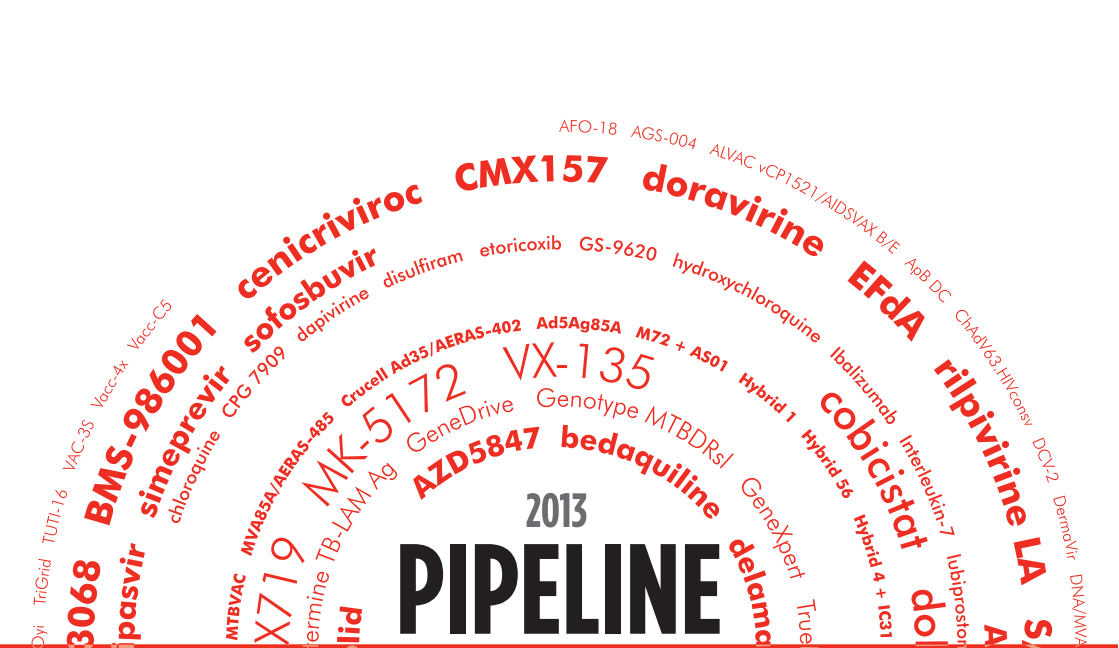

June 2013

HIV
HCV
TB

Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward A Cure, And Immune-based And Gene Therapies In Development

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ABOUT HIV i-BASE

HIV i-Base is a London-based HIV treatment activist organization. HIV i-Base works in the United Kingdom and internationally to ensure that people living with HIV are actively engaged in their own treatment and medical care and are included in policy discussions about HIV treatment recommendations and access.

www.i-base.info

ABOUT TAG

The Treatment Action Group (TAG) is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information.

www.treatmentactiongroup.org

2013 PIPELINE REPORT

HIV, HEPATITIS C VIRUS (HCV), AND TUBERCULOSIS (TB)
DRUGS, DIAGNOSTICS, VACCINES, PREVENTIVE TECHNOLOGIES,
RESEARCH TOWARD A CURE, AND IMMUNE-BASED AND GENE
THERAPIES IN DEVELOPMENT

By Polly Clayden, Simon Collins, Colleen Daniels, Mike Frick,
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Edited by Andrea Benzacar

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This report is dedicated to Spencer Cox

Walter Kurtz Photography © 2006

March 10, 1968–December 18, 2012

Remarks on the Naming of the Spencer Cox Center for Health

Melanie Thompson, MD

New York City, June 11, 2013

I am so honored to be part of this ceremony to celebrate a man I loved dearly, my friend and patient, Spencer Cox.

When I met him in the very early 90s, Spencer was one of ACT UP's youngest stars, a leading member of the Treatment and Data Group, and later, chair of TAG's Antiviral Drugs Committee. He was bright and beautiful and charismatic. His wit did not disappoint.

I had been in HIV research for only a few years, fighting at the national level from the clinical side for accelerated access to, and approval of, potentially lifesaving drugs to fight HIV. Conducting trials of monotherapy ddI, ddC, d4T, my research colleagues and I were desperate for something to stem the tide of unrelenting death. AZT was approved after 19 died on the placebo arm, but ddI was approved on the basis of a 10 T-cell improvement, in spite of pancreatitis and neuropathy. And ddC and d4T won approval on similar shaky grounds in spite of even worse neuropathy. It was the common wisdom in those days that the chance at life was worth a few painful or numb feet. And protease inhibitors were in the wings, with rumors of unprecedented potency.

Then in September 1994, this young man, this Spencer Cox, appeared before the FDA (representing TAG) and everything changed. Having fought hard for accelerated drug access, he now chastised the agency, researchers, and pharma about the danger of rapid approvals in the absence of true efficacy data, potentially putting patients at risk for little or no benefit.

"The approval of therapies based on inadequate, ambiguous, uninterpretable, or incomplete data offers severe and often insurmountable difficulties in the future evaluation of new treatments," he said. "This is the deck with which the current therapeutic house of cards was built."

And then he ended: "In short you must ask yourselves, 'Can we do better?' Damn right you can."

When the protease inhibitor ritonavir appeared on the scene, it was in a trial designed by Spencer and others. The new trial design led to unambiguous proof of efficacy and ritonavir was licensed in record time, setting a clear and rapid path for others and leading to over 8 million people receiving combination antiretroviral therapies today.

Liquid ritonavir, by the way, in addition to being god-awful in taste, caused a change in taste perception, which was termed "taste perversion." Spencer defined this taste perversion as "the inexplicable desire to wear plaid." The mystery of his many plaid shirts is now solved.

These were the miracle times—the Cocktail Days. People were living instead of dying: going back to work, starting new careers, joking about buying long-playing records. The Plague Years appeared to be, themselves, dying. AIDS was over.

Spencer left activism in the late 90s. He had to. But in many ways, the Plague Years were the best of times for him. There was a cause for which to fight. Miracles happened, after a lot of hard work. For Spencer, and for many other (largely white) gay poz activists, there was true community in the committee meetings as well as die-ins at the FDA, St. Patrick's cathedral, and the NIH. There was love—the beloved community. People cared for one another in the most basic of ways: cooking meals, ferrying to doctor visits, cleaning the sick and then burying them—all done together.

But when AIDS died for Spencer, so did the beloved community. Now no longer a baby activist, now having graduated from the Universities of ACT UP and TAG, the 30-something-year-old began to revisit the life that the 20-something-year-old Spencer had put on pause in order to battle death. He was not well prepared for the realities of a harsh, individualistic world without the focus of a mission and safety net of its caring institutions. Survivors like Spencer were expected just to be grateful to be alive and to get on with it. Like many, Spencer had been in the foxhole and seen multiple losses, just barely escaping with his own life. For some survivors, getting on with it was not so simple, because what "it" was was not entirely clear. Michael Callen said, "AIDS is the day-to-day management of uncertainty." But in the Cocktail Days, it was the challenge of living instead of dying that was brimming with uncertainty.

Spencer and John Voelcker founded the Medius Institute. As Spencer struggled with depression, his keen insight led him to observe that many Plague Survivors shared a syndrome not unlike that of combat veterans, posttraumatic stress disorder. But for these gay men, PTSD included high-risk-taking behavior, drugs, guilt, and shame as well as depression. Crystal meth was the drug du jour. He wrote scholarly white papers on depression and PTSD for Medius. But in the heady days of viral suppression, there was eagerness on the part of the media and the LGBT community itself—just as there is today, unfortunately—to forget about AIDS. The Medius Institute did not survive.

In 2009, depression and despair led to crystal meth, abandonment of ART, and the onset of life-threatening illness that landed him in a coma in a New York hospital. When he was well enough for discharge, he was released to heal in his mother Beverly's loving custody in Atlanta. I was honored to be his doctor, but when he walked through the door I hardly recognized him. We saw a lot of each other, needless to say, over the ensuing months that stretched to years. One by one, we patched up residual illnesses and played whack-a-mole with new ones. But finally, he began to bloom again, like the purple morning glories he raised from seed and posted on Facebook. He became the old Spence, with T cells to spare, and suppressed virus.

Spencer became a social media animal, a regular on Gawker, Twitter, Facebook. He had 1,347 Facebook friends, all drawn to him because of his acerbic wit and his mushy soft center. He regaled us with Puppy Porn, pictures of baby otters, recipes for meals he cooked, date invitations for James Franco, and ongoing ruthless commentary on just about anything. He summed up the presidential election by observing: "They have Ann Coulter. We have Cher. We win."

When *How To Survive a Plague* came along, it further enlivened Spencer. He was a star and he lusted for the Red Carpet, mostly to provide ripe material destined for harvest in catty posts. He shared the trailer with me with great pride. And partially due to this energy and the reconnection with friends that came with it, he declared that he was now ready to move back to the City.

Then last December I received a call from a young intern at a New York hospital. Spencer was again at death's door. I provided a full medical history, as far as it went. "Looks like he just stopped taking his meds. It's a shame how these guys just don't get it," he said. Needless to say, the young intern got a vigorous "schooling" from me.

Unfortunately, we doctors are often the ones who just don't get it. Our patients have complex lives. For even the best and brightest, antiretroviral therapy is not enough. And that's why it's so important that this clinic is being named for Spencer Cox.

Our biggest challenge for HIV care in America in 2013 is not the absence of effective drugs. Our biggest challenge is that our medical system, in general, is not structured to help people with HIV to get in care, stay in care, and take their drugs successfully. We human beings have messy lives. We need navigation to help us get back on a path when we fall off, and care for our emotional and mental health as well as drug therapy for the virus. We need treatment for other illnesses like hepatitis C, cardiovascular disease, and diabetes. And as we grow older, we need all of the above times two.

So it is with pride that I see Spencer's name appear on the face of this excellent clinic. This is the type of clinic that has the potential to bridge these gaps. I urge you to remember Spencer as you go about your work here. Be angry that he died. Use your power to fix our system. Remember that health is more than the absence of illness, and care is more than drugs. I challenge you to work hand in hand with your patients to become that model for a new beloved community that all patients need.

I hope that every day, when we awake, we ask ourselves, "Can we do better?" And I hope we answer: "Damn right we can."

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Seven Ways to Speed Up the Pipeline

By Polly Clayden and Mark Harrington

This chapter will discuss how to get the best drugs to the most people as quickly as possible; this requires that the compounds and combination products be:

- Discovered and developed in a high-quality research program;
- Approved by a national or multinational regulatory authority;
- Recommended by national or multinational guidelines groups;
- Available in formulations suitable for use in the proposed population;
- Affordable to public-sector programs and through private insurance; and
- Accessible to patients through local health systems.

1. Continue to invest in better drugs and treatment combinations for all HIV indications.

From 1987 to 2013, the U.S. Food and Drug Administration (FDA) approved 36 drugs and fixed-dose combinations (FDCs) to treat HIV in the United States.[1]

Since the FDA initiated the tentative approval (TA) program in 2004 for sale of compounds in developing countries supported by the President's Emergency Program for AIDS Relief (PEPFAR), the FDA has approved 159 different generic antiretroviral (ARV) drugs, formulations, and combinations.[2]

Over the past decade since TAG's first pipeline report in 2003, research and development (R&D) on new anti-HIV drugs has been remarkably successful.

Since 2003, 47 anti-HIV drugs or combinations have been studied in phase II or later under FDA oversight. Of these, 34% (16/49) have been approved by the FDA, 6.4% (3) have been submitted for approval, 21% (10/49) are moving forward in phase II (9) or phase III (1), while 6.4% (3/49) stopped development in phase III, 4.25% (2/49) are stalled in phase II, and 27.7% (13/47) stopped development in phase II.

Table 1 shows what happened to each of the 47 drugs or combinations studied in phase II forward since 2003.

Table 1A. HIV treatment pipeline, 2003–2013: Drugs approved, submitted, or active in phase II/III

Generic Name (Acronym)	Brand Name	Sponsor	Status	Date	Class
Approved (16)					
atazanavir	Reyataz	BMS	Approved	2003	PI
emtricitabine (FTC)	Emtriva	Gilead	Approved	2003	NRTI
enfuvirtide (T-20)	Fuzeon	Roche	Approved	2003	FI
fosamprenavir	Lexiva	GSK	Approved	2003	PI
abacavir/lamivudine (ABC/3TC)	Epzicom	GSK	Approved	2003	NRTI 2-FDC
emtricitabine/tenofovir (FTC/TDF)	Truvada	Gilead	Approved	2004	NRTI 2-FDC
tirpanavir	Aptivus	BI	Approved	2005	PI
darunavir	Prezista	Janssen	Approved	2006	PI
efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF)	Atripla	BMS/Gilead	Approved	2006	NNRTI/2NRTI 3-FDC
maraviroc	Selzentry	Pfizer	Approved	2007	CCR5RI
raltegravir	Isentress	Merck	Approved	2007	InI
etravirine	Intelence	Janssen	Approved	2008	NNRTI
nevirapine-XL	ViramuneXR	BI	Approved	2011	NNRTI
rilpivirine	Edurant	Janssen	Approved	2011	NNRTI
rilpivirine/emtricitabine/tenofovir	Complera	Janssen/Gilead	Approved	2011	NNRTI/2NRTI 3-FDC
elvitegravir/cobicistat/emtricitabine/tenofovir	Stribild	Gilead	Approved	2012	InI/PK booster/2NRTI 4-FDC
Submitted (3)					
elvitegravir	–	Gilead	Submitted	2012	InI (single-agent approval postponed; approved in Stribild 2012)
cobicistat	–	Gilead	Submitted	2012	PK booster (single-agent approval postponed; approved in Stribild 2012)
dolutegravir	–	ViiV/GSK	Submitted	2013	InI
Active in Phase III (1) or Phase II (9)					
tenofovir alafenamide (TAF)	–	Gilead	In phase III	2013	NtRI
BMS-986001	–	BMS	In phase II	2013	NRTI
BMS-663068	–	BMS	In phase II	2013	AI
cencriviroc	–	Tobira	In phase II	2013	CCR5RI
doravirine (MK-1439)	–	Merck	In phase II	2013	NRTI
GSK126744	–	GSK/Shionogi	In phase II	2013	InI (injectable LA)
rilpivirine-LA	–	Janssen	In phase II	2013	NNRTI (injectable LA)
darunavir/cobicistat/emtricitabine/ tenofovir alafenamide	–	Janssen/Gilead	In phase II	2013	PI/PK booster/2NRTI 4-FDC
dolutegravir/abacavir/lamivudine (572-Trii)	–	GSK/ViiV	In phase II	2013	PI/2NRTI 3-FDC
elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide	–	Gilead	In phase II	2013	InI/PK booster/2NRTI 4-FDC

Table 1B. HIV treatment pipeline, 2003–2013: drugs stopped or stalled in phase II/III

Generic Name (Acronym)	Sponsor	Last Active Year	Class
Stopped in Phase III (3)			
capravirine (AG-1549)	Pfizer	2005	NNRTI
vicriviroc (SCH 417690)	Schering	2010	CCR5I
lersivirine (UK-453,061)	Pfizer	2013	NNRTI
Stalled in Phase II (2)			
PRO 140	Progenics/Cytodyn	2010	AI mAb
ibalizumab (TNX-355)	Tanox/Biogen	2011	anti-CD4 mAb
Stopped in Phase II (13)			
DPC-083 (AI-183)	BMS	2004	NNRTI
PRO 542	Progenics	2004	AI mAb
SCH-C	Schering	2004	CCR5RI
calanolide A	Advanced L.S.	2005	NNRTI
reverset (D-D4FC)	Incyte	2006	NRTI
brecanavir	GSK	2007	PI
alovudine (FLT)	Mefuvir Beijing	2008	NRTI
BILR 355/r BS	BI	2008	NNRTI
elvucitabine	Achillion	2008	NRTI
racivir	Pharmasset	2008	NRTI
amdoxivir (DAPD)	Gilead	2010	NRTI
apricitabine	Avexa	2010	NRTI
bevirimat (PA-457)	Panacos/Myriad	2010	AI

Legend:
AI = attachment inhibitor
CCR5I = CCR5 receptor inhibitor
FDC = fixed-dose combination
FI = fusion inhibitor
InI = integrase inhibitor
LA = long-acting
mAb = monoclonal antibody
MI = maturation inhibitor
NNRTI = non-nucleoside reverse transcriptase inhibitor
NRTI = nucleoside or nucleotide (Nt) reverse transcriptase inhibitor
PI = protease inhibitor
PK booster = pharmacokinetic booster

These data indicate that ARV drug development continues to be a successful investment for R&D companies even after the approval of 36 drugs and combinations.

The best way to improve treatment outcomes is to assure the most rapid uptake of the best first-line ARV drugs and regimens everywhere.

Barriers to this include:

- unnecessarily slow development of generic compounds/combinations for developing countries (until recently; there has been gradual improvement: for example, a generic version of dolutegravir is now being produced by Indian manufacturers in partnership with ViiV Healthcare);
- regulatory sloth or inexperience in developing countries;
- failure to use existing regulatory mechanisms to support Northern/Southern-hemisphere collaboration and development of regulatory capacity in the South;
- corporate eagerness for profits in the North before providing access in the South;
- pharmaceutical sponsors' preference for combinations of their own compounds;
- intellectual property restrictions on exploring the use of cross-company combinations;
- lack of transparency;
- delays, e.g., by the World Health Organization (WHO) and many national regulatory and normative authorities, in authorizing the use of the best drugs and combinations;
- irrational complexity of regimens available in both North and South; and
- excessively high prices of generic compounds in rich countries and of brand-name compounds in poor ones.

Here we examine each of these barriers and suggest ways to overcome them.

2. Expedite regulatory approval of new drugs/regimens everywhere.

Several current mechanisms exist to expedite regulatory approval of drugs in developing countries, including FDA tentative approval (TA), WHO prequalification (PQ), and European Medicines Agency (EMA) Article 58. They, along with some newer proposed mechanisms, are discussed here.

National regulatory authorities (NRAs)—also known as medicines regulatory agencies (MRAs)—in developing countries must take steps to compel the most rapid approval of new products, best adapted for their needs (including those in new regimens not available in rich countries) as soon as stringent regulatory authorities have approved them.

Regulatory delay has posed as much of an obstacle to timely access to antiretrovirals in developing countries as has patent protection, yet it has attracted none of the advocacy attention.

Back in 2004, according to the World Health Organization (WHO), only about 20 percent of member states, largely in developed countries, had the capacity to effectively regulate medicinal products.[3]

In 2010, the WHO published an assessment of regulation in 26 African countries; it found that while structures exist, in practice they are largely inadequate, failing to form coherent regulatory systems. There were multiple contributing factors, including a fragmented legal basis for regulation, weak management structures and processes, and a severe lack of staff and resources. Most countries lacked the capacity to control the quality, safety, and efficacy of medicines on their markets.[4]

Even South Africa, which the WHO concluded has a fully functional MRA, experienced considerable delay in registering medicines. Table 2 shows the delay in approval for several single-entity and combination antiretroviral products in South Africa.

Table 2: Regulatory delay by South Africa's Medicines Control Council (MCC) compared with the FDA's[5,6,7]

Antiretroviral drug/combo	FDA approval	MCC approval	Delay (years)
zidovudine (AZT)	1987	1992	5
lamivudine (3TC)	1995	1996	1
lopinavir/ritonavir (LPV/r; Kaletra*)	2000	2002+	2+
tenofovir (TDF)	2001	2007	6
atazanavir (ATV)	2003	2007	4
emtricitabine (FTC)	2003	2007	4
emtricitabine + tenofovir (FTC/TDF)	2004	2007	3
efavirenz + emtricitabine + tenofovir (EFV/FTC/TDF; Atripla)	2006	2010	4

*Aluvia (Abbott's lopinavir/ritonavir co-formulation produced for developing countries in a different color than Kaletra) was registered by the MCC in 2008.

Currently almost all developing countries are guided by regulatory decisions made by stringent regulatory authorities in developed countries, mainly the FDA and the EMA.

While countries must continue to build the capacity to perform evaluations of medicines for their own markets, the FDA and the EMA, as well as the WHO, have mechanisms that could assist with expediting applications.[8] Some of these are woefully underused and none of them are perfect, but they are a huge improvement on piling up regulatory in-trays or corridors, while people go without or put up with suboptimal treatment.

a. Tentative approval by the FDA

The FDA introduced TA in May 2004 to support PEPFAR. This process expedites review and approval of marketing applications for single-entity, combination, and co-packaged generic versions of previously approved antiretrovirals, even when there is patent exclusivity in the United States.[9]

The program was introduced despite concerted lobbying of the U.S. government by industry and right-wing think tanks, including the Hudson Institute, which raised alarms about the quality of generic antiretrovirals. This often succeeded in muddying the waters between generic drugs (which are used all the time in medicine) and counterfeit drugs.[10]

There are now 159 generic antiretroviral products approved through the process for adults and children. Although many products are no longer preferred options, the list includes novel combination products that are unavailable in rich countries, such as an FDC of efavirenz plus lamivudine plus tenofovir DF, and ritonavir-boosted atazanavir. There are no generic versions of regimens or components of regimens approved since 2006: tenofovir DF plus emtricitabine plus efavirenz being the most recent (innovator product Atripla). There is no generic version of darunavir/ritonavir.

Table 3. FDA delay from U.S. to tentative antiretroviral approval[11,12]

Antiretroviral drug/combo	FDA U.S. approval	FDA TA approval	Delay (years)	From 2004*
zidovudine (AZT)	1987	2005	18	1
lamivudine (3TC)	1995	2005	10	1
lopinavir/ritonavir (LPV/r)	2000	2009	9	5
tenofovir (TDF)	2001	2007	6	3
atazanavir (ATV)	2003	2008	5	4
emtricitabine (FTC)	2003	2008	5	4
tenofovir + emtricitabine (FTC/TDF)	2004	2009	5	5
efavirenz + emtricitabine + tenofovir (EFV/FTC/TDF)	2006	2009	3	–

* Tentative approval began in 2004.

In the past, license agreements were negotiated three to five years after products were already approved in rich countries. Table 3 shows the time lag. A trend is gaining momentum though and, more recently, companies have signed agreements a year or two before FDA approval: Gilead for cobicistat, elvitegravir, and Stribild with Mylan, Strides, Hetero, and Ranbaxy (also licensing these and tenofovir DF to the Medicines Patent Pool); Janssen for rilpivirine with Aspen, Emcure, Mylan, Strides, and Hetero; and ViiV, which is already negotiating licenses for dolutegravir.

The Clinton Health Access Initiative (CHAI) made some recommendations to innovators to encourage making new products available more quickly than they have been to date, including:[13]

- Sign license agreements early enough in product development so that generic licensees can file with the FDA or the WHO within one year of innovator filings (this is beginning to happen but needs to be even earlier in the cycle to further abbreviate the process).
- Agree on plans for technology transfer and the generic product development no later than the 48-week readout from phase III trials.
- Have joint FDA meeting (alongside the generic company) to discuss clinical data requirements for an FDC, if the regimen components are different from those of the innovator product.
- Innovator and generic file for registration in the generic-licensed territories within 12 months of their respective FDA approvals.

Despite concerns from innovator companies that such discussions with the generic companies might be slated for promoting their products prior to approval, some of this is starting to occur. A strong signal from the FDA (and EMA) that early negotiations will not be frowned on would not go amiss.

The FDA Guidance for *Industry Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV 2006* includes a list of regimens and components for which the agency is satisfied that safety and efficacy have been established (and demonstrated in product labeling or peer-reviewed literature).[14] It suggests that FDC or co-packaged products for combinations on this list could be developed without conducting new clinical studies.

Updated guidance from the FDA on a list of acceptable FDCs that can be approved without further clinical testing is badly needed, as is a clear regulatory pathway for the approval of FDCs that are different from the innovators.

b. WHO Drug Prequalification (PQ)

WHO established its vaccine prequalification program in 1987 to ensure the quality of products for immunization programs purchased through UN systems.[15]

WHO prequalification of medicines was established in 2001, initially focusing on drugs for HIV, tuberculosis, and malaria. More recently it expanded to include medicines and products for reproductive health, influenza, and acute diarrhea in children.[16] Several hundred products are prequalified to treat HIV.[17] Many developing countries rely on prequalification; the program has helped countries to build regulatory capacity as it engages their regulators in the process and offers training in evaluation.

There is an agreement with the FDA that tentatively approved antiretrovirals are also prequalified. Although generally considered to be useful, WHO PQ is horribly slow, taking about two years to prequalify a drug.

c. EMA Article 58

Article 58 is a mechanism of the EMA by which the agency, in collaboration with the WHO, can provide a scientific opinion for medicinal products intended for use in countries outside the European Union.[18,19]

With this mechanism, the EMA conduct an identical regulatory review to that which they would for a standard one for Europe, but with input from WHO-recommended experts, largely from developing countries. This process does not result in a regulatory approval, but instead the EMA's Committee for Medicinal Products for Human Use (CHMP) issues a scientific opinion on the product. Under Article 58, the EMA can also provide scientific advice.

Two published reviews of regulatory mechanisms[20,21] highlighted the pros and cons of this process. Among the advantages, both reviews emphasize that WHO experts and, in some cases, regulators from developing countries can participate in plenary discussions on the product and the inspection of manufacturing facilities, helping to build regulatory capacity. Assessments are quick and rigorous—averaging about two and a half months—and they incorporate risk/benefit considerations that reflect the countries where the products will be marketed.[22]

Although promising, there are several downsides: "Article 58 also has drawbacks. It has been poorly understood, poorly positioned, and has lacked good advocates and, as a result, has barely been used," stated one review.[20] Importantly, the obligations of developing countries and the WHO are not made clear in the process; nor is it clear who will be responsible for postmarketing surveillance and pharmacovigilance once the product is in use outside the E.U. A massive obstacle

is the article—unlike E.U. orphan-drug approval—has no incentives (such as tax breaks, research grants, free scientific advice, or marketing exclusivity) to tempt companies to use it in favor of other regulatory mechanisms. Notably with the FDA, sponsors can benefit from several incentive schemes simultaneously.

The collaboration with the WHO was also intended to support its prequalification mechanism.[23] Scientific opinions from Article 58 have been used for three antiretroviral products on the WHO List of Prequalified Medicinal Products: lamivudine,[24] lamivudine/zidovudine,[25] and lopinavir/ritonavir (Aluvia)[26] for adults and children, adults and children over 12, and adults and children over two years, respectively. Given that the WHO has prequalified several hundred HIV products, this mechanism is not performing impressively, nor does it compare well to TA.

"The procedure continues to be ill-suited and heavily underused," write Saidu et al. "In fact, since its inception in 2004, only six applications have been submitted to the process, five of which received a positive opinion, including three antiretroviral drugs."

d. "Twinned" Regulatory Review

Expediting regulatory review in high-burden countries will require new approaches. Some have discussed possibilities such as parallel or "twinned" reviews.[20]

With parallel approval, it is possible for product developers to submit dossiers to a stringent authority and MRAs in developing countries, which conduct their regulatory reviews simultaneously but independently. This approach is more typically taken by product development partnerships (PDPs) than companies. Although the review notes that the gains offered by this approach might be illusory, as in practice MRAs wait for WHO prequalification or approval by a stringent authority. They highlight with concern the exception of weaker MRAs—some of which have approved products prior to any other review despite their lack of capacity to conduct a rigorous review.

The drawback with parallel review is that it offers no assistance or capacity building to the MRAs. Twinned review is a process where a developing-country regulator could access a dossier with a reviewer from a stringent authority. A DNDi/George Institute for International Health review points out that a twinned review of a dossier has not yet occurred, but PDPs have taken steps in this direction since 2006.[20] This approach could potentially offer a superior outcome, as the twinning would combine experience with product assessment with local experience of the disease and its treatment.

Our recommendations are that:

a. FDA tentative approval should be broadened to include drugs for HIV, HCV, and TB, and should expand to include regulatory support for national regulatory authorities in developing countries.

b. WHO should maintain support for its prequalification program through the end of the current decade while supporting NRAs to scale up their in-country regulatory capacity.

c. EMA should broaden the use of Article 58 activities to foster regulatory modernization in developing countries.

d. Organisation for Economic Co-operation and Development (OECD) countries should partner ("twin") with NRAs in developing countries to foster regulatory modernization and allow modern regulatory authorities to emerge around the world.

e. Duplicative reviews should be avoided and regional reviews adopted where possible.

3. Address developing-world needs up front during drug development.

Key research questions for developing countries need to be addressed early on in drug development programs to meet their regulatory requirements.

The needs of people with HIV may differ between developed and developing countries—where populations include significantly larger proportions women of child-bearing age, children, and people with tuberculosis, malaria, and other coinfections. Yet antiretrovirals are primarily developed for markets in developed countries, so research is conducted in order to provide information to register them accordingly.

A review by Médecins Sans Frontières provides the example of concomitant treatment of HIV and malaria for which WHO guidelines provided no evidence-based guidance in spite of the fact that 80 percent of HIV-positive people live in regions where malaria is endemic.[27] They contrast this with the practice in the developed world, where drug regulatory authorities frequently insist that data regarding a drug's use in particular populations be submitted.

The review, conducted in 2008, examines four antiretroviral drugs that had been recently approved or advanced along the pipeline—maraviroc, raltegravir, etravirine, and rilpivirine—considering dose selection, comparability and compatibility with other antiretrovirals, and use in specific populations. They found a lack of free access to company information, which limited their analysis.

They noted that until information is made more freely available, the rationale for companies' clinical development decisions will remain unclear, and the scientific community will be unable to advise and contribute with research in developing countries.

Their recommendations can be summarized as follows:

a. Pharmaceutical companies have a responsibility to initiate and contribute to studies that are relevant for resource-limited settings if they are seriously committed to contributing to global health.

b. The scientific community should also play a bigger part than they do currently by conducting studies that are of global public benefit. Public funding could be sought for such research as long as there is very clear agreement between the private- and the public sectors on future accessibility in terms of price, in-country registration, and possible licensing to other producers.

c. Regulatory agencies also have an important role to play by requiring data for relevant populations in different settings as part of the drug approval process.

d. Originator companies that hold the intellectual property and clinical data for the compounds should also take proactive steps.

There are numerous recent examples of high-quality studies examining the interaction of, for example, new HIV or TB drugs with existing ones.[28,29,30,31]

4. Close development and regulatory approval gaps between adult and pediatric medications.

The FDA needs to be given legal authority to require sponsors seeking approval for new agents treating diseases that are important domestically or globally among infants and children to develop and submit to regulatory approval a pediatric investigational program (PIP), as has been done successfully by the EMA.[32] Although the FDA has included incentives to industry to encourage pediatric development since 1997[33] and the EMA regulations were only adopted in 2007, over the past years, these have been insufficient. Table 4 shows the time lag with recently approved pediatric indications—particularly for the youngest age group.

Table 4. Adult/pediatric ARV approval gap: delay between FDA approval in adults and for each age-banded pediatric group.[34]

Antiretroviral	Approval for adults	Approval for children ages				
		12–18	6–12	2–6	0–2	Delay (years)
atazanavir (ATV)	2003	2008	2008[i]			5 (incomplete)
darunavir (DRV)	2006	2008	2008	2011[ii]		5
raltegravir (RAL)	2007	2011	2011	2011[iii]		4 (incomplete)
etravirine (ETR)	2008	2012	2012[iv]			4 (incomplete)
tenofovir (TDF)	2000	2010	2012	2012[v]		10–12
efavirenz (EFV)	1998	1998	1998	1998	2013	0–15

i Studies >3 months to 6 years ongoing.
ii Waiver below 3 years old.
iii Studies >4 weeks to 2 years planned.
iv Studies >2 months to 6 years planned.
v Deferral until more data on bone toxicities.

Our recommendations include:

a. Accelerate the development and regulatory approval of pediatric drugs and combinations.

b. Change U.S. law to mandate the development of pediatric ARVs and other drugs.

5. Continue to simplify and streamline global and national ARV guidelines.

The WHO is releasing updated and consolidated antiretroviral treatment guidelines this summer.[35] These guidelines combine adult and adolescent, pediatric, and pregnancy treatment recommendations. They are laudably simpler than previous iterations.

TABLE 5. 2013 WHO Guidelines–Recommended ART Regimens

First-line	tenofovir DF + lamivudine (or emtricitabine) + efavirenz preferred (including pregnant women) zidovudine alternative to tenofovir DF nevirapine alternative to efavirenz
Second-line	atazanavir/ritonavir or lopinavir/ritonavir preferred + tenofovir DF + lamivudine preferred backbone (if zidovudine or stavudine first-line) + zidovudine + lamivudine preferred (if tenofovir DF first-line)
Third-line	No specific recommendations: Integrase inhibitor (INI) or second-generation PI or NNRTI are mentioned

The new WHO guidelines are simple, but they have missed a chance to move the optimal modern protease inhibitor, darunavir, into preferred second-line r ecommendations—particularly after Johnson & Johnson announced in late November 2012 that it would not enforce patents on darunavir in sub-Saharan Africa.[36] It is currently included as an alternative only because there is no generic, heat-stable, co-formulated version of darunavir/ritonavir. Hopefully, this cautious inclusion will spur on generic development, approval and access, and dose optimization work for this drug.

Our recommendations:

a. The WHO should drop the inferior legacy PI lopinavir/ritonavir in its 2013 guidelines as soon as possible and replace it with the superior darunavir/ritonavir for second-line treatment.

b. Johnson & Johnson should broaden its patent-free region to include all high-HIV-burden countries outside of sub-Saharan Africa and provide licenses for its HIV drugs to the Medicines Patent Pool (MPP).

c. The WHO should prioritize review of dolutegravir and the role of integrase inhibitors after this drug is approved by the FDA/EMA, particularly since dolutegravir appears to be superior to current first-line therapies and may be accessible and affordable if ViiV Healthcare carries out its planned collaborations with generic companies.

The U.S. Department of Health and Human Services (DHHS) preferred first-line therapy recommendations for adults and adolescents are commendably simple—just four combinations are offered. But there are still too many alternative first-line

therapy recommendations and a thoroughly confusing "less satisfactory" category of combinations that should not be included in first-line therapy recommendations at all.

Table 6. DHHS preferred and alternative first-line ARV regimens[37]

Regimen	Rating	Branded components	Pill count
DHHS preferred first-line regimens (4 regimens; 3 once-daily, 1 twice-daily)			
efavirenz + emtricitabine + tenofovir (EFV/FTC/TDF)	AI	Atripla	1
atazanavir/ritonavir + emtricitabine + tenofovir (ATV/r/FTC/TDF)	AI	Reyataz + Norvir + Truvada	3
darunavir/ritonavir + emtricitabine + tenofovir (DRV/r/FTC/TDF)	AI	Prezista + Norvir + Truvada	3
raltegravir + emtricitabine + tenofovir (RAL/FTC/TDF)	AI	Isentress twice-daily + Truvada	3
DHHS alternative regimens (15 regimens; 8 once-daily, 3 twice-daily)			
efavirenz + abacavir + lamivudine (EFV/ABC/3TC)	BI	Sustiva + Epzicom	2
rilpivirine + emtricitabine + tenofovir (RPV/FTC/TDF)	BI	Complera	2
rilpivirine + abacavir + lamivudine (RPV/ABC/3TC)	BIII	Edurant + Epzicom	2
atazanavir/ritonavir + abacavir + lamivudine (ATV/r/ABC/3TC)	BI	Reyataz + Norvir + Epzicom	3
darunavir/ritonavir + abacavir + lamivudine (DRV/r/ABC/3TC)	BII	Prezista + Norvir + Epzicom	3
fosamprenavir/ritonavir + abacavir + lamivudine (FPV/r/ABC/3TC)	BI	Lexiva once- or twice-daily + Epzicom	3–4
fosamprenavir/ritonavir + emtricitabine + tenofovir (FPV/r/FTC/TDF)	BI	Lexiva once- or twice-daily + Truvada	3–4
lopinavir/ritonavir + abacavir + lamivudine (LPV/r/ABC/3TC)	BI	Kaletra once- or twice-daily + Epzicom	3–4
lopinavir/ritonavir + emtricitabine + tenofovir (LPV/r/FTC/TDF)	BI	Kaletra once- or twice-daily + Truvada	3–4
elvitegravir/cobicistat + emtricitabine + tenofovir (EVG/COBI/FTC/TDF)	BI	Stribild	1
raltegravir + abacavir + lamivudine (RAL/ABC/3TC)	BIII	Isentress + Epzicom	2

Our recommendations:

d. Despite apparent simplification, DHHS ARV regimen guidelines are still too complicated.

e. DHHS should drop clinically inferior PIs with less simple dosing schedules (fosamprenavir/r and lopinavir/r) from the first-line alternative recommended category.

f. DHHS should eliminate the "less satisfactory" category from its first-line therapy recommendations. If they are "less satisfactory," they should not be recommended.

6. Rationalize optimal combinations and assure the rapid availability of preferred/alternative new compounds and regimens when their use can improve treatment outcomes in developing countries.

Innovator companies need to assure the rapid availability of preferred/alternative new compounds or combinations when their use can improve treatment outcomes in developing countries.

The antiretroviral and dose optimization chapters in the *2013 Pipeline Report* describe a number of FDCs, either filed with the FDA/EMA or in phase III, targeted to markets in rich countries. These are combinations of compounds from the same manufacturer, e.g., elvitegravir/cobicistat/tenofovir DF/emtricitabine (Stribild); elvitegravir/cobicistat/tenofovir AF/emtricitabine; and dolutegravir/abacavir/lamivudine (572-Trii). In her chapter, Tracy Swan discusses similar issues afflicting the HCV pipeline.

Alternatively, they are licensing agreements between companies where there is no competing alternative component, such as that between Gilead and Janssen to formulate darunavir/cobicistat/emtricitabine/tenofovir AF.

Gilead, Janssen, and BMS are also investigating cobicistat with darunavir and atazanavir as co-formulated boosted PIs, although it is unclear whether cobicistat offers any advantages over ritonavir.

Of the FDCs in development, Stribild is not expected to become a preferred option in developing countries, with dolutegravir on the horizon, elvitegravir requiring a boosting agent, and lamivudine preferred to emtricitabine.

572-Trii is also not entirely appropriate as the cost of abacavir and concerns about hypersensitivity have meant this NRTI is not recommended or widely used (except in pediatric treatment).

Governments and regulators must ensure that the best possible combinations are studied, validated, and produced together, regardless of who discovered or patented them, or who manufactures them. If studies result in proof that cross-company (or multicompany) combinations are safe and highly effective, regulators need to authorize them, and those who manufacture combinations and blister packs need to be able to co-package or co-formulate them so that people can receive optimal treatment. This will require flexibility on the part of regulators, innovators, generic companies, purchasers, and providers. Getting the best combinations to as many people as possible as quickly as possible should override commercial considerations.

If two drugs are generic and one is still patented, the patent holder should license the patented drug so it can be co-formulated or co-packaged with the generics. In the case of HCV, where everything is moving so fast, regulators and guide-lines panels should require that sponsors study the most promising combination therapies regardless of who discovered or makes them. This is just as important in developed as in developing countries—where occasionally more rational products are available such as an FDC of efavirenz/tenofovir DF/lamivudine and co-packaged atazanavir/ritonavir plus lamivudine/tenofovir DF.

Our recommendations:

a. Gilead needs to study optimal companion drugs for tenofovir AF, and tenofovir AF dosing without cobicistat, irrespective of the sponsor.

b. ViiV needs to study dolutegravir with tenofovir DF and lamivudine rather than abacavir—as in 572-Trii.

c. Expedite the availability of optimized fixed-dose combinations and blister packs using high-quality generics as soon as available in the United States and elsewhere.

7. People with HIV in developed countries should benefit from generics innovations, and the savings should be reinvested in high-quality HIV prevention and treatment programs to end HIV transmission and illness, and death from AIDS.

The next decade will see rich countries begin to benefit from the most astounding vigor and expansion of generics innovation in HIV treatment since Cipla's bold move in 2001 to manufacture a cross-sponsor off-patent combination, which revolutionized treatment access in developing countries.

Table 7. Schedule of ARV generic availability in the United States

Drug	U.S. Patent expiration	With 18-month extension	Plus 6-month exclusivity
zidovudine/Retrovir	September 2005	February 2007	August 2007
didanosine/Videx EC	August 2006	January 2008	July 2008
zalcitabine/Hivid	November 2006	April 2008	October 2008
stavudine/Zerit	September 2008	February 2010	August 2010
lamivudine/Epivir	February 2009	July 2010	January 2011
saquinavir/Invirase	December 2010	May 2012	November 2012
nelvirapine/Viramune	November 2012	April 2013	October 2013
efavirenz/Sustiva	August 2012	January 2014	July 2014
ritonavir/Norvir	December 2012	May 2014	November 2014
indinavir/Crixivan	May 2013	October 2014	April 2015
delavirdine/Rescriptor	October 2013	March 2015	September 2015
nelfinavir/Viracept	October 2013	March 2015	September 2015
From E-MedTV - earliest possible			
abacavir/Ziagen	June 2012	November 2013	May 2014
enfuvirtide/Fuzeon	June 2013	November 2014	May 2015
emtricitabine/Emtriva	March 2016	August 2017	February 2018
lopinavir/Kaletra	June 2016	November 2017	May 2018
atazanavir/Reyataz	April 2017	September 2018	March 2019
tenofovir/Viread	June 2017	November 2018	May 2019
fosamprenavir/Lexiva	December 2017	May 2019	November 2019

We see the coming decade as an opportunity for the introduction of high-quality generic ARV drugs and the most rational combinations in both developed and developing countries, with billions of dollars and millions more lives saved.

However, data on 2011 expenditures from the United States AIDS Drug Assistance Programs (ADAPs) indicate that generic ARV procurement represented just 0.7% of expenditures (the data are on total costs and do not demonstrate sales by volume).

Table 8: U.S. ADAP ARV Expenditures FY 2011

Drug name	Company	Total	Adjusted for missing	% of total
DHHS preferred first-line regimens/drugs				
efavirenz + emtricitabine + tenofovir DF (Atripla)	BMS/Gilead	$431,120,237.66	$452,495,957.75	30.19%
emtricitabine + tenofovir DF (Truvada)	Gilead	$292,104,331.29	$306,587,391.65	20.46%
atazanavir (Reyataz)	BMS	$158,616,528.61	$166,481,022.60	11.11%
darunavir (Prezista)	Janssen	$95,579,834.05	$100,307,883.21	6.69%
raltegravir (Isentress)	Merck	$95,569,380.70	$100,307,883.21	6.69%
ritonavir (Norvir)	Abbott	$60,813,528.16	$52,524,628.65	3.50%
tenofovir DF (Viread)	Gilead	$26,329,560.99	$27,635,028.18	1.84%
efavirenz (Sustiva)	BMS	$19,774,996.94	$20,755,477.01	1.38%
emtricitabine (Emtriva)	Gilead	$1,459,579.54	$1,531,948.13	0.10%
DHHS preferred first-line subtotal		**$1,181,367,977.94**	**$1,228,627,220.39**	**81.98%**
DHHS alternative first-line regimens/drugs				
abacavir + lamivudine (Epzicom)	ViiV/GSK	$55,834,785.63	$58,603,175.15	3.91%
lopinavir + ritonavir (Kaletra)	Abbott	$50,043,387.13	$52,524,628.65	3.50%
fosamprenavir (Lexiva)	ViiV/GSK	$19,928,279.49	$20,916,359.58	1.40%
abacavir (Ziagen)	ViV/GSK	$8,795,481.78	$9,231,577.65	0.62%
lamuvudine (Epivir)	ViiV/GSK	$5,674,252.91	$5,955,592.62	0.40%
rilpivirine + emtricitabine + tenofovir (Complera)	Janssen/Gilead	$2,864,832.88	$3,006,876.47	0.20%
rilpivirine (Edurant)	Janssen	$1,096,477.71	$1,150,843.06	0.08%
DHHS alternative first-line subtotal		**$144,237,497.53**	**$151,389,053.18**	**10.10%**
DHHS "other" or not recommended for first-line				
nevirapine (Viramune)	BI	$24,988,441.21	$26,227,413.26	1.75%
lamivudine + zidovudine (Combivir)	ViiV/GSK	$22,315,624.03	$23,422,072.98	1.56%
etravirine (Intelence)	Janssen	$19,928,279.49	$20,916,359.58	1.40%
abacavir + lamivudine + zidovudine (Trizivir)	ViiV/GSK	$12,959,115.09	$13,601,651.42	0.91%
nelfinavir (Viracept)	ViiV/Pfizer	$8,557,770.47	$8,982,080.19	0.60%
lamivudine + zidovudine (generic)	generic	$7,211,626.31	$7,569,191.77	0.51%
maraviroc (Selzentry)	ViiV/Pfizer	$5,336,449.20	$5,601,039.99	0.37%
saquinavir (Invirase)	Roche	$3,348,907.36	$3,514,952.24	0.23%
enfuvirtide (Fuzeon)	Roche	$2,292,461.56	$2,406,125.94	0.16%
didanosine (generic)	generic	$1,396,960.75	$1,466,224.60	0.10%
lamivudine (generic)	generic	$1,142,613.47	$1,199,266.31	0.08%
tipranavir (Aptivus)	BI	$1,086,042.91	$1,139,890.88	0.08%
zidovudine (Retrovir)	ViiV/GSK	$619,694.00	$649,555.30	0.04%
indinavir (Crixivan)	Merck	$618,870.58	$649,555.30	0.04%
stavudine (Zerit)	BMS	$496,566.23	$521,186.88	0.03%
didanosine (Videx)	BMS	$347,914.45	$365,165.68	0.02%
zidovudine (generic)	generic	$287,349.94	$301,597.27	0.02%
delavirdine (Rescriptor)	ViiV/Pfizer	$57,854.10	$60,772.61	0.00%
DHHS "other" / not recommended for first-line subtotal		**$112,992,541.15**	**$118,594,102.20**	**7.91%**
U.S. ADAP ARV 2011 total		**$1,438,598,016.62**	**$1,498,610,375.77**	
All generics combined		**$10,038,550.47**	**$10,536,279.95**	**0.70%**

Source: National Alliance of State and Territorial AIDS Directors (NASTAD)

Our recommendations:

a. Generic ARVs in the United States and other developed countries should be priced at 25 percent of the brand-name/innovator price or less.

b. Ideally, given the U.S. taxpayers' generosity to people with HIV in other countries though the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and PEPFAR, the U.S. generic price should equal the best global generic price of an equivalent FDA TA regimen; similar benefits should accrue to other developed countries when patents expire.

c. Prices of generic ARVs are far too high in the United States. For example, generic abacavir and nevirapine cost about 90 percent of that of the innovator, while generic AZT costs about 65 percent as much as branded Retrovir.

d. This year's imminent patent expiration of efavirenz provides an opportunity to begin a much-needed transition to generic preferred drugs and combinations. The coming decade will see a number of such innovator/generic transitions.

e. The potential of these changes to accelerate a reduction in ARV drug prices must be realized.

f. Countries such as the United States must carry out public tenders to accelerate the availability of inexpensive high-quality generic drugs and combinations as soon as practicable.

g. Savings from their use should be reapplied to allow broader, earlier treatment of HIV and related conditions such as HCV, and to improve HIV prevention, care, and support services.

Conclusion: Summary of Recommendations to Speed Up the Pipeline

The best way to improve treatment outcomes is to assure the most rapid uptake of the best first-line ARV drugs and regimens everywhere.

1. **Continue to invest in better drugs and treatment combinations for all HIV indications.**

2. **Expedite regulatory approval of new drugs/regimens everywhere.**

   a. FDA tentative approval should be broadened to include drugs for HIV, HCV, and TB, and should expand to include regulatory support for national regulatory authorities in developing countries.

   b. The WHO should maintain support for its prequalification program through the end of the current decade while supporting NRAs to scale up their in-country regulatory capacity.

   c. The EMA should broaden the use of Article 58 to foster regulatory modernization in developing countries.

   d. OECD countries should partner ("twin") with NRAs in developing countries to foster regulatory modernization and allow modern regulatory authorities to emerge around the world.

   e. Duplicative reviews should be avoided, and regional reviews adopted where possible.

3. **Address developing-world needs up front during drug development.**

   d. Pharmaceutical companies have a responsibility to initiate and contribute to studies that are relevant for resource-limited settings if they are seriously committed to contribute to global health.

   e. The scientific community should also play a bigger role, conducting studies that are of global public benefit. Public funding could be sought for such research as long as there is very clear agreement between the private and the public sectors on future accessibility in terms of price, in-country registration, and possible licensing to other producers.

   f. Regulatory agencies also have an important part to play by requiring data for relevant populations in different settings as part of the drug approval process.

g. Originator companies that hold the intellectual property and clinical data for the compounds should also take proactive steps.

4. **Close development and regulatory approval gaps between adult and pediatric medications.**

   a. Accelerate the development and regulatory approval of pediatric drugs and combinations.

   b. Change U.S. law to mandate the development of pediatric ARVs and other drugs.

5. **Continue to simplify and streamline global and national ARV guidelines.**

   a. WHO should drop the inferior legacy protease inhibitor lopinavir/ritonavir in its 2013 guidelines and replace it with the superior first-line regimen darunavir/r.

   b. Johnson & Johnson should broaden its patent-free region to include all high-HIV-burden countries outside of sub-Saharan Africa and should provide licenses for its HIV drugs to the Medicines Patent Pool.

   c. The WHO should prioritize review of dolutegravir and the role of integrase inhibitors after drug is approved by the FDA/EMA, particularly since dolutegravir appears to be superior to current first-line therapies and may be accessible and affordable if ViiV Healthcare carries out its planned collaborations with generic companies.

   d. Despite apparent simplification, DHHS ARV regimen guidelines are still too complicated.

   e. DHHS should drop clinically inferior PIs with less simple dosing schedules (fosamprenavir/r and lopinavir/r) from the first-line alternative recommended category.

   f. DHHS should eliminate the "less satisfactory" category from its first-line therapy recommendations. If they are "less satisfactory," they should not be recommended.

6. **Rationalize optimal combinations and assure the rapid availability of preferred/alternative new compounds and regimens when their use can improve treatment outcomes in developing countries.**

    a. Gilead needs to study optimal companion drugs for tenofovir AF, and tenofovir AF dosing without cobicistat, irrespective of the sponsor.

    b. ViiV needs to study dolutegravir with tenofovir DF and lamivudine rather than abacavir (as in 572-Trii).

    c. Expedite the availability of optimized fixed-dose combinations and blister packs using high-quality generics as soon as available in the United States and elsewhere.

7. **People with HIV in developed countries should benefit from generics innovations, and the savings should be reinvested in high-quality HIV prevention and treatment programs to end HIV transmission and illness, and death from AIDS.**

    a. Generic ARVs in the United States and other developed countries should be priced 25 percent of the brand-name/innovator price or less.

    b. Ideally, given the U.S. taxpayers' generosity to people with HIV in other countries though GFATM and PEPFAR, the U.S. generic price should equal the best global generic price of an equivalent FDA TA regimen; similar benefits should accrue to other developed countries when patents expire.

    c. Prices of generic ARVs are far too high in the United States. For example, generic abacavir and nevirapine cost about 90 percent of that of the innovator, while generic AZT costs about 65 percent as much as branded Retrovir.

    d. This year's imminent patent expiration of efavirenz provides an opportunity to begin a much-needed transition to generic preferred drugs and combinations. The coming decade will see a number of such innovator/generic transitions.

    e. The potential of these changes to accelerate a reduction in ARV drug prices must be realized.

    f. Countries such as the United States must carry out public tenders to accelerate the availability of inexpensive high-quality generic drugs and combinations as soon as practicable.

    g. Savings from their use should be reapplied to allow broader, earlier treatment of HIV and related conditions such as HCV, and to improve HIV prevention, care, and support services.

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2013 HIV, HCV, and TB Pipeline Executive Summary and Research Policy Recommendations

2013 HIV pipeline executive summary

The 2013 HIV pipeline comprises adult and pediatric antiretroviral therapy (ART) development and dose-optimization research as well as antiretroviral preventive technologies, research toward a cure, and immune-based and gene therapies. Adult and pediatric ART clinical research continues to move forward robustly, with encouraging movement on the dose-optimization front. In 2012, for the first time, the U.S. Food and Drug Administration (FDA) approved the use of an antiretroviral combination, emtricitabine/tenofovir DF (FTC/TDF, Truvada) as preexposure prophylaxis (PrEP) for sexual transmission of HIV. HIV vaccine research made encouraging progress in basic science, while clinical trials continued to experience setbacks, which moved the field back toward early-stage, preclinical, and phase I activities. Cure-related research moved forward slowly but with encouraging surprises, while immune-based and gene therapies – many of them now being drawn into the cure-related space – remain promising but unproven for individuals with suboptimal immune responses despite viral suppression (so-called immunologic nonresponders, or INRs) and for those with HIV-related immunologic senescence and inflammatory end-organ disease.

ADULT ANTIRETROVIRAL PIPELINE

The three themes of the "Antiretroviral Pipeline" by Simon Collins and Tim Horn[1] are the continuing wave of innovations bringing broader and in some cases better treatment options for people with HIV; the possible conflicts these innovations will encounter due to global economic austerity; and the potential for combining generic antiretrovirals as they move off-patent in many developed countries with innovator compounds to produce synergistic, often cross-sponsor, combinations and fixed-dose combinations (FDCs) that could offer people with HIV the best of the new and the old while saving cash-strapped health systems billions of dollars.

The 2013 adult ARV pipeline is robust, with one drug, dolutegravir, awaiting FDA expedited review in August 2013, two 2012 submissions, elvitegravir and cobicistat, still undergoing extended review, and a triple fixed-dose single-pill once-daily combination of dolutegravir, abacavir, and lamivudine (3TC) following rapidly on the single drug in the pipeline.

Ten compounds – the prodrug tenofovir alafenamide (TAF, formerly GS-7340), the CCR5 inhibitor cenicriviroc, the NNRTI MK-1439, another tenofovir prodrug, CMX-157, the novel nucleosides EFdA and BMS-986001, the attachment inhibitor BMS-663068, three long-acting (LA) injectables S/GSK1265744 LAP, rilpivirine-LA, and the long-acting fusion inhibitor albuvirtide – are progressing at a healthy pace.[1]

Three compounds covered in previous pipelines, apricitabine, ibalizumab, and PRO 140, are stalled, generally awaiting outside investment from a new sponsor, while one compound, the NNRTI lersivirine, was terminated in February 2013.

Last year, Gilead secured a first-ever FDA approval of an FDC containing two new drugs, the integrase inhibitor elvitegravir (EVG) and the pharmacokinetic booster cobicistat (COBI) with two approved ones, FTC/TDF, in the quadruple single-day pill branded as Stribild. This apparent slam-dunk was mitigated by the U.S. federal HIV treatment guidelines' relegation of the new FDC to an alternative first-line regimen due to concerns about efficacy and tolerability in comparison with preferred first-line regimens containing boosted atazanavir or darunavir, efavirenz, or raltegravir in combination with FTC/TDF;[2] and by the FDA's decisions in early 2013 to defer approval of both new single agents, EVG or COBI, as single drugs due to unspecified concerns with their dossiers.[3,4] Gilead's FDC-first strategy was clever, but may foreshadow an unfortunate tendency on the part of some sponsors to privilege combinations from their own companies, which may not be those best suited for individual patient management.

This year's leading compound for FDA approval, the integrase inhibitor from ViiV known as dolutegravir (DTG), demonstrates many advantages over the other two approved agents in its class, including a low molecular weight permitting once-daily 50 mg dosing in treatment-naive patients, and no food or pharmacokinetic boosting requirements. The sponsor's impressive data report superiority to Atripla (efavirenz/FTC/TDF) in treatment-naive patients, noninferiority to raltegravir (RAL) in the same population, and interim results reported at CROI 2013 in treatment-experienced, integrase-naive patients report greater viral suppression on DTG vs. RAL.[1]

The development plan is progressive with respect to key drug-drug interaction studies such as those with methadone or combined oral contraceptives (already complete), a pediatric development plan (already under way), and the sponsor's already-undertaken negotiations with generic manufacturers to make the product available globally at accessible prices in low- and middle-income countries (LMICs).[1]

Collins and Horn warn, however:

> The model of pricing newly approved antiretrovirals (ARVs) higher than current drugs is increasingly difficult to sustain….The demand for ARVs is well established and it will continue to expand for many years: life expectancy has been dramatically extended; treatment is lifelong and is now being recommended [in rich countries] regardless of a person's CD4 T-cell count; rates of new infections and diagnoses remain high in many countries and in specific populations….[Yet] [h]igher pricing in an increasingly competitive market will ultimately translate into a missed opportunity to recoup development costs, and potentially better drugs will be barely used….So the compounds reviewed in this year's ARV report—many with great potential—must be considered against a backdrop of a changing economic landscape.[1]

The good news is that use of high-quality generic ARV combinations has already enabled programs such as the U.S. President's Emergency Program for AIDS Relief (PEPFAR) to treat three times as many people in 2012 as it did in 2008 despite flat funding levels.[2] Now, due to a coming wave of expiring ARV patents in rich countries, the possibility exists to save billions of dollars in HIV treatment costs by combining newly generic preferred ARVs with branded compounds – if the government and industry (both innovator and generic) collaborate to make the right products available; one paper estimated that if the United States switched to generic efavirenz, generic 3TC, and still-on-patent TDF, the country could save $920 million in the first year alone.[3] The FDA has already tentatively approved many of the right combinations for sale in developing countries, but it is not clear what the United States is doing to ensure that the cheap, high-quality drugs it's providing to 5.1 million people in developing countries can also be made available to people here at home.

It will be critical for the United States – and for other programs such as Britain's National Health Service (NHS) – to reinvest the savings generated by sensible use of generic-containing antiretroviral combinations into massively expanded HIV-prevention and treatment programs to end HIV transmission and progression to AIDS and death, and to achieve an "AIDS-free generation" in the United States and around the world.

The danger, as Collins and Horn point out, is that the world and even rich-country formularies will move even further toward two-tier ARV regimens, where the wealthy and those with private insurance will be able to access newer compounds which in some cases will be more tolerable and sometimes more durable than older

regimens, while those receiving public-sector treatment in rich countries and nearly everyone in developing ones will receive older, suboptimal combinations (see "Seven Ways to Speed Up the Pipeline").

PEDIATRIC ANTIRETROVIRAL PIPELINE

In this year's "Pediatric Antiretroviral Pipeline," Polly Clayden notes that 2012's "bumper year for ARV approvals" has been followed by one "in which new approvals were fewer and far between," with "only two new...[U.S. FDA] approvals: an expanded indication for efavirenz to include children at least three months old, and once-daily dosing of darunavir in treatment-naive children three years and older," while "[t]wo development programs—the granule formulation of ritonavir-based protease-inhibitor ritonavir, and the integrase inhibitor dolutegravir—remained attention-worthy."[5]

While it took efavirenz 15 years from adult approval to reach very young children (there were admittedly formulation difficulties, and preclinical toxicology results of concern), it's impressive that dolutegravir is already being studied in children, with a granule formulation in development for the youngest ones. In recent years, concerted efforts by a number of players including the Clinton Health Access Initiative (CHAI), the Drugs for Neglected Diseases Initiative (DNDi), and UNITAID, have stepped in to rationalize pediatric ARV access and development and drive it forward in a coordinated way.

RETROFITTING FOR PURPOSE: TREATMENT OPTIMIZATION PIPELINE

Lower doses of effective ARVs have the potential to be both more tolerable (in some cases) and cheaper (in most cases) than existing ones. As Clayden notes in "Retrofitting for Purpose: Treatment Optimization," reformulation and process-chemistry efficiencies also have the potential to reduce the prices of common ARVs.[6] CHAI, the Bill & Melinda Gates Foundation, the Johns Hopkins University, Médecins Sans Frontières (MSF), the Medicines Patent Pool (MPP), and the WHO have been working on various strategies to this end since 2010. Clayden presents a wish list for an ideal ARV regimen [Table 1: Target product profile of a dream ARV regimen] and notes the plunging global best price of first-line fixed-dose combined efavirenz/3TC/TDF, which has dropped 21 percent in just one year, down to US$131 per person per year (pppy). (This is the combination that Walensky et al. found could save the U.S. health system $920 million dollars in the first year alone, and their model used the prior, 2012 price, so the actual savings

are likely over $1 billion.)[3] The tenofovir prodrug, described here and by Collins and Horn, could potentially drive prices down further, since its active dose is 25 mg/day vs. 300 mg/day with TDF – and down to 10 mg/day when coadministered with cobicistat.

The WHO 2013 ARV treatment guidelines provide another opportunity for treatment optimization with simpler consolidated recommendations.[7] One concern, however, is that the WHO still includes lopinavir/ritonavir as a recommended second-line therapy (alongside atazanavir/ritonavir) while developed-country guidelines such as those in the United States prefer the more potent, durable, tolerable darunavir/ritonavir to the outdated lopinavir/ritonavir. At present, a heat-stable, generic combination darunavir/ritonavir product does not exist, which led to this decision, but with such products on the way, the WHO could rectify this oversight rapidly, and we recommend that they do so.

Clayden notes the potential for lower, cheaper dosing with TDF, zidovudine (AZT), efavirenz, atazanavir/ritonavir, darunavir/ritonavir, and boosting ritonavir itself. An outlier, stavudine (d4T), is being studied at a lower dose, but most activists and many clinicians oppose the continued use of this toxic relic of the 1990s. A recent agreement by UNITAID to subsidize the difference in cost between stavudine and TDF-containing regimens, in turn bringing the cost of TDF down still further, offers a way forward that will hasten the long overdue phasing-out of stavudine both in adults and – it is to be hoped – in children.[8]

Looking further ahead, Clayden notes the potential of new compounds such as low-dose, once-daily dolutegravir (50 mg/day) and – if provided as a single pill and at acceptable, affordable prices – the tenofovir prodrug TAF (25 mg/day, 10 mg/day if boosted with cobicistat) to bring down global ARV prices still further. Long-acting (LA) agents such as Shionogi/ViiV's integrase follow-up compound, GSK1265744, and Janssen's LA rilpivirine offer the possibility of monthly or even quarterly injectable dosing.[6]

PREVENTIVE TECHNOLOGIES, RESEARCH TOWARD A CURE, AND IMMUNE-BASED AND GENE THERAPIES PIPELINE

Richard Jefferys provides a sweeping overview of the complex developments in biomedical HIV preventive therapies, cure-related research, immune-based, cell and gene therapies.[9] For the first time ever, his broad chapter has yielded an FDA-approved product, FTC/TDF (Truvada) for prevention of sexually transmitted HIV. Uptake of the intervention—which is effective if taken daily—is hindered by the high price ($11,000 pppy or more in the U.S.) and by uncertainties about how

best to use PrEP. Intermittent dosing studies are under way, as is a study of another agent, the CCR5 receptor blocker maraviroc, in an ongoing study among men who have sex with men (MSM). The long-acting ARVs mentioned above have the potential to work as PrEP, and microbicide researchers have turned to vaginal rings, which release anti-HIV agents slowly over a period of weeks.[9]

Vaccine research has seen impressive advances in basic science with the discovery of antibodies in chronically infected individuals that can neutralize an extensive array of clinical HIV strains. The work of turning this discovery into a candidate vaccine remains ahead. An injectable gene therapy–like approach, which appeared effective in mice and generates host resistance to HIV, is moving forward into human trials. Vaccine efficacy trials, however, are stalled after multiple reverses seen with adenovirus-vectored products, which in several trials appeared not only to be ineffective, but actually to increase incidence.[9]

Cure-related research generated many headlines, not always accurate, after a report at the 2013 Conference on Retroviruses and Opportunistic Infections (CROI) demonstrated that an infant treated very early during infection, whose mother subsequently was lost to care in the chaotic health system of Mississippi, and whose treatment was therefore interrupted, appeared to have cleared HIV, lost antibodies to the virus, and be functionally cured.[10] Additional excitement was generated by a cohort of very-early-treated individuals in France who appear to have experienced long-term ART-free virological control for periods of up to several years.[11] These advances give additional impetus to ongoing efforts to design scalable, broadly usable, and safe therapeutic approaches that would produce a functional or sterilizing cure of HIV-1.

Jefferys notes that many immune-based and gene therapeutic approaches have now been subsumed under the cure-related research umbrella, but that two other potential indications remain understudied and potentially amenable to such therapeutic approaches—therapies that would increase immunologic recovery among INRs and those directed at sequelae of HIV infection that involve immuno-senescence and hyperimmune-activation-induced end-organ disease.[9]

2013 hepatitis C virus (HCV) pipeline executive summary

In "Hepatitis C Drug Development Catapults Onward," Tracy Swan describes the astonishing therapeutic revolution currently under way in HCV treatment research:

> Over the past 24 months, duration of treatment and assessment of posttreatment outcome have been dramatically abbreviated. Old-school, 48-week regimens with SVR-24 [sustained viral response 24 weeks after therapy ends] are gone. Now, duration of treatment is usually 12 to 24 weeks, and SVR-12 is the endpoint that is commonly used as a surrogate for cure….This acceleration in, and rapid evolution of, HCV drug development has left some drugs behind: they are shackled to lumbering development programs, such as the strategy being used in many phase III trials—adding a DAA [direct-acting antiviral] to 24 or 48 weeks of response-guided therapy with peginterferon (PEG-IFN) and ribavirin (RBV). This approach is likely to have limited clinical relevance, given the rapid development of peginterferon-sparing and peginterferon-free regimens.
>
> The confluence of a robust HCV drug pipeline, shortened regimens, and posttreatment follow-up are extraordinary. The new FDA breakthrough therapy designation may speed things up as well. By the end of 2014, DAAs from four different classes and fixed-dose combinations (FDCs) are likely to be approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), offering the potential for off-label mixing and matching.[12]

HCV treatments in phases II or III include three nucleoside or nucleotide polymerase inhibitors, six non-nucleoside polymerase inhibitors, eight nonstructural 5A (NS5A) protein inhibitors, eight protease inhibitors, one microRNA targeting compound, and two fixed-dose combinations (FDCs) (see table 1). Two drugs—Janssen/Medivir's once-daily protease inhibitor simeprevir and Gilead's nucleotide polymerase inhibitor—were submitted to the FDA for expedited review in spring 2013, meaning that—barring unexpected surprises—they are likely to be approved before the end of the year. Their regulatory submissions, however, were suboptimal, and the combinations studied used ribavirin with or without peginterferon. By contrast, an astonishing 28 interferon-free regimens are in development for HCV genotype 1, with 11 under study for genotypes 2, 3, and 4 (see table 2).

Of necessity [see "Cross-company Trials"], some sponsors are codeveloping certain compounds in order to optimize outcomes, but others[13] are eschewing promising cross-company collaborations in order to develop combinations of

their own molecules so as to seize market share regardless of whether their combinations are the best.

Swan's command of the HCV pipeline is unparalleled, and anyone who wants to know what's going on in the field needs to read her chapter. Research progress will not be reflected in public health advances, however, until and unless health systems adapt to meet the needs of the world's 185 million people living with HCV.

> The buck stops—and shrinks—when it comes to HCV treatment. The extortionate pricing of first-generation HCV protease inhibitors—added to the already high cost of peginterferon and ribavirin—limits treatment access even in wealthy countries. Oversight of complex treatment algorithms, frequent monitoring requirements during treatment, and management of nasty side effects add to the expense….The swift and astounding progress against hepatitis C virus will have a negligible impact on public health if medicines are too costly. In low- and middle-income countries (LMICs) millions of people with hepatitis C will go without treatments if governments cannot afford drugs, or the health care systems that will administer them.[1]

In "Low- and Middle-Income Countries Defuse Hepatitis C, the 'Viral Time Bomb,'" Karyn Kaplan describes how a worldwide movement is forming to ensure that when new all-oral HCV cures are approved, that governments, health systems, and providers will be ready for them.

> A growing movement of global activists is responding to this crisis… demanding access to affordable, quality drugs and diagnostics as well as high-level political commitment to testing and treatment scale-up in their countries. They will continue to fight until they defuse what the World Health Organization (WHO) has called the "viral time bomb."[14]

Despite a 2010 World Health Assembly (WHA) resolution[15] demanding that governments develop comprehensive programs that

> enhance access to affordable treatment in developing countries….outrage that little has been done [since] to address the epidemic…has motivated a diverse coalition of stakeholders….A global movement for HCV treatment access has begun.

> From Ukraine to India, and from Georgia to Egypt, activists from LMICs are adapting relevant lessons from the HIV treatment-access movement about how to reduce the cost of drugs and diagnostics, integrate services, and simplify the package of care. They are demanding that their governments take action to address local epidemics and include civil-society representatives meaningfully in the response.[3]

Some governments have stepped up to the challenge.

- Egypt "developed the world's largest nationally subsidized viral hepatitis–control program… [with] more than 220,000 people…already treated for hepatitis C."[3] The country sponsored a local competitor to peginterferon to force Roche and Merck to lower prices—a tactic successfully used by Brazil over the years to reduce the price of expensive brand-name anti-HIV drugs.
- Thailand responded to a multiyear activist campaign by making "a government commitment to expand HCV treatment access through the national health care program. In August 2012, Thailand put PEG-IFN on its national EML;" meanwhile "[t]he government, propelled by grassroots activists, successfully negotiated a significant [fourfold] price reduction from Roche and Merck: US$4,800 per treatment course."[3]
- India's Intellectual Property Appellate Board (IPAB) "overturned Roche's patent [on PEG-IFN]…[and] ruled that [a local competitor's] effort could 'help break the monopoly' on PEG-IFN and 'bring the drug within reach'…."[3]
- Ukrainian activists protesting as "the Condemned" secured a government commitment to "develop a funded national plan."[3]
- Georgian activists and harm reduction advocates secured a commitment by Georgia's Ministry of Corrections "to treat 300 people in prison who have HCV, expanding to 500 in the next year."[3]

These victories show the way forward for activists from other low- and middle-income countries—and indeed for those from rich countries with deep disparities in health care access, such as the United States—who by using combinations of legal, political, scientific, media, and mass-mobilization strategies can bring the promise of all-oral cures to the 185 million people who will need them over the next decade.

2013 tuberculosis (TB) pipeline executive summary

Lack of investment and political will make the TB pipeline the most anemic covered in the 2013 Pipeline Report.

Globally, one-third of active TB cases are never diagnosed, reported, or treated, meaning that 3 million people are walking around with undiagnosed disease, in danger of progression, death, and onward transmission.

Recent advances in molecular diagnostics in the form of the Hain GenoType and Cepheid GeneXpert platforms for detecting drug-resistant forms of TB and, in the case of GeneXpert, diagnosing TB itself faster than any other test are, where available, helping to guide smarter treatment decisions. Hain, however, has recently doubled the price of its test kits, while Cepheid cannot keep up with demand for GeneXpert, in spite of a recent agreement with the President's Emergency Plan for AIDS Relief (PEPFAR), UNITAID, USAID, and the Bill & Melinda Gates Foundation (BMGF) that dropped the price of its Xpert MTB/RIF test cartridges to below $10 apiece. In any case, a $17,000 test platform that needs to be returned annually to Toulouse, France, for calibration is never going to be used in field settings where most TB cases occur.

Several other companies are making molecular tests to compete with Xpert; some made in middle-income countries such as India have the potential to be cheaper, if they work. Regulatory standards are much lower for diagnostics than they are for drugs or vaccines, and few peer-reviewed data on these new molecular tests are available in the scientific literature.

Through the TB diagnostics research forum, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) is teaming up with the Gates foundation, Stellenbosch University in South Africa, and others to expedite the development of more rapid molecular tests for TB organisms resistant to drugs such as pyrazinamide, the fluoroquinolones, and the newer batch of TB drugs coming through the pipeline.

Progress is slow. A urine dipstick made by Alere that diagnoses lipoarabinomannan (LAM), a TB surface protein, can add diagnostic specificity among people with HIV whose CD4 counts are below 100 cells/mm^3, making this test a useful add-on in high-HIV burden areas where many people with advanced AIDS present for care. The test, however, is insensitive among the 85 percent of TB cases without HIV and among those on HIV treatment with CD4 counts above 100 cells/mm^3.

Relatively small investments are under way to discover antibody or antigen targets for use in a point-of-care (POC) test, but none appear likely to turn up any time soon without greater investment.

Clinical research on new TB drugs and novel regimens, some containing mixtures of new and older drugs, is moving forward slowly. Forty years after last approving a new TB drug from a new class—rifampicin in the early 1970s—in December 2012, the U.S. Food and Health Administration (FDA) granted Janssen's bedaquiline (TMC207, Sirturo) accelerated approval for treatment of drug-resistant TB. European approval is pending, and Janssen has filed in China, Russia, South Africa, and Thailand. Last month the World Health Organization (WHO) released early advice on how to use bedaquiline in developing countries. Despite its potency and ability to shorten time to culture conversion, many will await the results of further research before feeling comfortable using bedaquiline due to an unexpected mortality difference observed in one of the phase II studies, which were generally too small to reliably show whether this difference was a true drug effect or a statistical fluke.

Meanwhile Otsuka's novel compound delamanid (OPC-67683) has been languishing at the European Medicines Agency (EMA) for over a year despite the drug's evident safety, ability to shorten time to conversion in drug-resistant TB, and an apparent survival benefit among patients who received more than two months of the drug. The EMA does not seem to be aware that the European region has the highest burden of drug-resistant TB, and that new drugs and regimens to treat it are urgently needed.

The Global Alliance for TB Drug Development's innovative new-combination trials NC-002 and NC-003 are moving along rapidly. Results are expected later this year. The Alliance has also proposed NiX-TB, a salvage trial for people with extensively drug-resistant (XDR) and pre-XDR-TB, using all-new compounds to which no resistance can have evolved. This study should start as soon as possible, as nearly one million people are living with drug-resistant TB and fewer than five percent of them are receiving appropriate treatment for the disease.

Several industry compounds are moving forward slowly. Pfizer seems to have virtually frozen clinical development of the new oxazolidinone sutezolid, which will be needed in the forthcoming trials of the NIAID-funded AIDS Clinical Trials Group (ACTG), the NiX-TB study, and the TB Alliance's studies of novel TB regimens.

Regulatory agencies in developing countries are unprepared to deal with even one or two new TB regulatory submissions, let alone the new combination studies now being planned. They are also generally unfamiliar with pre-approval expanded access mechanisms such as compassionate use, requiring sponsors such as Janssen to create open-label safety studies among people with DR-TB. As we note elsewhere in this report, national regulatory authorities in developing countries must rapidly bring their capacity for 21st-century regulation up to par. Global bodies such as the WHO and technical partners such as the U.S. Centers for Dis-

ease Control and Prevention (CDC) and the FDA can help, but they too are suffering from the effects global financial austerity, and—in the United States—sequestration is hitting the CDC's TB program and its research programs particularly hard.

Greater investment in the fundamental science of TB and its relation to the human host, and in vaccine discovery and development will be critical to developing new safe and effective TB vaccines that can prevent all forms of the disease. This research is moving forward slowly at this time due to a lack of investment.

Countries are doing a poor job of scaling up TB programs, particularly for people with drug-resistant, HIV-associated, or pediatric disease. The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) has awarded countries US$2 billion to scale up TB programs in the coming two years, but many countries have been unable to deliver the promised scale-up. There is a danger that these funds committed to TB may be shifted to more successful HIV or malaria programs if in-country TB programs continue to fail their populations. This bodes poorly for the forthcoming GFATM replenishment meeting next year, at least for TB.

Ongoing stock-outs of key first-line drugs such as isoniazid and rifampicin and second-line drugs such as amikacin and kanamycin, as well as of assays such as tuberculin skin testing, continue to occur in developing countries as well as the United States. The underlying the lack of political will, and the failure to project program needs and to deliver the right drugs to the right patients at the right time, indicate that despite having a burden of disease almost as great as HIV, and a death rate to match, TB remains far too low on the world's political or scientific agenda. This must change, or millions of unnecessary cases of TB and deaths from the disease will continue to occur over the coming years and decades.

2013 HIV pipeline recommendations

ADULT ANTIRETROVIRAL PIPELINE

The demand for ARVs is well established, and it will continue to expand for many years: life expectancy has been dramatically extended; treatment is lifelong and is now being recommended regardless of a person's CD4 T-cell count; rates of new infections and diagnoses remain high in many countries and in specific populations; and even optimistic reviewers see advances toward a cure as a long-term goal, at least a decade away.[1]

1. Restricted budgets for most health care systems and steadily approaching patent expiries for several commonly used ARVs mean that new drugs also need to match or undercut existing products on price to earn their place as better treatments. When a new product's efficacy, safety, and dosing convenience are broadly similar to those of currently used ARVs, the drug price increasingly determines use. Higher pricing in an increasingly competitive market will ultimately translate into a missed opportunity to recoup development costs, and potentially better drugs will be barely used.[1]
2. The forthcoming introduction of dolutegravir, with its multiple advantages including impressive clinical trials data, low molecular weight, single daily dosing, and lack of need for boosting, gives its sponsor, ViiV Healthcare, a chance to price the drug competitively (e.g., lower than existing integrase inhibitors) to broaden access to this class, potentially changing globally recommended first- and/or second-line preferred regimen choices. "To date, integrase inhibitors as a class have been a good example of the pitfalls of inappropriate pricing. After more than a decade of careful and intensive research, the first integrase inhibitor was approved over five years ago. But the potential global benefits from this new class, given their impressive results, have hardly been realized because of premium pricing."[1] Both raltegravir and elvitegravir (approved last year as part of Stribild) have been too expensive to make an impact globally.
3. "Savings from generics are essential if we are to retain public health services for those who remain uninsured or underinsured."[1] Generic manufacturers and governments must seize the opportunity posed by the coming wave of patent expiries to offer optimal combinations (either fixed-dose or blister-pack) at prices much lower than for innovator compounds. It will be critical for the United States – and for other programs such as Britain's National Health Service (NHS) – to reinvest the savings generated by sensible use of generic-

containing antiretroviral combinations into massively expanded HIV prevention and treatment programs to end HIV transmission and progression to AIDS and death and achieve an "AIDS-free generation" in the United States for everyone.

4. Innovator companies must ensure that novel compounds are studied and made available on the market as single pills as well as in fixed-dose combinations (FDCs) to enable people with HIV to assemble optimal combinations based on their own needs. Thus, Gilead needs to ensure that elvitegravir, cobicistat, and – when available – tenofovir alafenamide (TAF) are each available as single pills to maximize patient and provider choice. This is particularly critical for TAF. The current development plan will not inform its use outside Gilead's FDCs, which rely on a pharmacokinetic interaction with cobicistat to determine the dose under investigation.
5. Governments, donors, guidelines panels, innovator and generic companies, providers, independent investigators, people with HIV and activists must work together to ensure that the best drugs and combinations are available for all, regardless of date of market entry, patent expiry, or individual manufacturer. The ongoing emergence of some dual-sponsor fixed-dose combinations is meritorious and should be expanded to allow the combination of generic and innovator compounds as expeditiously as possible to enable the best therapeutic options to be provided.
6. People with HIV resistant to three classes of drugs or more need new treatment options, which will require regulatory flexibility in developed countries and greater access to third-line therapy in developing ones. Recent moves by the FDA[3] to define a registration path for treatment of multidrug-resistant HIV, ongoing consultations among FDA and the HIV community[4] and the inclusion by WHO in its new consolidated HIV treatment guidelines[16] of recommendations for third-line antiretroviral therapy (ART) are necessary, but not sufficient, steps in the right direction.

PEDIATRIC ANTIRETROVIRAL PIPELINE

To repeat from the 2012 Pipeline Report: there is a danger of pediatric HIV becoming an old story against a backdrop of targets to eliminate vertical transmission by 2015, which though they are laudable, must not happen at the cost of continual scale-up for children. And back to the reality check: currently only 28 percent of children with HIV in need of treatment are receiving it.[17] Most of what is recommended below is spillover from previous years, but unfortunately has not been done yet.[18]

1. The new WHO guidelines for treating children strike a fairly good balance between aspirational and pragmatic. It is important that nevirapine-containing regimens still remain an alternative as the recommended lopinavir/ritonavir first-line regimens (including for rural neonates) will frequently not be feasible with the formulation currently available. If recommendations become too complex, children often do not receive anything. As a simpler formulation of lopinavir/ritonavir becomes available, countries must ensure that it is swiftly approved and distributed, with appropriate training for health workers.
2. Other missing formulations needed to implement the guidelines must be made available. If the market is too tiny to interest generic companies, donors need to step in to support this.
3. The news of the infant with a "functional cure" provoked much discussion. Researchers and implementers are already planning pilot programs and studies to advance research findings. The news should stimulate all programs to do infant PCR as early as possible and intensify post exposure prophylaxis (or early treatment) for neonates of at risk pregnancies (not to mention identifying and treating pregnant women). Successes must be followed by rapid advice from the WHO.
4. Support new models of research and development. There is a lot of hope resting on the successful development and delivery of the Drugs for Neglected Diseases Initiative (DNDi) product. That an initiative focusing on diseases of the poor has selected pediatric HIV as a focus speaks volumes. More innovative models of research and development, and appropriate agreements between originator companies and generic ones to produce child-adapted formulations in a timely fashion must be made.
5. Ensure that patents are not an obstacle. The Medicines Patent Pool (MPP) is putting a lot of emphasis on pediatric antiretrovirals. Even the most hesitant innovator companies, as far as adult drugs are concerned, must recognize that pediatrics will never be much of a market let alone a moneymaker. Gilead's license agreement with the MPP always has royalties waived for any new pediatric formulations.[19] ViiV will grant MPP a voluntary license for pediatric formulations of abacavir.[12] [20]There is also a commitment to do the same for dolutegravir. Other companies must follow suit and is very important to ensure availability beyond sub-Saharan Africa. What AbbVie decides to do about the lopinavir/ritonavir granules will be closely watched.
6. Rationalize available formulations. Development, approval, and distribution of new formulations need to happen in ways that are timely and do not further fragment the market. The time from first approval to when products are

available where they are most needed must shorten. This will require earlier access by generic companies to new products (which must include the possibility to develop FDCs with components from different innovators) and registration by the WHO and in-country. To reduce the current situation with too many formulations and too few real options, products need to be rationalized, and unsuitable ones phased out.

7. Consolidate procurement. CHAI needs to continue with its successful model of price negotiations.[21] Concerted efforts by international donors, including the Global Fund and PEPFAR, need to be made to facilitate the transition from previous reliance on UNITAID funding of pediatric products. In the many individual countries where orders do not meet manufacturer volume requirements, buyers must get together.

RETROFITTING FOR PURPOSE: TREATMENT OPTIMIZATION PIPELIN

1. Treatment optimization must be in the interests of people with HIV.
2. Trials like the one of low-dose stavudine, conducted for the sake of cost alone, and against much opposition from people with HIV and activists, are unacceptable. Activist and patient acceptability is always important. This will become increasingly true as indications for starting become broader, and more asymptomatic people with HIV are offered treatment.
3. Drugs and regimens need to be designed with resource-limited settings in mind. The target product profile has been widely described by now. Currently approved and pipeline compounds fit for this purpose need to be studied and produced in appropriate formulations.
4. The time between full FDA/EMA approval and WHO prequalification, FDA tentative approval of generics in association with PEPFAR's expedited review process, and approval by local regulatory agencies must be shortened.
5. Eliminate the delay between availability of the best new drugs and combinations in one country and their availability everywhere. Delays with the registration process, in addition to production by generic manufacturers and recommendations in national guidelines, means that it takes years from promising results in trials and initial approval to wide availability for the majority of people in need of antiretroviral treatment. Despite over 150 single agents and combination products having FDA tentative approval, the majority are older drugs and those with expired patents.[7]

PREVENTIVE TECHNOLOGIES, RESEARCH TOWARD A CURE, AND IMMUNE-BASED AND GENE THERAPIES PIPELINE

1. Basic and translational science on potential HIV vaccines must continue, incorporating the best scientific understanding of new developments in basic science, and learning from recent setbacks.
2. Research on antiretroviral-based pre- and postexposure prophylaxis (PrEP and PEP) must continue as a high priority, with attention given both to optimizing delivery methods (e.g., long-acting parenteral or barrier delivery systems) as well as understanding how best to use newly licensed approaches such as TDF/FTC PrEP to reduce new HIV infections in the real world.
3. Immune-based therapy research must continue to explore the possibilities of improving immunologic recovery among immunologic nonresponders (INRs).
4. New research is needed to address ongoing "residual dysfunction of the immune system that can persist in individuals on ART, [including] elevated levels of inflammation and features resembling the age-related immunologic wear and tear seen in the elderly."[9]
5. Given the overwhelming efficacy of existing strategies for prevention of mother-to-child transmission (PMTCT) with antiretroviral therapy (ART), an independent panel of the Institute of Medicine (IOM) should review proposed studies of passive immunization for this purpose before they are undertaken.
6. Following up on the intriguing results presented by Persaud at CROI 2013 and by the VISCONTI cohort, research should further investigate the role of very early treatment with potent antiretroviral therapy (ART) combinations in both infants and adults infected with HIV.
7. Research is needed to better understand and quantify the cells and tissue sources of the latent HIV-1 infected cell reservoir, which is the target for HIV cure research, and to enable the development of assays, which can be automated and used to quantify the effects of potential curative therapy approaches on the size and dynamics of the reservoir.
8. The potential contribution of therapeutic vaccine approaches as part of combination curative therapy needs to be further explored.
9. Funders, manufacturers, and researchers conducting research which may be relevant to potential HIV curative approaches should carefully modulate their public statements and presentations to ensure that they contain accurate scientific information rather than hype and speculation.

10. Current funding limitations on basic, vaccine, prevention, and cure-related research on HIV infection must be overcome or all the potential promise of the coming years will be deferred or denied, potentially extending the toll of the pandemic deep into the current century.

2013 hepatitis C virus (HCV) pipeline recommendations

HCV TREATMENT AND RESEARCH PIPELINE

1. Regulators, activists, patient groups, and legislators need to revisit the design of early access programs, and create a framework to allow access to potentially lifesaving treatment for people who are too ill or otherwise ineligible for clinical trials, while safety and efficacy data are collected.
2. Governments, pharmaceutical companies, and foundations should support public-private research networks, and civil-society representatives should participate in development and oversight of these networks.
3. Regulatory agencies need to identify metrics that will facilitate reimbursement for off-label use, keeping in mind both class-specific and within-class-specific differences in drug potency, resistance barrier, safety, and side effects profile.
4. Regulators, clinicians, and other stakeholders should discuss requirements for HCV drug development, given the rapid evolution of HCV treatment.
5. Sponsors should be obligated to conduct relevant drug-drug interaction studies prior to phase III, to facilitate preapproval trials in HIV/HCV coinfection.

HCV POLICY AND ACCESS

These changes are required to achieve universal access to high-quality HCV prevention and treatment services:

1. Governments must immediately repeal laws that criminalize people who use drugs. These laws perpetuate unsafe injection practices and drive people underground and away from essential health services.[22]
2. Governments must provide comprehensive harm reduction services, such as provision of clean injecting equipment, methadone, and buprenorphine.
3. Governments, in partnership with civil society, must create and fully fund national plans that address concentrated and generalized hepatitis C epidemics.

4. Merck and Roche must drastically reduce the price of PEG-IFN in low- and middle-income countries. Currently, treatment cost can exceed the per capita gross domestic product (GDP) by over tenfold.[23]
5. The WHO, the European Medicines Agency (EMA), and the U.S. Food and Drug Administration (FDA) must create a clear and harmonized regulatory pathway for biosimilars. The WHO must clarify, simplify, and streamline the prequalification process for biosimilar products (and diagnostics). In turn, biosimilar manufacturers should collect appropriate data and be transparent with regulatory agencies.
6. Donor agencies must support development of simple, accurate, and affordable HCV diagnostics and disease-staging tools, since their cost and complexity are major barriers to treatment.

2013 tuberculosis (TB) pipeline recommendations

TB DIAGNOSTICS PIPELINE

Funding

1. Donors must increase funding and work to bring more scientists and innovators into the field to develop an optimal point-of-care TB test that is affordable, patient- and user-friendly, accurate in people with any form of TB, and will result in TB treatment decisions in one visit or encounter.
2. The private sector and middle-income countries need to increase investment in TB diagnostics development. The BRICS countries (Brazil, Russia, India, China, and South Africa) must increase their investment in TB R&D for new tools as well as the infrastructure to evaluate and demonstrate their field-effectiveness.

Biomarkers

1. Donors must prioritize increased investment in basic science to quantify biomarkers as surrogate clinical endpoints for clinical trials of new drugs, regimens, and vaccines.

DST

1. Donors must fund and prioritize decentralized DST for fluoroquinolones, pyrazinamide, and other drugs, particularly second-line drugs.

2. Country programs and donors must implement the recommendation to do rapid DST of isoniazid and rifampicin, or of rifampicin alone, over conventional testing or no testing at the time of diagnosis of TB.
3. Donors and industry must work to develop universal DST and newer DST methods to rapidly identify regimens to which every patient's bacterial organism is susceptible.

Specimen bank

1. Donors need to fund repositories of useful, viable specimen samples that are available openly and freely.

Policies and strategies

1. Donors, national programs, and implementers must develop policies and strategies that move toward active case-finding and integrate TB services across the health system.
2. Donors and national programs must integrate new TB diagnostic tools such as Xpert MTB/RIF into HIV-, maternal and child–, and other health care services wherever possible.
3. Programs must work to develop national strategies that allow the flexibility to introduce any new tool or regimen whenever available and needed.
4. Regulatory agencies must develop stringent evidentiary standards for the introduction of new diagnostic tests to ensure that people have access to good, accurate tools without delay.
5. Programs in countries with high HIV burdens should assess the usefulness of tests that have not yet been endorsed by international agencies, in their own settings, particularly where TB kills many people before they are even diagnosed.
6. National programs should not wait for the WHO to make recommendations regarding the use of tools if they have the resources to do so themselves. However, programs should beware of promotional marketing by diagnostics developers that lacks supporting data.
7. Donors, in particular BRICS and other middle-income countries, must conduct operational research to determine at how low a level of the health system Xpert could be implemented.
8. Donors, industry, and national programs must develop policies that make

good tests more affordable to all sectors, public and private.

9. UNITAID, the BMGF, PEPFAR, USAID, and the WHO must ensure that Cepheid identifies the causes of Xpert cartridge shortages and fixes them quickly.

TB TREATMENT PIPELINE

1. Governments and donors need to increase funding for TB research at least threefold. Countries with high rates of TB, particularly middle-income ones such as the BRICS, must invest more in TB R&D.[24]
2. Sponsors must commit to developing their drugs and making them accessible to other research groups. In particular:
    - AstraZeneca should continue to invest in AZD5847, and begin to engage with community groups;
    - Janssen must quickly fulfill its postmarketing requirements for bedaquiline, and work to close other research gaps including potential drug-drug interactions with delamanid and other drugs, and dosing and safety concerns in special populations including children;
    - Novartis needs to make clofazimine available for TB research studies;
    - Otsuka should facilitate the NIH's interaction work combining delamanid with bedaquiline to ensure this key study advances as quickly as possible;
    - Pharmasyntez needs to make its full data available for peer review and create a sound, responsible development plan for perchlozone before pursuing further research studies or registration;
    - Pfizer must commit to developing sutezolid and making it available to research consortia for developing optimized combinations;
    - Sanofi should maintain its support for the CDC-funded TB Trials Consortium (TBTC) to enable further research on rifapentine amid public financial austerity; and
    - Sequella should be more transparent and amenable to sharing SQ109 data so its suitability for further development can be appropriately assessed.
3. More research is needed in vulnerable populations. TB drug sponsors and researchers must commit to studying TB drugs as thoroughly as possible, and as quickly as safety allows, in children, women (including pregnant women), people with HIV, people with hepatitis B and C, people who use alcohol, and

people who inject drugs or are on opioid substitution therapy. Regulatory authorities can play an important role by appropriately encouraging and providing incentives for research in these populations.

4. Trial sponsors and implementers should engage TB-affected communities in the design, implementation, and posttrial communications of TB research as laid out in the Good Participatory Practice Guidelines for TB Drug Trials (available from: http://cptrinitiative.org/downloads/resources/GPP-TB%20Oct1%202012%20FINAL.pdf).
5. The TB community needs to collaborate to develop an efficient path for testing new drugs and determining optimal combinations.
6. Regulatory authorities must build capacity and expertise to appropriately regulate clinical trials, early access, accelerated approval, postmarketing studies, and pharmacovigilance for new TB drugs and regimens. Regulatory agencies—particularly those in high-TB-burden countries—must scale up their ability to rapidly and carefully review submissions, and enforce conditions of approval. The Russian Federation and the Confederation of Independent States (CIS) in particular must improve their review processes to ensure that studies, especially registration trials, are appropriately designed and conducted, and that only drugs with robust and peer-reviewed data on safety, efficacy, and dosing receive marketing approval.
7. National TB programs need to improve their services, supply-chain management, and ability to rapidly adopt and appropriately implement new tools.
8. Drug sponsors and manufacturers must make licensed drugs accessible and affordable. In particular:
    - Janssen should continue to file for approval in a range of countries, and price bedaquiline accessibly.
    - Otsuka's compassionate use program for delamanid is overdue and needs to be initiated immediately, as it will likely be over a year until the drug is commercially available.
    - Pfizer needs to lower the price of linezolid.
    - Sanofi should quickly lower the price of rifapentine to enable the taxpayers who funded its development to benefit from its implementation.

TB VACCINE PIPELINE

1. Prioritize the science behind biomarker discovery to determine correlates of risk of TB acquisition, disease progression, response to therapy, as well as correlates of immune protection via innate or acquired immunity, including postvaccination.[25,26,27]
2. Develop and validate a human challenge model for TB infection and disease.[28,29]
3. Deploy modern molecular and systems biology approaches to better characterize and unpack the human host/TB pathogen interaction.
4. Pursue innovation within clinical trials.
5. Increase funding for TB vaccine research, including basic science.[30]

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THE ANTIRETROVIRAL PIPELINE

By Simon Collins and Tim Horn

Introduction

The model of pricing newly approved antiretrovirals (ARVs) higher than current drugs is increasingly difficult to sustain, even in a purely commercial context. The largest market for new drugs is not in first-line therapy, important though this is. The greatest potential comes from providing more effective, better-tolerated and easier-to-take drugs that expand switching options for people on potent but cumbersome regimens. Treatment should get better, because current treatments can be improved.

The demand for ARVs is well established and it will continue to expand for many years: life expectancy has been dramatically extended; treatment is lifelong and is now being recommended regardless of a person's CD4 T-cell count; rates of new infections and diagnoses remain high in many countries and in specific populations; and even optimistic reviewers see advances toward a cure as a long-term goal, at least a decade away.

However, restricted budgets for most health care systems and steadily approaching patent expiries for several commonly used ARVs mean that new drugs also need to match or undercut existing products on price to earn their place as better treatments. When a new product's efficacy, safety, and dosing convenience are broadly similar to those of currently used ARVs, the drug price increasingly determines use. Higher pricing in an increasingly competitive market will ultimately translate into a missed opportunity to recoup development costs, and potentially better drugs will be barely used. Whoever sets high prices for new drugs—and this is unlikely to be the scientists and researchers who have developed the breakthroughs—needs to realize this.

This might initially sound like an idealistic community demand, but similar points were made by GlaxoSmithKline (GSK) CEO Andrew Witty, who argued that recent efficiencies in research and development—that for GSK have reduced development costs by 30 percent—should be passed on to consumers with prices that could be lower than existing options, and that this is common in other industries. HIV drug development needs this new model. Witty also countered the frequently asserted US$1billion-plus cost for bringing a drug to market as "one of the great myths of the industry"— being inflated by the inefficiency of some companies with a higher rate of pursuing compounds that fail.[1]

Integrase inhibitors as a class are a good example of the pitfalls of inapproapriate pricing. After more than a decade of careful and intensive research, the first integrase inhibitor was approved over five years ago. But the potential global benefits from this new class, given their impressive results, have hardly been realized because of premium pricing. Drug price at launch is similarly likely to determine whether new drugs in this expanding class—elvitegravir was approved in the last year in the US (co-formulated in Stribild) and dolutegravir approval is expected shortly—fare any better.

So the compounds reviewed in this year's ARV report—many with great potential—must be considered against a backdrop of a changing economic landscape. The next approvals are likely to be dolutegravir and separate formulations of elvitegravir and the pharmacokinetic (PK) booster cobicistat. These will be followed by new formulations and fixed-dose combinations (FDCs) that include dolutegravir/abacavir/3TC; protease inhibitors (PIs) boosted with cobicistat (atazanavir/cobicistat and darunavir/cobicistat); new low-milligram reverse transcriptase inhibitors (RTIs); and co-formulations involving the newly generic 3TC. It is notable that Merck is expanding its interest in HIV by acquiring compounds, particularly the reverse transcriptase inhibitors CMX157 and EFdA, with co-formulation potential for weekly dosing. Advances in drug delivery for long-acting formulations also continue.

The following review covers these compounds and formulations and others that are moving into phase II/III studies based on interesting early data, as well as potential targets on the horizon, still in preclinical development.

Health care changes and generic access

The impact of the economy on healthcare and the potential changes from new generics was already sufficiently important to be a focus of the *2012 Pipeline Report*. More recently, the potential economic savings to public health programs in rich countries was widely highlighted last year by a mathematical model presented by Rochelle Walensky at the International AIDS Conference (IAC) in July 2012 and published early in 2013.[2,3]

According to the model, a regimen comparable to Atripla (efavirenz, FTC and tenofovir DF [TDF]) consisting of generic 3TC (approved in 2011), generic efavirenz (availability expected in 2014–2015), and branded TDF (Viread; not expected to go off patent until at least 2017), prescribed as individual once-daily tablets, was associated with a 50 percent reduction in drug costs, resulting in savings of US$920 million in the first year of availability alone. Even if combined with the branded co-formulation of TDF and FTC (Truvada), broad utilization of generic efavirenz would translate into US$560 million in savings in the first year alone.

Advocacy efforts surrounding the development, optimization and availability of generic ARVs have primarily focused on nations in the global south, where greatly expanded access to affordable HIV treatment has saved 14 million life-years, including nine million in sub-Saharan Africa, since 1995.[4] With patent expirations pending over the next four to five years for several preferred and alternative drugs listed in the US Department of Health and Human Services (HHS) guidelines;[5] attention to the potential for cost savings—along with the safety, efficacy, and convenience of generic options to be made available in the US and other high-income countries—is now critical. Indeed John Bartlett, the respected co-chair of the guideline panel was quoted in *Nature* magazine predicting that HIV combinations in the US will commonly be less than $200 for many patients within 10 years.[6]

Because, in the US, a large percentage of Medicaid, private insurance, and Ryan White expenditures are directly related to prescription drug costs, compounded by growing political intolerance for disease-specific funding and nationwide efforts to reduce health care spending, a shift toward generic ARVs is not so much a desire as it is a necessity. This seems to accept that the two-tier access to choice of medicine in the US—based on insurance coverage and ability to pay—will widen further.

The near future will require a balance between use of branded and generic treatment, recognizing that both will be essential to maintain the opportunity to advance better treatments and support highly individualized care. One strategy for maintaining options in the short term is to ensure that people prescribed a generic efavirenz-based combination who have residual side effects are switched to brand-name alternative drugs. Switching stable patients back to less tolerable combinations is far more of an unsettling clinical decision, whatever the cost savings.

In both Europe and the US, the financial pressures on many public health systems with access to generic 3TC, are already operating within such restraints that multiple-pill regimens combining generic and brand ARVs are being favored over FDCs, even when savings are relatively modest (given the cost effectiveness of all current combinations) and with the additional inconvenience of an additional pill count.

Summary of pipeline progress

A summary of key developments over the last year is included in table 1. These include both updates from last year's report and data on new compounds that advanced from preclinical phases of development.

Each of the compounds is discussed in more detail below.

Table 1. Summary of pipeline compounds in 2013

Agent	Sponsor	Class/Type	Status	Comments
Stribild FDC (elvitegravir/ cobicistat/ FTC/TDF)	Gilead	Fixed-dose combination (boosted INSTI + 2 RTIs)	US approval in August 2012.[7] EU approval in May 2013.[8]	Inclusion in US guidelines was as an alternative rather than preferred combination. The treatment-naive and experienced indication was limited to patients with eGFR >70 mL/min.[9]
cobicistat	Gilead	Pharmaco-kinetic (PK) booster	Phase III	See Stribild, above. Ongoing studies include co-formulations with darunavir, atazanavir, and another four-drug FDC. Submitted as separate compound in June 2012[10] but required further review in April 2013.[11] New phase III data report similar efficacy and safety to ritonavir.[12]
elvitegravir	Gilead	INSTI	Phase III	See Stribild, above. Other studies ongoing as component of other FDCs.[13] Submitted to FDA as separate compound in June 2012,[14] but, as with cobicistat, required further review in April 2013.[11]
dolutegravir (S/GSK1349572)	Shionogi/ ViiV	INSTI	Phase III/ EAP	Phase III in naive patients reported superiority to Atripla and noninferiority to raltegravir.[15,16] Submitted to US, EU and Canadian regulatory authorities in December 2012.[17] Decision expected by August 2013.
tenofovir alafenamide (TAF, GS-7340)	Gilead	Nucleotide (tenofovir prodrug)	Phase III	Oral abstract at CROI 2013 reported similar safety and efficacy to tenofovir DF with potentially reduced side effects reported.[18] The 25 mg dose is selected for development (10 mg in FDC with cobicistat). Ongoing studies prioritize co-formulations including a PI-based FDC.[19]
BMS-663068 (prodrug of BMS-626529)	BMS	Attachment inhibitor (gp120)	Phase IIb	No efficacy update since CROI 2011. Phase II dose-finding study vs. atazanavir/ritonavir, each with raltegravir + tenofovir DF yet to report.[20]
BMS-986001	BMS	NRTI (similar to stavudine/d4T)	Phase IIb	Dose-finding study compared to tenofovir DF, both with efavirenz + 3TC, still ongoing. New animal and in vitro safety and resistance data.[21,22,23]

Agent	Sponsor	Class/Type	Status	Comments
lersivirine (UK-453061)	ViiV	NNRTI	Ended	Further development stopped in February 2013 after phase IIb results.[24]
apricitabine	Avexa	NRTI	Phase II	No update since last report. Still dependent on finding new commercial backing.
cenicriviroc (TBR-652)	Tobira	CCR5 inhibitor (also active against CCR2)	Phase II	Phase II results reported in March 2013 in treatment-naive patients compared to efavirenz, both with tenofovir DF/FTC.[25] New formulation in development for phase III.
doravirine (MK-1439)	Merck	NNRTI	Phase II	New NNRTI. Mean –1.4 log VL reductions after 7 days monotherapy at 25 mg dose. Dose-ranging study uses up to 200 mg.[26]
ibalizumab (TMB-355; formerly TNX-355)	TaiMed Biologics	CD4-specific humanized IgG4 monoclonal antibody	Phase II	Although there have been no treatment updates for several years, a recent review in *JAIDS* suggested potential use for HIV prevention.[27]
PRO 140	CytoDyn	CCR5-specific humanized monoclonal antibody	Phase II	No new data since 2010. Acquired from Progenics by Cytodyn in 2012.[28]
S/GSK1265744 oral and long acting parenteral (LAP) formulations.	Shionogi/ GSK	Integrase inhibitor (follow-up to dolutegravir)	Phase II	No update on oral use. New in vitro data based on a monthly injection.[29,30,31]
albuvirtide	Chongqu-ing Biotech-nologies	Long-acting fusion inhibitor	Phase I	A single dose of this long-acting version of T-20 reduced viral load by 1 log copies/mL, maintained for 6–10 days.[32]
CMX157	Merck	NRTI (similar to tenofovir)	Phase I	No new data since 2008 but acquired from Chimerix by Merck in August 2012.[33]
EFdA	Merck	NRTI	Phase I	Limited in vivo data, but encouraging in vitro potency and activity against NRTI-resistant HIV.[34,35]
rilpivirine-LA (long-acting SC and IM injections)	Janssen	NNRTI	Phase I	Ongoing studies are in HIV negative people, with monthly and quarterly injections, including with S/GSK1265744. Current research focused on prevention use.[36,37]

AIDS: Acquired Immune Deficiency Syndrome; BMS: Bristol-Myers Squibb; CROI: Conference on Retroviruses and Opportunistic Infections; EAP: expanded access programme; eGFR: estimated glomerular filtration rate; EU: European Union; FDA: US Food and Drug Administration; FDC: fixed-dose combination; GSK: GlaxoSmithKline; IM: intramuscular; INSTI: integrase strand transfer inhibitor (integrase inhibitor); *JAIDS: Journal of AIDS*; NRTI: nucleoside/tide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; US: United States; SC: subcutaneous; VL: viral load.

New and expected approvals

The only new drug approval since the *2012 Pipeline Report* was the US and EU decisions for the four-in-one boosted integrase inhibitor FDC Stribild.[7,8]

FDA approval was for a treatment-naive indication only; the European Commission approval extends to HIV-positive people with virus without mutations associated with resistance to elvitegravir, tenofovir DF (TDF), or emtricitabine (FTC). Additionally, its use is limited to patients with good renal function (defined as eGFR >70 mL/min), which is one reason that its listing in the US HHS guidelines is as an alternative rather than preferred combination.[9]

Regulatory decisions on separate formulations of the new component drugs in Stribild—the integrase inhibitor elvitegravir and the PK booster cobicistat—are expected in 2013, as FDA submission for both compounds was in June 2012.[10,14] However, these agents are "not wonderful yet," with a further setback to individual approval with the FDA formal response letter referring to "deficiencies in documentation and validation of certain quality testing procedures and methods".[11]

Dolutegravir, the lead integrase inhibitor in development by ViiV Healthcare, was submitted simultaneously to US, European, and Canadian regulatory authorities in December 2012, with approval and access expected by the summer of 2013.[17]

Update on compounds with phase II and III results

Several compounds with exciting early data are steadily progressing and several co-formulations are in advanced phase III studies.

The pipeline can be categorized broadly as "advanced," "progressing," "trailing," and "stopped."

Advanced – generally phase III

- Stribild (treatment-experienced indication), elvitegravir (single compound), cobicistat (single compound), co-formulated darunavir/cobicistat and atazanavir/cobicistat, two new four-in-one combinations (elvitegravir/cobicistat/FTC/TAF and darunavir/cobicistat/FTC/TAF).
- dolutegravir, 572-Trii (dolutegravir/abacavir/3TC).

Progressing – generally in active phase I or II

- tenofovir alafenamide (TAF, GS-7340).
- cenicriviroc (CCR5 inhibitor).
- MK-1439 (NNRTI), CMX157, EFdA.
- BMS-986001 (d4T-like nuke) and BMS-663068 (attachment inhibitor).
- long-acting injections: S/GSK1265744 LAP and rilpivirine-LA, albuvirtide.

Trailing – generally little or no progress irrespective of development phase

- apricitabine, ibalizumab, PRO 140.

Stopped

- Lersivirine (NNRTI halted February 2013).

Stribild (Quad): elvitegravir/cobicistat/TDF/FTC

This once-daily four-in-one FDC tablet is a significant breakthrough, but it has had limited uptake following US approval in August 2012. Only licensed in Europe in May 2013, studies during the last year contributed sustained safety and efficacy data with no unexpected new events.

The US and EU indications for Stribild are primarily for treatment-naive patients, with only tentative moves into treatment-experienced patients. Ongoing studies are switch studies for people with viral suppression rather than virological failure.

Updated results included 96-week data from two phase III studies, each in approximately 700 treatment-naive patients, presented at the Glasgow conference in November 2012.[38,39] These results were also combined in a poster at CROI 2013 that included subgroup analyses by baseline CD4 and viral load.[40]

Viral suppression rates at 96 weeks, compared to 48-week results, were slightly reduced across all arms, but Stribild remained non-inferior to Atripla (in Study 102) and to atazanavir/ritonavir (ATZ/r) plus TDF/FTC (in Study 103).

Viral suppression to <50 copies/mL in Study 102 was 84% vs. 82% (difference: 2.7%; 95% CI, –2.9% to +8.3%) compared to 88% vs. 84% (difference 3.6%; 95% CI, –1.6% to +8.8%) at week 48, Stribild vs. Atripla, respectively. In the subgroup analysis, by baseline viral load below and above 100,000 copies/mL, viral suppression rates were 81% vs. 83%. Mean CD4 increases were 295 vs. 273 cells/mm^3.

In Study 103, 83% vs. 82% of patients (difference: 1.1%; 95% CI, –4.5% to +6.7%) achieved viral load <50 copies/mL at week 96 compared to 90% vs. 87% (difference: 3.0%; 95% CI, 1.9% to 7.8%) at week 48 for Stribild compared to atazanavir/ritonavir plus TDF/FTC, respectively.

Results in patients with baseline viral load >100,000 copies/mL were 82% vs. 80% (all comparisons, Stribild vs. ATZ/r, respectively). Mean CD4 cell increases at week 96 were also similar between arms (256 vs. 261 cells/mm^3).

Among those with low baseline CD4 counts (<50 cells/mm^3), Stribild achieved lower viral response rates (58%; 11/19) compared to Atripla (83%; 5/6) or the atazanavir (100%: 5/5) arms in the combined subanalysis presented at CROI.

Discontinuation rates due to side effects were approximately 5 percent in each arm in each study. Two patients in Study 102 discontinued Stribild after week 48 due to serum creatinine increases, but without features of proximal renal tubulopathy; in Study 103, one person in each arm discontinued between weeks 48 and 96 due to elevated serum creatinine. Median changes in serum creatinine at week 96 in both studies were similar to those at week 48.

Lipids generally favored Stribild, which lead to smaller median increases (mg/dL) in total cholesterol (9 vs. 18; $p < 0.001$) and LDL cholesterol (9 vs.16; $p = 0.011$), and similar increases in triglycerides (4 vs. 8; $p=0.41$) when compared to Atripla; and smaller increases (mg/dL) in triglycerides (5 vs. 16; $p = 0.012$) but greater increases in total cholesterol (14 vs. 8; $p = 0.046$) with similar changes in LDL and HDL cholesterol when compared to atazanavir/ritonavir.

A combined analysis of glomerular function, renal blood flow, and the relationship to drug levels in Stribild studies presented at CROI 2013 reported a lack of effect on actual GFR, and no relationship between renal, bone or other events and drug exposure levels of elvitegravir, cobicistat or TDF.[41] In Study 103, Stribild produced smaller mean decreases (%) in BMD (hip: 3.16 vs. –4.19; $p = 0.069$, spine: 1.96 vs. 3.54; $p = 0.049$).[39]

Elvitegravir (GS-9137)

Elvitegravir is a once-daily integrase inhibitor that, with boosting (150 mg cobicistat or 100 mg ritonavir), was licensed as a component of Stribild, but has still to be

approved as a separate drug, either with or without co-formulated cobicistat. Elvitegravir has the potential for cross-resistance to raltegravir, but a mutation profile that suggests patients are likely to remain sensitive to dolutegravir, especially if switched early.[42]

Elvitegravir is metabolized primarily by CYP3A and secondarily via UGT1A1/3, requiring a reduced dose (from 150 mg to 85 mg daily) if used with atazanavir.

Additional information over the last year in treatment-naive patients included longer follow-up from Stribild studies (see above). New data in treatment-experienced patients, comparing elvitegravir/ritonavir to raltegravir, included continued efficacy and safety out to 96 weeks.[43,44]

This phase III study randomized 712 treatment-experienced patients to either the investigational integrase inhibitor elvitegravir (150 mg once daily) or raltegravir (400 mg twice daily), each with matching placebo, plus a background regimen of a boosted PI, plus a third drug.

Baseline characteristics included mean age 45 years; 18% women; mean CD4 count 260 cells/mm^3 (45% with CD4 <200); median viral load 20,000 copies/mL (with 26% >100,000 copies/mL); and 5% and 15% of patients were coinfected with HBV or HCV in the evitegravir and raltegravir arms, respectively. Approximately 63% had primary resistance to drugs in two or more classes (PI 33%, NRTI 72%, and NNRTI 61%), balanced between arms. Choice of background PI was largely darunavir (58%), lopinavir/r (19%), or atazanavir (16%). The third drug was an NRTI in 80% of patients (TDF 59%, TDF/FTC 27%, abacavir 4%, 3TC 3%, other 7%) with 13% using etravirine and 6% using maraviroc.

The primary endpoint of viral load <50 copies/mL through week 48 (time to loss of virological response [TLOVR] analysis) was achieved by 59% of elvitegravir vs. 58% raltegravir patients respectively.

Virological response out to 96 weeks dropped similarly in each arm (to 48% vs. 45%), maintaining noninferiority for the comparison (difference: 2.6; 95%CI: –4.6 to 9.9). Approximately 40% of patients in each arm discontinued before week 96. Reasons were balanced between arms (non-compliance: 39 vs. 34; loss to follow-up: 29 vs. 31, lack of efficacy: 17 vs. 21) except for withdrawal of consent (30 vs. 17), all elvitegravir vs. raltegravir, respectively. The respective percentages of patients with virological failure increased to 26% vs. 29%, and 26% of patient in each arm had discontinued for other reasons (including side effects). CD4 increases were similar at +205 vs. +195 cells/mm^3.

Genotypic resistance test results were available for approximately 25% of patients with virological failure in each arm, with a quarter of those in each arm (23/87 vs.

26/93) having integrase inhibitor-associated mutations. Although some mutations were shared, elvitegravir was associated with T66I/A (n=8), E92Q/G (n=7), N155H (n=5), T97A (n=4), S147G (n=4) and Q148R (n=4); and raltegravir with N155H (n=16), Q148H (n=7) and T97A (n=4). Resistance mutations associated with NRTIs (3%), PIs (1%), and NNRTIs (2–3%) were similar in each arm. A more detailed analysis of the resistance results is available.[45]

Grade 2–4 side effects were similar (68% in each arm) with slightly higher rates of diarrhea with elvitegravir (13% vs. 7%). Limited details were provided for the 20% rate of serious side effects in each group but these only led to discontinuation in 4% vs. 3% of patients. Grade 3/4 laboratory abnormalities were also similar, except for slightly higher liver enzyme levels (ALT/AST/GGT) in the raltegravir arm (2–3% vs. 5–7%).

Other ongoing phase III studies of Stribild include those in specific treatment-naive populations (women, impaired renal function) and various switch studies as part of the yet-to-be-named Quad II (elvitegravir/cobicistat/FTC/TAF).[46]

Elvitegravir/cobicistat has no interaction with methadone and modest increases in buprenorphine and are not considered clinically relevant.[47]

Elvitegravir was submitted to the FDA as a separate compound in June 2012 but received a Complete Response Letter from the FDA in April 2013 stating that it cannot approve the applications in their current form.[11,14]

Cobicistat (formerly GS-9350)

Cobicistat is currently approved as one component of the four-in-one FDC Stribild, where it boosts the integrase inhibitor elvitegravir. It is a strong inhibitor of cytochrome P450 3A4 and a weak inhibitor of CYP2D6. It does not impact other CYP or UGT pathways and has a similar effect to ritonavir on other drug transporters including P-gp, BCRP, and OATP1B1/3. Unlike ritonavir, cobicistat has no activity against HIV, but it is not always interchangeable with ritonavir (for example, it can't be used to boost tipranavir).

Although the side-effect profile appears similar to ritonavir, cobicistat is being co-formulated with both atazanavir and darunavir to simplify dosing. These studies provide a clearer data set for the efficacy and safety of cobicistat compared to ritonavir.

In a randomized, double-blind, double-dummy, phase III study in 692 treatment-naive patients published in March 2013, cobicistat was noninferior to ritonavir as a booster for atazanavir based on viral suppression rates (<50 copies/mL) at 48 weeks.[12]

Mean baseline characteristics included: age 37 years, 350 CD4 cells/mm^3 (17% <200 and 14% >500) with median viral load of 4.8 log copies/mL. Approximately 17% were women; 60% were white; 18% were black; and 28% were Hispanic. As with studies evaluating Stribild, baseline entry criteria included stable renal function, defined as eGFR levels >70 mL/min.

TDF/FTC were used as background NRTIs for all patients. Response rates were 85% vs. 87% (difference: –2.2%; 95% CI, –7.4% to 3.0%, P = 0.40) in the cobicistat vs. ritonavir groups respectively, using FDA intention-to-treat (ITT) snapshot analysis, with no difference for the approximately 40% of patients with viral load >100,000 copies/mL at baseline (86% suppressed in each arm). CD4 counts increased by a mean of approximately 215 cells/mm^3 in each arm.

Side effects were generally mild and broadly comparable, accounting for 7% of patients discontinuing in each arm. The most commonly reported side effects (in >10% patients) included jaundice (21% vs. 16%), scleral icterus (yellow eyes, 18% each arm), nausea (~17%), diarrhea (15% vs. 20%), headache (11% vs. 15%) and hyperbilirubinaemia (11% vs. 100%); all cobicistat vs. ritonavir, respectively, with no statistically significant differences.

Median increases in serum creatinine were 0.13 vs. 0.09 mg/dL, with the greater of the two documented in the cobicistat group ($p < 0.001$). This was associated with a corresponding decrease in eGFR (–12.9 vs. –9.1 mL/min respectively; $p < 0.001$). These changes usually occurred by week 8 and stablized thereafter. There were six discontinuations in the cobicistat group because of renal events; one was due to reduced eGFR and five were due to laboratory markers associated with proximal tubulopathy. In the ritonavir group, there were five renal-related discontinuations, two of which were due to possible proximal tubulopathy. These resolved on discontinuation.

Increases in total cholesterol (+5 vs. +9 mg/dL; $p = 0.081$) and triglycerides (+19 vs. +32 mg/dL; $p = 0.063$) were numerically higher with ritonavir but not statistically different.

Cobicistat inhibits tubular secretion of creatinine which reduces estimated, but not actual, GFR.[48] For clinical management, a serum creatinine increase of 0.4 mg/dL or greater may be able to be used as a conservative cut-off to address concerns about potential tenofovir renal tubular toxicity.[49]

Cobicistat increases drug levels of TDF[50] and requires a reduced dose of TAF in co-formulations.

Other ongoing formulations include:[51]

- elvitegravir/cobicistat/FTC/TAF (phase III);
- darunavir/cobisitat (phase III);
- darunavir/cobicistat/FTC/TAF (phase II); and
- atazanavir/cobicistat (phase I).

Cobicistat was submitted to the FDA as a separate compound in June 2012 but received a similar decision to elvitegravir in April 2013 stating that further questions still need to be answered.[11]

Tenofovir alafenamide (TAF, formerly GS-7340)

While the potential benefits of this new prodrug formulation of tenofovir have been known for over a decade,[52] in vivo efficacy data were not presented until 2011,[53] by which time co-formulation in FDCs had been prioritized over the individual compound, with no current single formulation programme. This delay now sets any future approval conveniently close to the patent expiry for TDF.

Earlier dose-ranging studies (at CROI in 2011 and 2012) with different formulations reported more potent viral suppression with TAF compared to TDF, and that this was achieved with 90% lower plasma levels and sevenfold higher intracellular concentrations.[53,54] However, a phase II dose-finding study presented at CROI in 2013 reported that this had no additional impact on virological endpoints when TAF was compared to TDF as part of a potent FDC with elvitegravir/cobicistat and FTC.[55]

This is an ongoing, double-blind, treatment-naive study that randomized 170 patients 2:1 to TAF or TDF formulations respectively. The four-drug combination uses a 10 mg TAF as cobicistat boosts TAF by 2.4-fold.

This was a largely male (97%), white (67%) group in early infection. Baseline CD4 and viral load were approximately 400 cells/mm^3 (15% were <200) and 40,000 copies/mL (17–28% were >100,000 copies/mL), respectively. Entry criteria included eGFR >70 mL/min, with median baseline levels at 115 mL/min, as with previous studies using cobicistat and TDF.

For the primary endpoint of virological suppression at 24 weeks, 87% vs. 90% in the TAF vs. TDF arms, respectively, had viral loads <50 copies/mL (weighted difference: –4.9%, 95%CI, –15.7 to +5.9; p = 0.36). CD4 increases were similar (+163 vs. +177 cells/mm^3).

With efficacy expected to be high (the study was underpowered to determine differences in virological response), the focus on side effects showed similar short-term results. The five side effects occurring in ≥10% of patients were: nausea (18% vs. 12%), diarrhea (12% vs. 12%), fatigue (12% vs. 9%), headache (10% vs. 10%), and upper respiratory tract infection (7% vs. 12%); any grade, TAF vs. TDF, respectively. Both arms had an increase in serum creatinine and reduction in eGFR related to use of cobicistat. These occurred by week 2 but then stabilized to week 24, and were greater with TDF (–4.9 mL/min vs. –11.8 mL/min, $p = 0.032$). There were no cases of proximal renal tubulopathy or discontinuations for renal events.

Mean (+/–SD) bone mineral density (BMD) was reduced less in the TAF arm for both spine (–0.8 [+/–3.4] vs. –2.5 [+/–2.5]; $p = 0.002$) and hip (–0.3 [+/–1.8] vs. –2.0 [+/-2.7]; $p < 0.001$).

Unlike TDF, there are data to support the potential to use TAF without dose adjustment in patients with renal impairment. This comes from a study in HIV-negative patients presented as a poster at CROI in 2013.[56]

Perhaps most importantly, 25 mg TAF leads to an intracellular IQ95 that is five times higher than TFV/TDF intracellular IQ95 with in vitro data that this is sufficient to overcome the TDF-associated K65R mutation, the multinucleoside T69S and Q151M mutations, and with up to three but not with higher numbers of TAMs if they generate greater than 15-20 fold change in phenotypic sensitivity. This would make TAF essential for use in resource-limited settings, especially as tenofovir is becoming more widely used in first-line combinations.[57]

Dolutegravir

As a once-daily drug (in treatment-naive patients) with a low-milligram dose (50 mg) and no requirement for food restrictions or pharmacological boosting, dolutegravir may have advantages over other integrase inhibitors including raltegravir and elvitegravir. It is also included in an FDC with abacavir/3TC called 572-Trii, with the development for the FDC running behind that of the dolutegravir single agent, but regulatory submission expected by the end of 2013.

New phase III results this year included data from the SINGLE, SPRING, and FLAMINGO studies in treatment-naive patients and the VIKING 3 and 4 studies in treatment-experienced patients (where dolutegravir was dosed at 50 mg twice-daily).

The SINGLE study, presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in September 2012, reported that dolutegravir was superior to Atripla in 833 treatment-naive patients, with the difference driven largely by reduced side effects.[58]

Median CD4 count and viral load at baseline was approximately 340 cells/mm^3 (with 14% below 200) and 50,000 copies/mL (31% above 100,000).

Viral suppression at week 48 was 88% vs. 81% (difference: 7.4%; 95%CI, 2.5% to 12.3%; p = 0.003), with no differences between arms by baseline viral load and CD4 count. This is important: abacavir/3TC is not recommended when the pretreatment viral load exceeds 100,000 copies/mL. There was a lower rate of discontinuations due to side effects in the dolutegravir arm (2% vs. 10%).
The median time to <50 copies/mL was 28 days vs. 84 days (hazard ratio: 2.3; 95%CI, 2.0 to 2.7; p<0.0001) and CD4 increases were 267 vs. 208 cells/mm^3 (difference: +59; 95%CI, 33 to 84; p<0.001), in the dolutegravir vs. Atripla arms, respectively.

Dolutegravir was also statistically noninferior compared to raltegravir in the SPRING-2 study, presented at IAC 2012 as an oral late breaker[59] and published in the *Lancet* earlier this year.[60]

This was another randomized, double-blind, double-placebo-controlled, noninferiority study in treatment-naive patients. Participants (from Canada, US, Australia and Europe) were randomized (1:1; n=411 in each arm) to receive either 50 mg dolutegravir once-daily or 400 mg raltegravir twice daily (plus matching placebo) and stratified by baseline viral load (above and below 100,000 copies/mL) and by NRTI choice. This was investigator selected: TDF/FTC (60%) or abacavir/3TC (40%). The primary endpoint was viral suppression to <50 copies/mL with a lower-margin confidence interval set at –10% to determine noninferiority.

As with the SINGLE study, this was a largely white, male study population in patients with early-stage HIV. Approximate baseline characteristics for the study included median age of 36 years, 85% male, 85% white, and 10% black. Median viral load and CD4 count were approximately 35,000 copies/mL and 360 cells/mm^3, respectively. About 28% of patients had baseline viral load >100,000 copies/mL and 12% had a CD4 count <200 cells/mm^3. Approximately 2% and 10% were coinfected with hepatitis B and C, respectively.

Viral-suppression rates were 88% for dolutegravir and 85% for raltegravir, which, after adjusting for baseline viral load and NRTI, met the criteria for noninferiority (difference: 2.5%; 95%CI, –2.2% to +7.1%). Dolutegravir had a similarly rapid, or perhaps slightly faster, response compared to raltegravir, with 70% of patients undetectable by week 4 and >80% by week 8.

Discontinuations were similar between the dolutegravir and raltegravir arms (11% vs. 14%) and occurred for similar reasons (4% vs. 6% for lack of efficacy, 3% each for protocol violations; 2% each for side effects; and <1% vs. 2% for loss to follow-up and withdrawal of consent in both groups).

Median CD4 counts increases were superimposable at weeks 8, 24, and 48: +88, +182, and +230 cells/mm^3 in each arm.

Stratification by baseline viral load and nucleoside/tide use also met noninferiority endpoints. Response rates were 90% vs. 89% with <100,000 copies/mL (difference: +0.4; 95%CI, –4.5 to 5.3) and 82% vs. 75% (difference: +7.5; 95%CI, –3.1 to 18.0) with >100,000 copies/mL; and 86% vs. 87% using abacavir/3TC (difference: –0.8; 95% CI –8.2 to 6.6) and 89% vs. 85% using TDF/FTC (difference: +4.6; 95%CI –1.3 to 10.6) – all dolutegravir vs. raltegravir, respectively.

There were slightly fewer patients with virological failure, defined as confirmed viral load >50 copies/mL at week 24 or after, in the dolutegravir arm (5% vs. 7%; n=20 vs. 28) with most (19/20) being between 50 and 400 copies/mL. Two patients in the raltegravir arm rebounded to 10,000–50,000 copies/mL and one to >100,000 copies/mL. One of these patients developed integrase inhibitor– and NRTI mutations, with NRTI resistance in only three others. No mutations were detected in the dolutegravir arm.

Serious adverse events occurred in 7% vs. 8% (n=29 vs. 31), but were only judged to be drug-related in 3 vs. 5 patients. These included arrhythmia, hypersensitivity, and hepatitis (dolutegravir) and convulsion (2), hypersensitivity/hepatitis, diarrhea (raltegravir). Only 2% of patients in each arm discontinued due to side effects.

Grade 3/4 laboratory abnormalities were infrequent and included increases in creatinine phosphokinase (5% vs. 3%), AST (3% vs. 2%) ALT (2% vs. 2%), and lipase (2% vs. 3%), all dolutegravir vs. raltegravir, respectively. Slightly higher increases in mean creatinine (+0.14 vs. +0.05 mg/dL; p=NS) and changes in creatinine clearance (–15.5 vs. –5.4 mL/min; p=NS) occurred in the dolutegravir arm, but dolutegravir does not affect glomerular filtration and there were no discontinuations related to renal events in either arm.

At CROI in March 2013, interim 24-week results were presented from the ongoing phase III SAILING study in 715 treatment-experienced (integrase-naive) patients randomized to either 50 mg dolutegravir once-daily or 400 mg raltegravir twice daily, each plus matching placebo.[61] Patients could use an additional two investigator-selected ARVs, at least one of which had to be fully sensitive. The background combinations were generally robust (PI/ritonavir plus TDF 40%, lopinavir/ritonavir only 10%, darunavir/ritonavir plus etravirine 10%).

At baseline, median CD4 count and viral load were approximately 200 cells/mm^3 and 15,000 copies/mL, respectively, with approximately half of participants having resistance to three or more classes and a median six years prior ART. Approximately 30% were women, 50% white and 40% African American, and 15% had HIV/HCV coinfection.

At week 24, the dolutegravir arm had greater viral suppression compared to raltegravir (79% vs. 70% with VL <50 copies/mL; difference: 9.7%; 95% CI, 3.4 to 15.9; p = 0.003). However, this was in an analysis that adjusted for baseline viral load, phenotype sensitivity, and use of darunavir without PI mutations. The differences were based on fewer discontinuations in the dolutegravir arm (14% vs. 17%) and lower rates of virological failure (4% vs. 7%). Side effects were broadly similar in each arm.

In patients with hepatitis B or C coinfection, IRIS-related liver complications were reported more frequently in the patients using dolutegravir (6 vs. 3 patients). The primary endpoint for the study will be results at week 48.

A second late-breaker poster at CROI 2013 reported that dolutegravir achieved levels in the CSF that were similar to the unbound fraction in plasma and that this was above the IC50 for wild-type virus (0.2 ng/mL), indicating likely therapeutic levels. This was an open-label, single-arm intensive PK study in 13 men receiving dolutegravir with abacavir/3TC.[62]

Baseline viral loads in CSF and plasma were 3.64 and 4.73 log copies/mL, with 12/13 men achieving undetectable levels at week 16 (using test with <2 and <50 copies/mL cutoffs for CSF and plasma, respectively). Levels in the patient with detectable levels were 5 and 77 copies/mL, respectively.

A lack of interaction between dolutegravir and either methadone or combined oral contraceptives (ethinyl estradiol 0.035 mg and norgestimate 0.25 mg) was also reported in a poster showing two drug interaction studies in HIV-negative volunteers.[63]

Although many of these studies are in patients with earlier and easier-to-treat HIV infection, dolutegravir has produced strong results, even in patients with abacavir/3TC in patients with baseline viral load >100,000 copies/mL for whom abacavir is contraindication due to potency concerns. If appropriately priced, the low-milligram dose has the potential to make first-line INSTI-based combinations a reality in both rich and resource-limited countries.

Update on other compounds in earlier development

Doravirine (MK-1439)

Doravirine is a once-daily NNRTI in development at Merck that has in vitro activity against common NNRTI resistance mutations (K103N, Y181C, and G190A) and is dosed with or without food. First efficacy and safety data in HIV-positive people were presented at CROI 2013.[26]

This was a double-blind, placebo-controlled, single-site, phase Ib study in 18 treatment-naive men randomized (1:1:1) to 25 mg (n=6), 200 mg (n=6) or placebo (n=3 for each placebo), taken once-daily for seven days as monotherapy. All participants started standard ART from day eight for 10 days to minimize risk of drug resistance during the washout phase.

Mean viral-load reductions compared to placebo were –1.37 (95%CI, –1.60 to –1.14) and –1.26 (95% CI, –1.51 to –1.02) log copies/mL in the 25 and 200 mg arms, respectively, with nonsignificant differences between active doses at all time points.

A total of 21 non-serious side effects were reported in 13/18 participants, including headache (n=5), nausea (n=2), common cold (n=2), and sore throat (n=2). Night sweats, headache (at 200 mg) and loss of appetite (at 25 mg) were considered possibly related to doravirine. The single serious event was an increase in LFT in one patient on day 7, judged related to acute HCV infection between screening and study entry.

Pharmacokinetic results were similar to those seen in HIV-negative studies, with mean concentrations at 24 hours post dose that were 14-fold (25 mg dose) and 87-fold (200 mg dose) higher than the adjusted IC95 for wild-type virus (19 nM, in 50% serum).

Phase Ia pharmacokinetic results in HIV-negative people receiving multiple doses up to 750 mg for 10 days showed a lack of significant interactions with or without food, and that at steady-state, a 12 mg dose produced 24-hour postdose drug levels that remained above the adjusted IC95 for wild-type virus.[64] Other phase I studies in 140 HIV-negative people have reported no relevant side effects, including rash or CNS events.[26]

Phase IIb studies continue using 25, 50, 100, and 200 mg doses.

Cenicriviroc

Cenicriviroc is a CCR5 inhibitor that is also active against CCR2. This compound has been in development in various formulations by Tobira for several years (previously as TBR-652). Results from a randomized double-blind, double-placebo phase IIb study in 143 treatment-naive patients were presented as a late-breaker at CROI 2013.[25]

The study used a 50 mg formulation and randomized patients 2:2:1 to either 100 mg or 200 mg cenicriviroc compared to efavirenz 600 mg, all with matching placebo and open-label TDF/FTC. This was a twice-daily combination with a requirement for cenicriviroc/placebo to be taken as a morning dose following breakfast and efavirenz/placebo to be taken at night.

Baseline characteristics included approximate baseline CD4 and viral load of 400 cells/mm^3 (range: 77 –1090) and 25,000 to 40,000 copies/mL (14–25% were >100,000), respectively. The study population was 94% male, 62% Caucasian, 32% African American and 24% Hispanic. Mean age was 36 (range: 19–63).

At week 24, viral suppression to <50 copies/mL was achieved by 76% and 73% vs. 71% of patients in the 100 mg and 200 mg vs. efavrienz arms, respectively. Virological nonresponse was higher in the cenicriviroc arms (12% and 14% vs. 4% efavirenz). Cenicriviroc arms appeared less effective compared to efavirenz in the small percentage of patients with baseline viral load >100,000 copies/mL (50% and 60% vs. 75%) although discontinuations due to nonresponse were similar (20% and 29% vs. 25%). Interpretation of the results stratified by baseline viral load was complicated by a range of non-responders, due to lack of virological data at week 24 related to early discontinuation (from 0% with efavirenz at >100,000 copies/mL to 29% with efavirenz at <100,000 copies/mL).

Efficacy with cenicriviroc appeared to be related to drug exposure: a higher viral response rate was reported with upper quartile (141–400 ng/mL) of modeled Cmin trough concentrations of 100% compared with 12%, 9%, and 17% non responders in Q3 (70–141 ng/mL), Q2 (40–71 ng/mL) and Q1 13–40 ng/mL), respectively. This also shows a wide range of interpatient variability. CD4 changes from baseline were similar (+147 and +170 vs. +135 cells/mm^3).

Discontinuation related to side effects was significantly more frequent with efavirenz (0% and 2% vs. 18%) as were grade 3 events (2% and 4% vs. 11%). There were no grade 4 events, serious events, or deaths in the study.

Laboratory abnormalities were higher in the 200 mg arm—principally increased creatinine phosphokinase—but these generally resolved without treatment discontinuation.

Resistance mutations in patients with viral load rebounding to >400 copies/mL were predominantly M184V/I in 5 patients taking cenicriviroc (vs. none in the efavirenz arm).

The impact of CCR2 blocking on the monocyte activation pathways was seen by dose-related increases in the CCR2 ligand MCP-1 of approximately 450 ng/L in the 100 mg arm and 750 ng/L in the 200 mg arm. Both cenicriviroc arms also reported a reduction in levels of the monocyte activation marker of soluble CD14 of –0.2 vs. +1.3 x 10(6) pg/mL in the efavirenz group. Soluble CD14 has been associated with an increased risk of all-cause mortality independent of CD4 and viral load, and this potential was highlighted in the conclusion as a property of cenicriviroc that warranted additional research.

A new formulation of cenicriviroc will be used for phase III studies, although the dose for future research has still to be decided. The company intends to co-formulate cenicriviroc with other ARVs, although this is currently only at a preliminary planning stage.

BMS-986001

BMS-986001 is a once-daily NRTI with a similar structure to stavudine (d4T) but with greater potency (75-fold) and without evidence of mitochondrial toxicity (it is >200-fold less active as an inhibitor of mitochondrial polymerase-gamma), that is in development by Bristol-Myers Squibb. Although there are no new clinical data since the *2012 Pipeline Report*, a phase II dose-finding study (100, 200 and 400 mg QD) is currently enrolled with TDF as a comparitor arm and with efavirenz/3TC as background ARVs.[65]

However, new in vitro safety and resistance data were presented during this year.

Drug-susceptibility results to a panel of NRTI mutations were interesting but may have limited clinical potential.[21] HIV harboring key reverse transcriptase mutations associated with tenofovir and abacavir resistance (0.43 fold change to K65R and 0.65 fold change to L74V) was hypersusceptible to BMS-986001; in the presence of M184V this reverted to similar activity as wild-type virus. HIV harboring the multidrug-resistant Q151M RT mutation was also hypersusceptible to BMS-986001, but this steadily reduced in the presence of other mutations including M184V (from 0.17 fold to 1.24-fold). One isolate that included mutations at RT positions 151 and 184 demonstrated a >40-fold loss in sensitivity. BMS-986001 is not active against the multidrug-resistant T69SSS substitution (also by >40-fold). Other common thymidine analogue mutations (TAMs), including M41L, L210W, T215Y or D67N, K70R, T215Y significantly reduced susceptibility (by 6-8 fold).

In vitro results from exposing renal, muscle and fat (preadipocytes and differentiated adipocytes) cells to therapeutic dose concentrations of BMS-986001 and four other NRTIs (TDF, AZT, d4T and abacavir) for 5, 10, 14 and 19 days reported that BMS-986001 was not cytotoxic in any of the four cell cultures.[22] This was in contrast to TDF, which showed toxicity in muscle cells and preadipocytes, and to both AZT and d4T, which were cytotoxic in all four cell types and for all measured parameters. Abacavir was only significantly cytotoxic at a 200 uM concentration.

BMS-986001 also had no effect on a wide panel of renal or bone biomarkers in rats and cynomolgus monkeys following oral six-month dosing at any dose tested compared to control group.[23]

BMS-663068

BMS-663068 is an attachment inhibitor that blocks HIV gp120 from binding to the surface of CD4 cells.

No further in vivo results have been presented since viral-load reductions of approximately –1.6 logs were reported in an eight-day monotherapy dose-ranging proof-of-concept study at CROI 2011, although these and other study results have recently been published in full.[66,67]

No results have been presented from the phase II 24-week dose-ranging study (follow-up is out to 96 weeks, expected 2017) using various doses (400, 600, 800 mg twice daily or 1,200 mg once daily) and compared to atazanavir/ritonavir, with raltegravir and TDF as backbone in all arms.[20]

Long-acting formulations

Several companies have formulations with extremely long elimination half-lives that have the potential for weekly, monthly, or even quarterly dosing.

S/GSK1265744

S/GSK1265744 is an integrase inhibitor that is in development both as a long-acting parenternal (LAP) formulation and the backup oral formulation to dolutegravir. Phase I data shown at 2012 International AIDS Conference (IAC) used a 200 mg/mL nanosuspension administered by intramuscular—dosed at 100 to 800 mg—or subcutaneous abdominal injection—at 100 to 400 mg—in HIV-negative people. Single doses maintained therapeutic levels (previously associated with –2.5 log reductions as monotherapy) beyond three months, supporting parenteral monthly or perhaps quarterly dosing.[29]

In vitro resistance data presented a few months later at ICAAC 2012 also looked promising.[30]

Passaging HIV-1 IIIB in MT-2 cells with increasing concentrations of S/GSK1265744 showed an IC50 of 0.22 nM in human peripheral blood mononuclear cells (PBMCs). IC50s for dolutegravir, raltegravir, and elvitegravir were 0.51, 2.0, and 2.0 nM, respectively. The fold potency shift for 100% human serum was 408 for S/GSK1265744, and 75, 4.7, and 22 for dolutegravir, raltegravir and elvitegravir. The protein-adjusted IC50 estimate for S/GSK1265744 was 102 nM compared to 38, 5.6, and 20 nM for dolutegravir, raltegravir, and elvitegravir respectively.

Exposure for up to 112 days did not produce highly resistant mutants with a maximum 8.4-fold phenotypic change. Raltegravir/elvitegravir-resistant signature

mutation site-directed molecular clones had a < 2-fold change in susceptibility to S/GSK1265744, except for Q148K/R, which had a 5.6/5.1-fold change, respectively. Fold changes of 14 double mutants among 15 site-directed molecular clones were less than 12.

A phase I, open-label, two-cohort, single-sequence crossover study looking at the effects of oral coadministration of rilpivirine with S/GSK1265744 or dolutegravir found no clinically significant interaction, supporting use in combined formulations.[31]

The oral formulation of S/GSK1265744 is being studied at once-daily doses of 10, 30 and 60 mg as part of a dual therapy maintenance therapy with rilpivirine in a phase IIb treatment naïve study, following 24 weeks induction with S/GSK1265744 plus investigator-selected dual NRTIs and compared to a control of efavirenz plus two NRTIs.[68]

Rilpivirine LA

Aside from the drug interaction studies with S/GSK1265744 detailed above, there have been no further human studies of the long-acting parenternal formulation of the NNRTI rilpivirine since presentation of initial pharmacokinetic results in HIV-negative individuals presented at CROI 2012, and this study was focused on its potential role as PrEP.[69]

Ongoing studies are in HIV-negative people, with monthly and quarterly injections, including with S/GSK1265744. Current research is focused on use in HIV prevention.[36,37]

CMX157

CMX157 is a nucleoside analogue that reported promising phase I results more than four years ago[70] but saw no further development until acquired by Merck in August 2012.[33]

The compound is a prodrug of tenofovir (tenofovir diphosphate as the active moiety), with an improved pharmacokinetic profile compared to tenofovir, and initial results suggesting a potential for once weekly dosing. The in vitro resistance profile includes sensitivity to K65R with some but not all thymidine analogue mutations.

EFdA

EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine) is a reverse transcriptase inhibitor being developed by the Japanese biotech division of the Yasama Corporation (which has a history that includes brewing soy sauce since the time of the English civil war) and which has been studied with support from amfAR and the US National Institutes of Health.

A poster presented at IAC 2012 reported a significantly stronger in vitro resistance profile compared to TDF following multiple passaging with a mixture of 11 multinucleoside-resistant viral mutations.[34]

In macaque studies EFdA was significantly more potent than TDF, AZT or FTC.[35]

EFdA was recently acquired by Merck, and its long half-life has the potential for use in FDC combinations.[33]

Albuvirtide: long-acting formulation of T-20

Albuvirtide is a new long-acting formulation of the fusion inhibitor T-20 with potential for weekly dosing that is in development by the Chinese company Chongquing Biotechnologies.

Limited in vivo virological data have been presented from a dose-finding study in HIV-positive Chinese patients who received single IV injections daily for three days, followed by once-weekly injections for a further two weeks.[32]

Mean maximum reductions of 0.68 and 1.05 log copies/mL were reported with 160 mg and 320 mg doses respectively. In this single-dose study, viral reduction was maintained for 6–10 days, with albuvirtide showing a plasma half-life of 10–13 days.

Multidrug resistance

One area with little advance this year has been research into options for people with multiple drug resistance.

This is an increasingly smaller percentage of patients each year, thanks largely to a good run on second-line and new-class drugs over the last five years: maraviroc, raltegravir, darunavir, etravirine, rilpivirine, and dolutegravir. For those at the sharp edge—technically probably few enough to derive orphan-drug status from a regulatory perspective—and who are already waiting for drugs, there have been few research or regulatory changes.

The hope that pulling together several early-stage compounds, even with limited potency, to use in a research setting has never materialized. This leaves compounds that might be useful in this setting, such as apricitabine, ibalizumab, and new classes like maturation inhibitors, out of active reach.

New targets and compounds of interest

Monoclonal Antibodies

The study of ibalizumab, a monoclonal antibody that binds to CD4, seems to have been on hold for many years. Even though a few treatment-experienced people may still be using ibalizumab (possiblely less than a handful), no new clinical or follow-up results have been presented for five years.[71] Although a recent review in JAIDS suggested a potential use for HIV prevention, no current studies are underway.[27]

There is also PRO 140, CytoDyn's monoclonal antibody targeting CCR5. Phase I and II studies exploring single-dose intravenous infusions of PRO 140 at doses of 5 mg/kg or 10 mg/kg reported mean maximum viral-load reductions of 1.8 log in the absence of other antiretrovirals.[72,73] Weekly (162 and 324 mg) and biweekly (324 mg) subcutaneous administration has also been evaluated, yielding mean viral-load reductions of 1.37 log to 1.65 log and no serious adverse events.[74] Though no new data have been reported since 2010, additional phase II studies are planned.[75]

Maturation inhibitors

Maturation inhibitors target the final stage of HIV gag processing that inhibits release of fully formed capsid, and as a new class would overcome currently drug-resistant HIV.

Early studies focused on the compound beviramat (PA-457), which featured in earlier *Pipeline Reports*. Beviramat produced viral-load reductions of approximately –1.2 log in treatment responders, but common polymorphisms at baseline, principally V370A (present in 50% of patients), correlated with nonresponse. Although early phase I/II studies raised no safety concerns, the development of beviramat was discontinued in June 2010 (by Myriad which had bought the compound from Panacos).

However, new results presented at CROI 2013 provided in vitro data on second-generation maturation inhibitor molecules developed to overcome V370A.[76]

This research is under DFH Pharma (and includes previous members of the Panacos team), and the group collaborated with researchers at the US National Cancer Institute.

The IC50 for DFH-055 had similar activity (at 0.032 uM) to wild-type and V370A (compared to <0.08 and >32.0 uM for wild-type and V370, respectively, for beviramat). Current best compounds (DFH-068 and DFH-070) further improved

on activity against V370A with five-fold greater sensitivity compared to DFH-055 at 30.1 and 38.3 nM, respectively. Although these results are encouraging, the presenter cautiously avoided announcing whether either molecule had been selected as a lead compound for further development.

Transcription Factors: RNase H Inhibitors

After reverse transcriptase has copied RNA into DNA, ribonuclease H (RNase H) must degrade the HIV RNA that remains attached to the newly created DNA so that HIV's genetic material can be successfully integrated into the host cell's genome.[77] The critical role of RNase H in the HIV life cycle makes it an ideal target, and the development of high-throughput screening assays has enabled an increased pace for inhibitors of the enzyme's activity.

Though numerous small molecules with good inhibitory potency against RNase H have been published since 2003, none has moved beyond the laboratory due to poor antiviral activity in cell-based HIV replication assays,[78] This year, however, investigators at the University of Pittsburgh School of Medicine and the University of Missouri School of Medicine plan to launch a publicly accessible database of RNase H inhibitors with validated screening hits. The teams also recently received a $4.3 million grant from the National Institutes of Health to develop and advance promising compounds through preclinical development.[79]

Transcription Factors: Tat, Rev, Nef, Vpu, Vpr and Vif Inhibitors

Tat is a regulatory protein that allows full-length transcripts, an essential component of HIV replication, to be produced. BPRHIV001, a derivative of coumarin (found in vanilla grass, cassia cinnamon, and sweet clover), has demonstrated in vitro activity against Tat transactivation and has synergistic effects when combined with reverse transcriptase inhibitors.[80]

Rev is another regulatory protein needed to synthesize major viral proteins during the replication process. Though a number of compounds have been explored in vitro, efficacy, toxicity, and oral absorption challenges have arisen for some, and none has moved beyond preclinical evaluations.

The accessory protein Nef is involved in multiple functions during the life cycle of HIV and is required for high replication and disease progression. The Akt inhibitor triciribine, originally developed as a cancer chemotherapeutic, targets Nef and has a wide range of activity against HIV, but has been associated with severe adverse events.[81,82]

Vpu, an accessory protein involved in the release of HIV from the surface of infected cells, is the target of BIT225, a small molecule inhibitor being developed by the Australian biotech Biotron Limited.[83] BIT225 targets HIV in monocytes and macrophages and is currently in early-stage clinical trials.

Vpr is an accessory protein that plays a role in the preintegration stages of HIV and is required for the virus to replicate in nondividing cells such as macrophages. Vipirinin, another coumarin-based compound, has recently been used to expose Vpr's binding sites, though it is unclear if this particular compound will be explored further in preclinical evaluations.[84]

Vif inhibits APOBEC3G, an important cellular protein that plays a role in innate antiviral immunity. RN-18, a small molecule identified in 2008 by University of Massachusetts Medical School researchers, has been shown to inhibit Vif and increases cellular levels of APOBEC3G.[85] RN-18 remains in preclinical development and has not made any significant advances since it was mentioned in the *2012 Pipeline Report*.

Cellular Factors: LEDGF/p75

There has been growing interest in lens-epithelial-derived growth factor (LEDGF/p75), a cellular protein that binds to HIV integrase and is needed for replication. Inhibitors of this interaction, a series of compounds dubbed LEDGINs, were first described in 2010 and remain in pre-clinical development.[86] More recent evaluations suggest LEDGINs may be synergistic with approved integrase inhibitors and are active against integrase inhibitor–resistant strains of HIV, and therefore hold promise for further clinical development.[87]

Nanosuspensions

Novel nanoscale drug-delivery platforms provide a tremendous opportunity to improve the efficacy, safety, administration, and cost of approved and experimental compounds for HIV. Drivers for controlled-release nanotechnology-based formulations of antiretrovirals include drugs with insoluble active pharmaceutical ingredients (APIs), patient variability, high pill burden, dietary requirements, adverse drug reactions, formulation difficulties during development, poor patient uptake of the product, low efficacy, low bioavailability, high dose requirements, and the cost of conventional processing.[88]

As discussed above, long-acting nanosuspensions of rilpivirine and S/GSK1265744 may allow for infrequent dosing, at least during maintenance phases of antiretroviral treatment. Nanotechnology is also being applied to efavirenz, a drug with very

poor water solubility that requires high doses in order to reach therapeutic plasma concentrations after oral administration. In two recent assessments, efavirenz nanosuspensions employing freeze-drying techniques resulted in improved bioavailability;[89,90] one of the studies, conducted by a University of Liverpool team, also found greater in vitro cellular distribution and enhanced antiviral activity using the efavirenz nanosuspension compared to dissolved efavirenz.[90]

University of Liverpool studies involving HIV-negative volunteers to evaluate the bioequivalence of a low-dose efavirenz are expected to begin this year.

Nanosuspensions of atazanavir/ritonavir and lopinavir/ritonavir are also being developed.[88,91]

Conclusion

The ARV pipeline this year is remarkably strong, and includes compounds and technologies that look to advance options for HIV-positive people who are able to afford them.

This will drive further competition among companies to achieve and maintain a share of the HIV market. It will also drive intercompany collaborations for FDCs that are rarely seen in other health areas. Projecting forward 10 years, this might include combinations that are given by monthly or perhaps quarterly injections.

Use of generics is inevitable. Implicit in the patent process is the recognition that market exclusivity is granted to companies for a limited period in recognition of the costs of developing new drugs. Competition among generic manufacturers will be needed for this to dramatically reduce drug costs though, and brand companies are able to use their experience and skills to retain some of these markets by also reducing medicine costs.

Many of the global differences in treatment use have largely depended on geographic region and economic factors, and it is expected that these will increasingly occur within rich countries. These will inevitably result in a two-tier system of access to treatment in wealthier countries, similar to that that has always existed between rich and poor countries.

Drug innovation will continue—but drug access to the newest drugs is likely to become a global issue wherever someone lives, which will invariably be a new activist challenge for many.

Savings from generics are essential if we are to retain public health services for those who remain uninsured or underinsured, and it will ultimately be up to activists to ensure that savings on ARV expenditures are siphoned back into HIV care delivery systems. Ensuring universal access to the latest drugs will be more difficult.

Sources

Information about clinical trials is based on the U.S.-based clinical trials registry (clinicaltrials.gov) and for study results on the online U.S. National Library of Medicine (pubmed.gov) current in May 2013, as a result of the following search terms:

APOBEC3G, apricitabine, BIT225, BPRHIV001, BMS-986001, BMS-663068, cenicriviroc, cobicistat, CMX-157, CTP-518, dolutegravir, efavirenz, elvitegravir, GS-7340, GS-9137, GSK-1265744, ibalizumab, LEDGINs, MK-1439, PF-3716539, PRO 140, rilpivirine, RAP101, RN-18, RNase H, SPI-251, TBR-652, tenofovir alafenamide fumarate, tetherin, TMB-355, TMC-310991, TMC-558445, TNX-355, triciribine, TRIM5-alpha.

Company press statements have been used for some updates, with the usual caveat that they may include forward-looking statements.

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IAC: International AIDS Conference
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The Pediatric Antiretroviral Pipeline

By Polly Clayden

The last *Pipeline Report* described a bumper year for pediatric antiretroviral approvals. This one reports after a year in which new approvals were fewer and far between.

Although the pipeline for children continues to look promising, pediatric investigational programs mostly sauntered along, with only two new United States Food and Drug Administration (FDA) approvals: an expanded indication for efavirenz to include children at least three months old, and once-daily dosing of darunavir in treatment-naive children three years and older.[1,2]

Two development programs—the granule formulation of ritonavir-boosted protease inhibitor lopinavir, and the integrase inhibitor dolutegravir—remained attention-worthy.[3,4]

This year's headline-hogging news, of the Mississippi cure baby,[5] was accompanied by a plague of bad journalism. *Pipeline Report* co-author Richard Jefferys provided a much-needed voice of reason on this case of a potential "functional cure" in an HIV-infected infant.[6] The news would be good if the attention it grabbed helps to sharpen the focus of research and implementation of maternal/infant HIV programs in places where they are badly needed.

Finally the World Health Organization (WHO) has revised its HIV guidance—this time recommendations for adults (including pregnant women) and children are consolidated into one document.[7] This chapter updates the pediatric antiretroviral pipeline in the context of the new recommendations.

Efavirenz

The FDA expanded indication for efavirenz to infants at least three months old and weighing at least 3.5 kg was approved on May 2, 2013. For children unable to swallow capsules, these can be broken and the contents (dispersible sprinkles) given with a small amount of soft food, or formula milk if they are too young for solids.

The updated labeling includes a table for dosing showing the number of capsules or tablets and strength by weight band. See Table 1.

Table 1. Efavirenz Weight Band Dosing for Children 3.5 to Less Than 40 kg

Weight/kg	Daily Dose/mg	Number of Capsules[a] or Tablets [b] and Strength
3.5 to less than 5	100	two 50 mg capsules
5 to less than 7.5	150	three 50 mg capsules
7.5 to less than 15	200	one 200 mg capsule
15 to less than 20	250	one 200 mg + one 50 mg capsule
20 to less than 25	300	one 200 mg + two 50 mg capsules
25 to less than 32.5	350	one 200 mg + three 50 mg capsules
32.5 to less than 40	400	two 200 mg capsules
at least 40	600	one 600 mg tablet OR three 200 mg capsules

[a]Capsules can be administered intact or as sprinkles. [b] Tablets must not be crushed.

Source: FDA. Sustiva (efavirenz) pediatric patients labeling update. 2013 May 2.

The update was based on three open-label trials to investigate the pharmacokinetics, safety, tolerability, and antiviral activity in antiretroviral-naive and experienced children age three months to 21 years.

Pharmacokinetic parameters at steady state were based on data predicted by a population pharmacokinetic model by weight ranges that correspond to the recommended doses.[8]

This approval came as a bit of a surprise as the pediatric formulations for efavirenz took some time to develop (adult approval was in 1998). An appropriate one for the youngest children has remained elusive for many years. The 2010 Pediatric Antiretroviral Pipeline described the hurdles:[9]

> *"Development of a liquid formulation of efavirenz has been besieged by setbacks for years. Efavirenz has potential for oral mucosa irritation; it also has poor aqueous solubility. Early development focused on palatable alternatives to the aqueous suspensions using oily vehicles that were known to mask irritation. The original oral solution, a suspended sugar solution, was found to have a low level of bacterial contamination; the culprit was confectioner's sugar. A heating step was then incorporated into the process to destroy the bacteria, but this then led to clumping. The current liquid formulation is a sugar-free strawberry mint flavor 30mg/mL solution. It does not provide sufficient drug exposure for children less than three years of age."*

Formulation glitches aside, a strong influence of CYP2B6 genotype polymorphisms on efavirenz pharmacokinetics and safety has been shown in children less than three years old.[10] In one study, using aggressive dosing (approximately 40 mg/kg) with the opened capsules, produced therapeutic efavirenz concentrations in most

(68 percent) children of the children in this age group (with GG or GT genotype), but this led to excessive exposure in the remainder (with TT genotype). This suggested that optimal use of efavirenz in children less than three years requires pretreatment genotyping. A related study, using modeling to predict the pharmacokinetics of efavirenz in children with different CYP2B6 genotypes, also indicated genotype-guided dose optimization might be used in young children.[11]

Efavirenz could be important for use with concomitant tuberculosis (TB) treatment, but WHO has just recommended boosted lopinavir first-line for infants and children less than three, and triple nucleoside reverse transcriptase inhibitors (NRTIs) during treatment of TB.[12] For older children, tentatively approved reduced strength (50 and 100 mg) and scored adult tablets (200 mg twice on one side and once on the other) are available.[13,14]

Concerns about non-nucleoside reverse transcriptase (NNRTI) resistance acquired through in utero exposure, as well as comparative potency to protease inhibitors (PIs) that led to nevirapine being only recommended if boosted lopinavir is not available, could also apply to efavirenz.[15,16]

It is unclear whether this new formulation and indication is an important breakthrough. But the tenacity of the sponsor to finally produce one—albeit without a clear role (including in rich countries)—is impressive.

WHO Guidelines 2013

The new guidelines include antiretroviral treatment recommendations for adults and children (including pregnant women). Guidance is also given on implementing the recommendations.

When to Start?

- Infants and children should initiate antiretroviral therapy:
- Less than five years old regardless of CD4 count or WHO stage. Strong recommendation for children up to one year and conditional from one to five years.
- At five years and older with 500 CD4 cells/mm^3. Strong recommendation 350 cells/mm^3 and below, and conditional 350 to 500 cells/mm^3.
- With severe or advanced symptomatic disease (WHO stage 3 or 4) regardless of age or CD4 count. Strong recommendation.
- With a presumptive HIV diagnosis below 18 months. Strong recommendation.
- With active TB. As soon as possible within eight weeks following the start of TB treatment regardless of CD4 or WHO clinical stage. Strong recommendation.

What to Start?

First-line for infants and children less than three years old:

- Lopinavir/ritonavir-based regimens regardless of previous NNRTI exposure. If lopinavir/ritonavir is not feasible, nevirapine-based. Strong recommendation.
- Consider substituting lopinavir/ritonavir with an NNRTI after sustained virological suppression (defined as viral load less than 400 copies/mL at six months, confirmed at 12 months from starting treatment). Conditional recommendation.
- Children who develop active TB while on boosted lopinavir- or nevirapine-based regimens should be switched to abacavir plus lamivudine plus zidovudine during TB treatment. They should switch back to the original regimen when their treatment for TB is completed. Strong recommendation.
- The NRTI backbone should be one of the following (in order of preference): abacavir or zidovudine plus lamivudine; stavudine plus lamivudine. Strong recommendation.

First-line for children three years and older:

- Efavirenz preferred and nevirapine alternative. Strong recommendation.
- Less than 12 years (or weighing less than 35 kg) the NRTI/nucleotide reverse transcriptase inhibitor [N(t)RTI] backbone should be (in order of preference): abacavir plus lamivudine; zidovudine or tenofovir disoproxil fumarate (DF) plus lamivudine or emtricitabine. Conditional recommendation.
- Adolescents 12 years (weighing more than 35 kg) should align with adults, the NRTI backbone should be: tenofovir DF plus lamivudine or emtricitabine; abacavir or zidovudine plus lamivudine. Strong recommendation.

Which Second-line?

- After first-line NNRTI failure, a boosted PI; lopinavir/ritonavir is preferred. Strong recommendation.
- After failure of first-line lopinavir/ritonavir, children less than three should remain on the regimen with improved adherence support. Conditional recommendation.
- After failure of first-line regimen containing abacavir or tenofovir DF plus lamivudine or emtricitabine, the preferred NRTI backbone is zidovudine plus lamivudine. Strong recommendation.

- After failure of first-line regimen containing zidovudine or stavudine plus lamivudine or emtricitabine, the preferred NRTI backbone is abacavir or tenofovir DF plus lamivudine or emtricitabine. Strong recommendation.

Missing Formulations

One of the goals of treatment optimization is to align pediatric antiretroviral regimens with recommendations for adults. With current options, the youngest children need to be considered differently, and there is some room for interpretation in the guidelines as to what age this harmonization should begin.

In order to implement the revised guidelines, child-sized solid dosing forms of recommended antiretrovirals, in appropriate strengths, are needed to facilitate dosages according to WHO simplified tables.[17] Where possible these should be fixed-dose combination (FDC) dispersible tablets. For compounds that cannot be formulated in this way (large and/or insoluble molecules) granules are preferable to liquids. These formulations are expensive, have short shelf lives, and often require a cold chain, making them hard to store and transport.

Lopinavir/ritonavir

For the youngest infants and children, implementing lopinavir/ritonavir-based regimens with the currently available formulations is easier said than done. There is an 80/20 mg/mL liquid formulation, but it is unsuitable for most settings for the aforementioned reasons. It also tastes appalling. There are also scaled down 100/25 mg heat stable tablets available for children, but these are only suitable for those weighing10 kg or more. The tablets are formulated with the active ingredient embedded in a matrix of insoluble substances, so cannot be split or crushed as they lose bioavailability.

Cipla and the Drugs for Neglected Diseases initiative (DNDi) are developing a more acceptable granule formulation of 40/10 mg lopinavir/ritonavir as part of a first-line regimen for infants and young children. They are also working on either abacavir or zidovudine plus lamivudine granules as backbone and aim to produce adapted 4-in-1 regimens for children under three.

In recognition of the urgency of a suitable formulation for this age group DNDi was awarded a substantial grant by UNITAID to expedite 4-in-1 development and delivery.[18] The plan is to have the new formulation and regimen by 2015 and to help to consolidate rather than further fragment the market—that is, have this regimen replace many existing and not always very useful formulations currently available for infants and young children.

Tenofovir Disoproxil Fumarate

Last year a 40 mg/1 g oral powder formulation, and 150 mg, 200 mg, and 250 mg tablets of tenofovir DF, and dosing recommendations for children age two to less than18 years were approved.[19] The recommended dose is 8 mg/kg (up to a maximum of 300 mg).

Tenofovir DF for young children also took its time—the FDA approved it for adults in 2001. Like efavirenz, there were problems with the pediatric formulation—the original liquid-suspension formulation tasted too bitter for further development. The powder for younger children is an improvement, but its nasty taste is not well masked and it is hard to administer, making adherence problematic (sometimes called the "new nelfinavir"). The pediatric tablets appear to be more palatable, although exposure can be variable with the approved dose.[20]

Also last year the WHO published a review of the current literature and unpublished data on the safety and efficacy of tenofovir DF in children.[21,22,23] The review found it to be efficacious in children and adolescents at current FDA-approved doses, but further studies are needed to confirm the dose and investigate its side effects, particularly in combination with efavirenz.

The main toxicities are decreased bone mineral density, and glomerular and renal tubular dysfunction. Data in children are scant but suggest that the toxicities are similar to those seen in adults.

Bone turnover is higher in young children and adolescents because they are growing. Children's bone mineral density increases over time whereas in adults it remains constant or decreases with age, so comparisons between adults and children are difficult. Plus children with HIV have lower bone mass than background population for their age and sex. The impact of lower bone mineral density on longer-term risk of fracture and osteoporosis is not known. This long- term risk is concerning.

Several studies have suggested significant glomerular and renal tubular toxicity in children on tenofovir DF, but the role of concomitantly used antiretrovirals, such as didanosine and ritonavir-boosted lopinavir is unclear.

At present there are still questions about its use in children and the guidelines are a bit ambiguous as to what age it should be recommended. It is introduced for the three to less than12 age group third in order of preference after abacavir and zidovudine. For adolescents 12 years and older it takes first place in line with adult recommendations.

To facilitate simplified dosing with the current formulations, 2.5 scoops of the oral powder could be used for a child 10 to 13.9 kg and one 150 mg tablet for the next weight band, 14 to 19.9 kg etc. Triple FDCs, scaled down to a quarter of the

adult tablets, 75/75/150 mg tenofovir DF/lamivudine/efavirenz (or with 60 mg emtricitabine), as well as dual 75/75 mg and 75/60 mg with tenofovir and lamivudine or emtricitibine, respectively, are needed to make this a realistic option.

The WHO pediatric group considered the feasibility of scoring adult FDC tablets once on one side and twice on the other. The doses delivered by tablets divided into thirds and halves would be acceptable,[24] but there is concern that in practice it might be difficult to manufacture, score and split large, multilayered FDC tablets in this way. If such tablets are possible, it will be important to establish feasibility, pharmacokinetic and bioavailability data to support this dosing strategy.

Darunavir/ritonavir

At the end of 2011, a 100 mg/mL oral suspension formulation of darunavir was approved, with dosing recommendations for children three to less than six years old.[25] There is a waiver for children under three, due to very high darunavir concentrations in animals (of an analogous age) and, in turn, toxicities in preclinical studies.

Ritonavir-boosted darunavir is increasingly used in children and adolescents in rich countries, particularly in those with treatment experience.[26] This could be a useful option for third-line regimens for children, and for second-line regimens where boosted lopinavir has been used as first-line.

The Pediatric Antiretroviral Group of the WHO considered darunavir to be of high priority and in the 2011 Updated List of Missing Drug Formulations listed a tablet or sprinkle formulation of darunavir/ritonavir as urgently needed.[27]

Using boosted darunavir with the currently approved doses does not lend itself to harmonized, simplified weight-band dosing or to appropriate use in combined tablets to facilitate this. The establishment of a single ratio at best, or at least a simpler dosing range would make wider use of darunavir more feasible. As the varied ratios were because of the limits of ritonavir formulations, there seems no reason why a 6:1 ratio twice daily, as for adults, shouldn't be possible.

For the 2013 guidelines, the WHO group lists a 240/40 mg darunavir/ritonavir tablet for twice-daily dosing as a priority for children weight bands 10 kg and above.

Atazanavir/ritonavir

The capsule formulation of atazanavir is approved in the United States and the European Union for children ages six years and older who are treatment-naive and -experienced children weighing 15 kg or more. Capsules are available in 100, 150, 200, and 300 mg atazanavir.

For boosting, the atazanavir/ritonavir ratio is 3:1 and, as with darunavir, this is complicated by the currently available formulations. A heat stable tablet once daily 100/33 mg atazanavir/ritonavir could help to align second-line treatment for children 10 kg and above, who received an NNRTI first-line, with adult recommendations.

Generic heat stable 300/100 mg atazanavir/ritonavir tablets for adults are already produced, including one that is tentatively approved.[28] A reduced-strength tablet for children, scaled down to one third of the adult one, is another priority.

The Pipeline

Formulations for young children for all but one drug in the current pipeline are granules, dispersible tablets, or powder, some of which might be useful for resource-limited settings in the future.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Etravirine

A scored 25 mg etravirine tablet, and dosing recommendations for treatment-experienced children and adolescents ages six to less than18 years of age and weighing at least 16 kg, are currently approved.[29] The recommended dose is based on 5.2 mg/kg twice daily.

IMPAACT P1090 is evaluating the drug in treatment-naive and -experienced children ages two months to six years.[30] Phase I/II studies in the younger age groups are currently enrolling treatment-experienced children sequentially from the older to younger age groups. There is a waiver for infants less than two months.

Etravirine might be a useful second-line NNRTI option for children as its resistance profile is different from those of nevirapine and efavirenz; it should not be co-administered with rifampicin.

Rilpivirine

The PAINT phase II trial is currently enrolling treatment-naive adolescents ages12 to less than18, weighing more than 32 kg, and receiving 25 mg once daily plus two NRTIs. The trial will evaluate steady-state pharmacokinetics and short-term antiviral activity in this age group.[31]

IMPAACT 1111 is planned in children from neonates to less than12 years. This trial

is also taking a staggered approach and will study the drug in de-escalated age groups: six to twelve years, two to six years, six months to two years and less than six months. A granule formulation is in development.

PROTEASE INHIBITORS

Atazanavir

Treatment-naive and -experienced children ages three months to eight years receiving atazanavir boosted with ritonavir are being studied in PRINCE 1 and 2 and IMPAACT P1020A, phase II, IIB and I/II.[32,33,34] PRINCE 1 is now fully enrolled, and data are expected this year; PRINCE 2 is over half enrolled, and data are expected at the end of 2013 and IMPAACT P1020A is ongoing.

For younger children a powder formulation is in development, which is boosted with ritonavir liquid.

Lopinavir/ritonavir

The generic manufacturer Cipla is developing a pediatric formulation of lopinavir/ritonavir in partnership with DNDi. The original sprinkle formulation (40/10 mg lopinavir/ritonavir) consists of a finite number of mini-tablets in a capsule, which is opened and sprinkled on soft food.

Data from a randomized crossover pharmacokinetic study in healthy adults comparing a single dose of sprinkles from 10 capsules of lopinavir/ritonavir with a single dose of 5 mL Kaletra oral solution found most pharmacokinetic parameters fell within the conventional bioequivalence range of 80 to125 percent in this study. Where they fell outside, the differences were not large.[35] Both formulations were administered with about 150 g porridge and 240 mL water.

Initial data from CHAPAS-2—which compared twice-daily sprinkles to tablets in children ages four to 13 years, and sprinkles with syrup in infants ages three to 12 months in a randomized cross-over pharmacokinetic study—found high variability in the younger cohort with both sprinkles and syrup, with no significant differences in sub-therapeutic concentrations between formulations. In the older children, lopinavir/ritonavir concentrations were lower in children receiving the sprinkles than in those who got the tablets.[36]

The caregivers found the sprinkles were more acceptable for infants but not for older children, mainly due to the taste. Acceptability data showed storage, transport, and conspicuousness of treatment were less problematic for sprinkles compared with syrups, but for older children, several caregivers commented about

the number of capsules needing to be used. At week eight, when they could chose which formulation to continue with, the majority of caregivers chose to continue sprinkles rather than syrups for the infants, but only a quarter of the older children chose sprinkles over tablet, and taste was particularly to blame.

When the investigators performed the same comparison in one to four year olds, lopinavir exposure with sprinkles was higher than with syrup and historical data for children aged six months to12 years.[37] There was moderately high variability in with both formulations but neither gave subtherapeutic levels. Ritonavir pharmacokinetics were similar.

Poor taste was reported most frequently as a problem with both formulations, followed by swallowing difficulty. Although the majority of caregivers rated both formulations unpleasant, they reported easier storage and transportation with sprinkles compared to syrup.

The partnership is now working on further pharmacokinetic and acceptability investigations with an improved granule formulation (finer than the 0.8mm mini tablets and more sand-like in texture) with better taste masking. The new granules will be easier to mix with the NRTIs for the 4-in-1 regimens.

INTEGRASE INHIBITORS

Dolutegravir

The regulatory applications for dolutegravir have been submitted and include approval requests for adolescents ages 12 to less than18 years.

The ongoing IMPAACT P1093 phase I/II study is designed with de-escalated age bands of treatment naive and experienced children, from18 years down to four-week-old infants. The older children will receive tablets, and the younger ones the pediatric formulation.

A granule formulation is in development, and results from a phase I pharmacokinetic study in healthy adult volunteers shown.[38] The granules were given with and without 30 mL of various liquids and compared to the current tablet formulation given with 240 mL of tap water.

Participants received a single dose of dolutegravir as a 50 mg tablet (adult formulation) and as 10 g of granule given: with no liquid; with purified water; with mineral water containing high-cation concentrations; or with infant-formula milk.

Dolutegravir exposures of the granule formulation were all moderately higher than those of the tablet formulation, with or without liquids. Exposure was highest when the granule formulation was given with formula milk.

Two reduced-strength 10 mg and 25 mg tablets have also been developed for children.

Preliminary data for dolutegravir from treatment-experienced adolescents, ages 12 to less than18 years from IMPAACT P1093 showed good short-term safety and tolerability at four weeks. Concentrations were within the target range with approximately 1mg/kg and pharmacokinetic data supports the selection of a 50 mg once daily for this age group weighing 40 kg or more.[39]

Enrollment for the next cohort in children ages six to less than12 years is now ongoing evaluation, both tablets and granules.

A possible PENTA 20 trial of dolutegravir in all age groups of children is also under discussion.

A reduced strength pediatric FDC of dolutegravir plus abacavir plus lamivudine, (572-Trii)—currently under investigation for adults—is also planned. Following the results from the ARROW trial[40], which found once-daily dosing of abacavir and lamivudine non-inferior to twice-daily in children, ViiV is submitting data for this indication, which will support the once-daily pediatric FDC. The development of this formulation will depend on the dolutegravir dosages across the age groups and the dosing ratios of the regimen components.

Further along the adult pipeline, the follow-up integrase inhibitor S/GSK-1265744, under investigation as a long-acting formulation, has provoked interest as a potential treatment of adolescents (as has the long-acting formulation of rilpivirine).

The company is working in partnership with Clinton Health Access Initiative (CHAI), and Mylan on a dispersible tablet FDC of abacavir plus lamivudine. They will transfer the technology and resources to the generic company for production, registration, and distribution of this at the lowest possible cost for low-income countries.[41] Any lessons learned with the collaboration should be used to ensure that dolutegravir—assuming it fulfils its early promise—is available, including in appropriate FDCs, for children in poor countries without delay.

Elvitegravir/cobicistat

GS-US-183-0152, a phase Ib open-label non-randomized trial, conducted in treatment-experienced adolescents 12 to less than18 years receiving 150 mg once daily elvitegravir plus a ritonavir-boosted protease inhibitor-optimized background regimen, showed comparable exposures to that seen in adults.[42]

GS-US-183-0160 will evaluate elvitegravir with ritonavir boosted protease inhibitors in non-suppressed children ages 4 weeks to less than18 years old.

PENTA 17 will evaluate elvitegravir with darunavir/ritonavir in stable, virologically suppressed children.

Reduced strength tablets and dispersible tablets for suspension of the booster, cobisistat, are in development.

GS-US-216-0128 is planned to start enrolment this year and will switch children from ritonavir to cobicistat ages three months to less than18 years, who are suppressed and on an atazanavir- or darunavir-containing regimen.

Cobicistat-boosted elvitegravir will be studied in de-escalated weight bands, and a suspension formulation is in development for the youngest children.

Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir DF) is being studied in treatment naive adolescents ages 12 to less than 18 years in GS-US-236-0112. Reduced strength tablets are planned for children ages six to less than12 years.

An adolescent study of the FDC of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (AF), GS-US-292-0106, began in May 2013. Gilead plan to submit regulatory applications that include approval requests for adolescents ages 12 to less than18 years for this FDC. As with adults, the plan for tenofovir AF as a standalone is unclear. As with adults the drug might be important in regimens other than those in development.

Raltegravir

The adult 400 mg film-coated raltegravir tablet is approved in the United States for use in children ages six to less than18 years, weighing above 10 kg, and 100 mg and 25 mg chewable tablets are approved for children above two to less than 12 years at a maximum dose of 300 mg.[43] The 100 mg tablet is scored so it can be divided in half.

Raltegravir's approval was the first in a new therapeutic class—integrase inhibitors—for young children that might offer some advantages over the currently available drugs. Like darunavir, raltegravir has been suggested as a future option for third-line treatment for children. But like darunavir, it is currently very expensive, with no generic options yet—even for adults.

The pediatric program is ongoing in IMPAACT P1066, and a granule formulation for suspension is being studied in the youngest children and babies down to four weeks old. Children ages six months to less than two years old receiving a dose of approximately 6 mg/kg, twice daily showed similar exposure to that achieved in the two to 12 year old age group receiving chewable tablets. Preliminary 24-week safety and efficacy at 12 weeks showed 78 percent of the nine children achieved virological suppression, and by 24 weeks, 85 percent were suppressed.[44] The twice-daily dose of 6 mg/kg will be investigated in this age group.

Raltegravir also has the potential for use as prophylaxis to prevent vertical transmission to infants, and for treatment of HIV-infected infants. IMPAACT P1097 is an ongoing phase IV washout (passive) phamacokinetic and safety study of infants, born to women who received at least two weeks of raltegravir (400 mg twice daily) in pregnancy and through labor.[45,46]

This is the first clinical trial of an investigational antiretroviral to look at neonatal pharmacokinetics. Raltegravir crosses the placenta well. It is metabolized primarily by a liver enzyme (UGT-1A1), which is immature in neonates. UGT pathways increase in activity hugely in the first weeks of life, reaching adult levels within three to six months.

Early results from this study show good placental transfer with cord blood to maternal plasama concentration ratio of approximately 1.5. Transplacental half-life is long—24 to 36 hours—in neonates. Neonatal raltegravir elimination is highly variable.

IMPAACT P1110 is an open label pharmacokinetic and safety single and multiple dose study of raltegravir granules in high-risk HIV-exposed neonates. Multiple dosing will be from birth to six weeks and HIV-infected infants will continue after six weeks.

CCR5 RECEPTOR ANTAGONIST

Maraviroc

The A4001031 study is ongoing in children aged two to less than18 years old who are infected with the CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). This drug will not work for people with the CXCR4-tropic virus or in dual- or mixed-virus (CCR5/CXCR4) populations.[47]

Preliminary data in 29 children showed body surface area–based doses of maraviroc provided adequate exposures when administered with a protease inhibitor as part of their background regimen. Children who were not receiving a boosting agent in their background regimen required at least doubling of the initial dose.[48]

A body surface area–scaled twice-daily tablet dose of maraviroc in treatment-experienced children six years and above concomitantly receiving boosted protease inhibitors (darunavir and lopinavir) achieved concentrations similar to those in adults receiving 150 mg maraviroc twice daily with a boosted protease inhibitor.[49]

TABLE 2. Pediatric Antiretroviral Pipeline

Compound	Class	Sponsor	Formulation(s) and Dose	Status and Comments
Atazanavir (ATV)	Protease inhibitor (PI)	Bristol-Myers Squibb	Powder 50mg sachet Capsules 100, 150, 200, 300mg	Phase II/IIb RTV boosted 3 months to <6 years ongoing
Dolutegravir (DTG)	Integrase inhibitor (INI)	Shionogi/ ViiV	Tablets 10, 25, 50mg Granule formulation being evaluated for younger children	Adolescents 12 to <18 years included in regulatory submissions Phase I and II 6 weeks to <18 years
Dolutegravir/ ABC/3TC (572-Trii)	INI/2NRTIs FDC	Shionogi/ ViiV	Pediatric formulation development planned Dosing to be determined	Dependent on ongoing studies confirming DTG dose in children
Elvitegravir (EVG) Cobicistat (COBI)	INI/booster	Gilead	EVG reduced-strength tablets and suspension in development COBI dispersible tablets for suspension	EVG PK completed, RTV boosted 12 to <18 years RTV- and COBI-boosted EVG to be studied in all age groups
EVG/COBI/ FTC/TDF (Stribild)	INI/booster /2NRTIs FDC	Gilead	Reduced strength tablets in development	Studies underway in treatment naïve 12 to <18 years 6 to <12 years planned (waiver <6 years)
Etravirine (ETR)	NNRTI	Janssen	Dispersible tablets 25mg (scored), 100mg	Phase I and II treatment experienced 2 months to <6 years enrolling
Lopinavir-ritonavir (LPV/rtv)	Boosted PI	Cipla/DNDi	Granules 40/10mg (equivalent to 0.5mL liquid)	Phase I
LPV/rtv/ABC or AZT/3TC (4-in-1)	Boosted PI/2NRTIs	Cipla/DNDi	Granules FDC	Phase I Granule regimen for use in infants and young children in resource-limited settings
Maraviroc (MVC)	CCR5 receptor antagonist	Pfizer/ViiV	Suspension 20mg/mL	Phase IV Treatment-experienced CCR5 tropic 2 to <18 years
Raltegravir (RAL)	INI	Merck	Granules for suspension 6mg/kg (100mg sachet)	Phase II 2 weeks to <2 years Neonate passive PK study Neonate prophylaxis study

Rilpivirine (RPV)	NNRTI	Janssen	Tablet 25mg Granules 2.5mg base/g	Phase II Adolescents 12 to <18 years >32kg enrolling Planned 0 to <12 years

What Needs to Be Done?

To repeat from last year's *Pipeline Report*: there is a danger of pediatric HIV becoming an old story against a backdrop of targets to eliminate vertical transmission by 2015, which though they are laudable, must not happen at the cost of continual scale-up for children. And back to the reality check: currently only 28 percent of children with HIV in need of treatment are receiving it.[50] Most of what is recommended below is spillover from previous years, but unfortunately has not been done yet.

Implementing recommendations

The new WHO guidelines for treating children strike a pretty good balance between aspirational and pragmatic. It is important that nevirapine-containing regimens still remain an alternative as the recommended lopinavir/ritonavir first-line regimens (including for rural neonates) will frequently not be feasible with the formulation currently available. If recommendations become too complex, children often do not receive anything. As a simpler formulation of lopinavir/ritonavir becomes available, countries must ensure that it is swiftly approved and distributed, with appropriate training for health workers.

Other missing formulations, needed to implement the guidelines, must be made available. If the market is too tiny to interest generic companies, donors need to step in to support this.

The news of the infant with a "functional cure" provoked much discussion. Researchers and implementers are already planning pilot programs and studies to advance research findings. The news should stimulate all programs to do infant PCR as early as possible and intensify post exposure prophylaxis (or early treatment) for neonates of at risk pregnancies (not to mention identifying and treating pregnant women). Successes must be followed by rapid advice from WHO.

Support new models of research and development

There is a lot of hope resting on the successful development and delivery of the DNDi product. That an initiative focusing on diseases of the poor has selected pediatric HIV as a focus speaks volumes. More innovative models of research and

development, and appropriate agreements between originator companies and generic ones to produce child-adapted formulations in a timely fashion must be made.

Ensuring that patents are not an obstacle

The Medicines Patent Pool (MPP) is putting a lot of emphasis on pediatric antiretrovirals. Even the most hesitant originator companies, as far as adult drugs are concerned, must recognise that pediatrics will never be much of a market let alone a money-spinner.

Gilead's licence agreement with the MPP always has royalties waived for any new pediatric formulations.[51] ViiV will grant MPP a voluntary licence for pediatric formulations of abacavir.[52] There is also a commitment to do the same for dolutegravir. Other companies must follow suit and is very important to ensure availability beyond sub-Saharan Africa. What Abbvie decides to do about the lopinavir/ritonavir granules will be closely watched.

Rationalizing available formulations

Development, approval, and distribution of new formulations need to happen in ways that are timely and do not further fragment the market. The time from first approval to when products are available where they are most needed must shorten. This will require earlier access by generic companies to new products (which must include the possibility to develop FDCs with components from different innovators) and registration by the WHO and in country.

To reduce the current situation with too many formulations and too few real options, products need to be rationalized and unsuitable ones phased out.

Consolidated procurement

CHAI needs to continue with its successful model of price negotiations.[53] Concerted efforts by international donors, including the Global Fund and PEPFAR, need to be made to facilitate the transition from previous reliance on UNITAID funding of pediatric products. In the many individual countries where orders do not meet manufacturer volume requirements, buyers must get together.

Endnotes

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Retrofitting for Purpose: Treatment Optimization

By Polly Clayden

Last year's *Pipeline Report* saw the addition of a new chapter exploring research into antiretroviral treatment optimization. This strategy includes the optimization of approved compounds, and possible future opportunities with those in late-stage development. This 2013 chapter is largely an update from the original one, as the goals and target product profile for a "dream regimen" are unchanged. Any resemblance to the previous version is entirely intentional.

Treatment 2.0—a strategic approach by the World Health Organization (WHO) and UNAIDS to the achievement of universal access to antiretroviral therapy and to making the most of the role of antiretrovirals in preventing new infections—includes treatment optimization as one of its critical components.[1]

Discussions about optimization—particularly through appropriate dose reduction—of approved antiretrovirals have been ongoing now for over a decade,[2,3] the rationale being that when developing new drugs, the highest tolerated doses in phase II are often selected for phase III and, in turn, approval, where in some cases lower doses may have equivalent efficacy. Efficiencies can also be achieved by reducing the amount of active pharmaceutical ingredient (API) with improved bioavailability through reformulation, or by tweaking the process chemistry.

The Conference on Dose Optimization (CADO)—a collaborative project of the Clinton Health Access Initiative (CHAI), the Johns Hopkins University School of Medicine, and the Bill & Melinda Gates Foundation, held in 2010 and attended by process chemists, clinical pharmacologists, infectious disease specialists and experts in regulatory and ethical issues—led to a consensus statement on optimizing the manufacturing, formulation, and dosage of antiretroviral drugs for more cost-efficient delivery in resource-limited settings.[4,5]

As the statement explains, the API is the largest part of the product cost of generic drugs; a reduction in this would potentially decrease the total cost of the product. The cost of a marketed generic drug typically consists of: API (65 to 75 percent of the total market price), formulation (10 to 20 percent), and packaging and profits (5 to15 percent).

There are several ways through dose optimization that API reduction might be accomplished:

Dose reduction. In order to achieve regulatory approval for a dose lower than that currently approved, fully powered non-inferiority studies (phase III)—similar to those conducted by industry for the approval of a new drug—need to be done. It would take about three to six years to generate sufficient data to file with regulatory agencies, plus time to approval (about three months to a year). The estimated cost would be US$15 to 22 million.

Reformulation. This strategy makes use of technologies and/or inactive ingredients to increase the bioavailability of a drug, which enables reduction of the approved dose. A reformulated compound will need bioequivalence studies with the approved formulation (phase I). The estimated time frame to regulatory filing is two to three years, at a cost of US$2 to 8 million.

Process chemistry. It may also be possible to alter the manufacturing process leading to more efficient and less expensive API production. For this strategy to be successful, regulatory authorities would need to see only equivalent stability and purity data. This would take about one to two years, at an estimated cost of US$1 to 2 million.

Other factors in price reduction:

- Sourcing less expensive raw materials. This price depends on the volume needed, an increase in demand can attract new suppliers and in turn competition.
- Improvements in the manufacturing process can mean raw materials are converted to API more efficiently.
- Shelf life extension. To extend a typical two-year shelf life, real-time stability testing would be required with clear regulatory pathways.

In 2011 WHO held a follow up meeting to the first CADO, to work out ways to incorporate treatment optimization into future guidelines and the Treatment 2.0 initiative.[6] This yielded a number of short-term research priorities and recommendations including increased harmonization of adult and pediatric regimens, through FDCs and other simplified formulations.

Subsequent discussions at meetings led by Médecins Sans Frontières (MSF) and WHO as well as the recent Conference on Dose Optimisation II (CADO2), have explored medium- and longer-term horizons for future treatment strategies. [7,8,9]

The plans, established at the first CADO to increase API cost-efficiencies, remain unchanged, and this research continues to gain momentum. In the three years since the original meeting, there has been an increasing emphasis on patient acceptability and preferences. Discussions have included a broader group of representatives from the community and caregivers with consensus that improved efficiencies of the API need, not only reduce costs, but also improve tolerability and outcomes for people with HIV. It is acknowledged that these factors will be increasingly critical as indications for treatment grow and more asymptomatic people with HIV are offered antiretroviral treatment. All potential treatment options must be measured against these factors.

Dream Regimen

The ideal characteristics of a dream regimen have been variously described, and the target is one that is "so safe, effective, tolerable and durable that the need for switching to a new regimen would be very rare."[7]

TABLE 1. Target Product Profile of a Dream ARV Regimen

Safe and Effective	Superior or Equivalent to Currently Recommended Drugs
Simple	Possible to be given in decentralized facilities or the community. One pill once a day (less frequently might be possible in the future). No lead-in dosing. No dose adjustments when given with other common medicines. Heat-stable. Shelf life of two or more years.
Tolerable	Minimal toxicity. Reformulation and/or dose reduction might improve tolerability.
Durable	High genetic barrier to resistance. Low pharmacokinetic variability. Forgiving of missed doses. Tolerable for easier adherence.
Universal	Safe and effective across all CD4 strata; in people with high viral load; in men and women; during pregnancy; across age groups and with common coinfections such as tuberculosis or viral hepatitis.
Affordable	ARV coverage does not meet the estimated current need. Meanwhile, evidence is growing for earlier and wider use of treatment.

For adult first-line treatment, a one pill, once-a-day FDC of efavirenz plus tenofovir disoproxil fumarate (DF) plus lamivudine is agreed—across all expert consultations as well as in the 2013 WHO Consolidated ART Guidelines[10]—to be the current preferred option in the short- and medium-term. The 2013 CHAI ceiling price for this FDC is now US$131, which is a 21 percent reduction since 2012.[11] With successful optimization work, this regimen could be expected to be less than $100

per patient per year (pppy).[12] Future changes to this regimen must either offer efficiencies with its components (such as a reduced dose with the same durability and improved tolerability), or superiority with new compounds.

The WHO 2013 guidelines-recommended second-line regimen remains ritonavir-boosted protease inhibitor-based and, unlike recommendations in rich countries, boosted lopinavir rather than darunavir is included alongside boosted atazanavir. An optimized boosted atazanavir-based regimen could be expected to be less than $275 pppy.

TABLE 2. 2013 WHO Guidelines–Recommended ART Regimens

First-line	tenofovir DF + lamivudine (or emtricitabine) + efavirenz preferred (including pregnant women) zidovudine alternative to tenofovir DF nevirapine alternative to efavirenz
Second-line	atazanavir/ritonavir or lopinavir/ritonavir preferred + tenofovir DF + lamivudine preferred backbone (if zidovudine or stavudine first-line) + zidovudine + lamivudine preferred (if tenofovir DF first-line)
Third-line	No specific recommendations: Integrase inhibitor (INI) or second-generation PI or NNRTI are mentioned

Treatment-limiting central nervous system toxicities that are a concern with efavirenz could possibly be reduced with a lower dose. Fears about its use during pregnancy are steadily being assuaged, and more permissive recommendations—in line with the British HIV Association guidelines—are made in the WHO 2013 guidelines.[13,14,15,16,17]

Despite direct comparisons as monotherapy, lamivudine and emtricitabine are largely considered to be interchangeable in terms of efficacy and safety, and the WHO systematic review concluded this to be true.[18] Both are nucleoside reverse transcriptase inhibitors (NRTIs) and are structurally similar molecules with low toxicity, and both are effective against hepatitis B virus. Cost comparisons make lamivudine the preferred option—using emtricitabine instead in combination with efavirenz and tenofovir DF adds an annual patient cost of US$25 to a combined product with tenofovir DF.

Work on the bioavailability of tenofovir DF could bring down the price (currently US$54 pppy as a single agent), and further reductions still might be possible with the new pro-drug, tenofovir alafenamide (AF).

The United States Food and Drug Administration (FDA) has tentatively approved a heat-stable formulation of atazanavir/ritonavir.[19,20] This 300/100 mg one-pill once-daily formulation is now US$220 pppy and compares favourably to heat-stable lopinavir/ritonavir costing US$300 pppy, with four pills a day and twice-daily dosing. Mylan Pharmaceuticals has developed a two pill once-a-day co-packaged regimen of this plus lamivudine and tenofovir DF; the ceiling price is US$306 pppy.

Once-daily heat-stable boosted darunavir would offer a better option to lopinavir second line. At present a suitable formulation (and suitable price) remains elusive. With expected comparable price to boosted lopinavir (there is potential to reduce the current cost of boosted darunavir $900 to below $350 pppy, if it was used in comparable volumes to that of lopinavir currently) and a better profile, boosted darunavir should be a second-line option and not just considered for third-line treatment.

WHO recommendations for third-line treatment were introduced for the first time in 2010 and they remain much the same in 2013, suggesting, as well as boosted darunavir, the integrase inhibitor, raltegravir, and second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), etravirine in nucleos(t)ide sparing regimens. None of these yet have generic versions, and the cost is considerable.

Can we Do Better with What we Have Already?

Optimization opportunities with some of the approved antiretrovirals could offer several advantages over the current doses and/or formulations, and work is underway or under discussion with several compounds.[21,22]

TABLE 3. Approved Antiretroviral Compounds with Potential for Dose Optimization

Compound (current approved dose)	Class	Sponsor/ approach	Outcomes	Status
Tenofovir DF (300 mg once daily)	NtRTI	CHAI Reformulation	Approx 33% reduction anticipated Cost reduction $50 to $35 pppy	Underway
Zidovudine (300 mg twice daily)	NRTI	Geneva University Hospital Dose optimization RCT	Dose reduced to 200mg twice daily Cost reduction $89 to $60 pppy	MiniZID Phase III To be completed January 2014

Stavudine (30 mg twice daily)	NRTI	Wits Reproductive Health Institute Dose optimization and comparison with TDF, RCT	Dose reduced to 20mg twice daily Cost reduction $25 to $20 pppy	WHCS-001 Phase III To be completed end 2015/early 2016
Efavirenz (600 mg once daily)	NNRTI	Kirby Institute Dose optimization RCT CHAI Reformulation	Dose reduced to 400 mg once daily Potential additional 33% reduction by reformulation Cost reduction $63 to $31 pppy	ENCORE 1 Phase III To be completed July 2013 Underway
Atazanavir/ritonavir (300/100 mg once daily)	PI	HIVNAT/Kirby Institute Dose optimization RCT CHAI Process chemistry	Dose reduced to 200/100 Cost reduction $355 to $200 pppy Additional potential price reduction by process chemistry	LASA Phase III To be completed early 2014 Underway
Darunavir/ritonavir (800/100 mg once daily or 600/100 mg twice daily)	PI	Under discussion Process chemistry, dose optimization and reformulation	API reduced from above $2000 to below $1000. Dose reduced from 800/100 to 400/100 mg once daily. Cost reduction $835 to below $350 pppy	Standard of care needs to be established. Process chemistry underway
Ritonavir (100 mg)	Booster	Dose optimization	Boosting dose of atazanavir and darunavir reduced to 50 mg	Under discussion

Source: Crawford KW, et al. Lancet Infect Dis. 2012 Jul; 12(7): 550-60, Hill A. Clinical Pharmacology Workshop. 2013. CADO2 2013. ClinicalTrials.gov

Tenofovir

Tenofovir DF is preferred as part of first-line treatment everywhere. It is considered to be the best NRTI /NtRTI (nucleotide reverse transcriptase inhibitor) on the market, and this is likely to continue for several years.

The price of tenofovir DF has dropped considerably since its introduction into the generic market. This is largely due to efficiencies in raw material sourcing and improved processing, which led to a 57 percent drop in price between 2006 and 2010. [23,24,25] It is now available for US$54 pppy, a 74 percent drop since 2006: a tenofovir DF-based FDC regimen is US$131 pppy.

There are, however, limits to tenofovir DF's lowest possible price due to its high milligram dose (300 mg) with the current formulation. This also makes it less easy to co-formulate with other antiretrovirals.

Clinton Health Access Initiative (CHAI) is working on reformulation of tenofovir DF in partnership with a generic manufacturer. Through reformulation of the excipients, they aim to increase bioavailability and, in turn, lower the dose of the drug, while maintaining equivalent exposure.[26] Although the new dose has yet to be determined, the researchers anticipate a reduction by about a third.

Additionally there are two new pro-drugs of tenofovir in development: tenofovir alafenamide (AF formerly known as GS-7340) and CMX-157 (not much obvious progress but recently acquired by Merck).

Zidovudine

If tenofovir DF remains the preferred first-line NRTI/NtRTI, zidovudine is likely to be used second-line in the short term.

The dose of zidovudine was reduced considerably from the initial 300 mg every four hours to 250 to 300 mg twice daily, after similar efficacy and increased safety was demonstrated.[27]

Although zidovudine is generally better tolerated than stavudine over a long-term period, its hematologic toxicities (anemia/neutropenia) remain a concern in many resource-limited settings (RLS).

The ongoing MINIZID study is looking at 200 mg versus 300 mg zidovudine twice daily (as part of a regimen with lamivudine plus an NNRTI), with reduction of anemia as the primary endpoint. This is a 48-week phase II study in 136 treatment-naive patients, sponsored by the University of Geneva and being conducted at the Hôpital de la Caisse Nationale de Prévoyance Sociale, Yaoundé, Cameroon. Recruitment began in August 2011 and will be completed in January 2014.[28]

The study will not generate sufficient data for regulatory approval of the lower dose, but will provide proof of principle.

Some Asian countries such as Thailand and India already use the zidovudine 250 mg tablet twice daily, and Thailand is currently using 200 mg twice daily in patients weighing less than 50 kg.

Stavudine

Of all the dose optimization strategies proposed or ongoing, the decision to use stavudine is the most controversial. Unlike the other antiretrovirals for which these strategies are being suggested or conducted, stavudine is no longer a preferred option in any guideline, anywhere, due to its toxicity profile.

The Wits Reproductive Health Institute in South Africa is leading a phase IIIb trial comparing 20 mg stavudine twice daily to 300 mg tenofovir DF once daily in approximately 1,000 patients in South Africa, India and Uganda. The trial is sponsored by the Bill & Melinda Gates Foundation.

The primary objective is to demonstrate the non-inferiority of stavudine to tenofovir DF (both in a regimen with lamivudine plus efavirenz) in treatment-naive patients. The proportion of patients receiving each regimen with undetectable viral load (less than 200 copies/mL) at 48 weeks, will determine this. The secondary endpoints are to evaluate the tolerability, overall safety, and efficacy of 20 mg stavudine compared to tenofovir DF.

The trial is concerning, as it will not answer stavudine's long-term toxicity question. The 20 mg stavudine dose might be acceptable in a short-term 48- or even 96-week virological endpoint study. However, because mitochondrial toxicity is both dose- and time dependent, many of stavudine's most serious side effects (such as peripheral neuropathy and lipoatrophy) would not necessarily emerge until after such a study was completed. Although it looks at lipoatrophy, this study does not include monitoring of surrogate markers for mitochondrial toxicity, so it cannot shed light on the incidence of this serious adverse event.

The stavudine parallel track program, which randomized over 10,000 patients to receive 40 (30) mg or 20 (15) mg (between October 1992 and February 1994), showed a higher incidence of neuropathy in the high-dose arm (21percent). Nonetheless, the incidence of neuropathy observed in the lower dose arm was also unacceptably high (15 percent).[29]

In addition to concerns about cumulative toxicities, stavudine-related cost savings might become irrelevant by the trial's end. Through other dose optimization strategies and the expected approval of promising pipeline compounds (such as tenofovir AF and dolutegravir), alternatives are likely to become available in a similar time frame that could drive regimen costs down with less risk to patient safety.

Importantly, stavudine is extremely unpopular with people with HIV and activists all over the world. Many of us have expressed our opposition.[30,31,32] In South Africa and India, people with HIV and activists have had several protests and petitions

against the trial and the slow phase out of stavudine.[33,34,35] As *Bad Science*'s Ben Goldacre asked: "Why is the Gates Foundation supporting this trial of a rubbish AIDS drug?"[36]

Efavirenz

Efavirenz is currently the preferred anchor drug. Price and possibly central nervous system (CNS) toxicities could be reduced if a lower dose than the currently recommended 600 mg is possible.

The ENCORE1 study, which began recruitment in September 2011 and will be completed in July 2013, is looking at 600 mg versus 400 mg of efavirenz in 630 treatment-naive patients. The ENCORE studies are designed to compare lower doses with approved doses of antiretrovirals. Pharmacokinetic studies of lamivudine and lopinavir (ENCORE2 and ENCORE3) have already been conducted as part of this program, with the conclusion that neither is a suitable candidate for dose reduction.[37,38,39]

The primary endpoint for ENCORE1 is the comparison between treatment groups of proportions of patients with viral load less than 200 copies/mL 48 weeks after randomization. The complete follow up is 96 weeks, and there are sites in Europe, Australasia, Latin America, Asia, and Africa.

ENCORE 1 has two substudies designed to look at pharmacokinetics and CNS exposure.[40,41] If successful, this trial should generate sufficient data to gain regulatory approval and change WHO and other key treatment guidelines.

There are concerns about the drug/drug interaction with rifampicin used in TB/HIV coinfection if the efavirenz dose is reduced.

The high API of efavirenz is due in part to its poor water solubility. CHAI is looking at reformulation, targeting the inactive ingredients, to improve this.

Nanosuspensions of efavirenz, using freeze-drying technology are also in development, which could result in improved bioavailability and possibly greater antiviral activity.[42, 43] The research group at the University of Liverpool developing an efavirenz nanosuspension will begin studies in HIV-negative volunteers to evaluate bioequivalence later this year.

Atazanavir

Dose reduction may also be possible with atazanavir, and the HIV Netherlands Australia Thailand Research Collaboration, with some support from the Kirby Institute, is conducting a trial that will provide some evidence for this strategy.[44]

The low-dose atazanavir/ritonavir versus standard-dose atazanavir/ritonavir (LASA) study is comparing the efficacy and safety of atazanavir/ritonavir at either 200/100 mg or 300/100 mg once daily in Thai patients in combination with two NRTIs. This non-inferiority, phase IV study with about 600 patients began recruiting in March 2011 and will be completed in early 2014.

This study is enrolling patients who are already virologically suppressed to switch to the lower or standard dose of atazanavir. This research is important for Thailand as patients tend to have a lower body weight, and hyperbilirubinemia occurs quite frequently. It will be difficult to generalize the results from this research beyond the study population, but positive results would provide good reason to conduct a study in treatment-naive patients from a broader population.

CHAI is also working on optimizing the process chemistry.

Darunavir

Darunavir is generally considered to be the most durable protease inhibitor, but there is no generic formulation, and cost has been a barrier to its wide use. As it is not yet recommended for second-line treatment by WHO there has been limited work on its optimization.

This drug has different approved doses for treatment-naive (including treatment-experienced but with no darunavir-associated mutations) and protease inhibitor-experienced patients. Treatment-naive patients receive darunavir/ritonavir at an 8:1 (800/100 mg) ratio once daily, and experienced patients at a 6:1 ratio (600/100 mg) twice daily. There might be potential for dose reduction to 400/50 mg.

The ratios also vary for children depending on their weight band and treatment experience.

The establishment of single ratios for adults and children (as well as recommendations for when best to use it) would make simpler darunavir-based regimens and formulations more feasible.

CHAI is working on optimizing the process chemistry.

Ritonavir

It might be possible to give atazanavir and darunavir with a lower boosting dose of ritonavir. Lower doses could be better tolerated, cheaper, and easier to co-formulate with PIs than the current dose.

If a 50 mg heat-stable tablet of ritonavir could be manufactured or 50 mg

co-formulated with either protease inhibitor, new bioequivalence trials would be needed to ensure that boosting effects were similar to those that have been achieved previously in small pharmacokinetic trials with the liquid formulation. A 50 mg ritonavir tablet would also be very useful for pediatric dosing, as the liquid is expensive, impractical (particularly for resource-limited settings) and tastes dreadful.[45]

Opportunities with Pipeline Drugs—Ones to Watch

Antiretrovirals in the pipeline might also offer advantages, in the future, over those currently recommended.

The integrase inhibitor dolutegravir, expected to be approved this year, is a compound with high potential, and it is predicted to cost US$30 pppy: 90 percent cheaper than raltegravir.[46,47] The milligram dose is relatively low (50 mg), compared to elvitegravir (150 mg once daily plus 150 mg cobicistat) and raltegravir (400 mg twice daily), with once-daily dosing in treatment-naive patients. Early data suggest that a dose increase (to 50 mg twice daily) will be needed with TB treatment.[48]

Dolutegravir appears well tolerated, and with the potential to be low-cost might replace efavirenz first-line or be used second-line. Trials in children, including in neonates, are underway or planned and a granule formulation is in development.

Tenofovir AF is in phase III and also could also be a useful new drug. With doses 10 times or more lower than that of tenofovir DF, the cost of tenofovir AF is predicted to be appropriately lower, and could come in at an annual patient cost of as little as US$20.[49]

The dose and plans for development as a single agent are still to be announced, but it is expected to be 25 mg.[50] It is critical that Gilead recognizes the potential for this compound as a component of FDCs other than its own incestuous ones. For the single tablet regimen tenofovir AF-containing combinations currently being investigated (with boosted elvitegravir or darunavir plus emtricitbine) an interaction with cobicistat makes it possible to use a 10 mg dose when it is co-formulated with the boosting agent.[51] After approval, data from these products will not inform the development of other, potentially more useful, FDCs. It will not look good if tenofovir AF miraculously appears as a standalone just as the patent for tenofovir DF expires.

Unlike Gilead, which gained approval for its latest FDC Stribild before making New Drug Applications (NDAs) for two components, elvitregravir and cobicistat (and recently got its fingers burned when these were rejected by the FDA[52]), ViiV

has submitted the NDA for dolutegravir first as a standalone. But, it too has an incestuous FDC in the pipeline of dolutegravir, abacavir and lamivudine.[53]

New compounds with the potential for high impact worldwide must be studied in rational combinations and compared to the first-line standard of care of efavirenz plus tenofovir DF plus lamivudine. Dolutegravir needs to be studied in combination with tenofovir DF, and with tenofovir AF, and efavirenz in combination with tenofovir AF (all plus lamivudine or emtricitabine).[54]

This must be done in a timely way, long before the expiry of the various patents, and will require commitments from both innovator and generic companies as well as WHO, regulatory agencies and investigators.

Looking to the Future? Long Acting Formulations

With the potential to completely alter standard of care, discussions about, and early development of, long-acting formulations are also under way for monthly or weekly depot injections. Potential candidates might be the NNRTI rilpivirine and the integrase inhibitor GSK1265744, both in early stages of development and studies are planned with the two together.[55] CMX-157, a novel version of tenofovir, also has a long half-life. Last seen in phase I, it has recently been acquired by Merck, but so far there has not been a lot of news about the plans.[56,57]

For long acting formulations, there is not yet clarity on the target product profile—both for the molecules and for patient acceptability—nor is it clear if the right combination of compounds required to construct a suitable regimen are available or even in development.

What Needs to Be Done?

- Treatment optimization must be in the interests of people with HIV.
- Trials, like the low dose stavudine one, conducted for the sake of cost alone, and against much opposition from people with HIV and activists, are unacceptable. Activist and patient acceptability is always important. This will become increasingly so as indications for starting become broader and more asymptomatic people with HIV are offered treatment.
- Drugs and regimens need to be designed with resource-limited settings in mind. The target product profile has been widely described by now. Currently approved and pipeline compounds fit for this purpose need to be studied and produced in appropriate formulations.
- The time between full FDA/EMA approval and WHO prequalification, FDA tentative approval, and approval by local regulatory agencies must be shortened.
- Delays with the registration process, in addition to production by generic manufacturers and recommendations in national guidelines, means that it takes years from promising results in trials and initial approval to wide availability for the majority of people in need of antiretroviral treatment. Despite over150 single agents and combination products having FDA tentative approval, the majority are older drugs and those with expired patents.

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Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies

By Richard Jefferys

Until last year, no product inching through the pipelines covered in this chapter had ever emerged into the marketplace. That changed on July 16, 2012, with the approval in the United States of the antiretroviral drug combination pill Truvada (tenofovir/emtricitabine) for preexposure prophylaxis (PrEP).[1] The labeling for the drug now notes that, in addition to its longstanding indication for HIV treatment, it is "indicated in combination with safer sex practices for preexposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk."[2]

Consistent with the complexity that attends the topic of biomedical HIV prevention, Truvada PrEP exited the pipeline into a sea of questions and uncertainty. The overall message from the trial data is that Truvada offers a high degree of protection against HIV acquisition if taken daily as prescribed. The acceptability of the approach is less clear, and has varied in different populations. In trials where adherence was low, efficacy was not observed. The challenges associated with daily administration have led both the PrEP and microbicide fields to pursue potentially simpler strategies, such as long-acting antiretrovirals that might be given once-monthly (or less) and vaginal rings that deliver microbicides continuously for several weeks at a time.

For the HIV vaccine field, achieving the levels of efficacy observed in the most successful PrEP trials (>70% reduction in HIV acquisition risk) remains a distant dream. In 2013, the storm clouds that have lingered over the use of adenoviruses as vaccine vectors rained bad news, first with the failure of a DNA-plus-adenovirus serotype 5 (Ad5) prime-boost regimen in the only ongoing HIV vaccine efficacy trial, HVTN 505,[3] and second with extended follow-up from a prior study in South Africa showing a significant enhancement of HIV risk associated with receipt of Merck's discontinued Ad5-based HIV vaccine.[4] Researchers and funders are now scrambling to assess whether the many other earlier-phase trials of adenovirus-based HIV vaccine vectors can safely continue.

All is not lost, however. The multi-stakeholder collaboration named the Pox-Protein Public-Private Partnership (P5) continues to work toward launching efficacy trials that will attempt to improve on the slender but significant protection against HIV infection documented in the RV144 trial in Thailand in 2009.[5] In the sphere of basic research, evidence is emerging that it may be possible to design vaccines

capable of cajoling B cells into producing broadly neutralizing antibodies against HIV, a challenge that once seemed insurmountable. Scientists are also pursuing a potential alternative, more radical strategy using an approach akin to gene therapy to deliver genes for making broadly neutralizing antibodies into muscle tissue.

The research effort to cure HIV infection achieved its highest-ever profile over the past year, garnering extensive—though not always accurate—media coverage. The ascendancy began in July 2012, just ahead of the International AIDS Conference in Washington, D.C., with the launch of the International AIDS Society's global scientific strategy, *Towards an HIV Cure*.[6] The document is essentially a lengthy scientific review describing the current understanding of the issues that will need to be addressed in order for a globally accessible cure to be developed.

An assemblage of case reports provided encouragement that a cure is possible, with the most widely publicized being that of an HIV-infected child from Mississippi said to be devoid of active virus after receiving very early antiretroviral therapy (ART) that was stopped after around 18 months.[7] Timothy Ray Brown remains the lone adult considered cured of HIV, but two other men who received stem cell transplants for concomitant cancers have been reported to show no evidence of viral reservoirs; ART interruptions are planned in both cases to assess whether the virus returns.[8]

Researchers in France described 14 individuals treated with ART during acute infection exhibiting "post-treatment control" of viral load after lengthy periods off treatment (an average of 7.4 years).[9] Known as the VISCONTI cohort, these individuals are not considered cured but rather in virological remission, and follow-up is continuing.

While these case reports offer hope, they all involve circumstances that are relatively unusual. When it comes to curing the vast majority of HIV-positive people—those with chronic infection, and lacking cancers requiring stem cell transplants—progress is painstaking, and significant scientific obstacles remain. Currently there are only a few preliminary trials of potential interventions ongoing, none of which is expected to cure anyone.

To a large extent, the immune-based and gene-therapy pipelines have become intertwined with the cure research agenda. Therapeutic vaccines in particular have multiple possible roles: enhancing HIV-specific immunity with the aim of improving control of HIV replication,[10] stimulating the release of virus from latently infected resting CD4 T cells that are specific for HIV antigens,[11] and increasing the ability of HIV-specific CD8 T cells to kill latently infected CD4 T cells (after they are prompted to produce virus by latency-reversing strategies).[12] Several ongoing and planned trials intend to evaluate the ability of therapeutic vaccines to perform these tasks.

Gene therapies converge on the goal of creating CD4 T cells that are resistant to HIV, using a variety of mechanisms including disrupting expression of the HIV coreceptor CCR5. The key challenge faced by these approaches is the modification of enough cells to confer measurable benefits.

The effectiveness of ART has narrowed the pipeline of immune-based therapies (IBTs) for potential disease-management indications. There are two main areas where there might still be opportunity for adjunctive IBTs to offer benefits:

- For the subset of HIV-positive people who experience limited CD4 T-cell recovery despite viral suppression by ART (referred to as immunologic nonresponders, or INRs). The main risk factors are low CD4 T cells at the time of ART initiation and older age.[13] INRs face a significantly increased risk of morbidity and mortality,[14] which an effective IBT might conceivably be able to lessen.
- To address the subtler, residual dysregulation of the immune system that can persist in individuals on ART. Most concerning are elevated levels of inflammation, and features resembling the aging-related immunologic wear and tear seen in the elderly, such as inverted CD4:CD8 ratios and increased numbers of senescent immune cells.[15]

Table 1. HIV Vaccines Pipeline 2013

Agent	Class/Type	Manufacturer/ Sponsor(s)	Status
ALVAC-HIV vCP1521	Canarypox vector including HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol gene, and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins	Sanofi Pasteur/U.S. HIV Military HIV Research Program (USMHRP)/ National Institute of Allergy and Infectious Diseases (NIAID)	Phase IIb
pGA2/JS7 DNA + MVA/HIV62	Prime: DNA vaccine Boost: MVA vector Both including Gag, Pol, and Env genes from HIV-1 clade B	GeoVax/NIAID	Phase IIa

Agent	Class/Type	Manufacturer/ Sponsor(s)	Status
HIVIS 03 DNA + MVA-CMDR	Prime: HIVIS DNA including Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) genes Boost: MVA-CMDR including Env (E), Gag (A), and Pol (E) genes	Vecura/Karolinska Institutet/Swedish Institute for Infectious Disease Control (SMI)/ USMHRP	Phase II
LIPO-5	Five lipopeptides comprised of CTL epitopes from Gag, Pol, and Nef proteins	Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS)	Phase II
VICHREPOL	Chimeric recombinant protein comprised of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidonium adjuvant	Moscow Institute of Immunology/Russian Federation Ministry of Education and Science	Phase II
DNA-C + NYVAC-C	Prime: DNA vaccine including clade C Env, Gag, Pol, and Nef genes Boost: NYVAC-C attenuated vaccinia vector including clade C Env, Gag, Pol, and Nef genes	GENEART/Sanofi Pasteur/Collaboration for AIDS Vaccine Discovery (CAVD)	Phase I/II
MYM-V101	Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env	Mymetics Corporation	Phase I/II
Ad26.ENVA.01	Prototype adenovirus serotype 26 vector including the HIV-1 subtype A Env gene	Crucell/IAVI/NIAID/ Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost phase I w/ Ad35-ENVA
Ad35-ENVA	Prototype adenovirus serotype 35 vector including the HIV-1 subtype A Env gene	Crucell/IAVI/NIAID/ Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost phase I w/ Ad26.ENVA.01
Ad35-GRIN/ENV	Two adenovirus serotype 35 vectors, one including HIV-1 subtype A Gag, reverse transcriptase, integrase, and Nef genes, and the other including HIV-1 subtype A Env (gp140)	International AIDS Vaccine Initiative (IAVI)/ University of Rochester	Phase I Prime-boost phase I w/ GSK HIV vaccine 732461

Agent	Class/Type	Manufacturer/ Sponsor(s)	Status
Ad5HVR48.ENVA.01	Prototype hybrid adenovirus vector consisting of a backbone of serotype 5 with the hexon protein from serotype 48; includes HIV-1 subtype A Env gene	Crucell/NIAID	Phase I
Cervicovaginal CN54gp140-hsp70 conjugate (TL01)	HIV-1 clade C gp140 protein with heat shock protein 70 (Hsp70) adjvant, delivered intravaginally	St George's, University of London/European Union	Phase I
DCVax + poly ICLC	Recombinant protein vaccine including a fusion protein comprising a human monoclonal antibody specific for the dendritic cell receptor, DEC-205, and the HIV Gag p24 protein, plus poly ICLC (Hiltonol) adjuvant	Rockefeller University	Phase I
DNA-HIV-PT123, NYVAC-HIV-PT1, NYVAC-HIV-PT4, AIDSVAX B/E	DNA and NYVAC vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	IPPOX/EuroVacc/HVTN	Phase I
DNA + Tiantian vaccinia vector	DNA and recombinant Tiantian vaccinia strain vectors encoding Gag, Pol, and Env genes from HIV-1 CN54	Chinese Center for Disease Control and Prevention/National Vaccine and Serum Institute/Peking Union Medical College	Phase I
EN41-FPA2	Gp41-based vaccine delivered intranasally and intramuscularly	PX'Therapeutics/ European Commission	Phase I
GEO-D03 DNA + MVA/HIV62B	Prime: DNA vaccine with GM-CSF adjuvant Boost: MVA vector Both vaccines include Gag, Pol, and Env genes from HIV-1 clade B and produce virus-like particles (VLPs)	GeoVax/NIAID	Phase I
GSK HIV vaccine 732461	Gag, Pol, and Nef proteins in proprietary adjuvant	GlaxoSmithKline	Phase I Prime-boost phase I w/ Ad35-GRIN
HIV-1 Tat/delta-V2 Env	Tat and oligomeric ΔV2 Env proteins	Istituto Superiore di Sanità/ Novartis Vaccines	Phase I

Agent	Class/Type	Manufacturer/ Sponsor(s)	Status
MAG-pDNA, Ad35-GRIN/ENV	Multi-antigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system, two adenovirus serotype 35 vectors, one including HIV-1 subtype A Gag, reverse transcriptase, integrase, and Nef genes, and the other including HIV-1 subtype A Env (gp140)	IAVI/Profectus Biosciences/ Ichor Medical Systems Incorporated	Phase I
MAG-pDNA, $rVSV_{IN}$ HIV-1 Gag	Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences/ HVTN	Phase I
MV1-F4-CT1	Recombinant measles vaccine vector including HIV-1 clade B Gag, Pol, and Nef	Institut Pasteur	Phase I
MVA.HIVA	MVA vector including a synthetic copy of a major part of HIV's Gag gene and 25 CD8 T-cell epitopes	Impfstoffwerk Dessau-Tornau (IDT)/ University of Oxford/ Medical Research Council/University of Nairobi/Kenya AIDS Vaccine Initiative	Phase I in infants born to HIV-positive (PedVacc002) and HIV-negative mothers (PedVacc001)
MVA HIV-B	MVA vector including HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I
PENNVAX-G DNA + MVA-CMDR	Prime: DNA vaccine including HIV-1 clade A, C, and D Env proteins and consensus Gag protein Boost: MVA-CMDR live attenuated MVA vector including HIV-1 clade CRF_AE-01 Env and Gag/Pol proteins DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device	NIAID/USMHRP/ Walter Reed Army Institute of Research	Phase I

Agent	Class/Type	Manufacturer/ Sponsor(s)	Status
PolyEnv1 EnvDNA	Vaccinia viruses including 23 different Env genes and DNA vaccine with multiple Env genes	St. Jude Children's Research Hospital	Phase I
pSG2.HIVconsv DNA + ChAdV63.HIVconsv, or MVA.HIVconsv	Prime: DNA vaccine pSG2 Boost: chimpanzee adenovirus vector ChAdV63 or MVA vector All contain the HIVconsv immunogen, designed to induce cross-clade T-cell responses by focusing on conserved parts of HIV-1	University of Oxford	Phase I
rAd35 VRC-HIVADV027-00-VP	Adenovirus serotype 35 vector	Vaccine Research Center, NIAID	Phase I
$rVSV_{IN}$ HIV-1 Gag	Attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences/ HIV Vaccine Trials Network (HVTN)	Phase I
SAAVI DNA-C2, SAAVI MVA-C, subtype C gp140/MF59	SAAVI DNA and MVA vectors encoding an HIV-1 subtype C polyprotein including Gag-reverse transcriptase-Tat-Nef and an HIV-1 subtype C truncated Env Novartis protein subunit vaccine comprising a subtype C oligomeric V2 loop-deleted gp140 given with MF59 adjuvant	South Africa AIDS Vaccine Initiative/ HVTN/Novartis	Phase I
SeV-G(NP), Ad35-GRIN	Sendai virus vector encoding HIV-1 Gag protein delivered intramuscularly or intranasally, adenovirus serotype 35 vector including HIV-1 subtype A Gag, reverse transcriptase, integrase, and Nef genes	IAVI/DNAVEC	Phase I

More Bad News for Adenovirus Vectors

In the early 2000s, there was a great deal of excitement regarding prospects for adenovirus-based vaccine vectors. Adenoviruses are common in nature, causing severe colds, and are categorized into different serotypes dependent on the types of antibody response they induce. Adenovirus serotype 5 (Ad5) was attenuated and modified for use as an HIV vaccine by Merck, and early trials showed that it effectively addressed a problem that scientists had been trying to solve for more

than a decade: the reliable induction of virus-specific CD8 T-cell (also known as killer T-cell) responses in the majority of recipients. Prior to Ad5, the best results had been achieved with the ALVAC canarypox vector, which created low-level but detectable HIV-specific CD8 T cells in around 10 to 20 percent of immunized individuals.[16] In stark contrast, more than 70 percent of individuals given Merck's Ad5 candidate developed HIV-specific CD8 T-cell responses, sometimes of high magnitude.[17] These immune responses were not expected to protect against HIV infection, but there was hope that they might be able to suppress the virus in vaccinated individuals who became infected.

An efficacy trial named the Step study was conducted by the HIV Vaccine Trials Network (HVTN), but had to be stopped early after a review by the Data Safety Monitoring Board (DSMB) concluded that there was no possibility of the vaccine's proving efficacious. Further dissection of the data revealed an unwelcome surprise: a subset of vaccine recipients (those with preexisting antibody responses to Ad5) had experienced a statistically significant increase in risk of HIV infection compared with placebo recipients. Extended follow-up ultimately showed that the increase in risk was statistically significant in the overall vaccine group (hazard ratio of 1.40 for vaccine vs. placebo; $P = .03$), but a subset of men who have sex with men (MSM) who were circumcised and lacked preexisting antibody responses to Ad5 did not appear to be affected (hazard ratio 0.97; $P = 1.0$).[18] Receipt of the vaccine did not alter viral-load levels or CD4 counts in Step study participants who acquired HIV.

Two other HIV vaccine efficacy trials were directly and immediately affected by the cessation of Step. HVTN 503 (also known as the Phambili trial) was a placebo-controlled assessment of the same vaccine in heterosexuals in South Africa that had only partially enrolled; immunizations were discontinued and the study arms were unblinded, with counseling provided to participants regarding the Step results. Although the study was not completed, data from the trial were published in 2011, and were consistent with the lack of efficacy observed in Step; at that juncture, however, there was no evidence that the Ad5 vaccine had enhanced the risk of HIV infection.[19] A separate trial named PAVE 100 was days away from beginning at the time of the Step DSMB review, aiming to evaluate a prime-boost vaccine regimen comprising a DNA construct followed by an Ad5 vector similar to Merck's (designed by the National Institutes of Health's Vaccine Research Center in collaboration with GenVec, Inc.). PAVE 100 was stopped, extensively redesigned in light of the Step findings, and rechristened HVTN 505, finally getting under way in the spring of 2009.

On April 25, 2013, any hopes of Ad5's being rehabilitated were dashed when it was announced that vaccinations in HVTN 505 were ending due to an interim DSMB review, which found that the trial would be unable to demonstrate efficacy,

either in terms of preventing HIV infection or lowering viral load in participants who acquired HIV. A total of 2,494 participants were included in the efficacy analysis: 1,250 in the vaccine arm and 1,244 in the placebo group. To try to address the safety concerns raised by Step, HVTN 505 limited enrollment to Ad5 antibody-negative circumcised men and male-to-female transgender persons who have sex with men. Despite this restriction, there was a noticeable—but not statistically significant—imbalance in the number of HIV infections: a total of 41 in the vaccine group and 30 in the placebo group after a median of 15 months of follow-up. The primary efficacy analysis focused on infections that occurred after the full immunization series (week 28 onward), but this didn't favor the vaccine either: there were 27 infections among vaccinees and 21 in placebo recipients. As with Step, vaccination had no significant effect on viral loads and CD4 T-cell counts in study participants who became infected.

On the heels of the HVTN 505 denouement came more grim tidings: during extended follow-up of participants in the Phambili trial, significantly more HIV infections occurred in vaccine compared with placebo recipients (63 vs. 37). Although the differential has to be interpreted with caution because the study was no longer blinded, and drop-out rates may have had some influence, when summed with the concerning outcomes of Step and HVTN 505, the findings bode a bleak future for adenovirus vaccine vectors. Because the mechanism for the apparent increase in HIV acquisition risk remains unclear, it is not yet certain if studies of serotypes other than Ad5 might still move forward. Sponsors of ongoing trials are currently convening meetings to discuss the issue.

Pox-Protein Public-Private Partnership (P5)

The early termination of HVTN 505 means that there are no ongoing HIV vaccine efficacy trials, and none are anticipated before 2015 at the earliest. Next in line are a suite of studies that will be conducted under the aegis of the Pox-Protein Public-Private Partnership (P5), a coalition consisting of the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS, the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network, the U.S. Military HIV Research Program, Sanofi Pasteur, and Novartis Vaccines and Diagnostics.[20] The goal of P5 is to improve upon the modest protection documented in the RV144 ALVAC-HIV vCP1521/AIDSVAX B/E prime-boost trial in Thailand. Current plans include two efficacy trials to be conducted in South Africa: a traditional evaluation of a poxvirus vector/protein boost combination and a novel "adaptive" design[21] that will allow multiple different prime-boost tandems to be assessed in a single trial. An additional efficacy trial in Thailand, in a population of MSM at high risk of HIV infection, is in the early planning stages.

The Future

Outside of the efforts of P5, it is not clear where the next candidate for an HIV vaccine efficacy trial might come from. In early-phase trials are relative newcomers to the vector armamentarium: recombinant vesicular stomatitis virus (VSV) from Profectus BioSciences,[22] and recombinant Sendai virus (SeV) from DNAVEC,[23] but it remains to be seen if the immune responses induced by these candidates offer any advantages over those created by previous approaches. Also in the first phase of testing are two protein-based vaccines that aim to induce antibodies against HIV at mucosal surfaces CN54gp140 and EN41-FPA2; both have been reported to be immunogenic in animal models, but human trial data are pending.[24,25]

Much of the progress that has occurred in HIV vaccine research over the past year has been in basic rather than clinical territory. Most notably, an ever-increasing number of antibodies have been identified that can neutralize a broad array of different primary HIV isolates from around the globe, and there is intense scientific focus on solving the problem of inducing similarly effective antibodies with vaccines.[26] Substantial support for this research comes from the Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID) grant awarded to Duke University and the Scripps Research Institute by NIAID in July 2012.[27]

A common feature of the broadly neutralizing antibodies (bNAbs) identified to date is that the B cells that produce them have undergone unusually extensive somatic hypermutation. Somatic hypermutation is the process by which the B cell's antibody-producing genetic code is progressively revised as the cell undergoes repeated rounds of proliferation, leading to an increase in the affinity of the antibody for its target. The genetic code that the B cell starts out with is known as the germline sequence, and it is typically altered by around 5–15 percent to produce antibodies against common infections, whereas the range is 19–46 percent for the bNAbs against HIV. This requirement for extensive mutation appears to be connected to the unusual shapes the bNAbs must form to access hard-to-reach conserved areas of the HIV envelope (Env) protein, which are shielded by highly variable decoy targets. The key challenge for vaccine design is to stimulate a B cell with the appropriate germline sequence to start making antibodies, and then provide additional stimulation that guides the B cell along a somatic hypermutation pathway that ultimately generates a bNAb. Recent progress has included a detailed tracing of the evolution of this process in an HIV-infected individual, from the starting B cell to the somatically hypermutated bNAb-producing B cell,[28] and the publication of several studies identifying antigens capable of activating B cells with germline sequences that can ultimately give rise to bNAbs.[29,30,31]

Two research teams are working on a more radical approach to delivering bNAbs. Both projects involve the use of adeno-associated viruses (AAVs), not as vaccine vectors but as gene-delivery vehicles that take up residence in the episome of cells and serve as long-lived bNAb-making factories. Rather than traditional vaccination, this approach resembles gene therapy, similar to the current experimental use of AAV vectors to deliver factor IX as a treatment for hemophilia B.[32] The International AIDS Vaccine Initiative (IAVI) is collaborating with Phillip Johnson at the Children's Hospital of Philadelphia on plans to launch a phase I trial of an AAV vector that encodes the bNAb PG9, while David Baltimore's laboratory at the California Institute for Technology has published encouraging preclinical results using AAV to deliver multiple bNAbs in humanized mice[33] and also hopes to ultimately translate the approach to humans.

A far less technological method for delivering bNAbs is passive immunization, wherein the antibodies are manufactured on a large scale and given intermittently via infusion. Plans are afoot to assess whether passive immunization with bNAbs can help protect against mother-to-child transmission (MTCT) of HIV, primarily as a "test-of-concept" to ensure that the antibodies are as protective as they appear to be in laboratory and animal studies. However, the efficacy of antiretroviral therapy in preventing MTCT has led to questions about the ethics of this type of study,[34] and an editorial in the journal *Nature Medicine* has called for a rigorous independent assessment of the issue by the Institute of Medicine prior to initiation of any trial.[35] TAG supports this recommendation.

On the T-cell front, macaque studies of a CMV-based vaccine vector conducted by Louis Picker's research group at Oregon Health & Science University continue to suggest that, under some circumstances, virus-specific T-cell responses can offer a high degree of protection. Picker's published work has shown that the vaccine consistently leads to strict control of a highly pathogenic SIV challenge virus in 50 percent of immunized macaques.[36] At the 2013 Conference on Retroviruses and Opportunistic Infections (CROI), Picker presented evidence that these animals actually clear the SIV infection over time—an unprecedented finding.[37] Analysis of the SIV-specific CD8 T-cell responses in the protected macaques has revealed two unusual and potentially important features: they target a far larger number of virus epitopes than has been seen with other vaccines, and in many cases recognize their targets via a pathway that was thought to only be used by CD4 T cells (the major histocompatibility complex class II pathway).[38] Although there are some concerns as to whether CMV can be rendered safe enough to use as an HIV vaccine vector in humans, this research is shedding new light on the type of T-cell response vaccines need to induce in order to be effective.

Table 2. PrEP and Microbicides Pipeline 2013

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
dapivirine vaginal ring	Reverse transcriptase inhibitor	International Partnership for Microbicides/Microbicide Trials Network	Phase III
Viread (tenofovir)	Nucleotide reverse transcriptase inhibitor	Gilead Sciences/NIAID/CDC	Phase III
tenofovir gel	Nucleotide reverse transcriptase inhibitor	CONRAD/CAPRISA/South Africa Department of Science Technology/ South Africa National Department of Health/USAID/Bill & Melinda Gates Foundation	Phase III Phase II
Truvada (tenofovir/emtricitabine) (intermittent dosing)	Combined nucleoside and nucleotide reverse transcriptase inhibitors	ANRS/HIV Prevention Trials Network	Phase III Phase II
maraviroc, maraviroc + emtricitabine, maraviroc + emtricitabine and tenofovir	CCR5 inhibitor	HIV Prevention Trials Network	Phase II
dapivirine (TMC120) gel	Reverse transcriptase inhibitor	International Partnership for Microbicides	Phase I/II
maraviroc (standard or reduced-dose in women)	CCR5 inhibitor	Emory University	Phase I
maraviroc + dapivirine vaginal ring	CCR5 inhibitor, reverse transcriptase inhibitor	International Partnership for Microbicides/Microbicides Trials Network/NIAID/NIMH	Phase I
maraviroc vaginal ring	CCR5 inhibitor	International Partnership for Microbicides/Microbicides Trials Network/NIAID/National Institutes of Mental Health (NIMH)	Phase I
rilpivirine long-acting (RPV-LA)	Non-nucleoside reverse transcriptase inhibitor, long-acting injectable formulation	St Stephens AIDS Trust/Janssen Pharmaceuticals	Phase I
tenofovir gel (rectal formulation)	Nucleotide reverse transcriptase inhibitor	Microbicides Trials Network	Phase I
UC-781 (vaginal and rectal gels)	Reverse transcriptase inhibitor	Biosyn	Phase I
Vaginal tablets containing tenofovir and/or emtricitabine	Nucleoside and nucleotide reverse transcriptase inhibitors	CONRAD	Phase I

Preexposure Prophylaxis (PrEP)

The approval of Truvada for PrEP in the United States has largely shifted the drug out of the pipeline and into the realm of implementation or operational research. A number of demonstration projects are getting under way to evaluate Truvada PrEP in the real world (described in detail in the 2012 AVAC report *Achieving the End: One Year and Counting*[39]), and there are community-based educational efforts such as the AIDS Foundation of Chicago's "My PrEP Experience" project.[40] A formal guidance document for clinicians is due to be released by the U.S. Centers for Disease Control and Prevention later this year.

Truvada's approval was based on positive results from three large trials: iPrEx, conducted among 2,470 MSM and 29 transgender women at high risk of HIV infection (primarily in Peru and Ecuador, with some participants from Brazil, the United States, South Africa, and Thailand);[41] Partners PrEP, which recruited 4,758 serodiscordant heterosexual couples in Uganda and Kenya;[42] and CDC TDF2, involving 1,219 men and women in Botswana.[43] But the FEM-PrEP trial, which enrolled 2,120 women in Kenya, Malawi, South Africa, and Tanzania, did not show efficacy.[44] Additionally, in March 2013, it was announced that the VOICE study—a multi-arm randomized comparison of Truvada, tenofovir, or tenofovir gel versus placebo that recruited 5,029 women in South Africa, Uganda, and Zimbabwe—found no significant reduction in HIV incidence in participants assigned to Truvada PrEP.[45]

The major factor that has emerged to account for the conflicting results is adherence; analyses of the iPrEx and Partners PrEP trials indicate that among Truvada recipients with detectable levels of tenofovir, protective efficacy was 92% and 90%, respectively (higher than the reported Truvada efficacy results in the overall trial populations: 44% and 75%).[46] In the FEM-PrEP and VOICE trials, drug-level testing indicated that less than 40% of participants were taking the drug regularly. Another suggested contributor to differential efficacy in men and women is lower drug penetration into vaginal tissues;[47] however, an analysis of women in the Partners PrEP trial at the highest risk of HIV infection found that protection was equivalent to that observed in the study as a whole.[48]

The varying adherence to Truvada PrEP has highlighted the need for approaches that are more broadly acceptable among populations at risk for HIV infection. Particular focus is now being placed on next-generation PrEP candidates that can be dosed intermittently or as needed, rather than daily, in the hope of providing more convenient and user-friendly means of achieving protection. A phase I study of a long-acting formulation of the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV-LA), which may allow for monthly or quarterly dosing, has offered encouragement that such approaches might be feasible.[49] More recently, a

macaque study of a long-acting injectable version of an integrase inhibitor, GSK744LAP, has demonstrated protective efficacy against intrarectal virus challenges; the investigators believe that, like RPV-LA, the drug might be given as infrequently as four times a year.[50] A phase I study involving HIV-negative volunteers is exploring the pharmacokinetics and safety of RPV-LA combined with GSK744LAP, though it is unclear if this regimen will be explored in PrEP efficacy studies.[51]

The CCR5 inhibitor maraviroc, an approved HIV treatment, is being evaluated as a possible novel PrEP agent in an ongoing phase II trial conducted by the HIV Prevention Trials Network (HPTN).[52] But the potential of the drug for this indication has been called into question by a study in macaques, which found that it failed to protect against intrarectal SHIV162p3 challenges despite high concentrations in rectal tissue.[53] Administration of maraviroc also caused an unanticipated increase in the percentage of CCR5-expressing T cells in the blood, leading the researchers to note that "the implications of these immunological effects on PrEP with MVC [maraviroc] require further evaluation."

Microbicides

As with PrEP, the acceptability of microbicides has been affected by the downsides of frequent product administration, leading to the prioritization of approaches amenable to intermittent application. The International Partnership for Microbicides (IPM) is leading the way with a vaginal ring that delivers the antiretroviral dapivirine for four weeks before it needs replacing. The dapivirine ring is now being tested in two efficacy trials: the IPM-sponsored Ring Study, involving 1,650 women at sites in South Africa, Rwanda, and Malawi, and ASPIRE, led by the Microbicide Trials Network (MTN), which aims to recruit 3,476 women in Malawi, South Africa, Uganda, Zambia, and Zimbabwe.

Tenofovir gel—which reduced risk of HIV acquisition by 39 percent in the CAPRISA 004 study,[54] but did not prove efficacious in the VOICE trial[55]—is the subject of two ongoing trials in South Africa: FACTS 001, a confirmatory efficacy trial in 2,200 women, and CAPRISA 008, a randomized study of the feasibility of delivering tenofovir gel to women who participated in CAPRISA 004 via family planning clinics compared with research clinics.[56]

Analyses of tissue drug levels in CAPRISA 004 have echoed results from PrEP trials, revealing a correlation between the presence of drug and protective efficacy.[57] But follow-up studies have also highlighted another contributor to diminished microbicide activity: inflammation, measured both in the genital tract[58] and systemically.[59] These findings add to the evidence that immunomodulators capable

of dampening inflammation—such as glycerol monolaurate, which has already shown potential in the macaque model[60]—deserve evaluation in human trials, and may be able to play a valuable adjunctive role combined with antiretroviral approaches.

A rectal formulation of tenofovir gel is making progress through the pipeline; safety results from a phase I trial have been published,[61] and the MTN is now planning to launch a larger phase II evaluation.

CONRAD has developed vaginal tablet formulations of tenofovir, emtricitabine, and tenofovir/emtricitabine (the combination contained in Truvada); a phase I study is under way to assess the safety, pharmacokinetics, pharmacodynamics, and disintegration time of the tablets.[62]

Table 3. Research Toward a Cure 2013

Clinical Trial	ClinicalTrials.gov Identifier(s)	Manufacturer/Sponsor(s)
ACE inhibitors	NCT01535235	University of California, San Francisco/ amfAR
Allogeneic transplant in individuals with chemotherapy-sensitive hematologic malignancies and coincident HIV infection (BMT CTN 0903)	NCT01410344	National Heart, Lung, and Blood Institute (NHLBI)/National Cancer Institute (NCI)/Blood and Marrow Transplant Clinical Trials Network
Alpha interferon intensification	NCT01295515	NIAID
ChAdV63.HIVcons, MVA.HIVconsv vaccines	NCT01712425	IrsiCaixa/Fundació Lluita contra la SIDA/Hospital Clinic of Barcelona/ HIVACAT/University of Oxford
disulfiram (Antabuse)	NCT01286259 (closed to enrollment)	University of California, San Francisco/ the Johns Hopkins University
DNA/Ad5 HIV vaccine, ART intensification	NCT00976404 (closed to enrollment)	Vical/GenVec/U.S. National Institutes of Health (NIH) Vaccine Research Center/ Objectif Recherche VACcin Sida (ORVACS)
Dual anti-HIV gene transfer construct	NCT01734850	Calimmune
Genetically modified peripheral blood stem cell transplant in treating patients with HIV-associated non-Hodgkin's or Hodgkin's lymphoma	NCT01769911	Fred Hutchinson Cancer Research Center
Intravenous Ig in primary HIV infection	No ID yet. Study name: CHERUB 001	CHERUB (Collaborative HIV Eradication of viral Reservoirs: UK BRC)

Clinical Trial	ClinicalTrials.gov Identifier(s)	Manufacturer/Sponsor(s)
panobinostat	NCT01680094 (closed to enrollment)	University of Aarhus/Massachusetts General Hospital/Monash University/ Karolinska Institutet/Novartis
Prime-boost therapeutic vaccine (MAG-pDNA, $rVSV_{IN}$ HIV-1 Gag)	NCT01859325	NIAID/Profectus Biosciences
Redirected MazF-CD4 autologous T cells for HIV gene therapy (MazF-T)	NCT01787994	Takara Bio/University of Pennsylvania
SB-728-T, autologous CD4 T cells genetically modified at the CCR5 gene by zinc finger nucleases	NCT01543152 (with cyclophosphamide) NCT01044654 NCT00842634 (closed to enrollment) NCT01252641 (closed to enrollment)	Sangamo BioSciences
Tat Oyi vaccine	NCT01793818	Biosantech
vorinostat (SAHA)	NCT01319383 NCT01365065 (closed to enrollment)	Merck/University of North Carolina at Chapel Hill/NIAID/Bayside Health

Defining what constitutes the cure-research pipeline inevitably involves some subjective judgments; for the purposes of this report, we have included trials evaluating the impact of interventions on the latent HIV reservoir, as well as new studies looking to create HIV-resistant immune cells or induce immunologic control of viral replication. The latter two goals have historically been pursued by gene therapies and therapeutic vaccines, respectively, before the term "cure research" came into widespread usage, so there is some overlap with those pipelines (listed in tables 4 and 5).

The Mississippi Child

The most widely publicized scientific developments in the field over the past year have related to evidence from case reports that a cure is possible. Chief among them is the case of a child in Mississippi who may have been functionally cured of HIV infection, presented at the 2013 CROI by Deborah Persaud from the John Hopkins University.[63] The context is unusual in that the child's mother was not diagnosed with HIV until in labor, precluding the use of prophylaxis against mother-to-child transmission. Separate HIV DNA and RNA tests at 30 and 31 hours after birth indicated that the baby had acquired infection in utero. Prior to the test results' becoming available, the treating clinician—Hannah Gay from the

University of Mississippi Medical Center—initiated a combination ART regimen at treatment rather than prophylactic doses due to the high risk of infection. This judgment call was shown to be correct when the diagnostic results came in, and subsequent sequential viral-load tests documented the stepwise decline typical of the response to ART (the initial reading was 19,812 copies/mL, followed by 2,617 copies/mL, 516 copies/mL, 265 copies/mL, and then below the limit of detection of 48 copies/mL).

ART was continued for around 18 months, but the mother and child were then lost to care. Upon their return five months later, it transpired that ART had been discontinued. Gay performed new viral-load tests, expecting to observe the typical rebound, but surprisingly HIV RNA remained undetectable. This prompted Gay to contact Katherine Luzuriaga at Massachusetts General Hospital, an expert in pediatric HIV research, who in turn contacted Persaud (who was lead author on the first paper to describe the latent HIV reservoir in children[64]). In collaboration with several other laboratories, the researchers searched for HIV DNA and RNA in samples taken at 24 and 26 months of age. Only a minority of the samples showed trace amounts of viral genetic material, at the borderline of the limit of detection of the assays. Persaud looked for replication-competent virus in 22 million resting CD4 T cells using a viral outgrowth technique—the gold-standard approach for measuring the latent HIV reservoir—but the results were negative. HIV-specific antibody and T-cell responses were also not detected.

Based on these results, the research team concluded that the case is best defined—at least tentatively—as a functional cure: some trace amounts of HIV may be present, but no active virus is evident, and the child has remained off ART for over 10 months and counting. A number of scientists not involved in the studies expressed skepticism and tried to offer alternative interpretations of the data. Among the suggested possibilities were that the viral RNA and DNA detected in the infant came from maternal cells that would have been cleared anyway, or that HIV infection had not been established and ART acted as prophylaxis rather than treatment, or that the infant might have spontaneously cleared the virus without treatment (a phenomenon that several studies published in the 1990s claimed to have documented, albeit rarely[65,66,67]).

None of these scenarios seem likely based on the evidence in the scientific literature: the number of HIV-infected maternal cells that would have to have been transferred in order to account for the viral-load readings would be physiologically implausible, and there are no published data supporting the idea that HIV DNA and RNA from maternal cells are detectable in exposed infants who turn out to be uninfected. Similarly, studies of large numbers of infants receiving ART prophylaxis after birth—including those born to HIV-positive mothers who did not

receive prophylaxis themselves—do not offer evidence of detectable HIV DNA and RNA readings followed by an absence of infection.[68,69] Lastly, the reports of transient HIV infection in infants that were published in the 1990s were questioned by a paper published by Lisa Frenkel and colleagues in *Science* in 1998,[70] which evaluated several cases and showed that they were explained by problems such as PCR contamination and sample misattribution. Frenkel's study laid out criteria for formally proving transient HIV infection in infants, and it is notable that no cases have since been reported.

The implications of Persaud's report for the broader field are still being discussed. The most commonly mentioned hypotheses to explain the outcome are that very early ART prevented the establishment of a latent HIV reservoir, or that the reservoir is shorter-lived in a person so young and was eliminated before treatment was interrupted. The pediatric HIV trials network IMPAACT is planning trials to assess whether the apparent cure can be duplicated in other HIV-infected neonates by providing immediate ART. Another avenue of research suggested by the case is the study of HIV reservoirs in perinatally infected individuals who were treated early with ART and have remained on therapy long-term. Katherine Luzuriaga presented a poster at CROI showing that, in five such individuals, replication-competent HIV could not be detected, viral DNA levels were low, and viral RNA was below the limit of detection of a sensitive assay (<2 copies/mL) in four out of the five.[71] Based on these results, Luzuriaga noted that, "perinatally infected youth with marked curtailment of HIV reservoirs following early therapy are prime candidates for interventions to achieve functional cure or eradication."[72] That statement perhaps also captures the clearest message from the Mississippi case: pediatric and adolescent HIV-infected populations, who face the greatest burden of lifelong ART, must be included in the cure research agenda.

Duplicating the Case of Timothy Brown

At the current time, Timothy Ray Brown remains the only adult considered cured of HIV infection. Last year, the presentation of results from an intensive search for HIV in his body generated some controversy when three of the laboratories involved detected trace amounts of viral genetic material in a minority of samples. The study has since been published in the open-access journal *PLoS Pathogens* and, while the authors highlight the difficulty of formally proving a cure using assays that are operating at the limits of their sensitivity, they also state unequivocally that "the absence of recrudescent HIV replication and waning HIV-specific immune responses five years after withdrawal of treatment provide proof of a clinical cure."[73] Further evidence to support this conclusion was presented at the 2013 CROI by Joyce Sanchez from the University of Minnesota, who showed that the

amount of fibrosis—scarring damage caused by immune activation in HIV infection—in Brown's gut-associated lymphoid tissue was comparable to a group of HIV-negative controls (6.8% vs. 7%), and far lower than that observed in infected individuals, even those controlling viral load in the absence of ART (15.9%).[74]

Efforts to duplicate the outcome achieved in Brown in other people with HIV in similar circumstances—a diagnosis of concomitant cancer requiring stem cell transplantation as part of the treatment—are continuing. Gero Hütter, the hematologist responsible for treating Brown with adult stem cells from a donor homozygous for the CCR5-Δ32 mutation (which abrogates expression of the HIV coreceptor CCR5), has identified other potential candidates, but so far has not been able to attempt the same procedure (largely due to difficulties identifying an appropriate stem cell donor).[75] A trial in the United States that will attempt to identify CCR5-Δ32 homozygous adult stem cell donors for HIV-positive people with hematologic malignancies (BMT CTN 0903; see table 3) remains ongoing.

Cord Blood Stem Cell Transplantation

Researchers are also pursuing the possibility of using cord blood stem cells from CCR5-Δ32 homozygous donors; a company called StemCyte has led an effort to screen banked cord blood units for the mutation in order to facilitate this work.[76] At the 2013 CROI, a poster presentation described the outcome of two cases in which the aim was to employ these cells:[77] one individual in the Netherlands with progressive myelodysplastic syndrome received the CCR5-Δ32 homozygous cord blood stem cell transplant but died shortly afterward from severe pneumonia and a relapse of the cancer. In a second case in Madrid involving an individual with Burkitt's lymphoma, there was concern about the viability of the CCR5-Δ32 homozygous cord blood stem cells,[78] and cells from a donor lacking the mutation were used instead. The cancer is in remission, but the individual remains on ART and still has a low-level but detectable HIV reservoir.

The newly formed European HIV Cure and Transplant Consortium (EHCTC) plans to continue seeking opportunities to provide CCR5-Δ32 homozygous cord blood stem cells to HIV-positive people requiring transplants. In the United States, a team led by John Wagner at the University of Minnesota has recently administered a CCR5-Δ32 homozygous cord blood stem cell transplant to a 12-year-old boy with leukemia and HIV, in the hope of curing both diseases. The procedure took place on April 23, 2013, and information regarding the outcome is not likely to be available for several months.[79]

Two cases involving stem cell transplantation that drew media attention last year were presented by Timothy Henrich from Massachusetts General Hospital at the

International AIDS Society (IAS) "Towards an HIV Cure" symposium in Washington, D.C., in July 2012,[80] and subsequently published in the *Journal of Infectious Diseases*.[8] Henrich studied two people with HIV and cancer diagnoses who were originally heterozygous for CCR5-Δ32, but received successful stem transplants from donors lacking the mutation. ART was maintained throughout the procedures and continued afterward. Both individuals experienced periods of graft-versus-host disease (GVHD) that resolved with treatment. After 21 and 42 months of follow-up, respectively, neither has detectable levels of HIV DNA, RNA, or replication-competent virus in peripheral blood mononuclear cells, CD4 T cells, or plasma. Henrich and colleagues are planning careful ART interruptions to assess if HIV levels rebound. The outcome of these studies may help shed light on which factors were important in achieving a cure in Timothy Ray Brown.

The VISCONTI Cohort

Another widely discussed presentation at the IAS symposium—given by Asier Sáez-Cirión from the Institut Pasteur—described the VISCONTI cohort, a group of 14 HIV-positive individuals in France who received ART soon after acquiring infection, but later stopped (after a median time on treatment of three years) and have maintained undetectable or extremely low viral loads ever since (currently, a median of 7.4 years). Although some media stories have characterized members of the cohort as examples of a functional cure, Sáez-Cirión and colleagues are more circumspect, and refer to the outcome as "long-term virological remission."[81] Analyses to date suggest a number of potential contributing factors: low levels of HIV infection in long-lived central memory CD4 T cells, low levels of T-cell activation and, possibly, the extended duration of ART compared with some other studies of acute HIV infection treatment. HIV-specific CD8 T-cell responses in the VISCONTI cohort are generally weak, and participants lack the favorable HLA alleles that have been associated with control of viral replication in elite controllers. In fact, HLA alleles that have been associated with more rapid progression in untreated HIV infection appear to be overrepresented. Additional studies are ongoing, with the goal of extracting lessons to guide the development of therapies capable of promoting control of HIV in the absence of ART.

HDAC Inhibitors and Toll-Like Receptor Agonists

HDAC inhibitors remain the lead compounds for awakening long-lived latent HIV reservoirs. Results from a phase I trial of the HDAC inhibitor vorinostat were presented at the 2013 CROI by Sharon Lewin from Monash University in Australia.[82] A total of 20 participants on ART received 14 days of the drug, and a significant increase in cell-associated HIV RNA expression of close to threefold

was documented (consistent with the drug prompting at least some latently infected cells to start actively transcribing viral RNA). These results appear congruent with those in the single-dose trial of vorinostat published by David Margolis's research group in 2012.[83] HIV DNA levels did not change, however, indicating that additional approaches will likely be needed to kill latently infected cells even if HIV RNA expression is successfully stimulated.

In Denmark, Ole Søgaard and colleagues at Arhus University Hospital are conducting a phase I evaluation of the effects of the HDAC inhibitor panobinostat on latent HIV,[84] after finding it to be highly active in vitro.[85] Preliminary results are due to be presented at the June 2013 "Towards an HIV Cure" symposium in Kuala Lumpur. Unfortunately, the trial became the subject of intense and extremely misleading media hype after a journalist for the U.K. newspaper the *Daily Telegraph* wrote that the scientists were "on brink of HIV cure."[86] The article was eventually corrected after considerable outcry from activists and the issuance of a correction by Arhus University Hospital.[87]

The same group of researchers has identified a potential complementary immune-modulating strategy that may help prompt elimination of latently infected cells: a compound that stimulates Toll-like receptor 9 (referred to as a TLR9 agonist). TLRs are a family of cell receptors involved in the recognition of pathogenic organisms, and the TLR9 agonist CPG 7909 has been studied in people with HIV as an adjuvant to improve immune responses to a pneumococcal vaccine.[88] The Danish researchers used samples from this trial to conduct an unplanned, exploratory analysis of the effects of CPG 7909 on the latent HIV reservoir, finding that it was associated with a significant reduction in HIV DNA that correlated with increases in markers of improved CD8 T-cell function.[89] Further studies are now in the works.

Gilead Sciences is considering a similar dual approach against HIV latency: the HDAC inhibitor romidepsin, which has shown potency in vitro,[90] and a TLR7 agonist (GS-9620), which is already being studied in humans as a candidate hepatitis B therapeutic.[91] The AIDS Clinical Trials Group (ACTG) is currently collaborating with Gilead to plan a phase I trial of romidepsin.

There are, however, some clouds on the HDAC inhibitor horizon. At the 2013 CROI, Anthony Cillo from the laboratory of John Mellors at the University of Pittsburgh presented evidence that vorinostat only induces HIV expression by a small fraction of latently infected CD4 T cells,[92] raising the possibility that the approach may leave a significant proportion of the viral reservoir unperturbed. The data suggest that a variety of mechanisms may be involved in HIV latency, not all of which can be reversed by HDAC inhibition—underscoring the importance of pursuing combination approaches to address the problem.

SB-728-T

Trials of Sangamo BioSciences' SB-728-T gene therapy—which uses zinc finger nucleases to disrupt the CCR5 gene and prevent expression of the CCR5 coreceptor on modified CD4 T cells—remain ongoing. Limited news of progress has trickled out in the past few months: at the 2013 CROI, Rafick-Pierre Sékaly presented data showing that increases in central memory CD4 T cells are the main component of the immune reconstitution that has previously been described in a study of nine immunologic nonresponders (INRs), but also that the magnitude of the reconstitution was negatively affected by baseline levels of inflammation.[93] At the 16th Annual Meeting of the American Society of Gene and Cell Therapy in May 2013, Dale Ando from Sangamo BioSciences revealed the interesting finding that seven of nine participants in the INR trial showed significant decreases in HIV DNA levels over 12 months of follow-up, which correlated with the proportion of detectable gene-modified CD4 T cells (the higher the number of cells, the lower the HIV DNA).[94]

Ando also offered a glimpse at some data from an ongoing study in individuals heterozygous for the CCR5-Δ32 mutation. The rationale behind this work is that one of the pair of CCR5 genes that exists in cells is already nonfunctional in CCR5-Δ32 heterozygotes, leaving less work for SB-728-T to do, and potentially increasing the number of CCR5-negative CD4 T cells created by the therapy. Ando described four study participants, two of whom experienced a decline in viral load during an ART interruption and two who did not. The viral-load declines were associated with increased polyfunctional HIV-specific CD8 T-cell responses, hinting that the protection of CD4 T cells by SB-728-T may, in some cases, be able to have positive effects on other important components of the immune response. Furthermore, when looking at all SB-728-T recipients to date who have undergone an ART interruption, there was a statistically significant correlation between the estimated proportion of gene-modified CD4 T cells and reductions in viral load. Lastly, Ando reported preliminary data from a trial investigating whether transient immune suppression with the drug cyclophosphamide (Cytoxan) can improve the uptake and survival of gene-modified CD4 T cells; so far no significant impact has been observed, but results from participants receiving the highest cyclophosphamide dose are not yet available.

Emerging Gene Therapies

Two new clinical trials involving gene therapies have opened over the past year. Calimmune, a company founded by David Baltimore, has developed a dual gene therapy dubbed LVsh5/C46 (also known as Cal-1) that comprises a lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5, and a fusion inhibitor, C46 (a peptide with a mechanism of action similar to the approved

fusion-inhibitor drug Fuzeon). The trial will explore the modification of both CD4 T cells and hematopoietic stem cells with LVsh5/C46; cells are harvested from study participants, modified in the laboratory, and then reinfused. Some participants will receive transient immune suppression with the chemotherapy drug busulfan to assess if this enhances the uptake of gene-modified cells.[95]

Drexel University is collaborating with the Japanese company Takara Bio to conduct a trial[96] in which autologous CD4 T cells are modified with a retroviral vector encoding the MazF endoribonuclease gene.[97] The gene has been shown to strongly inhibit HIV replication in CD4 T cells in vitro.[98] A team at the Fred Hutchinson Cancer Center led by Anne Woolfrey is also employing C46 to modify hematopoietic stem cells in a pending study for individuals with HIV and non-Hodgkin's or Hodgkin's lymphoma requiring autologous peripheral blood stem cell (PBSC) transplants.[99]

Therapeutic Vaccines

Therapeutic vaccines are the subject of separate studies in Bethesda and Barcelona. In the former, a prime-boost combination of DNA and recombinant vesicular stomatitis virus constructs developed by Profectus Biosciences will be administered to individuals treated with ART soon after acquiring HIV infection.[100] The protocol has generated some concern due to the inclusion of a placebo control and an ART interruption after 56 weeks; these issues are due to be discussed by the NIH's Recombinant DNA Advisory Committee (RAC) at a meeting on June 12, 2013. The trial in Barcelona involves chimpanzee adenovirus and modified vaccinia Ankara strain (MVA) vectors, and also aims to recruit HIV-positive people treated with ART early after infection.[101] The primary endpoint is safety, but secondary analyses will evaluate changes in HIV-specific CD8 T-cell responses—including measuring the ability of CD8 T cells to suppress viral replication in vitro—and levels of both integrated and unintegrated HIV DNA in peripheral blood. Although adenovirus-based vectors are under review in the preventive context due to the potential for enhanced acquisition risk, a study of Merck's Ad5 HIV vaccine as a therapy did not uncover any safety issues. On the contrary, receipt of the vaccine was associated with a strong trend toward lower viral load during an ART interruption.[102]

Intravenous Immunoglobulin

The National Institute for Health Research in the United Kingdom has funded a new collaborative cure research endeavor named CHERUB (Collaborative HIV Eradication of viral Reservoirs: UK BRC). The first clinical trial, CHERUB 001, is evaluating the effects of a combination of ART and intravenous immunoglobulin

(IVIG) on virus reservoirs in ten people with primary HIV infection. A prior "proof of concept" study conducted at the Karolinska Institutet in Sweden reported that the addition of high-dose IVIG to ART for seven days led to a transient decline in HIV reservoirs (as measured by the viral outgrowth assay).[103,104]

ART Intensification Plus IL-7

One cure-related clinical study has exited the pipeline since last year. The Eramune 01 trial investigated ART intensification with maraviroc and raltegravir, either with or without the addition of the cytokine IL-7. A total of 29 HIV-positive individuals were enrolled. No decrease in the HIV reservoir was observed in any participant. IL-7 significantly improved CD4 and CD8 T-cell numbers, consistent with previous reports, but also increased the amount of HIV DNA, likely by inducing the proliferation of latently infected CD4 T cells.[105] The results do not mean that IL-7 cannot benefit INRs—in whom the need to reconstitute CD4 T cells in order to prevent excess morbidity and mortality is more important than small changes in HIV DNA levels—but indicate that the cytokine is unlikely to have a role as an anti-latency agent (as was once proposed[106]).

An overarching question for all cure research is how best to measure the HIV reservoir. Sobering results from a comprehensive, multilaboratory effort to compare currently available assays were published in February 2013.[107] The different techniques studied showed little to no correlation with each other or the gold-standard (but cumbersome) viral-outgrowth assay for replication-competent HIV. The explanation likely pertains to the large number of defective HIV proviruses that can be detected by PCR methods but cannot generate replication-competent viruses. The findings indicate that more work is needed to develop tests that can accurately quantify the number of latently infected cells capable of releasing infectious virus. A step in this direction has been reported by the laboratory of Robert Siliciano at the Johns Hopkins University; his team has streamlined the viral outgrowth assay to increase the speed with which it can be performed and reduce associated labor and costs.[108]

Table 4. Immune-Based and Gene Therapy Pipeline 2013

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
mesalamine (5-aminosalicylic acid)	Oral anti-inflammatory drug approved for the treatment of inflammatory bowel disease	University of California, San Francisco/ Salix Pharmaceuticals	Phase IV
Chloroquine phosphate	Antimalarial, anti-inflammatory	NIAID/ACTG	Phase II
etoricoxib	Cox-2 inhibitor, anti-inflammatory	Oslo University Hospital	Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Interleukin-7 (CYT 107)	Cytokine	Cytheris	Phase II
lubiprostone	Apical lumen ClC-2 chloride channel activator	Ruth M. Rothstein CORE Center/ Chicago Developmental Center for AIDS Research	Phase II
LVsh5/C46	Dual anti-HIV gene transfer construct	Calimmune	Phase I/II
Prebiotics + glutamine	Gut microbiota modifiers	Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal	Phase I/II
Umbilical cord mesenchymal stem cells (UC-MSC)	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	Phase I//II
Gene transfer for HIV using autologous T cells	Infusions of autologous CD4 T cells modified with by a lentivirus vector encoding three forms of anti-HIV RNA: pHIV7-shI-TAR-CCR5RZ	City of Hope Medical Center/Benitec	Phase I
HLA-B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I
hydroxychloroquine	Antimalarial, antirheumatic, anti-inflammatory	St Stephens Aids Trust	Phase I
M87o	Entry inhibitor gene encoded by a lentiviral vector, introduced into CD4 T cells ex vivo	EUFETS AG	Phase I
Redirected high affinity Gag-specific autologous T cells for HIV gene therapy	Gene therapy that introduces an HIV-specific T-cell receptor into CD8 T cells and reinfuses them	University of Pennsylvania	Phase I
Redirected MazF-CD4 autologous T cells for HIV gene therapy (MazF-T)	Autologous CD4+ T cells genetically modified with a retroviral vector expressing the MazF endoribonuclease gene (MazF-T), given via intravenous infusion.	University of Pennsylvania	Phase I
SB-728-T	Autologous T-cells genetically modified at the CCR5 gene by zinc finger nucleases	University of Pennsylvania/ Sangamo BioSciences	Phase I

Table 5. Therapeutic Vaccines Pipeline 2013

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Vacc-4x	Synthetic peptides from the HIV-1 Gag p24 protein + adjuvant	Bionor Immuno	Phase IIb
AGS-004	Mature dendritic cells electroporated with autologous HIV-1 RNA and CD40L RNA	Argos Therapeutics	Phase II
DCV-2	Autologous myeloid dendritic cells pulsed ex vivo with high doses of inactivated autologous HIV-1	University of Barcelona	Phase II
DermaVir patch (LC002)	DNA expressing all HIV proteins except integrase formulated to a mannosylated particle to target antigen-presenting cells	Genetic Immunity	Phase II
FIT-06, GTU-MultiHIV vaccine	DNA vaccine encoding complete sequences of HIV-1 clade B Rev, Nef, Tat, and p17/p24 proteins, and T-cell epitopes from Pol and Env proteins	FIT Biotech	Phase II
GSK HIV vaccine 732462	p24-RT-Nef-p17 fusion protein in proprietary adjuvant AS01B	GlaxoSmithKline	Phase II
HIV-1 Tat vaccine	Tat protein vaccine	National AIDS Center at the Istituto Superiore di Sanità, Rome	Phase II
VAC-3S	3S peptide from gp41	InnaVirVax	Phase I/IIa
Autologous HIV-1 ApB DC vaccine	Autologous dendritic cells pulsed with autologous, inactivated HIV-infected apoptotic cells	University of Pittsburgh	Phase I/II
DNA/MVA	DNA vaccine and an MVA vector encoding HIV-1 Gag and multiple CTL epitopes	Cobra Pharmaceuticals/ Impfstoffwerk Dessau-Tornau/University of Oxford/U.K. Medical Research Council	Phase I/II
Tat Oyi vaccine	Synthetic Tat protein vaccine	Biosantech	Phase I/II
TUTI-16	Synthetic HIV-1 Tat epitope vaccine	Thymon	Phase I/II
Vacc-C5	Peptides from the C5 region of gp120	Bionor Pharma	Phase I/II
AFO-18	18 peptides representing 15 CD8 T-cell epitopes and 3 CD4 T-cell epitopes from HIV-1 in an adjuvant (CAF01)	Statens Serum Institut/ Ministry of the Interior and Health, Denmark/ European and Developing Countries Clinical Trials Partnership	Phase I
Autologous dendritic cell HIV vaccine	Autologous dendritic cells pulsed with conserved HIV-derived peptide	University of Pittsburgh	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
ChAdV63.HIVconsv, MVA.HIVconsv	Chimpanzee adenovirus vector and MVA vector containing the HIVconsv immunogen	IrsiCaixa/Fundació Lluita contra la Sida/Hospital Clinic of Barcelona, HIVACAT/University of Oxford	Phase I
DC vaccine	Autologous dendritic cells generated using GM-CSF and interferon alpha, loaded with lipopeptides and activated with lipopolysaccharide	Baylor University/ANRS	Phase I
HIVAX	Replication-defective HIV-1 vector pseudotyped with VSV-G envelope	GeneCure Biotechnologies	Phase I
HIV-v	Lyophilized mixture of polypeptide T-cell epitope sequences	Seek	Phase I
MAG-pDNA vaccine, GENEVAX, TriGrid	Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system	ACTG/NIAID/Profectus BioSciences/Ichor Medical Systems	Phase I
MAG-pDNA vaccine, $rVSV_{IN}$ HIV-1 Gag	Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences/ NIAID	Phase I
mRNA-transfected autologous dendritic cells	Dendritic cells transfected with vectors encoding consensus HIV-1 Gag and Nef sequences	Massachusetts General Hospital	Phase I
MVA HIV-B	MVA vector including HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I
MVA.HIVconsv	MVA vector	University of Oxford/U.K. Medical Research Council	Phase I
PENNVAX-B biological: GENEVAX IL-12-4532, pIL15EAM	DNA vaccine including HIV-1 Env, Gag, and Pol, with GENEVAX IL-12 and IL-15 adjuvants	University of Pennsylvania/ Drexel University	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
PENNVAX-B (Gag, Pol, Env) + electroporation	DNA vaccine encoding Gag, Pol, and Env genes of HIV-1 + electroporation	Inovio Pharmaceuticals/ University of Pennsylvania	Phase I
pGA2/JS7 DNA MVA/HIV62B	Prime: DNA vaccine Boost: MVA vector Both including Gag, Pol, and Env genes from HIV-1 clade B	GeoVax/AIDS Research Consortium of Atlanta/ University of Alabama at Birmingham/AIDS Research Alliance	Phase I
SAV001-H	Whole-killed HIV-1 vaccine	Sumagen	Phase I

Immune-Based and Gene Therapies, and Therapeutic Vaccines

In the area of adjunctive therapies for ART, pickings are relatively slim. Several years of accumulated data—covered in past TAG pipeline reports—support the potential for IL-7 to benefit INRs, but plans to evaluate clinical efficacy in this population have yet to come to fruition.

During the past year, researchers from China have published promising-looking data regarding the ability of umbilical cord mesenchymal stem cells (UC-MSC) to promote immune reconstitution in INRs.[109] In a small placebo-controlled phase I trial, significant increases in naive- and central memory CD4 T cells were documented, along with declines in markers of immune activation and inflammation. Expanded studies are under way to further explore the efficacy and mechanism of the approach.[110] However, because UC-MSC are obtained from donated fresh human umbilical cords, it is uncertain if the therapy can be made practical for large-scale use.

Concern about residual immune activation and inflammation in people on ART has prompted interest in therapies that might address one of the contributing factors: microbial translocation (the leakage of normally friendly digestive bacteria from the GI tract into the systemic circulation). A trial in Spain is investigating whether a combination of prebiotics and glutamine can improve markers of microbial translocation, inflammation, immune activation, and endothelial dysfunction—both in HIV-positive individuals on ART and those who have yet to start treatment.[111] Researchers in Chicago are planning a similar evaluation of lubiprostone, a drug that is FDA-approved for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation.[112] Additional impetus for these types of studies has come from recent research in the SIV/macaque model, demonstrating that a probiotic/prebiotic combination improved gut CD4 T-cell levels and reduced inflammatory damage to GI tract lymphoid tissue.[113]

On the therapeutic vaccine front, salutary results were published from a study of a dendritic cell-based strategy that has been lurking in the pipeline for several years, DCV2.[114] Immunization was associated with a statistically significant decline in viral load compared with placebo at the 24-week time point after ART interruption (−0.80 vs. −0.19 log; P = .01). While relatively meager compared with ART-mediated viral-load reductions, this rates as one of the largest effects seen with therapeutic vaccination in a controlled study. However, the impact was transient: after 48 weeks of follow-up, the viral-load difference between groups was no longer significant. Despite this limitation, the researchers suggest their findings support the idea that beneficial modulation of HIV-specific immunity is possible.

Scientists from the Statens Serum Institut in Denmark published results from a small phase I trial of their AFO-18 peptide-based vaccine, conducted in Guinea-Bissau with HIV-positive participants naive to ART. The construct was safe but induced new T-cell responses in only 6 of 14 participants.[115]

Although vaccines based on the HIV Tat protein have a checkered history,[116] a new candidate named the Tat Oyi vaccine has entered human testing in France.[117] The researchers developing the vaccine have reported positive results from studies in the SHIV/macaque model.[118]

Conclusion

Despite the many setbacks, the development of an HIV vaccine remains an urgent priority—an effective product would make a vast and vital contribution to ending the epidemic. New opportunities for progress are being opened up by technological advances, such as those that have allowed the detailed dissection of bNAb-producing B-cell responses, and the advent of systems biology as a means of analyzing and understanding the dauntingly large sets of data that can now be generated. A group of respected vaccine researchers, led by Wayne Koff from IAVI, have proposed the creation of a "Human Vaccines Project" to capitalize on the availability of these tools and focus on identifying and generating effective immune responses against the most intractable pathogens, including HIV, TB, and malaria.[119]

Demonstration projects will be crucial to understanding the acceptability and effectiveness of PrEP in different settings and populations, as well as how to integrate the intervention into a comprehensive package of situation-appropriate prevention options. Now that Truvada PrEP is approved in the U.S., there are unresolved questions about how the drug should be incorporated into control groups in biomedical prevention trials (particularly whether PrEP should be optional

or mandatory) that need to be addressed.[120] For both PrEP and microbicides, results from trials of long-acting approaches will be central to determining the future directions of the fields.

The spotlight on HIV cure research continues to intensify, but challenging problems persist. Among them is how exactly a cure should be defined: as has been learned from the cases of both Timothy Brown and the child in Mississippi, formally proving the complete absence of virus—a sterilizing cure—is essentially impossible. The term "functional cure," to indicate an end to the requirement for ongoing treatment despite the possible presence of HIV, is increasingly invoked, but is still somewhat loosely defined since long-term follow-up is needed to prove that an individual with controlled virus is not still burdened by elevated immune activation and inflammation (and facing the risk of adverse clinical consequences that can result over the long haul). Solving the conundrum of an HIV cure continues to require a multidisciplinary scientific effort. For this work to bear fruit, it will need not only significant contributions from laboratory science, but substantial additional investments of financial capital and sustained political will.

The achievements of ART have to some extent cast into shadow the areas where additional therapeutic options are required for HIV-positive people. Clinical efficacy trials for immunologic nonresponders are long overdue, and candidate therapies need to be pushed through the pipeline faster than at the current glacial pace. As the population on ART ages, the possibility arises that approaches similar to those being evaluated in the HIV-negative elderly (such as anti-inflammatories or even basic interventions like diet modification and exercise) could offer benefit, but this research portfolio is still nascent at the current time and demands expansion.

Success in all the spheres outlined in this chapter is critically dependent on funding support, and the looming specters that threaten the pipelines are the global economic downturn and U.S. budget sequestration. Advocacy continues to be crucial to ensure that shortsighted spending cuts are reversed, and scientific breakthroughs occur on the near—not distant—horizon.

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Hepatitis C Drug Development Catapults Onward

By Tracy Swan

Thanks to Jules Levin

The pace of, and progress in, hepatitis C virus (HCV) drug development are astonishing. In April 2011, proof-of-concept for safe, effective, peginterferon-free HCV treatment was announced. Since then, numerous trials have confirmed that hepatitis C virus is curable with direct-acting antivirals (DAAs), regardless of HCV treatment history, cirrhosis, or host genotype.

Over the past 24 months, duration of treatment and assessment of posttreatment outcome have been dramatically abbreviated. Old-school, 48-week regimens with SVR-24 are gone. Now, duration of treatment is usually 12 to 24 weeks, and SVR-12 is the endpoint that is commonly used as a surrogate for cure.[1] Interim data are now available within a few months after trials start. This acceleration in, and rapid evolution of, HCV drug development has left some drugs behind: they are shackled to lumbering development programs, such as the strategy being used in many phase III trials—adding a DAA to 24 or 48 weeks of response-guided therapy with peginterferon (PEG-IFN) and ribavirin (RBV). This approach is likely to have limited clinical relevance, given the rapid development of peginterferon-sparing and peginterferon-free regimens.

The confluence of a robust HCV drug pipeline, shortened regimens, and posttreatment follow-up are extraordinary. The new FDA breakthrough therapy designation may speed things up as well. By the end of 2014, DAAs from four different classes and fixed-dose combinations (FDCs) are likely to be approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), offering the potential for off-label mixing and matching.

Table 1. HCV Treatments in Phase II and Phase III

Agent	Dosing	Sponsor	Status
Nucleoside/nucleotide polymerase inhibitors			
sofosbuvir (GS-7977)	Once-daily	Gilead Sciences	Phase III
mericitabine (RG7128)	Twice-daily	Hoffmann-La Roche/Genentech	Phase III
VX-135	Once-daily	Vertex Pharmaceuticals	Phase II
Non-nucleoside polymerase inhibitors			
ABT-333	Twice-daily	AbbVie	Phase III
BI 207127	Twice-daily	Boehringer Ingelheim	Phase III
GS-9669	Once-daily	Gilead Sciences	Phase II
setrobuvir (ANA-595)	Twice-daily	Hoffmann-La Roche/Genentech	Phase II
VX-222	Twice-daily	Vertex Pharmaceuticals	Phase II
TMC647055	Twice-daily	Janssen	Phase I/II
NS5A inhibitors			
ABT-267	Once-daily	AbbVie	Phase III
daclatasvir (BMS-790052)	Once-daily	Bristol-Myers Squibb	Phase III
ledipasvir (GS-5885)	Once-daily	Gilead Sciences	Phase III
ACH-3102	Once-daily	Achillion Pharmaceuticals	Phase II
GS-5816	Once-daily	Gilead Sciences	Phase II
GSK2336805	Once-daily	GlaxoSmithKline	Phase II
IDX719	Once-daily	Idenix Pharmaceuticals	Phase II
MK-8742	Once-daily	Merck	Phase I/II
Protease inhibitors			
ABT-450/r (ritonavir-boosted)	Once-daily	AbbVie	Phase III
asunaprevir (BMS-650032)	Twice-daily	Bristol-Myers Squibb	Phase III
faldaprevir (BI 201335)	Once-daily	Boehringer Ingelheim	Phase III
simeprevir (TMC435)	Once-daily	Janssen/Tibotec/Medivir	Phase III
danoprevir/r (RG7227) (ritonavir-boosted)	Twice-daily	Hoffmann-La Roche/Genentech	Phase II
GS-9451	Once-daily	Gilead Sciences	Phase II
MK-5172	Once-daily	Merck	Phase II
sovaprevir (ACH-1625)	Once-daily	Achillion Pharmaceuticals	Phase II
MicroRNA-targeting			
miravirsen	Once-weekly	Santaris Pharma A/S	Phase II
Fixed-dose combinations			
ABT-267/ABT-450/r	Once-daily	AbbVie	Phase III
sofosbuvir/ledipasvir	Once-daily	Gilead Sciences	Phase III

To Market, To Market

On March 28, 2013, Janssen Research and Development (R&D) and Medivir AB submitted an application to the U.S. Food and Drug Administration (FDA) for approval of simeprevir, a once-daily protease inhibitor used with peginterferon and ribavirin in HCV genotype 1.

On April 8, 2013, Gilead Sciences submitted an application to the FDA for approval of sofosbuvir, an HCV nucleotide polymerase inhibitor, for use with ribavirin in HCV genotypes 2 and 3, and in combination with peginterferon and ribavirin for HCV genotypes 1,4, 5, and 6.

The Best Combinations

HCV drug development has evolved from single drugs to complete regimens (see tables 2 and 3). But identifying and constructing optimal HCV treatment regimens is not straightforward due to differences in patient populations and individual drug characteristics. An ideal regimen is not always comprised of best-in-class drugs (even if one company owns all of them). Some drugs may not be appropriate for co-formulation or coadministration due to differences in dosing schedule, food and refrigeration requirements, resistance profile, activity against certain HCV genotypes and subtypes, side effects, and contraindications. Drug-drug interactions (DDIs) with other medications commonly used by people with hepatitis C—and possible interactions between drugs in the regimen—must be avoided to reduce the risk of worsened side effects from overdosing, or treatment failure from underdosing. Each drug needs to be good enough to get the job done without adding to side effects, safety concerns, monitoring requirements, or complexity of administering and undergoing HCV treatment.

Table 2. Interferon-Free Regimens in Development for HCV Genotype 1

Regimen	Status/ Sponsor	Population	Duration
ABT-267 + ABT-333 + ABT-450/r + RBV	Phase II AbbVie	Posttransplant (no prior DAA)	24 weeks
ABT-267 + ABT-450/r +/− RBV ABT-267 + ABT-333 + ABT-450/r +/− RBV ABT-333 + ABT-450/r +/− RBV	Phase II AbbVie	Treatment-naive or null responders (no prior DAA); non-cirrhotic	8 to 24 weeks
ABT-267 + ABT-450/r +/− RBV	Phase II AbbVie	Treatment-naive or treatment-experienced (no prior DAA); non-cirrhotic; HCV genotype 1b	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 +/− RBV	Phase III AbbVie	Treatment-naive; non-cirrhotic; HCV genotype 1b	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase III AbbVie	Treatment-experienced (no prior DAA); non-cirrhotic	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase III AbbVie	Treatment-naive; non-cirrhotic	12 weeks
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase III AbbVie	Treatment-naive or treatment-experienced (no prior DAA); compensated cirrhosis	12 or 24 weeks
sovaprevir + ACH-3102	Phase II Achillion	Treatment-naive	12 weeks
asunaprevir + daclatasvir + BMS-791325	Phase II BMS	Treatment-naive or non and null responders (no prior DAA)	12 or 24 weeks
daclatasvir + sofosbuvir +/− RBV	Phase II BMS/ Pharmasset	Treatment-naive; non-cirrhotic	12 or 24 weeks
daclatasvir + simeprevir +/− RBV + PEG-IFN/RBV (if necessary)	Phase II BMS/Janssen	Treatment-naive or null responders (no prior DAA)	12 or 24 weeks
asunaprevir + daclatasvir + PEG-IFN/RBV (if necessary)	Phase III BMS	Treatment-naive, interferon-ineligible or -intolerant; partial and null responders (no prior DAA); HCV genotype 1b	24 weeks
faldaprevir + BI 207127 + RBV	Phase III Boehringer Ingelheim	Treatment-naive; non-cirrhotic; HCV genotype 1b	16 or 24 weeks
sofosbuvir + GS-5816	Phase II Gilead	Treatment-naive; non-cirrhotic	12 weeks
FDC: sofosbuvir/ledipasvir or sofosbuvir + GS-9669	Phase II Gilead	Treatment-naive or null responders (no prior DAA)	12 weeks
FDC: sofosbuvir/ledipasvir +/− RBV	Phase II Gilead	Treatment-naive	8 or 12 weeks

Regimen	Status/ Sponsor	Population	Duration
sofosbuvir + RBV	Phase II Gilead	No prior treatment with HCV nucleoside/tide; portal hypertension with or without hepatic decompensation	48 weeks
		Posttransplant	24 weeks
		Pretransplant (for hepatocellular carcinoma)	24 weeks
ledipasvir + GS-9451 +/– tegobuvir +/– RBV	Phase II Gilead	Treatment-naive; non-cirrhotic	12 or 24 weeks
		Interferon-ineligible or -intolerant; non-cirrhotic	24 weeks
FDC: sofosbuvir/ledipasvir +/– RBV	Phase III Gilead	Treatment-naive or treatment-experienced (including prior use of an HCV protease inhibitor)	12 or 24 weeks
danoprevir/r + mericitabine +/– RBV + PEG-IFN/RBV in the no-RBV arm (if necessary)	Phase II Hoffmann-La Roche	Treatment-naive; no advanced fibrosis or cirrhosis	24 weeks +/– 24-week PEG-IFN/RBV
danoprevir/r + setrobuvir +/– mericitabine + RBV	Phase II Hoffmann-La Roche	Treatment-naive and treatment-experienced (PEG-IFN/RBV only); non-cirrhotic	12 weeks
sofosbuvir + simeprevir +/– RBV	Phase II Janssen/ Gilead	Null responders; mild/moderate liver damage	12 or 24 weeks
		Treatment-naive and null responders; bridging fibrosis/ cirrhosis	
simeprevir + TMC647055/r +/– RBV + PEG-IFN/RBV (if necessary)	Phase II Janssen	Treatment-naive, relapsers, or null responders; HCV genotype 1a and 1b	12 weeks +/– 12-week PEG-IFN/RBV
MK-5172 +/– RBV	Phase II Merck	Treatment-naive; non-cirrhotic; IL28B CC genotype only	12 or 24 weeks
MK-5172 + MK-8742 + RBV	Phase II Merck	Treatment-naive; absence of advanced fibrosis or cirrhosis	12 weeks
miravirsen	Phase II Santaris	Null responders (no prior DAA)	12 weeks
VX-135 + RBV	Phase II Vertex	Treatment-naive; non-cirrhotic	12 weeks
telaprevir + VX-222 + RBV	Phase II Vertex	Treatment-naive	12 or 16 weeks

Source: www.clinicaltrials.gov

Table 3. Interferon-Free Regimens in Development for HCV Genotypes 2, 3, & 4

Regimen	Status/ Sponsor	Population	Duration
ABT-267 + ABT-450/r +/− RBV	Phase II AbbVie	Treatment-naive; HCV genotypes 2 & 3	Not Specified
FDC: ABT-267/ABT-450/r + ABT-333 + RBV	Phase II AbbVie	Treatment-naive and treatment-experienced (no prior DAA)	12 weeks
asunaprevir + daclatasvir + BMS-791325	Phase II BMS	Treatment-naive; HCV genotype 4	12 or 24 weeks
daclatasvir + sofosbuvir +/− RBV	Phase II BMS/ Pharmas-set	Treatment-naive; non-cirrhotic; HCV genotypes 2 & 3	24 weeks
sofosbuvir + GS-5816	Phase II Gilead	Treatment-naive, non-cirrhotic; HCV genotypes 2, 3, 4, 5, & 6	12 weeks
FDC: sofosbuvir/ledipasvir or sofosbuvir + GS-9669	Phase II Gilead	Treatment-naive or null responders (no prior DAA); HCV genotype 4	12 weeks
FDC: sofosbuvir/ledipasvir +/− RBV	Phase II Gilead	Treatment-naive; HCV genotype 3	12 weeks
sofosbuvir + RBV	Phase II Gilead	Interferon-ineligible or -intolerant; HCV genotypes 2 & 3	12 weeks
sofosbuvir + RBV	Phase II Gilead	All genotypes; no prior treatment with HCV nucleoside/tide; portal hypertension with or without hepatic decompensation	48 weeks
		Posttransplant	24 weeks
		Pretransplant (for hepatocellular carcinoma)	24 weeks
sofosbuvir + RBV	Phase II Gilead	Treatment-naive and treatment-experienced Egyptian adults; HCV genotype 4	12 or 24 weeks
sofosbuvir + RBV	Phase III Gilead	Prior sofosbuvir study participants; HCV genotypes 2 & 3	12 weeks
		Treatment-naive; interferon-intolerant, -ineligible, or -unwilling	12 weeks
		Treatment-experienced (no prior DAA); HCV genotypes 2 & 3	12 or 16 weeks

Source: www.clinicaltrials.gov

Financial considerations play a significant role in HCV drug development. Competition for market share is fierce, since experts estimate that the HCV market in the "big 7" (Japan, the United Kingdom, Germany, France, Italy, Spain, and the United States) will reach US$14 billion to US$20 billion by 2018. Most pharmaceutical companies are developing in-house combinations to avoid sharing the jackpot. As a result, only three trials have combined DAAs from different sponsors. Sofosbuvir (Gilead's nucleotide polymerase inhibitor) has been paired with daclatasvir, an NS5A inhibitor from Bristol-Myers Squibb (BMS), and simeprevir (an HCV protease inhibitor from Janssen).

Sofosbuvir and daclatasvir have been tested in a phase IIa trial, with or without RBV—and results were spectacular. Cure rates ranged from 88 percent to 100 percent after 12 or 24 weeks of treatment, regardless of treatment history, ribavirin use, HCV genotype or subtype, IL28B genotype, or treatment duration. The study included 170 non-cirrhotic, treatment-naive participants with HCV genotypes 1, 2, and 3, and 41 treatment-experienced (with an HCV protease inhibitor-based regimen) participants with HCV genotype 1. The regimen was safe and tolerable.[2,3] Unfortunately, Gilead is unwilling to continue this clinical collaboration because they are developing their own NS5A inhibitor, ledipasvir, in a fixed-dose combination (FDC) with sofosbuvir (see Twinkle, Twinkle, Little (Lone) Star on page 177).

COSMOS, a 167-person, phase IIa trial, is pairing simeprevir and sofosbuvir for 12 or 24 weeks, with or without ribavirin. COSMOS includes two cohorts of null responders with HCV genotype 1 (people with very mild to moderate liver scarring versus people with extensive liver scarring and cirrhosis). Although most of cohort 1 had poor prognostic factors (IL28B non-CC genotype and HCV genotype 1a), early results were stellar: at posttreatment week 8 (referred to as SVR-8), 96 percent (or 26 of 27 people) in the sofosbuvir/simeprevir/RBV arm, and 92 percent (or 13 of 14 people) in the sofosbuvir/simeprevir arm maintained undetectable HCV RNA. There were no discontinuations, but two relapses occurred (one in each arm). So far, 24 people have been followed until posttreatment week 12 (SVR-12), and 100 percent remain undetectable. The regimen was safe and tolerable; the second cohort (87 people with serious liver damage) was fully enrolled as of March of 2013.[4] It is likely that Gilead's partnership with Janssen will be short-lived, regardless of the final results from COSMOS.

Simeprevir and daclatasvir are being tested, with or without RBV, for 12 or 24 weeks (plus an optional extra 24 weeks of peginterferon/ribavirin if needed), in an ongoing phase II trial of 180 treatment-naive and prior null responders with HCV genotype 1, including people with cirrhosis.

Off-label use of drugs on similar regulatory timelines (such as simeprevir and sofosbuvir) may be possible (although the cost may be prohibitive). Without larger phase III trials, securing reimbursement for mix-and-match regimens may be a challenge, although activists—and drug makers—are pressing for access.

Cross-company Trials

Some companies have chosen a collaborative approach to stay in the game.

- Boehringer Ingelheim and Presidio will collaborate on a phase IIa trial focusing on HCV genotype 1a, combining faldaprevir (an HCV protease inhibitor), BI 207127 (a non-nucleoside polymerase inhibitor), and PPI-668 (an NS5A inhibitor), with or without RBV.[5]
- Bristol-Myers Squibb and Merck will collaborate on a phase II trial pairing daclatasvir (an NS5A inhibitor) with MK-5172 (an HCV protease inhibitor) in genotype 1.[6]
- Janssen and Idenix will collaborate on a phase IIa trial of simeprevir and IDX719 (an NS5A inhibitor), with or without RBV.[7]
- Janssen and Vertex will collaborate on a phase II trial pairing simeprevir with VX-135 (a nucleotide polymerase inhibitor).[8]
- Vertex and BMS will collaborate on a pair of phase II trials pairing VX-135 with daclatasvir (an NS5A inhibitor), initially in treatment-naive people with HCV genotype 1, then in treatment-naive people with HCV genotypes 1, 2, and 3. Vertex plans to conduct "co-formulation activities" as part of the agreement.[9]
- Vertex and GlaxoSmithKline will collaborate on a phase II trial of VX-135 with GSK2336805 (an NS5A inhibitor), with or without RBV.[10]

Next in Line: Simeprevir, Faldaprevir, and Sofosbuvir

Simeprevir, a once-daily HCV protease inhibitor, is being developed in peginterferon-based and peginterferon-free regimens. Although simeprevir's approval hinges on trials with peginterferon, it is likely to be used in different ways as peginterferon phases out. Simeprevir is currently in trials with TMC647055, a ritonavir-boosted non-nucleoside polymerase inhibitor, with or without ribavirin, sofosbuvir (with or without ribavirin), and daclatasvir (with or without ribavirin, or PEG-IFN and ribavirin "rescue"). Additional studies are planned with VX-135 (a nucleotide polymerase inhibitor) and IDX719 (an NS5A inhibitor) plus TMC 647055.

QUEST-2, a trial of 391 treatment-naive people with HCV genotype 1, compared response-guided therapy (12 weeks of once-daily simeprevir plus PEG-IFN alfa-2a or alfa-2b and RBV, followed by 12 or 36 weeks of PEG-IFN and RBV to PEG-IFN and RBV alone). More than 90 percent (235 of 257) were eligible for shortened treatment, and 86 percent of them (202 of 235) were cured. Of the 8 percent who were not eligible for shortened treatment, 31 percent (7 of 22) were cured, leading to an overall cure rate of 81 percent (vs. 50% for PEG-IFN and RBV). With simeprevir-based treatment, cure rates were higher in people with the IL28B CC genotype (96%) than CT (80%) or TT (57%), although SVR did not differ by HCV subtype. People with little or no liver damage were more likely to be cured (84%) than people with widespread fibrosis and cirrhosis, although cure rates for this group were high (66% and 64%). Most treatment failures and relapses were associated with emergent drug resistance; primarily the R155K mutation, either alone or with additional mutations in position 80 or 168, in HCV genotype 1a, whereas in HCV genotype 1b, treatment failure was associated with either the D168V mutation or Q80R plus D168E. Of note, SVR rates were higher among people treated with peginterferon alfa-2a, whether they received simeprevir or placebo.

Simeprevir did not worsen side effects during the first 12 weeks of treatment, with the exception of (mostly) mild rash and photosensitivity. Simeprevir was associated with transient increases in bilirubin. Otherwise, there were no significant differences in mild, moderate, or serious adverse events.[11]

Results from QUEST-1, a trial in 394 treatment-naive people with HCV genotype 1, were remarkably similar to those reported from QUEST-2. The overall SVR rate was 80 percent (simeprevir arm) versus 50 percent for peginterferon, ribavirin, and placebo. Of the 85 percent in the simeprevir arm who were eligible for shorter treatment, 91 percent were cured. As in QUEST-2, baseline and emergent drug resistance were associated with unsuccessful treatment; this occurred more in HCV genotype 1a than HCV genotype 1b.The most common adverse events in both treatment arms were fatigue, pruritus (itching), and headache.[12]

Simeprevir is being studied in HCV genotype 4, null and partial responders, and HIV/HCV coinfection (treatment-naive and treatment-experienced). To date, 250 people with compensated cirrhosis (Child-Pugh class A only) have been in trials of simeprevir; dose adjustments may be needed in people with Child-Pugh class B or C.[13]

Faldaprevir, a once-daily HCV protease inhibitor, is nearing the finish line. STARTVerso 1, a phase III trial in 652 treatment-naive people with HCV genotype 1, compared different doses (120 mg vs. 240 mg) of faldaprevir-based response-guided therapy to PEG-IFN/RBV and ribavirin plus placebo. The trial was conducted in Europe and Japan (where body mass index is lower, and the IL28B CC genotype is more common—factors that increase likelihood of cure). Early responders were eligible for shorter treatment; 88 percent met the criteria and most (86–89%) were cured, regardless of faldaprevir dose. Of note, cure rates were higher in people with undetectable HCV RNA at week 4 versus those with a viral load of ≤25 copies IU/mL. With the lower dose of faldaprevir, elevated bilirubin, rash, and gastrointestinal side effects were less frequent.[14]

Faldaprevir is also being studied in treatment-experienced people, and in HIV/HCV coinfection. An all-oral regimen (faldaprevir, BI 207127, and ribavirin) is being developed in HCV genotype 1b, and a trial combining faldaprevir, BI 207127, and PPI-668, with or without ribavirin, is planned.

Without a PEG to Stand on: The Sofosbuvir Saga Goes on

Sofosbuvir offered the promise of highly effective, peginterferon-free, oral, short-course treatment for everyone. Small trials reported 100 percent cure rates in genotypes 2 and 3, and 84 percent in genotype 1 after 12 weeks of sofosbuvir and ribavirin. But rates plummeted when this regimen moved into groups with difficult-to-treat characteristics. Only 1 of 9 null responders with HCV genotype 1 was cured by 12 weeks of sofosbuvir and ribavirin.[15] In the SPARE trial, cure rates ranged from 68 percent to 48 percent after 24 weeks of sofosbuvir and weight-based or low-dose ribavirin (600 mg). Most SPARE participants were African American, and had non-CC genotypes, HCV genotype 1a, and high hepatitis C viral load; almost 30 percent had widespread liver scarring.[16]

Biting the (Magic) Bullet

Until peginterferon-free regimens are available for HCV genotype 1, the best option for treatment-naive people may be 12 weeks of sofosbuvir plus PEG-IFN and RBV: this regimen cured 90 percent (48 of 54) in the phase II ATOMIC trial, and 89 percent (260 of 292) in the phase III NEUTRINO trial (a subset of NEUTRINO participants had cirrhosis; 80 percent [44 of 55] were cured).[17,18]

Twinkle, Twinkle, Little (Lone) Star

Sofosbuvir-based, peginterferon-free treatment is on the way for HCV genotype 1. Swapping out peginterferon for a DAA seems to do the trick: in ELECTRON, 100 percent of 25 treatment-naive and 10 null-responder participants were cured by 12 weeks of sofosbuvir, ledipasvir, and ribavirin.[19] Sofosbuvir and ledipasvir have been co-formulated into a fixed-dose combination (FDC).

Ribavirin may be next to go, based on interim results from LONESTAR, a 100-person, phase II trial (60 treatment-naive; 40 treatment-experienced with an HCV protease inhibitor–based regimen). LONESTAR compared

8 weeks of the FDC, with and without ribavirin, to 12 weeks of the FDC, with or without ribavirin. In the treatment-naive cohort, 100 percent of the 19 people treated for 12 weeks maintained undetectable HCV RNA 4 weeks after finishing treatment (SVR-4); 40 of 41 participants in the 8-week arm maintained undetectable HCV RNA 8 weeks after treatment completion (SVR-8). In the treatment-experienced cohort, 95 percent achieved SVR-4.[20]

The FDC is currently in phase III trials. It is being studied with and without RBV in treatment-naive people with genotypes 1, 3, and 4 and treatment-experienced people with HCV genotype 1 for durations ranging from 8 to 24 weeks.

AbbVie: All Hands on Deck

AbbVie's powerhouse regimen (ABT-450/r, a boosted HCV protease inhibitor co-formulated with ABT-267, an NS5A inhibitor, plus ABT-333 [a non-nucleoside polymerase inhibitor] and ribavirin) has yielded almost universal cure rates in clinical trials among treatment-naive and null-responder participants, regardless of HCV subtype or IL28B genotype; over 90 percent were cured after 12 weeks of treatment.[21] The regimen is now being studied in people with compensated cirrhosis; a trial in HIV/HCV coinfection is expected in mid-2013.

Bristol-Myers Squibb: All In!

Bristol-Myers Squibb (BMS) is developing a three-drug, ribavirin-free, in-house combination for HCV genotype 1: daclatasvir plus asunaprevir (an HCV protease inhibitor) and BMS 791325 (a non-nucleoside polymerase inhibitor). So far, SVR rates have been close to 100 percent, and the regimen appears safe and tolerable. A phase II trial in both treatment-naive and null-responder participants with HCV genotypes 1 or 4 is planned.[22]

Note: Recently reported SVR rates from interferon-free and interferon-sparing trials for HCV genotypes 1, 4, 5, and 6 are available online at: www.pipelinereport.org/2013/hcv/svr-update.

(Genotype) 3 is the new 1

In the peginterferon era, HCV genotypes 2 and 3 were considered "easy to treat" in contrast to HCV genotypes 1 and 4: duration of treatment was shorter (24 vs. 48 weeks) and cure rates higher. Although genotypes 2 and 3 have historically been lumped together, there are differences: cure rates are higher in genotype 2 than genotype 3 (80–90% vs. 60–70%, respectively); hepatic steatosis (a condition that accelerates liver damage) is associated with genotype 3 infection; liver disease progresses more rapidly in genotype 3 than in genotype 2.[23,24]

But when it comes to DAA-based treatment, genotype 3 is an altogether different animal than genotype 2. Results from small DAA trials in genotype 3 created expectations that eradication would be a slam-dunk: cure rates ranged from 88 percent to 100 percent.[2,15] But larger trials of DAA-based regimens in treatment-naive and treatment-experienced participants with HCV genotypes 2 and 3 have consistently reported a disparity in cure rates, favoring genotype 2 (see table 4).

Finding effective regimens for HCV genotype 3 has proven to be a challenge. Options are limited: HCV protease inhibitors (including faldaprevir, simeprevir, and telaprevir) are inactive or have weakened activity (asunaprevir, danoprevir) against genotype 3; only three (ABT-450/r, boceprevir, and MK-5172) are being studied in HCV genotype 3.[25,26,27,28,29] Resistance to NS5A inhibitors has been detected in treatment-naive people with HCV genotype 3, and some are known to have weaker activity against genotype 3.[30,31] In fact, adding daclatasvir to PEG-IFN and RBV produced disappointing results.[32] Non-nucleoside polymerase inhibitors are inactive against genotype 3 (with the possible exception of a lone candidate in early development), leaving only nucleoside and nucleotide polymerase inhibitors (sofosbuvir and mericitabine are active against genotype 3).[33,34]

It is clear that DAA-based treatment for genotype 3—especially in people with cirrhosis—needs to be optimized: extending duration, and adding peginterferon and ribavirin or another DAA with activity against genotype 3 may do the trick.

Table 4. SVR in HCV Genotypes 2 and 3

Study/Drugs	Population/ Size	Genotype	Treatment Arms	SVR
AI444-040 daclatasvir + sofosbuvir +/− RBV Phase II BMS/Gilead	Treatment-naive, non-cirrhotic (N = 44)	Genotypes 2 & 3	24-week, 2-drug (7-day sofosbuvir lead-in, no RBV)	SVR-24: **88%**
			24-week, 2-drug (no RBV)	SVR-24: **100%**
			24-week, 3-drug	SVR-24: **93%**
COMMAND GT 2/3 daclatasvir + PEG-IFN/RBV vs. placebo + PEG-IFN/RBV Phase II BMS	Treatment-naive, 20% cirrhotic (G3 only) (N = 151)	Genotype 2	12-week	SVR-24: **88%**
			16-week	SVR-24: **83%**
			placebo	SVR-24:: **63%**
		Genotype 3	12-week	SVR-24: **69%**
			16-week	SVR-24: **70%**
			placebo	SVR-24: **59%**
ELECTRON sofosbuvir + RBV + 0, 4, 8, or 12 weeks of PEG-IFN vs. sofosbuvir monotherapy Phase II Gilead	Treatment-naive, non-cirrhotic (N = 60)	Genotypes 2 & 3	8-week, 3-drug	SVR-24: **100%**
			12-week, with 4-week PEG-IFN	SVR-24: **100%**
			12-week, with 8-week PEG-IFN	SVR-24: **100%**
			12-week, 3-drug	SVR-24: **100%**
			12-week, no PEG-IFN	SVR-24: **100%**
			12-week, sofosbuvir only	SVR-24: **60%**
FISSION sofosbuvir + RBV vs. PEG-IFN/RBV Phase III Gilead	Treatment-naive, 20% cirrhotic (N = 499)	Genotype 2	12-week sofosbuvir + RBV	SVR-12: **97%** Cirrhotic: **91%** Non-cirrhotic: **98%**
			24-week PEG-IFN/RBV	SVR-12: **78%** Cirrhotic: **62%** Non-cirrhotic: **82%**
		Genotype 3	12-week sofosbuvir + RBV	SVR-12: **56%** Cirrhotic: **34%** **Non-cirrhotic: 61%**
			24-week PEG-IFN/RBV	SVR-12: **63%** Cirrhotic: **30%** Non-cirrhotic: **71%**

Study/Drugs	Population/ Size	Genotype	Treatment Arms	SVR
FUSION sofosbuvir + RBV Phase III Gilead	Treatment-experienced, 34% cirrhotic (N = 201)	Genotype 2	12-week	SVR-12: **86%** Cirrhotic: **60%** Non-cirrhotic: **96%**
			16-week	SVR-12: **94%** Cirrhotic: **78%** Non-cirrhotic: **100%**
		Genotype 3	12-week	SVR-12: **30%** Cirrhotic: **19%** Non-cirrhotic: **37%**
			16-week	SVR-12: **62%** Cirrhotic: **61%** Non-cirrhotic: **63%**
POSITRON sofosbuvir + RBV Phase III Gilead	Treatment naive, interferon-ineligible, -intolerant, and -unwilling; 15% cirrhotic (N = 207)	Genotype 2	12-week	SVR-12: **93%** Cirrhotic: **94%** Non-cirrhotic: **92%**
		Genotype 3	12-week	SVR-12: **61%** Cirrhotic: **21%** Non-cirrhotic: **68%**
PROTON sofosbuvir + PEG-IFN/RBV Phase II Gilead	Treatment-naive, non-cirrhotic (N = 25)	Genotypes 2 and 3	12-week	SVR-12: **92%**

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Cirrhosis: From Frontier to Proving Ground

Demonstrating that DAAs were effective in null responders was the first proving ground for peginterferon-sparing and peginterferon-free regimens. But cirrhosis is clearly the true test: HCV treatment that is safe and effective for people with cirrhosis will work at least as well for everyone else.

DAAs can—and ought to—be studied in people with compensated cirrhosis once adequate pharmacokinetic data in people with renal and/or hepatic impairment and results from critical DDI studies are available, and evidence of safety and efficacy has been established. A phase II trial, SOUND-C, is an example of this proactive approach since it included a subset of 33 people with compensated cirrhosis and reported cure rates in this group as high as 67 percent.[35]

Prioritizing people with more serious liver damage for HCV treatment is both ethical and sensible, given the anticipated king's ransom charged for DAAs and the limited resources to pay for them. This strategy will avert near-term morbidity, transplantation, and mortality from liver disease. Yet patients with advanced liver disease have been underrepresented in, or excluded from, many clinical trials. Drugs are being brought to market with limited data in people with cirrhosis, who are most likely to be treated first. Serious side effects—and fatalities—have been reported from trials of boceprevir- and telaprevir-based regimens in people with compensated cirrhosis.[36] Even without peginterferon, safety issues are paramount for people with advanced liver disease.

Trials in people with compensated cirrhosis provide data to inform pre-approval access for the people who need treatment most. If no safety signals arise, early access programs open to people who are ineligible for clinical trials because they are too sick. The benefits of early access spread beyond people who receive potentially lifesaving treatment. Critical safety data are generated through early access programs to guide widespread use in people with urgent need once drugs are approved.

HIV/HCV Coinfection

HCV coinfection increases AIDS-related, liver-related, and all-cause mortality among people with HIV, despite use of antiretroviral therapy (ART).[37,38] The incidence of HCV-related complications has been rising sharply among HIV/HCV-coinfected people. Since 1996, the incidence of cirrhosis among HIV/HCV-coinfected patients in care at the Veteran's Administration (VA) has risen from 3.5% to 13.2%, and hepatocellular carcinoma from 0.07% to 1.62%— a shocking 23-fold increase.[39]

Clearly, people who are HIV/HCV-coinfected ought to be a priority population for DAA trials, since they are at risk for more rapid HCV progression. Sponsors stand to benefit from supporting these trials, since systems that deliver ART to HIV-positive people could be expanded to include DAAs for both HCV-coinfected and HCV-monoinfected people. But development of peginterferon-free trials has been lagging: as of May 2013, only one peginterferon-free trial (sofosbuvir and ribavirin) was open to HIV/HCV-coinfected people; ongoing trials with simeprevir, faldaprevir, and daclatasvir are peginterferon-based.

But there is welcome news: initial reports that HIV does not appear to be a prognostic factor when a DAA is added to peginterferon and ribavirin have been supported by data from trials of telaprevir-based treatment, as well as interim reports from STARTVerso 4 (faldaprevir-based treatment) and the TMC435-C212 (simeprevir-based treatment) study.[40,41,42]

Faldaprevir plus PEG-IFN/RBV

STARTVerso 4 is an ongoing, 308-person, phase III trial of faldaprevir plus peginterferon and ribavirin in HIV/HCV-coinfected people with HCV genotype 1 who were treatment-naive or relapsers; 17 percent were cirrhotic. The mean CD4 cell count was 545 cells/uL. Participants were randomized (if not on HIV treatment, or raltegravir- or maraviroc-based regimen) to either 120 mg or 240 mg of faldaprevir, or assigned to 120 mg of faldaprevir (for darunavir/r- or atazanavir/r-based-regimens) or 240 mg of faldaprevir (for efavirenz-based regimens) based on drug-drug-interactions. No HIV virological breakthrough occurred.

STARTVerso 4 participants were assigned to response-guided-therapy with either 120 or 240 mg of faldaprevir. In the high-dose group, participants were treated for 24 weeks (with triple therapy, or 12 weeks of triple therapy followed by 12 weeks of PEG-IFN/RBV). Early responders were randomized to stop treatment or continue with 24 weeks of PEG-IFN/RBV; participants without a protocol-defined early response (HCV RNA <25 IU/mL at week 4, and undetectable HCV RNA at week 8) were given 24 weeks of PEG-IFN/RBV.

In the low-dose group, participants were treated with 24 weeks of triple therapy; early responders were randomized to stop treatment or continue with 24 weeks of PEG-IFN/RBV, while those without an early response continued PEG-IFN for 24 additional weeks. Early response rates were high: 77 percent of treatment-naive participants and 88 percent of relapsers met criteria for shortened treatment; by week 12, HCV RNA was undetectable in 82 percent of treatment-naive participants and 91 percent of relapsers.

The most common side effects were nausea, fatigue, diarrhea, and headache. Serious adverse events (reported in <1% of participants) were fever, abdominal pain, diarrhea, rash, diarrhea, vomiting, dehydration, and gastroenteritis; anemia and neutropenia were also reported. Three deaths occurred: two were not considered related to study drug, and the third, due to drug reaction with eosinophilia and systematic systems (DRESS), is under review.[40]

Simeprevir plus PEG-IFN and RBV

TMC435-C212 is an ongoing HCV treatment trial in 106 treatment-naive or treatment-experienced people coinfected with HIV and HCV genotype 1. Prior relapsers and treatment-naive participants were assigned to response-guided therapy with 12 weeks of simeprevir plus PEG-IFN/RBV, followed by 12 or 36 weeks of PEG-IFN and RBV; partial and null responders and people with cirrhosis were assigned to 12 weeks of triple therapy, followed by 36 weeks of PEG-IFN and RBV. Of the 106 participants, 93 were receiving ART (with raltegravir-, rilpivirine-, maraviroc-, or enfuvirtide-based regimens. The median CD4 cell count was 629 cells/uL (561 in the ART arm vs. 677 in the no-ART arm). No HIV virological breakthrough occurred.

Interim results are promising: of the 88 percent (52 of 59) eligible for shortened treatment, 34 have reached posttreatment week 4 (SVR-4); 85 percent maintained undetectable HCV RNA. SVR-4 rates did not differ significantly by treatment history (84% of treatment-naive; 90% of relapsers). A subset reached posttreatment week 12; in this group, SVR-12 was 75 percent (9 of 12). Relapse has been reported only in people with HCV genotype 1a. At the time of analysis, 64 percent of null responders remained on treatment.

Safety was described as similar to that reported in HCV monoinfection, with four people discontinuing for adverse events. Common side effects were fatigue, headache, nausea, pruritus, and rash. Common laboratory abnormalities were anemia, neutropenia, elevated ALT/AST, and increased bilirubin; almost all were mild to moderate.[43]

A Novel Approach

MicroRNAs are present in human cells; they regulate gene expression. MicroRNA 122 (miR-122) is found in liver cells; it binds to hepatitis C virus, stabilizing it and stimulating viral replication.[44]

A drug targeting miR-122, called miravirsen, is being studied in HCV genotype 1 (although it is pangenotypic). Study participants were given five weekly injections of miravirsen (at doses of 3 mg, 5 mg, or 7 mg per kilogram) over 29 days, and followed for 18 weeks. Miravirsen had a dose-dependent effect: one participant in the 5 mg dosing group and four people in the 7 mg dosing group achieved undetectable HCV RNA during the study; and one person in the high-dose group maintained undetectable HCV RNA throughout 18 weeks of follow-up. No posttreatment viral resistance was observed.

Adverse events (headache, fatigue, nausea, rash, diarrhea, myalgia, flu-like symptoms, nasopharyngitis, pruritus, and injection-site reactions) were mild to moderate (with the exception of a single case of neutropenia). There were no discontinuations.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (GGT) decreased during treatment, while serum creatinine and alkaline phosphatase levels were slightly elevated.

Miravirsen has potential as a supplemental therapy: it could be administered once monthly, has a high resistance barrier, is pangenotypic, and is not expected to have significant drug-drug interactions with DAAs or other commonly used medications.[45,46] A phase II trial is evaluating 12 weeks of miravirsen in null responders with HCV genotype 1.

From Excess to Access

The buck stops—and shrinks—when it comes to HCV treatment. The extortionate pricing of first-generation HCV protease inhibitors—added to the already high cost of peginterferon and ribavirin—limits treatment access even in wealthy countries. Oversight of complex treatment algorithms, frequent monitoring requirements during

treatment, and management of nasty side effects add to the expense. A recent analysis from Mount Sinai Medical Center in New York City found that the median cost for telaprevir-based triple therapy was $98,348.[47] Although the future standard of care will be safer and more effective, require less monitoring, and be easier to administer, any savings will be eclipsed by the high cost of new drugs.

The swift and astounding progress against hepatitis C virus will have a negligible impact on public health if medicines are too costly. In low- and middle-income countries (LMICs) millions of people with hepatitis C will go without treatment if governments cannot afford drugs, or the health care systems that will administer them. For more information about movements to create and broaden access to HCV treatment in LMIC, (see Karyn Kaplan's *Low- and Middle-Income Countries Defuse Hepatitis C, the "Viral Time Bomb"* on page 191).

Where Should All the Research Go?

In the absence of public-private research networks, the race to dominate the HCV market has consequences for people with hepatitis C and their medical providers. People with the most urgent need for HCV treatment are almost always excluded from clinical trials. Enrolling healthier people in early-phase trials is sensible, but delaying trials in people with advanced liver disease until after drugs have already been approved is cruel and unacceptable.

- **Regulators, activists, patient groups, and legislators need to revisit early access programs, and create a framework that allows access to potentially lifesaving treatment for patients who are too ill or otherwise ineligible for clinical trials, while safety and efficacy data are collected.**

Activists deserve complete information about the HCV drugs they are fighting for. But the clinical definition of "hard to treat" relies on certain host and viral factors; it does not include poverty, incarceration, addiction, and mental illness—and these are rife among people with HCV. When these conditions are ignored, history demonstrates that epidemics flourish. Public-private research partnerships can integrate implementation science into drug development—by exploring and optimizing models to deliver HCV care and treatment to current and former injecting drug users and people with psychiatric disorders—without slowing down approval.

- **Governments, pharmaceutical companies, and foundations should support public-private research networks, and civil-society representatives should participate in development and oversight of these networks.**

Promising cross-company development programs have been nipped in the bud because sponsors are unwilling to split profits. This has prevented further exploration of highly effective regimens that people may want to use, despite the lack of information from larger trials.

- **Regulatory agencies need to identify metrics that will facilitate reimbursement for off-label use, keeping in mind both class-specific and within-class-specific differences in drug potency, resistance barrier, safety, and side-effect profile.**

People who are coinfected with HIV and HCV ought to be a priority population, since HIV is a known accelerant of HCV-associated liver disease, and some infrastructure for treatment delivery already exists. But trials in HIV/HCV coinfection are lagging: as of May 2013, there was only one peginterferon-free trial in coinfected people, amid dozens of trials in HCV monoinfection.

- **Sponsors should be obligated to conduct relevant DDI studies prior to phase III, to facilitate pre-approval trials in HIV/ HCV coinfection.**

The drugs are almost here. All we need is the political will to support research, develop or expand treatment infrastructure, and provide widespread access to HCV treatment.

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Low- and Middle-Income Countries Defuse Hepatitis C, the "Viral Time Bomb"

By Karyn Kaplan

As rich countries prepare for a hepatitis C virus (HCV) treatment revolution, people in low- and middle-income countries (LMICs) remain without access to information, prevention tools, diagnostics, care, and treatment. A growing movement of global activists is responding to this crisis. They are demanding access to affordable, quality drugs and diagnostics as well as high-level political commitment to testing and treatment scale-up in their countries. They will continue to fight until they defuse what the World Health Organization (WHO) has called the "viral time bomb."

An estimated 185 million people (three percent of the world's population) are infected with hepatitis C virus (HCV). Globally, the majority of new HCV infections are occurring among the estimated 15.9 million people who inject drugs (PWID); at least 10 million of them have HCV. Yet less than 10 percent of the world's PWID have access to harm reduction services such as needle and syringe programs and opioid substitution therapy (OST), promoting further HCV transmission.[1,2]

Untreated hepatitis C can lead to cirrhosis, liver failure, and liver cancer; each year, more than 350,000 people die from these complications.[3] Despite widespread prevalence and increasing morbidity and mortality, the global response to the HCV epidemic has been sluggish.

HCV finally gained recognition as a global public health priority in 2010, when the World Health Assembly (WHA; the decision-making body of the WHO) called for comprehensive programs that "enhance access to affordable treatment in developing countries."[4]

Since then, excitement around new, more effective HCV treatment—and outrage that little has been done to address the epidemic—has motivated a diverse coalition of stakeholders: people living with and at risk for HCV and HIV; people who use illicit drugs; researchers; health care and harm reduction providers; nongovernmental organizations (NGOs); and others, including progressive government leaders. A global movement for HCV treatment access has begun.

From Ukraine to India, and from Georgia to Egypt, activists from LMICs are adapting relevant lessons from the HIV treatment-access movement about how to reduce the cost of drugs and diagnostics, integrate services, and simplify the package of care. They are demanding that their governments take action to address local epidemics and include civil-society representatives meaningfully in the response.

We've Got to Get It Together, Because the Revolution Is Here

In LMICs, people living with hepatitis C and their allies are excited about the simpler, better treatments on the horizon, but they wonder what this treatment "revolution" will mean for them. Significant barriers, ranging from widespread lack of awareness about HCV to the high cost of diagnostics and medication, must be overcome in order to achieve widespread access to these safer, more effective treatments as well as to the current standard of care.

Strategies for addressing the HCV epidemic and increasing access to treatment include:

- the repeal of repressive laws that criminalize people who use drugs;
- massively increasing access to evidence-based harm reduction services including clean injecting equipment and OST;
- ensuring access to safe, effective, and affordable HCV treatment with or without pegylated interferon (peginterferon or PEG-IFN); and
- identifying and prioritizing people with urgent need for treatment.

Some Governments Have Begun the Revolution

EGYPT

One government stands out for its successful commitment to stopping HCV: Egypt. With six million people (10 percent of its population) who have chronic HCV, Egypt is home to the world's largest HCV epidemic.[5] Unsafe injections inadvertently given during a mass anti-schistosomiasis campaign spread HCV across the country. Schistosomiasis (caused by parasitic diseases) was the leading cause of liver disease before being eclipsed by HCV.[6] Unfortunately, HCV coinfection accelerates liver disease in people with this illness.[7]

In response to the HCV epidemic, the Egyptian government developed the world's largest nationally subsidized viral hepatitis–control program. Egypt's Ministry of Health and Population established a National Committee for the Control of Viral Hepatitis, which in turn developed a National Control Strategy for Viral Hepatitis. Egypt's initiatives include:

- conducting a national prevalence survey and ongoing surveillance;
- launching awareness campaigns and prevention programs;
- establishing clinical research programs, including programs to evaluate their work;
- developing national HCV treatment guidelines; and
- opening dozens of treatment centers to augment existing health care sites.

Egypt continues to enhance and develop its national program, which may serve as a model for other LMICs.

More than 220,000 people have already been treated for hepatitis C under Egypt's program. The government continues to negotiate lower drug prices to facilitate provision of treatment to everyone who needs it.

Lowering the cost of PEG-IFN has made it possible for Egypt to tackle its epidemic. A locally produced product (Minapharm's Reiferon Retard), a competing version of peginterferon, provided leverage for negotiations with Roche and Merck, the makers of Pegasys (PEG-IFN alfa-2a) and Peg-Intron (PEG-IFN alfa-2b), respectively. Over the past six years, the Egyptian government has obtained a sixfold price reduction, from US$12,000 to US$2,000 per 48-week treatment course.[8]

THAILAND

In Thailand, 2.2 percent of the population (1.4 million people) has HCV. Prevalence among PWID in Thailand is estimated to be over 90 percent.[9]

Over the past several years, civil-society groups have pressured the government to address Thailand's unchecked HCV epidemic, demanding that PEG-IFN be added to the National Essential Medicines List (EML). Through community organizing and education, policymaker lobbying meetings, and direct actions, Thai AIDS Treatment Action Group (TTAG), the Thai Network of People Living with HIV/AIDS (TNP+), and others, secured a government commitment to expand HCV treatment access through the national healthcare scheme. In August 2012, Thailand put PEG-IFN on its national EML.

The government, propelled by grassroots activists, successfully negotiated a significant (fourfold) price reduction from Roche and Merck: US$4,800 per treatment course. Because of powerful civil-society advocacy and government negotiations with pharmaceutical companies, Thailand was able to afford including HCV treatment in its universal health care program. But activists realize the price of

drugs and diagnostics must come down further to make widespread access possible—and they continue to pressure their government.

INDIA

At least 1.5 percent of India's population (nearly 2 million of more than 1 billion people) has hepatitis C, including most people who inject drugs.[10] India, whose generic drug industry is known as the "pharmacy to the developing world," recently issued two court rulings that defied efforts by two multinational drug companies to make claims on patents for old drugs they alleged to be new, including PEG-IFN. These rulings pave the way for people in India (and other places where these drugs are not patented) to gain access to more affordable medications by facilitating production of biosimilars.[11]

Biosimilars

Biologic drugs—such as peginterferon, insulin, and monoclonal antibodies—are made in living cells. In contrast, generic medications are made with the same active ingredients used in the innovator (branded) product. Generic drugs must demonstrate therapeutic equivalence to the original: they must be "the same chemically as their innovator counterparts and…act the same way in the body."[12] Generic biologics, which must demonstrate similarity (but cannot demonstrate equivalence) and show that they work as well as the branded product, are called "biosimilars." In addition, there are "alternative" types of PEG-IFN, which, unlike biosimilars, do not need to demonstrate similarity. Neither is identical to the innovator product; therefore, the regulatory pathway for determining the quality, safety, and efficacy of biosimilars and alternatives, which cannot be compared with original products, is less clear.

In 2012, Sankalp Rehabilitation Trust, a local NGO working with PWID, brought a court challenge to Roche's patent on peginterferon alfa-2a. The Intellectual Property Appellate Board (IPAB) ruled in favor of Sankalp as a "person interested," and therefore able to legitimately bring the case to court. The IPAB then overturned Roche's patent—Sankalp had successfully challenged its validity. The IPAB found that Roche's product was not innovative, and was therefore unworthy of a patent. It ruled that Sankalp's effort could help "break the monopoly" on PEG-IFN and

"bring the drug within reach of the community for whom it works, not only by reduction in cost, but also because of increase in supply."[13]

An activist campaign launched by Lawyers Collective and grassroots networks including the Indian Network of People Living with HIV/AIDS (INP+) and the Delhi Network of Positive People (DNP+) made these court cases possible. In April 2013, India's Supreme Court struck down an appeal by pharmaceutical giant Novartis. The court ruled that its anticancer drug, a beta-crystalline form of imatinib (known as Gleevec, or Glivec), was not patentable because it was too similar to an earlier version of the medicine, and no more effective.[14] In India, an alternative imatinib is available for US$2,500 for a year's course; in the United States, the branded product costs US$70,000.[15] As with PEG-IFN, people in India and others in countries where imatinib is not patented can now continue to access more affordable biosimilars.

These court-based wins bring affordable drugs—including hepatitis C treatment—closer to billions of people in the world, rather than keeping essential medications priced cruelly out of reach.

UKRAINE

In April of 2013, activists in Ukraine who called themselves "the Condemned," wore cloth hoods over their faces and protested in front of the offices of the Cabinet of Ministers, the country's highest executive political body. They demanded that the ministers immediately implement a presidential order to allocate funding for the treatment of life-threatening diseases, including HCV, which they estimate will kill at least 44,000 people in Ukraine this year.[16] Within weeks, the government agreed to develop a funded national plan.

GEORGIA

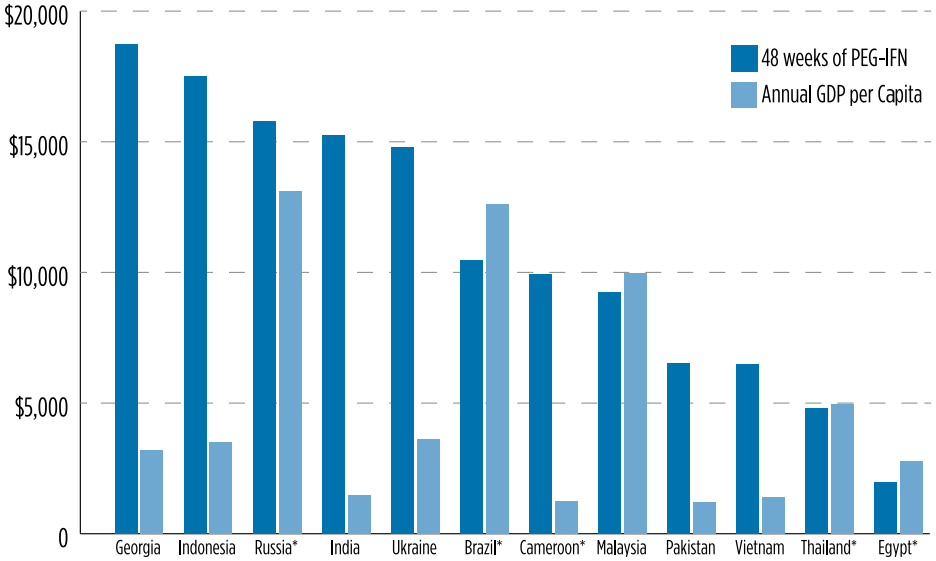
In Georgia, 6.7% of the population (or at least 200,000 people) has HCV, yet less than one percent has access to treatment. Civil-society advocates in Georgia, including the Georgian Harm Reduction Network (GHRN), have been pushing their government for a fully funded national program. Activists are making progress through lobbying parliamentarians and meeting with ministers.

This year, Georgia's Ministry of Corrections committed to treat 300 people in prison who have HCV, expanding to 500 in the next year. Activists are pushing the government to encourage the Ministry of Labor, Health and Social Affairs (MoLHSA) to also treat people with HCV.

Global Strategies for Access

Most people with hepatitis C live in LMICs, where the cost of treatment can exceed per-capita Gross Domestic Product (GDP) tenfold.[17] (See figure 1. Cost of a 48-Week Course of Brand-Name PEG-IFN Treatment vs. Gross Domestic Product (GDP) per Capita.) Activists are promoting a range of successful advocacy strategies, including price negotiations with pharmaceutical companies, the use of compulsory licenses, and promoting the use of quality, affordable biosimilars to push for access where even the standard of care is priced out of reach.

Figure 1. Cost of a 48-Week Course of Brand-Name PEG-IFN Treatment vs. Gross Domestic Product (GDP) per Capita



* indicates government procured prices of PEG-IFN, otherwise private market prices are used.

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PRICE NEGOTIATIONS

Roche and Merck must drastically cut the price of PEG-IFN for LMICs. New HCV drugs must also be affordable. In the United States, a single course of HCV treatment with peginterferon, ribavirin, and telaprevir (an HCV protease inhibitor)—including managing side effects and posttreatment follow-up—costs US$98,348.[18]

On Valentine's Day (February 14), 2013, international advocates joined Médecins du Monde and Treatment Action Group in launching an online social media campaign targeting Roche and Merck. The Valentine's Day card, sent via e-mail, Facebook, and Twitter to company executives, read, "Have a heart, save my liver!" More than 30,000 valentines were sent during this one-day action. The slogan was accompanied by an incisive message about the need to slash drug prices to avert more than 350,000 annual HCV-related deaths.

ESSENTIAL MEDICINES LIST

In 2012, Médecins Sans Frontières (MSF) submitted an application for PEG-IFN to be included on the World Health Organization's Essential Medicines List (EML).[19] Once a drug is on the WHO EML, it is easier to get access to quality, affordable versions, as the EML guides procurement and supply as well as essential drug choices. Adding PEG-IFN to the EML sends a strong message to countries: treating HCV is a priority, and PEG-IFN is safe, effective, and cost-effective.[20] It encourages countries to prioritize inclusion of PEG-IFN on their national EMLs, thereby increasing its accessibility.

COMPULSORY LICENSES

Some countries, including Brazil, Indonesia, Thailand, Ghana, and Cameroon, have issued compulsory licenses to increase access to drugs for HIV and hepatitis, as well as to other medications.[21,22] Under compulsory licensure, a government has the power to grant a license to local pharmaceutical producers, allowing them to use a patent without the patent holder's permission. In countries without production capacity, they may import the drug from elsewhere. A compulsory license is typically issued when a government determines that a disease is of high priority locally and urgent access to treatment is necessary. Drug companies that refuse to negotiate an affordable price leave countries with little choice but to issue compulsory licenses to produce or import otherwise inaccessible medications.

Compulsory licensing has allowed many leading middle-income countries (such as Brazil and Thailand) to provide affordable medicines for HIV/AIDS under nationally funded programs. Activists can encourage their governments to use this mechanism

if voluntary licensing (when the patent holder gives another party the right to manufacture, import, or distribute its pharmaceutical product) is not an option. Then governments can produce or import safe and effective PEG-IFN biosimilars.

ACCESS TO BIOSIMILARS

A number of countries are using locally produced peginterferon (both biosimilar and alternative). These are available at a fraction of the cost of the originator products, allowing governments (such as Egypt's) to treat large numbers of people. The availability of cheap PEG-IFN biosimilars has an impact on pricing: biosimilars and alternatives can be used as a leverage to negotiate cheaper prices with Roche and Merck.

The quality of internationally available biosimilar drugs and diagnostics must be assured if countries are to confidently scale up HCV treatment programs. Activists are demanding that the WHO immediately establish mechanisms for assessing the safety and efficacy of biologic medicines and diagnostic tests. Producers must prove that their products have been made using Good Manufacturing Process standards. A WHO prequalification process is also needed to facilitate access to safe and effective drugs and diagnostics.

Local manufacturers will increase global access to their product by improving data collection practices and transparency to regulators. In turn, the WHO, the European Medicines Agency (EMA), and the U.S. Food and Drug Administration (FDA) should create a clear and harmonized regulatory pathway for approval of biosimilars.

DIAGNOSTICS

The availability of affordable, effective point-of-care (POC) diagnostic and staging tools is essential to the scale-up of integrated hepatitis C screening, testing, treatment, care, and support programs in LMICs.

Simplified diagnostic tests such as dried blood spots from a single finger stick and noninvasive methods such as the use of routine blood tests to stage liver disease can be quickly administered and greatly increase access to treatment and care. These and other tools must be quality-assured to be useable. Donor agencies including the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID should support the development of simple, accurate, and affordable HCV diagnostics and disease-staging tools, since their cost and complexity are major barriers to treatment. The WHO should promote access to affordable POC diagnostics by facilitating their regulatory approval and prequalification.

CIVIL SOCIETY

Dozens of grassroots groups and regional networks across the world are demanding that their governments face up to the HCV crisis, and work together to respond. World Hepatitis Day (July 28) has provided a springboard for activists. In 2012, the Eurasian Harm Reduction Network marked World Hepatitis Day by presenting the WHO, Roche, and Merck with the Hepatitis C Treatment Waiting List, a petition calling for "affordable, high-quality hepatitis C treatment." They demanded high-level leadership, and deplored the monopoly on PEG-IFN. The petition was circulated globally, and now has nearly 6,000 signatories. At the International AIDS Conference in 2012, just prior to World Hepatitis Day, global activists interrupted a Roche side meeting to deliver a plate of decomposing liver to the organizers. While activists stood at the front of the room holding a banner that said "HIV/HCV: Silence = Death," International Treatment Preparedness Coalition—Russia staffer Denis Godlevskiy led a call to action for Roche to drop the price of Pegasys and "stop eating our liver."

In Ukraine, India, Thailand, and around the world, many people living with HCV contracted it through injecting drug use. The WHO considers people who inject drugs a high-priority group for targeted HCV prevention and treatment.[23] Evidence shows that scaling up HCV treatment in PWID is highly cost-effective when provided together with core harm reduction services such as OST and needle and syringe programs.[24] Until the rights of people who use drugs are fully realized, hepatitis C prevention and treatment efforts have little chance of success.

Defusing the Bomb

The availability of generics and biosimilars can dramatically reduce prices. Significant price reductions for medications and diagnostics will allow governments to integrate hepatitis C programs into national budgets. The AIDS movement proved this crucial point: drugs originally priced at US$10,000 per year could be generically produced for a fraction of the cost, thus greatly expanding access. Today, millions of people are on first-line HIV medications that cost US$100 per year. In sub-Saharan Africa, where countries face decimating HIV epidemics, access has increased 100-fold as a result.[25]

Providing HCV treatment benefits both individuals and communities. Treating HCV can also help prevent new cases, and potentially lead to the eradication of HCV globally.[26] Highly effective peginterferon-sparing and peginterferon-free regimens on the horizon that require shorter treatment duration and have fewer toxicities will facilitate treatment rollout.

The World Health Organization must agree to support governments to provide consistently high-quality, affordable PEG-IFN. Governments, in turn, must partner with civil-society organizations to develop and fully fund national plans to address their HCV epidemic. Both the Global Fund (which already subsidizes government HCV-testing and treatment programs), and UNITAID (whose market influence strategies help reduce the price of drugs and diagnostics) can affect global public health and access barriers. Their strategic interventions will help to overcome political and economic challenges in HCV treatment scale-up.

Activists are demanding that more must be done to dismantle the "bomb." The revolution in hepatitis C treatment is providing the tools to do this. But therapeutic advances will mean nothing without universal access to the new treatments, and programs to deliver them in a culturally competent way. The 194 member countries of the United Nations have agreed that the rights to health and life are to be enjoyed by all, equally, without discrimination. People living with and at risk for HCV and their activist allies must keep fighting for these rights to be realized. As American social reformer, abolitionist leader, and former slave Frederick Douglass said, "Power concedes nothing without a demand."

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The Tuberculosis Diagnostics Pipeline

By Colleen Daniels

Currently, smear microscopy and mycobacterial culture are the most widely used diagnostic tests, but microscopy, though relatively fast, is too inaccurate—missing over half of cases[1]—while culture is accurate but slow, taking from two to eight weeks to produce a definitive result. These tests are simply not accurate and rapid enough for proper diagnosis of TB, particularly in people living with HIV and in children. Early diagnosis of TB is essential to reducing transmission and mortality.[2] Five key barriers to the detection of TB are the difficulty of diagnosing latent TB infection and active TB disease; the lack of validated, accessible, and rapidly testable biomarkers; long delays before patients seek care; lack of an accurate, lab-free point-of-care (POC) test;[3] and the "widespread unavailability of facilities that can test for drug resistance."[4]

Sputum microscopy, the diagnostic tool developed in the 1880s, and still the most widely used diagnostic for TB despite its low sensitivity, finally has alternatives that are faster and more accurate.[5] The innovations in technology that transformed HIV diagnosis are finally being seen with TB. The price of HIV polymerase chain reaction (PCR) testing has decreased since it was first rolled out. In 2005, the minimum average price was US$31, and by 2012 it was US$21.[6,7,8] The potential for this technology to be developed and used in TB diagnosis is growing. However, current PCR platforms are too complex and technically demanding for community-level or true point-of-care use. Even with recent progress, we still lack a fast, cheap, accurate, and lab-free POC test that does not require sputum and can work at the lowest levels of health-service delivery.

Xpert MTB/RIF, which incorporates a nucleic acid amplification technology, is an automated device that tests for *Mycobacterium tuberculosis* (MTB) and rifampicin resistance. It has shown that new technologies have the potential to make diagnosis faster and more accurate. Since 2008, Treatment Action Group (TAG) has been working to change the diagnostic paradigm and increase resources for appropriate research and development (R&D) for new TB tools. In this and the next two chapters, we will review the pipeline for new TB diagnostics, treatments, and vaccines.

The introduction of Xpert MTB/RIF technology in high-burden settings such as South Africa and moderate-burden settings such as Brazil has encouraged R&D on new molecular diagnostics. Several fast followers are already on the market in some places, and more are in the pipeline. Today more than 50 diagnostic

companies and test developers are working on TB diagnostic technologies.[9] There is increased interest in developing better, broader, faster drug susceptibility testing (DST) approaches to guide rational use of therapies.[10] Most new technologies in the pipeline are dependent on electricity, require placement at reference- or peripheral laboratories, and still rely on sputum samples for detection of TB.

Table 1. 2013 TB Diagnostics Pipeline[11]

Test	Developer(s), Country	Type/Sample	Status
Molecular technologies			
❖Alere Q[12]	Alere, United States	Molecular diagnostic platform to screen MTB and drug resistance	In development; supported by the Bill & Melinda Gates Foundation (BMGF)
❖B-SMART	Laboratory Corporation of America Holdings (LabCorp), United States	Combines nucleic acid amplification and detection with phenotypic DST to detect MTB and determine resistance to anti-TB drugs[13] including pyrazinamide	In development; Sequella licensed technology to LabCorp
❖Genedrive MTB/RIF ID	Epistem, United Kingdom	Real-time PCR for TB and rifampicin resistance	Epistem was awarded CE/IVD accreditation (European Union accreditation for medical devices)[14]
❖GeneXpert XDR cartridge	Cepheid, United States	In-cartridge PCR to detect XDR-TB on GeneXpert platform	In development[15]
GenoType MTBDRs*l* line probe assay (LPA), second-line	Foundation for Innovative New Diagnostics (FIND), Switzerland/Hain Lifescience, Germany	Line probe assay for genetic mutations associated with resistance to fluoroquinolone antibiotics and the second-line injectable drugs amikacin, kanamycin, and capreomycin	On the market; not endorsed by the WHO. Field validation of the MTBDRs*l* assay in smear-negative and smear-positive patients under way in India, Moldova, and South Africa[16]

❖iCubate System	iCubate, United States	Multiplexed assay that detects TB and nontuberculous mycobacteria, and rifampicin-, isoniazid-, ethambutol-, and streptomycin-resistance in a single cartridge[17]	For research use only
❖INFINITI MTB Assay	AutoGenomics, United States	Multiplex PCR amplification/ microarray detection assay to detect MTB, common rifampicin (RIF) and isoniazid (INH) resistance mutations (i.e., MDR-TB) and Mycobacterium bovis[18]	Product is available for research use only
❖LATE-PCR with Lights-On/Lights-Off Probes and PrimeSafe technology	Stellenbosch University, South Africa; developed by Brandeis University, United States	PCR for simultaneous detection of MTB and resistance to INH, RIF, ethambutol, and injectables	In development; will be testing against clinical samples in South Africa[19]
Loopamp TB Detection[20]	FIND, Switzerland/ Eiken, Japan	Loop-mediated isothermal amplification (LAMP) for TB	On the market; CE-marked and registered in Japan; not endorsed by the WHO; evaluation studies completed in Brazil, Peru, South Africa, and Vietnam;[21] demonstration studies under way in Cambodia, Cameroon, Ethiopia, Gambia, India, Ivory Coast, Madagascar, Malawi, Mongolia, Romania, South Africa, Tanzania, Uganda, and Vietnam[22]

GenoType MTBDR*plus* 2.0	Hain Lifescience, Germany/Global Consortium for Drug-resistant TB Diagnostics, United States	Line probe assay (PCR)	On the market; version 1.0 endorsed by the WHO; version 2.0 not endorsed by the WHO; field validation of the assay in smear-negative and smear-positive patients in India, Moldova, and South Africa under way[23]
❖NATeasy TB Diagnostic Kit[24]	Ustar Biotechnologies, China	Isothermal nucleic acid amplification and lateral flow detection cartridge	On the market; not endorsed by the WHO. Regulatory submissions under way in China
❖TruArray MDR-TB	Akkoni, United States	Microarray-based NAAT	In development[25]
Truelab/Truenat MTB	Molbio/bigtec Diagnostics, India	Chip-based NAAT for MTB; runs on a portable battery-operated device	On the market in India. Independent studies incomplete[26]
Nonmolecular technologies			
Alere Determine TB-LAM Ag lipoarabinomannan (LAM) lateral flow test	Alere, United States	Lateral flow urine test detects TB protein in adults with HIV	On the market; field studies conducted and under way[27]
TB Rapid Screen[28]	Global BioDiagnostics, United States, with support from FIND, Switzerland	Reporter Enzyme Fluorescence (REF) to detect β-lactamase produced by live bacteria in sputum samples (1st generation substrate)	In development; expected to use simple, low-cost fluorescence reader
TBDx	Signature Mapping Medical Sciences, United States	Automated slide-loading and -reading system for smear microscopy[29]	In development; field studies ongoing[30]
Culture-based technologies			
❖BNP Middlebrook	NanoLogix, United States[31]	Culture	In development
MDR-XDR TB Color Test	FIND, Switzerland/ Imperial College, United Kingdom	Rapid colorimetric drug susceptibility test (DST)	In development; feasibility study to commence[32]

TREK Sensititre MYCOTB MIC plate	Trek Diagnostic Systems/Thermo Fisher Scientific, United States	A dry microdilution plate containing lyophilized antibiotics for determination of minimum inhibitory concentrations to first- and second-line TB drugs (except pyrazinamide)	In development; in field studies[33]
Volatile Organic Compounds			
BreathLink	Menssana Research, United States	Volatile organic compound	In development; in feasibility studies, but has received CE mark[34]
❖Prototype breathalyzer device[35]	Next Dimensions Technology, United States	To identify active TB and MDR-TB	In development; received continued funding from the BMGF to further develop

❖ indicates no published data available

The current pipeline for TB diagnostics is relatively robust for nucleic acid amplification-based technologies. Most of these technologies are targeted at levels of the health system that most people cannot easily access. A true POC diagnostic for TB will remain elusive if it is not specifically delivered at the peripheral health service-level or to communities and households for active case-finding—ideally with an electricity- and cold-chain-free, small, cheap, simple, and portable instrument.

The Cochrane Infectious Diseases Group, in its Diagnostic Test Accuracy (DTA) review of Xpert MTB/RIF,[36] and Dr. Madhukar Pai of McGill University have both noted that the effective rollout of Xpert MTB/RIF is not without challenges;[37] the system is still expensive and not available in peripheral centers. Last year, a consortium including UNITAID, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the U.S. Agency for International Development (USAID), and the Bill & Melinda Gates Foundation (BMGF) concluded a pooled purchase agreement with Cepheid to bring the price of Xpert cartridges down to US$9.98 for the public sector in high-burden countries .[38] Several projects are under way to roll out Xpert MTB/RIF over the next few years, including EXPANDx TB and TBXpert. The TBXpert project, a collaboration between the WHO and the Stop TB Partnership, is funded by UNITAID. Between 2013 and 2015, the project will provide 1.4 million Xpert MTB/RIF cartridges and 220 GeneXpert instruments in 21 countries.[39]

Stable Supply of Xpert MTB/RIF Cartridges

The lack of a stable supply of cartridges is a huge concern for those implementing Xpert MTB/RIF. In 2012, the Xpert MTB/RIF manufacturer, Cepheid, experienced difficulties in keeping up with the cartridge orders that were placed by countries, particularly after the price was lowered. In a press release dated January 8, 2013, then-CEO John Bishop said, "the underlying causes of our 2012 second half challenges have been resolved."[40] In a more recent web update, Cepheid now claims that they "expect to have considerably reduced—or even eliminated—any product allocations by the end of June [2013]."[41]

However, at the Xpert MTB/RIF Implementers Meeting held in Annecy, France, on April 16, 2013, new Cepheid executive vice president of emerging markets, Philippe Jacon (formerly CEO of FIND), indicated that the company would not be able to meet current back orders and demand until the third quarter of this year. Xpert MTB/RIF cartridges remain on allocation, which means that the company determines how much of an order to fulfill, and prioritizes orders. As professor Wendy Stevens of the National Health Laboratory Service in South Africa (the largest purchaser of Xpert MTB/RIF machines and cartridges) rightly pointed out, having only one global supplier of cartridges is far from ideal,[42] and Cepheid benefited from the pooled purchase agreement.

The lack of Xpert MTB/RIF cartridges is yet another of the ongoing drug- and diagnostic stock-outs. An inconsistent supply of Xpert MTB/RIF cartridges means that there will be fewer people who are accurately diagnosed and treated in a timely manner.

An adequate and consistent supply of diagnostic systems and assays must be guaranteed, and all stakeholders must be involved in ensuring the broadest possible access to useful new technologies where they are needed. The investment in the development and rollout of Xpert MTB/RIF must not be wasted.

Rather than rolling out TB-only laboratories, we need diagnostic tools and platforms that can be used in any laboratory (though tools at facility-level are optimal), and integration of tools such as Xpert MTB/RIF into HIV-, maternal and child–, and other health care services as soon as possible. This will facilitate more active case-finding instead of waiting for people to come to TB clinics.

The reactive nature of many TB control programs slows the development of aggressive national strategies to introduce new diagnostic tests.[43] Some countries implementing Xpert MTB/RIF are currently developing a strategy specifically for this one tool; a TB CARE project implementing Xpert outlined 37 steps necessary to roll it out—the first of which is to establish a working group.[44] Sometimes global agencies develop lengthy, overly complex diagnostic algorithms[45] that may be more confusing than useful to countries that may be deterred from trying the newer tests without FDA- or WHO guidance. Countries must work to develop national strategies that permit the introduction of any new tool or regimen whenever it is needed and available. As complex as the current system is, countries like South Africa, which rolled out GenoType MTBDR*plus* and then Xpert MTB/RIF, should be applauded for implementing these tests as quickly as they did.

Some countries have been slow to implement Xpert MTB/RIF as they wait for more data from fast followers such as Molbio's Truelab Real Time micro PCR System and Truenat MTB test for quantitative detection of MTB in sputum samples, which was launched this year in India. The system works on microchips with TB-specific genetic sequences and preloaded reagents for conducting a real-time PCR. Nikam et al. analyzed Molbio's Truenat MTB in a sample of 226 patients: the "Truenat MTB test was found to have sensitivity and specificity of 91.1% and 100% respectively, in comparison with 90.58% and 91.43% respectively for the in-house nested PCR protocol."[46] These data are hard, if not impossible, to interpret since no one else has an in-house nested PCR protocol, and the researchers did not compare Truenat with something more clearly validated, such as Xpert. While this product is available on the Indian market, there are few data about it. Efforts are now under way to evaluate this technology in the Indian public sector to inform the national TB policy.

Like Truenat, GeneDrive (Epistem) is a portable device developers say is targeted for use in low-resource settings. Unfortunately, although Truenat is CE-marked, there are no data about the product available at this time. A press release from August 2012 announced a partnership between Epistem and Becton Dickinson to supply and distribute the platform.[47]

These two molecular technologies, similar to Xpert MTB/RIF, aim to be cheaper. Independent studies are forthcoming. TAG believes that the evidentiary standards for the introduction of new diagnostic tests are far from rigorous. In fact, many

diagnostic companies make claims, which if they were made regarding new and untested drugs would likely result in the companies' facing civil or criminal sanctions for unjustified promotion of unvalidated medical commodities. However, in most parts of the world, diagnostics are not regulated as rigorously as drugs are.

The World Health Organization (WHO) approved the use of Xpert MTB/RIF in 2010[48] and, together with partners, has helped some countries roll out the technology by issuing documents such as the *WHO Policy Framework for Implementing New Tuberculosis Diagnostics 2010*[49] and *Prerequisites to Country Implementation of Xpert MTB/RIF and Key Action Points at Country Level: Checklist*,[50] as well as by sending rotating teams of technical experts from Geneva and other well-resourced centers to high–TB burden implementing countries.

In 2013, the WHO emphasized that the Hain GenoType MDRTBs*l* assay "cannot be used as a replacement test for conventional phenotypic drug susceptibility testing," due to lack of supporting evidence.[51,52] This was also the case with LAMP. Countries may use the tests, however, if they believe there is a role for them in their settings. A study (NIAID U01AI082229) currently being conducted by the Global Consortium for Drug-resistant TB Diagnostics, a group funded by the U.S. National Institutes of Health (NIH), is assessing the MTBDRs*l* assay in smear-negative and smear-positive patients in India, Moldova, and South Africa. Data should be available by fall 2013 and published in 2014.[53]

Based on the results of studies on the Alere Determine TB-LAM Ag, a urine-based TB LAM test, in HIV-infected adults with TB symptoms,[54] many authors concluded that the test holds promise for diagnosing TB faster in HIV-positive persons with CD4 counts under 100 cells/mm^3, who tend to have more extrapulmonary and smear-negative disease.[55] In most studies published to date, sensitivity is approximately 50 percent in patients with advanced immune suppression (CD4 count <100 cells/mm^3).[56]

Where should we be going?

Lawn and colleagues discuss the challenges related to cost-effectiveness as well as the clinical and programmatic effects of implementing GeneXpert.[57] They conclude that a rapid, accurate, affordable POC diagnostic test that can be "readily implemented is urgently needed."

The optimal point-of-care TB test would be affordable, patient- and user-friendly, accurate in people with any form of TB, and would result in TB treatment decisions in one visit or encounter. There is nothing in the pipeline that looks like it has even remote potential to fulfill these criteria. Médecins Sans Frontières, TAG, and

partners developed detailed specifications for such a test as long ago as 2008 (see http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_event_POC_meetingoutcomes_full_ENG_2008.pdf).

Despite the improvements being made in TB diagnostics, we still cannot quickly and accurately detect TB in those with suspected extrapulmonary disease, children, and people living with HIV.[58]

Funding

Funding for research and development for TB diagnostics is hugely inadequate. TAG's *Tuberculosis Research and Development: 2012 Report on Tuberculosis Research Funding Trends, 2005–2011*[59] indicates that funding for TB diagnostics in 2011 was US$55,043,541. *The Global Plan to Stop TB: 2011-2015* calls for annual funding for new TB diagnostics to be US$340 million. The largest funders of TB diagnostics remain the BMGF, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) at the NIH, and USAID.

According to David Walwyn's modeling study, spending on TB R&D in countries such as South Africa is disproportionately small relative to disease burden.[60] The cost of treating TB in South Africa for example, is over US$588 million per year. Walwyn's calculation, based on return on investment, indicates that South Africa should be spending at least US$92 million annually on TB R&D. It is crucial that the BRICS countries, (Brazil, Russia, India, China, and South Africa) now increase their investment in TB R&D. This investment should not only be for the search for new tools, but also for the infrastructure to evaluate and demonstrate their field effectiveness.[61]

Increased and sustainable investment in the TB diagnostics pipeline must remain a priority for funders and researchers. In a 2006 report, the World Health Organization estimated that US$1 billion is spent worldwide on TB diagnostics. This is a potentially huge market, and diagnostic developers must use this as an opportunity to invest in accelerating TB diagnosis, enabling rational use of therapies, and reducing TB mortality.[62] Since the TB diagnostics landscape has changed in the past few years, updated market estimates are required to guide test developers (see www.tbfaqs.org, a new website developed to address key questions by test developers).

Efforts are under way to quantify the current TB diagnostics market, accounting for the ongoing rollout of Xpert MTB/RIF and other changes in the landscape. This effort involves the BMGF, the McGill International TB Centre, UNITAID, FIND, the Stop TB Partnership's New Diagnostics Working Group, country partners, and national TB programs. The proposed project will conduct a rapid assessment of

the served available market (SAM) for TB diagnostics (i.e., current algorithms; regulatory and policy landscape; testing volumes/sales; total dollar-value spending on diagnostics; and market segmentation) in four high-burden countries: India, China, Brazil, and South Africa. This market analysis will cover 2012–13, providing a snapshot of the current market in these emerging economies, and is expected to be completed by early 2014.

In 2013, the BMGF granted Alere US$21.6 million and debt financing of up to US$20.6 million to develop a cartridge-based point-of-care molecular diagnostic platform. Called Alere Q, it is meant to rapidly and affordably screen TB patients. There are plans for a second cartridge, which will be used in people found to have active TB, to determine drug resistance; validation is expected in two years.[63] The Keck Graduate Institute of Applied Life Sciences and Claremont BioSolutions, LLC, received a US$3.6 million research grant from the NIH to develop a POC assay and device to diagnose MDR-TB. They aim to develop a handheld device that can be built for less than US$100.[64,65] This type of innovation must be nourished and fueled with more funding and by more partners.

Biomarkers for TB

There is still no accurate, validated TB biomarker, despite some progress in the past 10 years.[66] Research has been focused on curing active TB disease, reactivation of latent TB, and the induction of protective immune responses through vaccination. In order to address the main challenge—quantifying biomarkers as surrogate clinical endpoints for clinical trials of new drugs, regimens, or vaccines—there must be increased investment in basic science. In 2012, the BMGF invested US$7.7 million in a portfolio of 10 grants focused on TB diagnostic biomarkers that can result in a simple TB test like that for pregnancy.[67] Additional efforts are needed to accelerate progress.

Drug susceptibility testing

Another key area that lacks funding or priority by donors and sponsors is decentralized DST for fluoroquinolones, pyrazinamide, and other drugs, particularly second-line drugs. With the approval of bedaquiline and the potential for new drugs to enter the market soon, this must become more of a priority for funders and researchers.[68] The *WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis – 2011 Update* recommends "rapid drug susceptibility testing of isoniazid and rifampicin or of rifampicin alone…over conventional testing or no testing at the time of diagnosis of TB, subject to available resources."[69] It is essential that we move to implement this recommendation in all settings.

Specimen bank

Diagnostics developers need more information and access to specimens to validate their technology platforms. The WHO TDR TB Specimen Bank, in jeopardy of closing last year due to lack of funding, is now being managed through FIND (as of March 2013). Its specimens, as well as FIND's, are freely available to qualified investigators on application. FIND has funding to manage the two banks only until October 2014; it does not have funding for new collections.

The Tuberculosis Trials Consortium (TBTC) of the U.S. Centers for Disease Control and Prevention, the AIDS Clinical Trials Group (ACTG) of NIAID, and the Global Alliance for TB Drug Development (TB Alliance) have partnered to establish the Consortium for Tuberculosis Biomarkers (CTB2). The Consortium aims to develop agreed-upon standards for collection, processing, and storage of a core set of relevant samples and a high-quality biobank to facilitate discovery and qualification of biomarkers of TB drug effects. It will be made available to the broader scientific community through a peer-review system.[70]

It is crucial to diagnostics research that useful, viable specimen samples be available openly and freely; these resources need more and sustainable investments.

Policies and Strategies

Without adequately addressing the rollout of new tools, we will not change the number of people who die from preventable, curable TB. For example, if programs implementing Xpert MTB/RIF allow for starting TB therapy on the same day as diagnosis, this will result in quicker treatment initiation and reduced loss to follow-up and transmission.

The reduced, negotiated prices for Xpert MTB/RIF are not available to the private sector in the highest–TB burden countries like India, even though the private sector is the dominant health care provider. Even poor TB patients seek initial health care in the private sector in countries like Pakistan, Bangladesh, Cambodia, Nigeria, and Indonesia, and it is important that good tests are made available for such patients. This will require innovative business models. In Pakistan, Bangladesh, and Indonesia, a social-enterprise model is being launched to scale up implementation of Xpert MTB/RIF and improve quality of TB care.[71]

In India, the 2012 ban on inaccurate TB serological tests has resulted in a chaotic private market, since WHO-approved TB tests were costly. Some private labs continue to offer serology, while others have switched to blood PCR and QuantiFERON-TB Gold, tests that cannot accurately distinguish latent TB infection from active TB disease.[72]

The Initiative for Promoting Affordable, Quality TB tests (IPAQT), a coalition of accredited private labs in India supported by industry and nonprofit groups (e.g., Clinton Health Access Initiative), has made three WHO-approved tests (Xpert MTB/RIF, Genotype MTBDR*plus*, and BACTEC MGIT 960 TB System) available at affordable prices to patients in the private sector in India. Labs in IPAQT have access to lower, FIND-negotiated prices for the quality tests in exchange for their commitment to pass on the benefits to patients.

Such private-sector efforts need greater support from national TB programs and the public sector. It is insufficient to ban or eliminate inaccurate tests. Efforts must also be made to make good tests more affordable to all sectors, public and private.[73]

Recommendations

Funding

1. Donors must increase funding and work to bring more scientists and innovators into the field to develop an optimal point-of-care TB test that is affordable, patient- and user-friendly, accurate in people with any form of TB, and will result in TB treatment decisions in one visit or encounter.
2. The private sector and middle-income countries need to increase investment in TB diagnostics development. The BRICS countries (Brazil, Russia, India, China, and South Africa) must increase their investment in TB R&D for new tools as well as the infrastructure to evaluate and demonstrate their field-effectiveness.

Biomarkers

1. Donors must prioritize increased investment in basic science to quantify biomarkers as surrogate clinical endpoints for clinical trials of new drugs, regimens, and vaccines.

DST

1. Donors must fund and prioritize decentralized DST for fluoroquinolones, pyrazinamide, and other drugs, particularly second-line drugs.
2. Country programs and donors must implement the recommendation to do rapid DST of isoniazid and rifampicin, or of rifampicin alone, over conventional testing or no testing at the time of diagnosis of TB.

3. Donors and industry must work to develop universal DST and newer DST methods to rapidly identify regimens to which every patient's bacterial organism is susceptible.

Specimen bank

1. Donors need to fund repositories of useful, viable specimen samples that are available openly and freely.

Policies and strategies

1. Donors, national programs, and implementers must develop policies and strategies that move toward active case-finding and integrate TB services across the health system.
2. Donors and national programs must integrate new TB diagnostic tools such as Xpert MTB/RIF into HIV-, maternal and child–, and other health care services wherever possible.
3. Programs must work to develop national strategies that allow the flexibility to introduce any new tool or regimen whenever available and needed.
4. Regulatory agencies must develop stringent evidentiary standards for the introduction of new diagnostic tests to ensure that people have access to good, accurate tools without delay.
5. Programs in countries with high HIV burdens should assess the usefulness of tests that have not yet been endorsed by international agencies, in their own settings, particularly where TB kills many people before they are even diagnosed.
6. National programs should not wait for the WHO to make recommendations regarding the use of tools if they have the resources to do so themselves. However, programs should beware of promotional marketing by diagnostics developers that lacks supporting data.
7. Donors, in particular BRICS and other middle-income countries, must conduct operational research to determine at how low a level of the health system Xpert could be implemented.
8. Donors, industry, and national programs must develop policies that make good tests more affordable to all sectors, public and private.
9. UNITAID, the BMGF, PEPFAR, USAID, and the WHO must ensure that Cepheid identifies the causes of Xpert cartridge shortages and fixes them quickly.

Conclusion

TB diagnostics have the potential to revolutionize the way we diagnose TB and treat and cure people. After decades of neglect of TB R&D, we have now built the architecture to develop new drugs, vaccines, and diagnostics that together would eliminate TB. A simple, affordable, universally accurate point-of-care test is still attainable if diagnostics developers, funders, and patients make it a priority by increasing and sustaining higher levels of funding for new research and development.

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The Tuberculosis Treatment Pipeline

Better than Ever Is Not Good Enough

By Erica Lessem

Introduction

In December 2012, tuberculosis (TB) treatment reached a historic landmark with the first approval by a stringent regulatory authority of a new agent from a novel drug class in over 40 years. The U.S. Food and Drug Administration (FDA) approval of bedaquiline validates the recently revitalized global effort to develop new, better treatments for TB after decades of stagnation.

Yet the road to adequate treatment for people with TB is still a long one. First, bedaquiline has not begun to reach the up to 1 million people with drug-resistant tuberculosis who may need the drug. Delamanid, already in phase III trials, has yet to be approved by a stringent regulatory authority. As TB drugs are given in combination to prevent drug resistance, the need for improved companion drugs to truly simplify, shorten, and improve treatment for both drug-resistant TB (DR-TB) and drug-sensitive TB (DS-TB) is urgent. Yet other drugs lag even farther behind, such as the promising drug sutezolid, whose development has been thwarted by slow activity of its sponsor, Pfizer.

Faster-acting, better therapies to clear latent TB infection (LTBI) before it turns into active disease are necessary, especially for people latently infected with DR-TB, who lack evidence-based therapy to protect themselves from falling ill.

The TB drug pipeline is still scant compared to what is needed. The lack of accepted surrogate trial endpoints require phase III studies to be large, long, and expensive. Investment lags at a third of what is needed; in 2011 alone, there was nearly a US$500 million global funding gap.[1]

Lack of regulatory capacity threatens the ability of countries to rapidly review new treatment options, and ensure that postmarketing studies and pharmacovigilance are carried out. Inertia and inflexibility by policy makers at national and global levels may lead to slow adoption of new treatments even after approval. Continuing stock-outs around the world jeopardize access to both new and existing drugs. These market inefficiencies, plus lack of cooperation from drug manufacturers, have contributed to high prices for second-line drugs, which are utterly unaffordable in these times of austerity.

To reach the goal of zero TB deaths, zero new TB infections, and zero TB suffering and stigma, people with TB and LTBI must receive treatment regimens effective against the infecting strain. This points to the need for rapid universal drug susceptibility testing, as discussed in the TB diagnostics chapter. Shorter, more tolerable regimens are needed for all forms of TB; in the case of DR-TB, they must also be all-oral, faster to cure, and much less toxic. TB-affected communities must play a more meaningful role in the design, implementation, and uptake of research, in line with the *Good Participatory Practice Guidelines for TB Drug Trials* released in 2012.[2] Countries must rapidly build regulatory capacity, and national treatment programs need to become more flexible in adopting new tools. Programs should also ensure consistent drug stocks through improved supply-chain management and procurement, while manufacturers must provide steady, safe drug supply at lower prices. People with TB need better access to existing and new treatment options, and the auxiliary care and psychosocial support necessary to make care patient-centric.

Key Definitions and Acronyms

TB: tuberculosis

DOT: directly observed therapy

DR-TB: drug-resistant TB

DS-TB: drug-sensitive TB

LTBI: latent TB infection

MDR-TB: multidrug-resistant TB; TB resistant to at least isoniazid and rifampicin, the two most powerful TB drugs, which are used as part of the four-drug, first-line therapy

Pre-XDR-TB: pre-XDR-TB (see below); or MDR-TB resistant to either a second-line injectable drug (amikacin, capreomycin, or kanamycin) or a fluoroquinolone

XDR-TB: extensively drug-resistant TB; or MDR-TB also resistant to a fluoroquinolone and at least one injectable second-line drug

Drugs: where are they and why can't we get them?

Challenges and inadequacies in TB research and development are mirrored on the access side by an equally frustrating host of problems. Poor estimation and consolidation of demand, inefficient ordering systems, unstable drug markets, and a lack of diversity in manufacturers have contributed to a pandemic of drug stock-outs. Drug shortages plague TB programs, consuming vast amounts of staff time, causing patients to miss doses (potentially leading to drug resistance), forcing patients to switch to inferior regimens, and requiring the use of more expensive drugs.[15]

With new leadership, the Global Drug Facility (GDF) is attempting to resolve some of the procedural challenges that have contributed to stock-outs. The Clinton Health Access Initiative, with support from the Bill & Melinda Gates Foundation and the U.K. Department for International Development, is working to improve demand forecasting, commodity procurement, and supply chain management in key MDR-TB treatment programs (initially, in Ethiopia, India, Lesotho, South Africa, and Swaziland), and to engage supply-side partners.

In the meantime, drug-supply problems continue to crop up, increasingly so even in better-resourced countries such as the United States: in the past year alone, the CDC's *Morbidity and Mortality Weekly Report* has published articles on isoniazid- and second-line injectable shortages (as well as on shortages of Tubersol, an important product for TB diagnosis).[4,5,6,7] The FDA has also reported shortages of injectable rifampicin.[8] TAG has been working with key public, private, and community partners to better understand and address the causes of these issues.

> To learn more, see http://www.treatmentactiongroup.org/tagline/2012/fall/future-tb-united-states-going-or-growing.
>
> To view the videos or the meeting report from the January 2013 consultation on TB drug shortages, see http://www.treatmentactiongroup.org/tb/advocacy/silent-crisis-tuberculosis-drug-shortages-united-states.

Special populations: TB and people who use drugs, alcohol, methadone, or buprenorphine, or who have HIV or viral hepatitis

A recent review showed that the linkages between TB and injection drug use, alcohol consumption, HIV, hepatitis B, hepatitis C and incarceration are strong, and pose challenges for patients and care providers.[8a] These linkages are further complicated by drug interactions among TB, HIV, and hepatitis medicines, and—though too little research has been done—among TB medicines and methadone or buprenorphine. These special populations are more likely to have heart and liver conditions, and many TB drugs, particularly those for DR-TB, pose a safety concern with heart and liver toxicities.

Programmatic efforts to comprehensively care for people are also inadequate: treatment, if it occurs at all, too often exists in a silo. The majority of people with HIV are not screened for TB, and only 40 percent of TB patients have a documented HIV test result.[9] Data on TB testing among people with hepatits B or C are unavailable. Despite presenting an opportunity for entry into other health services, drug and alcohol treatment programs rarely screen for, let alone treat, TB. This vertical approach to addressing disease and substance use leaves people with TB or other comorbidities undiagnosed and untreated. Even those who do manage to obtain full but independent diagnoses and treatment have uncoordinated care, losing more time in health care visits, incurring greater costs, and becoming more vulnerable to potential harm from unmanaged drug interactions.

More research is urgently needed about the safety and suitability of TB drugs and regimens in these populations. On the programmatic side, integration of services is essential for patients to access timely diagnostic and comprehensive care, and to manage any drug interactions. The criminalization of drug use poses a number of barriers to rapid diagnosis and effective treatment, and to receiving humane and compassionate care.

> More information is available in the recently released *TB Advocacy Guide for People Who Use Drugs* from the Joint United Nations Programme on HIV/AIDS, the World Health Organization (WHO), HIT (a U.K.-based harm reduction organization), and the International Network of People who Use Drugs. Available at: http://www.stoptb.org/wg/tb_hiv/assets/documents/TBHIV_Advocacy_Guide.pdf.

Clinical trials science

Conducting TB clinical trials is challenging. The inefficient traditional paradigm of testing one new drug at a time for a disease that requires combination therapy is, fortunately, being overhauled, with several new combination trials for both DS- and DR-TB ongoing from the TB Alliance, and proposed studies from other groups pending. Adaptive designs that include multiple arms, some of which are dropped if they do not meet predetermined criteria after interim analyses have the potential to make TB drug development more efficient. For more information, see http://www.treatmentactiongroup.org/tagline/2013/spring/necessary-transformation.

Yet without accurate surrogate endpoints, TB trials will remain lengthy and large as required by the relatively rare endpoints of cure and relapse. Waiting for lengthy phase III data (or even phase IIb data with long follow-up times) for approval delays and potentially discourages the development of new treatments. A recent article posits that a better approach may involve pursuing adaptive licensing based

on two-month sputum culture conversion to shorten registration timelines, with a thorough global outcomes registry confirming safety and effectiveness.[10] However, an open-label registry would not provide sufficient information on safety and efficacy. Longer-term randomized studies with clinical endpoints are still required to change practice and will be required by the WHO to provide an evidence base for new regimens. Certainly, given the complexity, length, and expense of conducting TB clinical trials, along with the great need for new TB treatments, a better way is needed. More research into biomarkers and potential endpoints is critical, as is innovation and cooperation from researchers (and flexibility from regulators) to make TB drug development more efficient.

Latent TB Infection

With an estimated one-third of the human population infected with *Mycobacterium tuberculosis* (the bacterium that causes active TB disease), the need for short, affordable treatment of latent TB infection (LTBI) is urgent.

Table 1. Latent Tuberculosis Infection Studies as of May 2013

Study/Regimen	Status	Population	Sponsor(s)
PREVENT TB (TBTC Study 26, A5259) Once-weekly rifapentine + isoniazid for 12 weeks (directly observed)	Completed	Persons with LTBI and high risk of progression (close contacts, recent converters, fibrosis on chest X-ray) including children and people with HIV	TBTC/ ACTG
A5279 Daily rifapentine + isoniazid for 1 month	Enrolling	People with HIV with positive skin test/IGRA or living in high TB prevalence regions	ACTG
iAdhere (TBTC Study 33) Self-administered once-weekly rifapentine + isoniazid for 12 weeks	Enrolling	Adults with LTBI	TBTC
P4v9 4 months of self-administered daily rifampicin	Enrolling	Children with LTBI, including HIV-positive children	CIHR
A5300 To be determined	In discussion	Close contacts of individuals with MDR-TB	ACTG

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases
CIHR: Canadian Institutes of Health Research
IGRA: Interferon gamma release assay – QuantiFERON-TB Gold In-Tube or T-SPOT TB test
TBTC: U.S. Centers for Disease Control and Prevention's Tuberculosis Trials Consortium

In 2011, following research from the CDC's Tuberculosis Trials Consortium (TBTC), the U.S. Centers for Disease Control and Prevention (CDC) recommended a new three-month regimen of once-weekly isoniazid and rifapentine administered as directly observed therapy (DOT).[11] Cure was similar with this new regimen of 12 treatment doses compared with nine months of daily isoniazid. Programmatically, the 12-week, 12-dose regimen would save substantial patient costs compared with the nine-month daily isoniazid standard. Further studies in people with HIV and in children published this year further demonstrate the regimen's safety.[12,13,14]

The TBTC is now conducting the iAdhere study to see if this regimen can work as well when given as self-administered therapy (SAT)—with and without SMS reminders—as when given by DOT. However, rifapentine costs much more than isoniazid alone.[15] Sanofi is developing a fixed-dose combination of isoniazid and rifapentine to reduce the current high pill burden of the regimen, and will file with the FDA for a latent indication once this is complete. Unfortunately, however, despite receiving substantial public support for the development of its compound, Sanofi has yet to commit to lowering the drug price to make it affordable in either low- or high-incidence settings.

Study A5279 by the AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)—funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID)—is evaluating whether rifapentine and isoniazid can be given in a super–short course treatment for LTBI in 3,000 people coinfected with HIV.[16] This study is looking at daily administration of the two drugs for just one month. Results are expected in 2015–16.

The Canadian Institutes of Health Research and McGill University are conducting a study to determine the safety and tolerability of a four-month, once-daily rifampicin regimen in children to prevent active disease. Already recommended for adults, this regimen is readily accessible and is shorter than the current standard of care for children, which is nine months of isoniazid. The study is enrolling newborns to children 17 years of age; results should be available in 2016.[17]

While these regimens are promising, treatment-shortening options not based on rifamycins are desirable. Both rifapentine and rifampicin interact with a number of anti-HIV drugs, such as protease inhibitors (e.g., ritonavir), non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz) and integrase inhibitors (e.g., raltegravir), complicating treatment in people coinfected with HIV who are on antiretroviral therapy (ART).[18]

As MDR-TB is by definition resistant to isoniazid and rifampicin—closely related to rifapentine—existing and novel treatment options for LTBI are unlikely to work among those latently infected with MDR-TB (though some evidence suggests isoniazid

can prevent active disease in some instances, possibly due to mixed infection).[19] The millions of contacts of people with MDR-TB around the world desperately need an option to prevent their infection from progressing into active disease, which is lengthy, costly, and very difficult to treat. The ACTG is planning a study of novel LTBI treatment in close contacts of people with MDR-TB. The ACTG originally proposed a study of bedaquiline in close contacts of people with MDR-TB. However, risks and benefits of treating LTBI differ from those of treating active MDR-TB, and bedaquiline may not yet be proved safe enough to give to people without active disease. Current work in mice to identify the best drug or regimen for treating drug-resistant LTBI will inform the final study design.[20]

While researchers wait for new drugs to study, and programs wait for rifapentine to become affordable, isoniazid preventive therapy (IPT) continues to be an essential and effective treatment for LTBI. A systematic review assessing the effect of LTBI therapy on the risk for isoniazid-resistant TB did not find a statistically significant increased risk for resistance in those who had taken IPT; it is assumed that those given preventive therapy have undergone a diagnostic screen to rule out active disease.[21]

A recent paper modeling the effect of community-wide IPT points to its potential to drive increases in drug resistance at the population level.[22] While these results are from theoretical modeling exercises, and while human studies have shown that IPT does not increase DR-TB, it would be ideal if LTBI therapy involved different drugs than treatment for active disease. Until more drugs enter the pipeline and this becomes feasible, IPT will remain an important tool for preventing disease. Early diagnosis and appropriate treatment of all active TB disease will reduce transmission of infection.

Active TB

Table 2. Classes of Drugs with Antituberculosis Activity in Clinical Studies

Class	Drug(s)	Mechanism of Action
Diarylquinoline	**bedaquiline**	interferes with how bacterial cells make energy by targeting the proton pump adenosine triphosphate synthase[23]
Ethylenediamine	**SQ109**	disrupts bacterial cell-wall construction by disturbing the assembly of mycolic acids, possibly by targeting the MmpL3 protein;[24] in vitro activity has yet to be confirmed in humans
Fluoroquinolone	gatifloxacin, levofloxacin, moxifloxacin, ofloxacin	disrupts bacterial replication by inhibiting the DNA gyrase enzyme, thus preventing bacterial DNA from unwinding and duplicating[25]
Nitroimidazole	**delamanid, PA-824, TBA354** (preclinical)	destabilizes the bacterial cell membrane by blocking the synthesis of mycolic acids;[26] poisons the bacterial cell by releasing nitric oxide when metabolized[27]
Oxazolidinone	**AZD5847**, linezolid, **sutezolid, tedizolid** (for MRSA)	blocks protein synthesis (translation) by inhibiting the initiation step at the ribosome[28]
Rifamycin	rifabutin, rifampicin, rifapentine	blocks messenger RNA synthesis (transcription) by inhibiting the bacterial DNA-dependent RNA polymerase[29]
Riminophenazine	clofazimine	unclear, but it appears that the bacterium's ineffective attempts to metabolize drug lead to cycle (redox cycle), which generates toxic reactive oxygen species within the bacteria; may target the bacterium's outer membrane by inhibiting the bacterial respiratory chain and ion transporters[30]

Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds

MRSA: Methicillin-resistant *Staphylococcus aureus*

Table 3. Recently Completed Clinical Studies for Active Tuberculosis

Study/Regimen	Stage	Indication	Sponsor
OFLOTUB 4 months of gatifloxacin, isoniazid, pyrazinamide, rifampicin	Phase III	DS-TB	WHO-TDR, IRD
REMoxTB 4 months of moxifloxacin substituting isoniazid or ethambutol, plus pyrazinamide and rifampicin	Phase III	DS-TB	TB Alliance, Bayer, University College London, University of St Andrews, MRC-UK, EDCTP
RIFAQUIN ethambutol, moxifloxacin, pyrazinamide, rifampicin in intensive phase, rifapentine in continuation phase for treatment-shortening and intermittent dosing	Phase III	DS-TB	INTERTB
HR2 or HIGHRIF rifampicin 10, 15, 20 mg/kg daily, ethambutol, isoniazid, and pyrazinamide	Phase IIb (2-month)	DS-TB	PanACEA, EDCTP
Linezolid to treat XDR-TB delayed or immediate start of linezolid at 600 mg for 4 months or till culture conversion, then 600 mg or 300 mg for ≥18 additional months, plus individualized background regimen	Phase IIb	XDR-TB	NIAID
NC-002 moxifloxacin, **PA-824**, pyrazinamide	Phase IIb (2-month)	DS/DR-TB	TB Alliance
RIFAT0X rifampicin 900 mg and 1,200 mg daily for first 4 months of standard 6-month regimen	Phase IIb	DS-TB	INTERTB
RioMAR isoniazid, rifapentine, pyrazinamide, moxifloxacin	Phase IIb (2-month)	DS-TB	Johns Hopkins University, TBTC
TBTC Study 29 rifapentine 10 mg/kg, isoniazid, ethambutol, pyrazinamide 5 times/week	Phase IIb (2-month)	DS-TB	TBTC
TBTC Study 29X rifapentine 10, 15, 20 mg/kg daily, isoniazid, ethambutol, pyrazinamide in the intensive phase	Phase IIb (2-month)	DS-TB	TBTC

Study/Regimen	Stage	Indication	Sponsor
B1171003 **sutezolid** 600 mg twice daily vs. **sutezolid** 1,200 mg daily vs. isoniazid, rifampicin, ethambutol, pyrazinamide	Phase IIa (2-week EBA study)	DS/DR-TB	Pfizer
HR1 rifampicin 10, 20, 25, 30, or 35 mg/kg daily as monotherapy and with ethambutol, isoniazid, and pyrazinamide	Phase IIa (2-week EBA study)	DS-TB	PanACEA, EDCTP
NC-003 **bedaquiline**, clofazimine, **PA-824**, pyrazinamide in various combinations	Phase IIa (2-week EBA study)	DS/DR-TB	TB Alliance

Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds

DR-TB: Drug-resistant TB DS-TB: Drug-sensitive TB EBA: Early bactericidal activity

EDCTP: European and Developing Countries Clinical Trials Partnership

INTERTB: International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis

IRD: Institut de recherche pour le développement

MRC-UK: British Medical Research Council

NIAID: U.S. National Institute of Allergy and Infectious Diseases

PanACEA: Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics

TBTC: U.S. Centers for Disease Control and Prevention Tuberculosis Trials Consortium

WHO-TDR: World Health Organization–based Special Programme for Research and Training in Tropical Diseases

NOVEL COMPOUNDS

AZD5847

AstraZeneca's AZD5847 is an oxazolidinone. AZD5847—like sutezolid, described below—has promise as it is in the same class as Pfizer's linezolid, which is effective in treating drug-resistant TB, but comes with damaging side effects including vision loss, painful damage to the peripheral nervous system, and anemia.[31] AZD5847 has appeared well tolerated in the very short, small trials that have been conducted. The main effects were nonserious gastrointestinal events and reductions in white blood cells (important in immune functioning) and red blood cell counts (which can lead to anemia).[32,33,34]

AZD5847 moved into a phase IIa clinical trial in the fall of 2012. This two-week early bactericidal activity (EBA) study compares four different dosing schedules of AZD5847 (500 mg orally once daily, 500 mg orally twice daily, 1,200 mg orally once daily, or 800 mg orally twice daily) with a control arm of the standard four-drug, first-line therapy.[35] The study is currently enrolling; results are expected in the first half of 2014.[36] AstraZeneca's investments in developing AZD5847 made it the third-largest private funder of TB research and development in 2011.[37] AstraZeneca has been notably reticent when approached by community groups seeking discussions; it is time for the company to engage with research advocates and representatives from TB-affected communities in a meaningful way.

Bedaquiline (brand name: Sirturo; formerly known as TMC207)

Bedaquiline made history in late 2012, when the FDA granted it accelerated approval as part of combination therapy for MDR-TB. A diarylquinoline, bedaquiline is the first new drug from a new class of drugs to be approved in over 40 years. Bedaquiline is being developed for DR-TB by Janssen Infectious Diseases BVBA (a subsidiary of Johnson & Johnson formerly known as Tibotec), and for DS-TB by the TB Alliance.

FDA approval was based on data from two phase II studies of 440 people with DR-TB. These studies found that bedaquiline, when given with existing MDR-TB drugs, was extremely effective against TB. For example, in study C208 when a five-drug background regimen was administered with six months of bedaquiline or a placebo, 79 percent of those randomized to receive bedaquiline achieved culture conversion, versus 58 percent of those who received background regimen alone. Median time to conversion in the bedaquiline arm was 12 weeks versus 18 weeks for those in the placebo arm.[38]

Janssen's data were encouraging regarding bedaquiline's efficacy, but less so for its safety. Most drugs used to treat MDR-TB have serious side effects—bedaquiline's include moderate QT prolongation (a disturbance in the heart's electrical activity that could potentially lead to serious and even fatal rhythm disturbances) and elevated aminotransferase levels (increased liver enzymes in the blood, indicating potential liver damage).

The drug's long terminal half-life of about five and a half months means it lingers in tissues for a long time. This may mean longer exposures to bedaquiline's side effects. As bedaquiline remains in the body long after treatment ends and other TB drugs have cleared, if a patient had not yet cleared all bacteria and achieved cure, there is potential for resistance to bedaquiline to develop.[39] However, since it was taken for only six months over a background of therapy lasting 18 to 24 months, this has not been observed in the studies conducted to date.

One study found excess mortality in the bedaquiline arm: 13 percent (10/79) of patients who took bedaquiline and other drugs died, versus only two percent (2/81) in the placebo arm (P = 0.017). Drawing conclusions from these data is difficult, given that the overall number of people taking the drugs was small. There was no common cause of death other than TB (five of 10 deaths) among those who died in the bedaquiline arm, and all but one death occurred after bedaquiline administration ceased.[40] The mortality rate in the control arm was lower than expected in a population with DR-TB. Nevertheless, this increased mortality requires further investigation of bedaquiline's safety; it will be essential to monitor mortality not only during, but for at least six months after bedaquiline administration.

Because of safety and drug interaction issues, the FDA urged caution when using bedaquiline with clofazimine and fluoroquinolones, as all cause QT prolongation. Based on available data, bedaquiline should not be used with rifampicin or rifapentine.[41,42] The TB Alliance and NIAID recently completed a drug-drug interaction study with a single dose of bedaquiline added to rifabutin or rifampicin; pending results will further inform whether bedaquiline and rifamycins can be used safely together.[43] As delamanid also causes QT prolongation and is far along in the development pipeline, research is urgently needed to determine if it can be combined safely with bedaquiline—the National Institutes of Health (NIH) is arranging for this research, but the process is moving slowly.[44]

Bedaquiline interacts with anti-HIV protease and non-nucleoside reverse transcriptase inhibitors such as efavirenz (used globally in first-line HIV therapy) and lopinavir/ritonavir (used in second-line therapy), and should not be taken with the antifungal ketoconazole for more than two weeks, as both cause QT prolongation.[45,46,47] Bedaquiline may cause liver or heart damage, so more research is necessary to see if it is safe for people who use alcohol, methadone or buprenorphine, or other drugs, or have hepatitis B or C.

To address safety questions, confirm its efficacy, determine its optimal use, and comply with the conditions of FDA approval, Janssen is about to begin a phase III trial of bedaquiline and a patient registry of all those who receive the drug in the United States. The phase III trial will involve 600 subjects with sputum smear–positive pulmonary MDR-TB, including pre-XDR-TB. Participants in the first arm will receive nine months of bedaquiline and a background regimen (six months of prothionamide, high-dose isoniazid, levofloxacin, ethambutol, clofazimine, and pyrazinamide, with four months of kanamycin; followed by three months of levofloxacin, ethambutol, clofazimine, and pyrazinamide). Those in the control arm will receive placebo and the background regimen. Participants from the first two arms whose treatment failed will have access to rollover arms, where they will receive an individualized salvage regimen.[48]

People with HIV will be included in the study, but only if their viral load levels are below 400 copies/mL and their CD4 counts are above 250 cells/mm^3 at screening; participants cannot be on anti-HIV medicines other than triple nucleoside reverse transcriptase inhibitor–, nevirapine-, or lopinavir/ritonavir-based regimens.[49]

The primary endpoint will be the proportion of subjects with a favorable treatment outcome (i.e., two consecutive negative cultures 25 days apart or no signs or symptoms of active TB if no sputum can be produced) at 15 months for those in the first two arms, representing six months of treatment-free follow-up—this is a traditional endpoint for efficacy. The final analysis will look at the proportion of favorable outcomes at 21 months, or one year of treatment-free follow-up.[50] Janssen is looking into increasing community engagement at identified phase III trial sites. A strong community engagement program could benefit the required study's enrollment, which may be challenged by parallel marketing approvals in trial-site countries. Individuals may be reluctant to participate in a phase III trial if a drug is on the market; community outreach and education about the importance of research may help with recruitment and retention.

The FDA required Janssen to create a patient registry for all bedaquiline-treated patients in the United States to assess the incidence of serious adverse events including death.[51] This assessment must be completed and submitted to the FDA by 2019.

The IMPAACT network is currently completing protocol design for study 1108, a pharmacokinetic and safety study of bedaquiline in children with MDR-TB, which will begin by placing the oldest children (12–18 years) on an adult formulation of bedaquiline. All younger cohorts (6–12 years, 2–6 years, 6 months–2 years, 0–6 months) will be placed on a pediatric formulation currently in development by Janssen, sequentially from oldest to youngest, once adequate data from the preceding cohort are available. Enrollment is anticipated to start in the first quarter of 2014. The study plans to first enroll HIV-negative children in each age cohort, then enroll similar numbers of HIV-positive children in the oldest cohort, all with proven or presumed MDR-TB. A separate HIV-coinfection trial for the younger age groups is under discussion.[52]

Bedaquiline's potential to help shorten MDR-TB treatment or to replace existing, inferior drugs has not yet been verified, though it is plausible given evidence of the drug's ability to reduce time-to-culture conversion.[53] Janssen will pursue additional studies of interest in collaboration with others in the TB community. Some proposed treatment-shortening studies include ACTG 5319 (called the MDR-Additive Regimens Varying Experimental Layouts or MARVEL study), which plans to use bedaquiline as a backbone in various combinations with other new and existing drugs to determine optimal regimens. The recently completed NC-003 study tests bedaquiline with

various combinations of clofazimine, PA-824, and pyrazinamide to assess its safety and efficacy with these drugs. The TB Alliance's proposed NiX-TB open-label study involves bedaquiline given only with other new drugs—PA-824 and an oxazolidinone—to patients with pre-XDR/XDR-TB. Given the limited site capacity for conducting MDR-TB trials, the TB research community needs to come together to develop the most efficient path forward for testing bedaquiline and other new drugs to determine optimal combinations.

Bedaquiline Approval and the Evolving Regulatory Landscape

As the first new TB drug from a new drug class to be approved by the FDA in over forty years, and with filings in China, Europe, Russia, South Africa, and Thailand and more planned, bedaquiline is a wake-up call for regulators across the world to develop their capacity to review new drugs for TB. Janssen's laudable compassionate use program (which provides pre-approval access to the drug for individual patients in critical condition under select circumstances) has stimulated regulatory authorities in countries where these patients live, who must approve the importation of the drug.

Regulators are generally not equipped to rapidly convene a group of experts who can provide knowledgeable feedback on new TB drugs, as they have not been required to do so for over 40 years. Bureaucracy and financial and human resource constraints tend to slow down drug review processes, particularly in the countries most affected by TB. Countries must both scale up their capacity to rapidly review new drug applications and implement adequate systems for holding drug sponsors accountable postapproval. Particularly as bedaquiline and new drugs are approved under accelerated mechanisms with only phase II data, regulators must ensure their ability to enforce post-marketing surveillance and the sponsor's completion of required studies.

TB programs require similar improvements. Countries must dedicate more funding both for programs to scale up diagnosis of MDR-TB and linkage to care. National treatment programs need to prepare for the rapid adoption and rational use of approved new drugs to ensure access, and reduce the emergence of drug resistance, to both existing and new drugs. This includes both swift adaptation of guidelines and implementation on the ground. A commitment to proper TB treatment requires better forecasting of demand and supply-chain management from treatment programs.

Sponsors must do their share to rapidly register new drugs in countries where they are needed and to deliver drugs quickly once approval is obtained. For example, Janssen made bedaquiline available immediately upon approval in the United States under its compassionate use program, and four months later, the product became commercially available. Yet the burden of the disease remains outside of the U.S. Sponsors are responsible for pricing the drug affordably and for fulfilling any requirements of approval (e.g., further studies or postmarketing surveillance) rapidly and thoroughly.

Delamanid (OPC-67683)

Otsuka's compound delamanid, a nitroimidazole, shows great promise in treating MDR-TB. While it trails behind bedaquiline in terms of regulatory approvals—decisions from the European and Japanese regulatory agencies are pending, and Otsuka plans to file with the FDA in the near future—it has advanced further than bedaquiline in clinical trials. Enrollment for a phase III trial of an optimized background regimen plus six months of delamanid or placebo has been under way since mid-2012.[54] Indeed, Otsuka is the leading private investor in TB research, dedicating $65 million in 2011 alone.

Delamanid's apparent safety and efficacy in a two-month phase IIb trial were recently followed-up in a six-month open-label trial.[55] Patients who successfully completed the two-month trial were eligible to enter a longer observational study where they were given delamanid for an additional six months. All patients, including those who did not enter the six-month study, were observed for 24 months to evaluate long-term treatment outcomes. Of those who received delamanid for six months or more, favorable outcomes (defined as five consecutive negative cultures in the preceding 12 months, or treatment completed, but with fewer than five negative—and no positive—cultures) were observed in 74.5% versus 55% of those who received delamanid for two months or less. Only 1% of those receiving long-term delamanid treatment died, versus 8% of those who received short-term or no delamanid.[56]

Delamanid appears generally safe, although it does cause mild-to-moderate QT prolongation.[57] Delamanid is being tested for administration twice daily at 100 mg for the first two months of treatment, and once daily at 200 mg for the following four months.[58] Delamanid's pediatric formulation of small, dissolvable tablets is complete, and a pediatric study has begun in the Philippines.[59] Drug-drug

interaction studies have shown that delamanid plus efavirenz, tenofovir, or lopinavir/ritonavir does not cause any clinically relevant effects, though lopinavir/ritonavir does increase exposure to delamanid by 20 percent.[60,61] Delamanid has been safely administered with other second-line drugs, although QT prolongation is a concern with fluoroquinolones and clofazimine, and drug-drug interaction studies may be necessary to determine if they are safe to use together. Giving delamanid along with the first-line anti-TB drug rifampicin reduced exposure to delamanid by 40–50 percent.[62]

Delamanid is a promising drug. Data support pre-approval access to it for those in urgent need. Otsuka has been collaborating with Médecins Sans Frontières to develop a compassionate use program; however, this has been slow to start. It is imperative that Otsuka initiate compassionate use programs so those in urgent need can benefit from pre-approval access to delamanid, as it may be over a year before delamanid is actually rolled out. Janssen, with more experience in infectious disease drug development, opened a compassionate use program for bedaquiline before filing for approval or initiating phase III studies, while Otsuka has done the opposite with delamanid.

PA-824

PA-824, like delamanid, is a nitroimidazole—a new drug class for fighting TB. The TB Alliance is developing PA-824 for both drug-sensitive and drug-resistant TB in its novel combination studies, including NC-002 and NC-003. PA-824 is included in the previously described proposed NiX-TB and MARVEL study plans.

The TB Alliance and NIAID cosponsored a phase I thorough QT safety study to evaluate any effects PA-824 will have on the rate at which the heart conducts electrical impulses. The clinical trial studied whether PA-824 and moxifloxacin had additive or synergistic effects on the QT interval. Results should be available soon.[63]

The ACTG has completed enrollment of study A5306, a phase I safety, tolerability, and pharmacokinetic interaction study of PA-824 with two common antiretrovirals, lopinavir/ritonavir and efavirenz, as well as with rifampicin.[64] Results from the efavirenz/PA-824 arm showed that the two drugs were well tolerated when given together, and PA-824 did not affect efavirenz concentrations. Efavirenz reduced exposure to PA-824 modestly; the clinical implications of this reduction, though, are unknown and warrant further study.[65] Results from the lopinavir/ritonavir and rifampicin arms should be available soon.

Russian Regulatory Reforms Required

Two compounds, perchlozone and SQ109, are racing through Russian research and regulatory processes. Yet the paucity of promising peer-reviewed data on either drug raises concerns about the compounds themselves, the transparency of their developers, and Russian regulatory capacity.

Perchlozone

Perchlozone from JSC Pharmasyntez is a new drug from the thiosemicarbazone drug class. Perchlozone was approved in Russia for treating MDR-TB in November 2012, but has not yet been appropriately scrutinized via traditional clinical and peer-review processes. In fact, no peer-reviewed data in English are available.

Despite having only been studied for three months in humans, the drug was approved for use for six months on top of a background regimen. The drug's recommended dosage is 9.5–12.5 mg/kg, although it was studied at 20–30 mg/kg. Perchlozone costs EUR2,000–4,000 per six-month course depending on the patient's weight.

Pharmasyntez has initiated what they call a phase IV trial in Russia—although it will only involve 340 patients—to administer perchlozone for six months along with a 12–18 month course of fluoroquinolones and other drugs to people with DS- and DR-TB, and including HIV coinfected individuals. The company is considering registration in African countries and the Commonwealth of Independent States (CIS).[66] The company's failure to publish peer-reviewed data on the drug and its substandard clinical trial designs are unacceptable. It is essential that Pharmasyntez make all existing data available for external, unbiased peer review before additional clinical studies are initiated.

SQ109

SQ109 is an ethylenediamine antibiotic, in the same drug class as ethambutol, though with a novel mechanism of action—both affect cell-wall assembly, but SQ109 appears to do so by inhibiting the MmpL3 protein (see table 2), whereas ethambutol likely inhibits arabinosyl transferase.[67,68] Early in vitro and mouse studies showed SQ109 does not exhibit cross-resistance with ethambutol, and is effective at killing *Mycobacterium tuberculosis*.[69] The drug appeared synergistic in vitro with isoniazid, rifampicin, and bedaquiline, and additive with sutezolid; mouse studies indicated that SQ109 was more effective than ethambutol when given with isoniazid and rifampicin in reducing the number

of colony forming units.[70,71,72,73] The company claims that unpublished data show in vitro synergy with amikacin, capreomycin, clofazimine, and moxifloxacin, and additivity with cycloserine, ethionamide, kanamycin, and para-aminosalicylic acid.[74]

No evidence from humans yet supports the continued development of SQ109. The drug appears safe and well tolerated, but results from a phase IIa trial cosponsored by the European and Developing Countries Clinical Trials Partnership (EDCTP) showed that the drug has no early bactericidal activity (EBA).[75,76]

Sequella is optimistic that it will be effective in treating TB when given for longer periods, despite the lack of any clinical evidence to support that view. Sequella announced in November that the first person had been enrolled in a pivotal trial in Russia and Kazakhstan, which is being run by a little-known Russian company called Infectex.[77] In this trial, SQ109 is being given for six months on top of an 18-month background regimen, compared with the background regimen alone. This study will have two-year follow-up and both clinical and mycobacterial endpoints, although it will involve only 84 participants—unacceptably small for a registrational trial. Sequella assures that the trial is only for registration in Russia and the Commonwealth of Independent States (though the data may be included in other applications), is led by an esteemed principal investigator, and is being conducted according to International Conference on Harmonisation guidelines. However, as with perchlozone above, there are no data yet to support a registration trial, and approval standards are significantly lower in Russia or in the CIS than elsewhere in the world. We recommend that Russia and the CIS improve their regulatory capacity to oversee development of urgently needed TB drugs.

Sequella will conduct a conventional phase IIb MDR-TB study of SQ109 plus an optimized background regimen, compared with an optimized background regimen alone, if it is able to obtain sufficient resources.[78] In 2012, Sequella invested US$4.5 million in developing SQ109 and other TB products, which is not enough to adequately evaluate a new drug in humans.[79]

In the meantime, the recently initiated phase IIb Multi-Arm Multi-Stage (MAMS) study conducted with the assistance of the EDCTP includes SQ109 in two out of five study arms, in combination with moxifloxacin and high-dose rifampicin.[80] NIAID planned a thorough QT safety study in healthy volunteers that will occur in 2013. However, with TB research budgets under extreme pressure, and based on currently available evidence, expending resources on SQ109 does not appear to be an appropriate use of limited public research funding.

Sutezolid (PNU-100480)

Sutezolid, also known as PNU-100480, is an oxazolidinone, like linezolid and AZD5847. In vitro and mouse models suggest that sutezolid may be more active than linezolid against TB. As linezolid has serious side effects, including optic and peripheral neuropathy and anemia, safer oxazolidinones are needed. [81] Like linezolid, sutezolid does not induce or inhibit the enzyme CYP3A4, important to the metabolism of many other TB and HIV drugs, meaning its potential for drug-drug interactions may be lower.[82] Appropriate drug-drug interaction studies should be conducted to confirm this. Sutezolid is of great interest to the TB research community, yet since TAG first reported on the drug in the *2009 Pipeline Report*, Pfizer has only completed two phase I and one phase IIa clinical trials, in addition to preclinical work.[83,84,85,86]

In 2012, Pfizer reported results of its first study of sutezolid in TB patients, which showed the drug to be safe and active against TB. Fifty-nine South African participants with DS-TB with and without HIV, but not on antiretrovirals, were assigned to one of three arms: 600 mg of sutezolid twice daily, 1,200 mg daily, or the standard four-drug therapy for DS-TB for the first two weeks of treatment. The study found no treatment-related serious adverse events and no effect on QT interval, although temporary, asymptomatic liver-enzyme elevations were observed.[87] Other TB drugs such as pyrazinamide also raise liver enzymes. A recent mouse study revealed that combinations including sutezolid were more effective than the standard first-line regimen, and could improve HIV-associated TB treatment by avoiding the use of rifamycins, which often interact with antiretroviral therapy.[88]

Sutezolid warrants further research right now.[89] Several proposed new studies—including the previously described NiX-TB study evaluating a regimen of entirely new drugs in people with pre-XDR- and XDR-TB, and the MARVEL study of multiple proposed MDR-TB treatment arms—include sutezolid. However, Pfizer has been unwilling to make sutezolid available to clinical research consortia such as the TBTC, TB Alliance, or ACTG to advance it and test its potential with existing or other experimental TB drugs. Pfizer must commit to both more rapidly advancing the development of sutezolid on its own, and to making the compound available for collaborative study in combination with other new and existing drugs.

Table 4. Enrolling Clinical Studies for Active Tuberculosis

Study/Regimen	Stage	Indication	Sponsor
C213 **delamanid** for 6 months plus 18–24 months individualized background regimen, and 6–12 months follow-up	Phase III	DR-TB	Otsuka
STREAM 9 months clofazimine, ethambutol, moxifloxacin, and pyrazinamide, with prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of 4 months	Phase III	DR-TB	The Union, MRC-UK
MAMS-TB-01 3 months of different combinations of ethambutol, isoniazid, moxifloxacin, pyrazinamide, rifampicin (10, 20, or 35 mg/kg) and **SQ109**	Phase IIb	DS-TB	PanACEA, EDCTP
AZD5847 500 mg once or twice daily, 1,200 mg once daily, or 800 mg twice daily	Phase II (2-week EBA study)	DS/DR-TB	AstraZeneca

Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds

DR-TB: Drug-resistant TB DS-TB: Drug-sensitive TB EBA: Early bactericidal activity

INTERTB: International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis

MRC-UK: British Medical Research Council

The Union: International Union Against Tuberculosis and Lung Disease

EXISTING COMPOUNDS

Clofazimine

Clofazimine—already FDA-approved for treating Hansen's disease (leprosy) since 1986—has piqued the interest of TB researchers by appearing successful when administered off-label for DR-TB in several studies, and it was included in the nine-month standardized treatment regimen for MDR-TB known as the "Bangladesh regimen,"[90,91,92] though the work in question was not conducted according to good clinical practice (GCP) and thus would not be acceptable to a stringent regulatory authority. This enthusiasm is hampered by clofazimine's side effects: skin discoloration is common and QT prolongation is a concern; clofazimine is more rarely associated with depression, with two suicides reported.[93] The Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM) study, the phase III bedaquiline trial, study NC-003, and the proposed MARVEL

study all include clofazimine, and will provide more information on clofazimine's safety and efficacy for treating DR-TB. Novartis, clofazimine's sponsor, has refused to provide study drug for these efforts, and access has challenged both research and programmatic efforts. A wealthy drug company with little to lose by expanding access to the niche drug for an underserved population, Novartis must facilitate the development of improved treatment for patients with DR-TB.

Fluoroquinolones

Gatifloxacin and moxifloxacin are both fluoroquinolones with broad-spectrum antibiotic activity and TB treatment-shortening potential, but unfortunately face prevalent preexisting resistance in many parts of the world.

Preliminary results from the RIFAQUIN study from the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB) were recently reported, revealing that using moxifloxacin and rifapentine together for six months for active, drug-sensitive TB can simplify treatment to once-weekly dosing in the continuation phase—including in people with HIV with CD4 counts of 150 cells/mm^3 or higher and not on ART.[94] Prior studies of intermittent regimens, however, led to increased treatment failure, relapse or resistance among patients with TB and HIV, so this approach merits further study in coinfected populations.[95] The RIFAQUIN regimen, while promising for intermittent therapy, could not shorten effective treatment to four months.[96] Data from the phase III REMox TB study, comparing moxifloxacin substituted for either ethambutol or isoniazid to shorten treatment to four months, should be available by early 2014.[97]

The TBTC's RioMAR study examined the role of replacing ethambutol with moxifloxacin, as well as rifampicin with rifapentine, during the intensive phase of treatment; enrollment closed, and data analysis will begin shortly.[98] As described above, the TB Alliance and NIAID cosponsored a phase I thorough QT study of PA-824 and moxifloxacin; results are pending.[99]

Moxifloxacin is included in the New Combination 2 (NC-002) study and is featured in the STREAM study.

While gatifloxacin has taken a backstage to moxifloxacin due to moxifloxacin's rapid killing activity and to gatifloxacin's removal from the market in many countries due to side effects, information on gatifloxacin might help broaden the understanding of whether fluoroquinolone use has a role in first-line TB treatment shortening.[100] Two years ago, the European Commission's OFLOTUB consortium completed a trial replacing ethambutol with gatifloxacin to evaluate gatifloxacin's potential to shorten first-line treatment to four months. Results were delayed due to issues with funding and data management, but are expected by the end of 2013.

Gatifloxacin was used in the "Bangladesh regimen," an all-oral drug regimen that may have the potential to simplify MDR-TB treatment and shorten it to nine months. Follow-up studies based on this regimen such as the STREAM study, however, are using other fluoroquinolones such as levofloxacin or moxifloxacin.

Linezolid

Pfizer's linezolid was approved in 2000 to treat drug-resistant, gram-positive bacteria.[101] While TB is not gram-positive, linezolid has occasionally been in use to treat DR-TB, although information on the drug's safety for long-term use was minimal. Linezolid's efficacy against MDR- and XDR-TB appeared strong in vitro, but more modest in mice.[102,103,104,105,106,107]

NIAID and the South Korean Ministry of Health and Welfare sponsored a phase IIa study of linezolid in South Korea. Pfizer donated study drug. Forty-one patients without HIV whose current pulmonary XDR-TB treatment had been failing for at least six months were enrolled; participants had, on average, been treated five previous times for TB. Participants were randomized to add 600 mg of linezolid on top of background drugs daily, either immediately or after two months. After four months or after culture conversion, whichever came first, patients were randomized again to continue linezolid at a dose of either 600 mg or 300 mg daily for at least another 18 months.[108]

Starting linezolid immediately increased the percentage of patients whose TB converted after four months (79% vs. 35%; $P = 0.001$); 87 percent of patients had negative sputum culture within six months of first taking linezolid. Thirteen of 38 patients who received linezolid completed therapy without relapse, 17 patients were still receiving treatment per protocol, and eight patients withdrew early.[109] Follow-up of all patients will be completed at the end of 2013; investigators claim that, to date, no additional failures or relapses have been recorded.[110] With the early conversion rates, and supposed potential for high treatment success rates, these results could exceed previously documented XDR-TB treatment success rates. For example, in a Latvian study of 48 XDR-TB patients treated with individually tailored regimens, 38% were cured, 8% died, 6% did not complete treatment, and 48% had an unfavorable outcome.[111]

Linezolid's activity, however, came at a cost: 82 percent of patients had clinically significant adverse events possibly or probably related to linezolid, and three patients out of 38 discontinued therapy. Adverse effects included anemia, neutropenia (abnormally low amounts of certain white blood cells, which can affect immunity), optic neuropathy, peripheral neuropathy (causing pain or numbness in the limbs), and rhabdomyolysis (the breakdown of skeletal tissue, which can lead

to kidney failure). Patients switched to 300 mg of linezolid daily after the second randomization had fewer adverse events than those who continued taking 600 mg. Nearly all events resolved after drug discontinuation or dose reduction. Despite the addition of a single drug to a failing regimen, only four cases of linezolid resistance were observed. Drug resistance was determined by a lack of clinical response or relapse, an increase in minimum inhibitory concentrations as compared to baseline levels, and DNA sequencing revealing mutations previously shown to be associated with linezolid resistance.[112]

While linezolid may be effective at treating extreme cases of drug-resistant pulmonary TB, adverse events are frequent and require close monitoring. A safer drug in the same class would be better.[113] Until then, Pfizer, linezolid's sponsor, must make the drug more affordable—its current high cost is a major barrier to access.

Rifamycins

Several studies are ongoing to determine the effect and safety of using rifampicin for DS-TB therapy in higher doses than the currently used dose of 10 mg/kg, which was selected not based on a maximum-tolerated dose, but rather because the drug was originally expensive, so a low dose was selected. The EDCTP-funded HIGHRIF group within the Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics (PanACEA) has found with its HR1 two-week safety and early bactericidal study that administering up to 35 mg/kg of rifampicin is safe and well tolerated, and that early bactericidal activity increases with the dose.[114] The group is planning to extend this study further with even higher doses.

HIGHRIF was part of the larger HR2 two-month study that looked at rifampicin dosages up to 20 mg/kg. Final analysis will be conducted this summer, but preliminary results show that toxicity was limited.[115]

The group recently started the above-described MAMS study, which tests one group with 35 mg/kg of rifampicin, a second with 20 mg/kg of rifampicin combined with moxifloxacin, and a third with 20 mg/kg of rifampicin combined with SQ109.[116] The INTERTB group will soon publish the results of the RIFATOX trial, which tested the toxicity of rifampicin at 900 mg and 1,200 mg daily for the first four months of the standard six-month regimen (which typically includes up to 600 mg daily of rifampicin).[117] Based on these results, a phase III study called RIFASHORT is planned to look at the treatment-shortening potential of high-dose rifampicin.[118] The NIAID HIRIF study, due to start in Peru this year, features high-dose rifampicin.[119,120] Médecins Sans Frontières (MSF)/Epicentre is planning RIFAVIRENZ, a drug-drug interaction study of high-dose rifampicin and efavirenz expected to start in September 2013.[121]

Current enthusiasm around optimizing rifamycins to improve DS-TB treatment includes rifapentine, the approved drug from Sanofi recently shown to enable shortened courses of LTBI treatment. Rifapentine has a longer half-life than rifampicin, and may be suitable for regimens that shorten treatment or allow for less frequent dosing for active TB as well. Indeed, the above-described RIFAQUIN study showed that replacing rifampicin with rifapentine (and isoniazid with moxifloxacin) in the continuation phase of treatment allowed for once-weekly dosing.[122]

The TBTC conducted Study 29, which showed that substituting 10 mg/kg of rifapentine for rifampicin, and dosing only five days weekly in the intensive phase, was safe. However, it was not significantly more active than the standard rifampicin regimen, so studies of higher doses of rifapentine were proposed.[123] Therefore, the TBTC conducted Study 29X, to determine the safety and estimate the efficacy of using 10, 15, and 20 mg/kg of rifapentine daily with isoniazid, pyrazinamide, and ethambutol for the eight-week intensive treatment phase. All doses appeared safe and well tolerated.[124] Based on these results, the TBTC is planning a phase III, treatment-shortening trial of rifapentine.

ACTG 5311, a phase I safety and pharmacokinetic study at four U.S. sites, was designed to evaluate different strategies to optimize exposures to rifapentine: twice-daily dosing and use of different food types, including foods likely to be available in most international settings. The study was closed to new enrollment, and dosing was stopped in all patients at the end of May 2013.[125] Pending data from the RioMAR study, which replaces rifampicin with rifapentine and ethambutol with moxifloxacin during the intensive phase of treatment will further characterize the role of rifapentine in TB therapy.[126]

Even if these research endeavors prove successful, however, using rifapentine to improve treatment for people with TB may still be a long way off. Currently, rifapentine is just too expensive. Sanofi must match its commitment to TB research with a commitment to access by lowering the drug price.

Of all the rifamycins, rifabutin may be the most suitable for treating people on certain anti-HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, as it interacts less with them than rifampicin and rifapentine do. While rifabutin's importance in treating coinfected individuals is well established, there are some unanswered questions about optimal dosing, which some drug-drug interaction studies are seeking to answer. The British Medical Research Council's EARNEST rifabutin pharmacokinetics study is looking at whether rifabutin should be taken daily or three times weekly with the protease inhibitor lopinavir/ritonavir to find the right balance between drug levels and side effects in people with HIV and TB.[127] The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) will soon publish results from a study in people with HIV and pulmonary

TB in Vietnam on the most appropriate dose of rifabutin when given with protease inhibitors and other anti-HIV treatment. These results will inform the dosing for any future phase III trials comparing the safety, tolerability, and efficacy of rifabutin and rifampicin with protease inhibitor–based ART.[128]

Table 5. Planned Late-Stage Clinical Studies for Active Tuberculosis

Study/Regimen	Status	Indication	Sponsor
C210 9 months **bedaquiline**, clofazimine, ethambutol, isoniazid, kanamycin, levofloxacin, prothionamide, pyrazinamide	Phase III Protocol development	DR-TB	Janssen
NiX-TB **bedaquiline, PA-824, sutezolid**—proposed	Phase III (noncontrolled 6-month salvage study) Protocol development	Pre-XDR/ XDR-TB	TB Alliance
MARVEL (A5319) **bedaquiline**, clofazimine, levofloxacin, **PA-824**, pyrazinamide, **sutezolid** given for 8 weeks in various combinations	Phase II/III (2-month, with safety measures at 24 weeks) Protocol development	DR-TB	ACTG
HIRIF rifampicin 10, 15, 20 mg/kg daily, isoniazid, ethambutol, pyrazinamide in the intensive phase	Phase IIb (2-month) Not yet recruiting	DS-TB	Harvard University, NIAID

Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds

DR-TB: Drug-resistant TB DS-TB: Drug-sensitive TB XDR-TB: Extensively drug-resistant TB

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases

EDCTP: European and Developing Countries Clinical Trials Partnership

NIAID: U.S. National Institute of Allergy and Infectious Diseases

PanACEA: Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics

Research and Policy Recommendations

1. Governments and donors need to increase funding for TB research at least threefold.

At US$250 million per year in 2011 out of a target of US$740 million, funding for TB research and programs is only a fraction of what it needs to be, and these budgets are shrinking.[129] In the United States, sequestration (the automatic, across-the-board spending cuts triggered by congressional inaction earlier this year), as well as subsequent cuts to the NIH (the leading funder of TB research and development) and the CDC's extremely productive Tuberculosis Trials Consortium are undermining already underfunded research programs. A recent review points to the need for countries with high TB burdens to take a greater share in funding research and development for TB according to their gross domestic product, their disease burden, and the size of their treatment program.[130] Without increased research budgets, the new drugs and regimens urgently needed to improve TB care will not be developed.

2. Sponsors must commit to developing their drugs and making them accessible to other research groups.

For both new and existing drugs, a commitment from sponsors to ensuring rapid drug development is essential. This means investing in the development of compounds with human and financial resources. It entails working with research consortia and other TB drug developers early on to study drugs in combination, both to optimize their use and to make clinical research more efficient. Once new drugs or regimens are approved, sponsors must swiftly fulfill conditions of approval, including further studies and postmarketing surveillance. In particular:

- AstraZeneca should continue to invest in AZD5847 and begin to engage with community groups;
- Janssen must fulfill its postmarketing requirements quickly for bedaquiline, and work to close other research gaps including potential drug-drug interactions with delamanid and other drugs, and dosing and safety concerns in special populations including children;
- Novartis needs to make clofazimine available for TB research studies;
- Otsuka should facilitate the NIH's interaction work with bedaquiline to ensure it advances as quickly as possible;

- Pharmasyntez needs to make its full data available for peer review and create a sound, responsible development plan for perchlozone before pursuing further research studies or registration;
- Pfizer must commit to developing sutezolid and making it available to research consortia for developing optimized combinations;
- Sanofi should maintain its support for the TBTC to enable research on rifapentine to continue amid public financial austerity; and
- Sequella should be more transparent and amenable to sharing SQ109 data so its suitability for further development can be appropriately assessed.

3. More research is needed in important vulnerable populations.

TB is a disease of the vulnerable and marginalized, and yet research into important TB-affected communities is scarce or comes too late. TB drug sponsors and researchers must commit to studying TB drugs as thoroughly as possible, and as quickly as safety allows, in children, women (including pregnant women), people with HIV, people with hepatitis B and C, people who use alcohol, and people who inject drugs or are on opioid substitution therapy. Comprehensive drug-drug interaction studies or modeling need to be done with antiretrovirals, with methadone and buprenorphine, with hormonal contraception, and with other TB drugs, as many interact or have overlapping toxicities (such as heart and liver toxicity). Regulatory authorities can play an important role by appropriately encouraging and providing incentives for research in these populations.

4. Trial sponsors and implementers should engage TB-affected communities in the design, implementation, and posttrial communications of TB research.

Community engagement contributes to research that is ethical, efficient, and in the best interests of people affected by the condition being studied. As laid out in the *Good Participatory Practice Guidelines for TB Drug Trials*,[2] communities need to be engaged in the various stages of the development of new interventions, including design, research implementation, results dissemination, and posttrial access. TB-affected communities, including representatives from the special populations mentioned above, must be better included, particularly in key decisions affecting research. Communities should be engaged in trial design to push for efficacy outcomes that will adequately address community needs.

At each step of research, communities must be included to ensure participant safety and health, both during and after trials. In implementation stages, communities can be engaged to help maximize and streamline enrollment and retention. Posttrial, communities can help effectively disseminate results to participants, other advocates, and policy makers. Some sponsors and research consortia have made notable progress in including TB-affected communities in research in recent years, but more needs to be done to solicit and incorporate the perspective of communities, particularly in the design stages, when soliciting input in a timely fashion can actually make a substantive impact.

5. **TB researchers, drug sponsors, and regulators need to collaborate to develop an efficient path for testing new drugs and determining optimal combinations.**

With limited trial-site capacity and scarce financial resources, those involved in TB research should collaborate to determine an efficient way forward for testing new drugs and combinations. More investment in biomarkers and other basic research is required to identify endpoints that can shorten and simplify clinical trials. Researchers and regulators must be innovative and flexible to allow for clinical trial designs that make TB drug development more efficient. The use of promising novel drugs such as bedaquiline needs to be optimized through thoughtful research into combinations. Candidates without demonstrated efficacy, such as SQ109, are not an appropriate use of limited public research funding.

6. **Regulatory authorities must build capacity and expertise to appropriately regulate clinical trials, early access, accelerated approval, postmarketing studies, and pharmacovigilance for new TB drugs and regimens.**

Research and development of new TB drugs are ultimately meaningless if improved treatment options are not approved and available to those who need them. Regulatory agencies—particularly those in high TB burden countries—must scale up their ability to rapidly and carefully review submissions. This is as important in drug registration as it is in clinical research, where study design and drug importation approvals can be unnecessarily lengthy and cumbersome. Russia and the CIS in particular must improve their review process to ensure that studies—especially registration trials—are appropriately designed and conducted, and that only drugs with robust and peer-reviewed data on safety, efficacy, and dosing receive marketing approval. Regulatory authorities must build their capacity to enforce conditions of approval (i.e., drug registries and other postmarketing surveillance, and completion of required further studies).

7. National Treatment Programs need to improve their services, supply-chain management, and ability to rapidly adopt and appropriately implement new tools.

Countries must scale up TB diagnosis and linkage to care, particularly for drug-resistant TB. This includes remedying inadequate forecasting and drug-supply management to prevent stock-outs and address problems with commodity distribution. Programs need to increase their flexibility and capacity to rapidly adopt new drugs and regimens, through both adaptation of guidelines and actual implementation of those guidelines.

8. Drug sponsors and manufacturers must make licensed drugs accessible and affordable.

Drug sponsors and manufacturers have a responsibility to ensure access. When sufficient safety and efficacy data are available, sponsors of promising drug candidates need to provide their compounds through compassionate use or other responsible pre-approval access programs to people who cannot wait for treatment. Sponsors must move quickly to register new drugs in countries where they are needed. Once approved, companies must price drugs affordably, and manufacturers must work to maintain a steady, safe drug supply.

- Janssen should continue to file for approval in a range of countries, and price bedaquiline accessibly;
- Otsuka's compassionate use program for delamanid is overdue and needs to be initiated immediately, as it will likely be over a year until the drug is commercially available;
- Pfizer needs to lower the price of linezolid; and
- Sanofi should immediately lower the price of rifapentine to enable the taxpayers who funded its development to benefit from its implementation.

Conclusions

With a sparse drug pipeline and TB incidence and deaths declining slowly, we are not close enough to realizing the vision of zero TB deaths, new infections, and suffering. Budget cuts, the increase of DR-TB, and scientific challenges all threaten progress. But if donors, sponsors, researchers, regulators, and manufacturers all commit the necessary resources and will, the potential to improve TB care and ultimately end the disease is huge.

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The TB Vaccines Pipeline

Where are we going, where have we been?

By Mike Frick

Since the *2012 Pipeline Report*, results from phase II trials and advances in preclinical development have brought the pipeline for new TB vaccines into sharper focus, even as correlates of protective immunity against TB remain elusive. Nearly empty in 2000, the current pipeline includes 14 vaccine candidates in clinical trials and over 35 candidates in discovery or preclinical development. Compared to where the TB community stood just 10 years ago, the present pipeline attests to the reinvigorated investment in TB vaccine research and development over the last decade. Yet disappointing results from the phase IIb efficacy trial of vaccine candidate MVA85A in infants as a boost to neonatal BCG announced in February 2013 require that we reevaluate the strategies that have brought us this far, paying critical attention to gaps in our knowledge of how *Mycobacterium tuberculosis* (MTB) interacts with the immune system and to the metrics we use to advance vaccine candidates through the pipeline.

Where have we been? The last 45 years

Forty-five years elapsed between the phase IIb trial of vaccine candidate MVA85A and the last TB vaccine efficacy trial, which evaluated the effectiveness of the bacille Calmette-Guérin (BCG) vaccine in Chengalpattu, India, in 1968. Over the decades, BCG became the most widely administered vaccine in the world, given over one billion times at low cost. Created by weakening strains of *Mycobacterium (M.) bovis* (the bacterium that causes TB in cattle), BCG was first introduced in 1921 and remains the only licensed vaccine for tuberculosis.[1] While BCG protects children against meningeal and disseminated forms of TB disease and death, it offers adults and adolescents highly variable protection against pulmonary TB, the form of the disease responsible for the vast majority of transmission and TB-related morbidity and mortality. As a live attenuated vaccine, BCG also poses a risk of leading to disseminated TB disease in people living with HIV and other immunosuppressive conditions.[2]

There remains a pressing need to develop superior vaccines against TB given the incomplete protection BCG offers and the safety risks it poses to immune-compromised individuals. A safe, effective vaccine against TB would provide a powerful tool for achieving zero TB deaths, new infections, and suffering, a goal endorsed by over 500 individuals and organizations since November 2012.[3] A vaccine that achieves complete elimination of MTB after infection, or offers

complete protection against developing active TB, would offer the most direct path to zero.[4] Whether any of the vaccines under development can provide complete protection against TB remains unknown; yet the diversity of candidates in the pipeline could illuminate the degrees of protection afforded by different approaches.

Current TB vaccine candidates reflect several immunization strategies:

- **Prime:** Replace BCG with either live recombinant BCG (rBCG) or genetically attenuated MTB vaccines that confer greater safety and protective efficacy.
- **Prime-boost:** Boost the limited immunity conferred by BCG (or boost specific antigens presented by recombinant BCG or attenuated MTB) using either viral-vectored or adjuvanted subunit vaccines. Vaccines of this type would be administered as boosters to a BCG prime in infancy or in adolescence when BCG's protection begins to dissipate.
- **Immunotherapeutic:** Develop therapeutic vaccines that might synergize with chemotherapy to shorten treatment for active TB disease or latent tuberculosis infection (LTBI). The therapeutic vaccines under development include whole-cell and fragmented mycobacteria, although several of these candidates also demonstrate prophylactic potential.

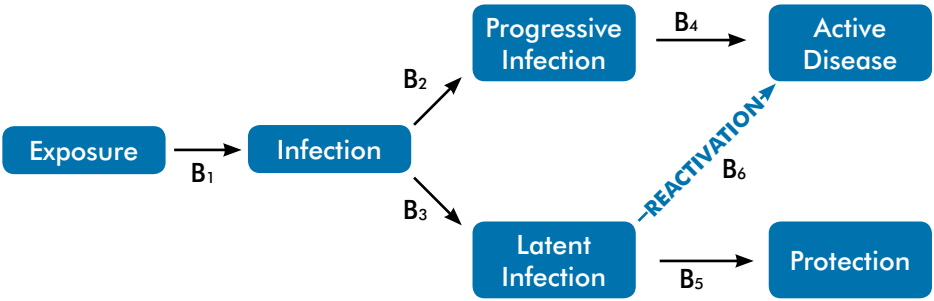
Common to these strategies is a focus on achieving cell-mediated immunity by inducing Th1 cytokines (e.g., IFNγ, TNFα, and IL-2) produced by either CD4 or CD8 T cells. These cytokines activate other cells capable of inhibiting the growth of MTB.[5,6] This approach differs from the majority of licensed vaccines, which work primarily by inducing humoral immunity: antibodies produced by B cells. Observations of how MTB interacts with both human and animal immune systems have led researchers to assess the immunogenicity of vaccine candidates by measuring Th1 cytokines associated with CD4 T-cell activity. Deficiencies in IFNγ and other Th1 cytokines appear to place MTB-infected individuals at increased risk of developing TB disease. The strong correlation between CD4 T-cell depletion and higher risk of TB among people with HIV has also focused attention on the cellular immune response.[7]

A truism among TB vaccine developers is that without clear correlates of immunity, testing the efficacy of potential vaccines requires advancing the most promising candidates to large, expensive phase III clinical trials. The aperture of the pipeline, however, opens only so wide, so testing one candidate means delaying others due to limited financial resources and the small number of research sites equipped to host large clinical trials. Biomarkers that signal protection against primary infection and reactivation of TB disease could serve as surrogate endpoints, enabling shorter trials and more rational selection of candidates in the preclinical and early stages

of clinical development. Yet biomarkers of protective immunity remain elusive, as do other important features of the dynamic human immune response to MTB infection.

The complexity of TB disease suggests that there is no single, silver-bullet biomarker of efficacy. Figure 1 illustrates where different biomarkers might fall in the immunologic life cycle of TB. Discovery of each would carry different implications for TB vaccine development. The ideal vaccine would offer protection across all populations and stages of TB's immunologic life cycle. It would prevent infection of healthy individuals, provoke the immune system to clear infection in a person recently exposed to MTB, and prevent reinfection and progress toward active disease.[8] If different biomarkers correlate with different stages of infection and disease, we may need multiple vaccines that protect distinct target populations through separate immunologic mechanisms. The absence of biomarkers of protective immunity has exerted a profound impact on the shape, composition, and strategies that define the current pipeline.

Figure 1: What do we talk about when we talk about biomarkers? Biomarkers for different stages of MTB's immunologic life cycle



B = biomarker. Prospective cohort studies may help to differentiate biomarkers of active disease (**B**$_4$) from latent infection (**B**$_5$). An open question remains whether such cohorts can distinguish markers of reactivated disease (**B**$_6$) from markers signaling the progression from initial infection to active disease (**B**$_2$, **B**$_4$). Human mycobacterial challenge models may help to identify biomarkers characterizing the transition from exposure to infection (**B**$_1$). Several preclinical studies in animals are exploring what enables 90 percent of those latently infected to resist disease (**B**$_5$). For example, studies in nonhuman primates are investigating the diverse activity characterizing granuloma formation and sterilization within a single host.[9] While these approaches may identify candidate biomarkers, only successful phase III trials can serve to validate biomarkers as surrogate endpoints for subsequent studies.

Image adapted from Ottenhoff TH, Ellner JJ, Kaufmann SH. Ten challenges for TB biomarkers. Tuberculosis (Edinb). 2012 Mar;92 Suppl 1:S17–20.

Where are we now? The clinical TB vaccine pipeline

There are currently 14 vaccine candidates undergoing or preparing to enter human clinical trials. Four of these candidates have reached phase I trials to demonstrate safety, and eight have reached phase II trials to assess their safety and immunogenicity. *M. vaccae* and *M. indicus pranii*, two whole-cell mycobacteria vaccine candidates, have completed phase III trials.

Table 1. Vaccine candidates under active development

Agent	Strategy	Type	Sponsors	Status
M. indicus pranii	Immunotherapeutic	Whole-cell *M. indicus pranii*	Department of Biotechnology (Government of India), Cadila Pharmaceuticals	Phase III
M. vaccae	Immunotherapeutic	Whole-cell *M. vaccae*	AnHui Longcom	Phase III pending
MVA85A/ AERAS-485	Prime-boost	Viral vector	Oxford University, Aeras	Phase IIb
M72 + AS01	Prime-boost	Adjuvanted subunit	GSK, Aeras	Phase IIb
Crucell Ad35/ AERAS-402	Prime-boost	Viral vector	Crucell, Aeras	Phase II (formerly phase IIb)
VPM1002	Prime	Live recombinant rBCG	Vakzine Projekt Management GmbH, Max Planck Institute for Infection Biology, TuBerculosis Vaccine Initiative (TBVI), Serum Institute of India	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase IIa
Hybrid 1 + IC31	Prime-boost	Adjuvanted subunit	Statens Serum Institut (SSI), TBVI, Intercell, European & Developing Countries Clinical Trials Partnership	Phase IIa
Hybrid 56 + IC31	Prime-boost	Adjuvanted subunit	SSI, Aeras	Phase IIa
Hybrid 4 + IC31/ AERAS-404	Prime-boost	Adjuvanted subunit	Aeras, Sanofi Pasteur	Phase IIa
ID93 + GLA-SE	Prime-boost	Adjuvanted subunit	Infectious Disease Research Institute, Aeras	Phase I
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
MTBVAC	Prime	Live genetically attenuated MTB	University of Zaragoza, Biofabri, TBVI	Phase I
Dar-901	Prime-boost	Whole-cell *M. vaccae*	Geisel School of Medicine at Dartmouth University	Phase I pending

Note: For each candidate under the prime-boost strategy, trials are evaluating the experimental vaccine in the left-hand column given as a boost to a BCG prime.

LIVE RECOMBINANT VACCINE CANDIDATES

Two live vaccine candidates designed to replace BCG remain in the pipeline: VPM1002 and MTBVAC. As a live recombinant form of BCG, VPM1002 aims to overexpress key MTB antigens. By contrast, MTBVAC contains live MTB weakened to become less virulent while still provoking a cellular immune response. A phase I trial of an earlier live recombinant candidate, AERAS-422, ended in 2011 due to adverse events (reactivation of shingles). Another live recombinant candidate, rBCG30, completed a phase I trial in 2004 but has been placed on hold without further development plans.[10]

VPM1002

Currently completing a phase IIa trial, VPM1002 remains the most advanced live recombinant BCG vaccine candidate. Lead developers for VPM1002 include Vakzine Projekt Management GmbH, the Max Planck Institute for Infection Biology, and the TuBerculosis Vaccine Initiative (TBVI). Vakzine Projekt Management GmbH recently formed a partnership with the Serum Institute of India to support VPM1002's development.[11] The phase IIa trial hosted by Stellenbosch University in South Africa enrolled its final participant in May 2012. The trial will compare the safety of VPM1002 and BCG in 48 BCG-naive, HIV-negative newborns. Preliminary data suggest the vaccine is safe and stimulates an immune response similar to an equivalent dose of BCG, as measured by CD4 and CD8 T-cell activity.[12]

A second phase IIa trial will begin by early 2014 and will assess the safety and immunogenicity of VPM1002, compared with BCG, in HIV-exposed and -unexposed newborns.[13] VPM1002 remains one of the few candidates with an infant or newborn product-development profile at a time when the pipeline is shifting toward vaccine development for adolescents and adults based on data showing that older age groups account for the majority of pulmonary TB transmission.

MTBVAC

A phase I trial of MTBVAC, a live attenuated MTB vaccine candidate, began in Lausanne, Switzerland, in January 2013. MTBVAC is the first live vaccine constructed from attenuated MTB to enter clinical trials and is being developed by the University of Zaragoza in partnership with Biofabri, a Spanish pharmaceutical company, and TBVI.[14] The trial will enroll 36 BCG-naive, HIV-negative adult volunteers to compare the tolerability and safety of MTBVAC with BCG. Since MTBVAC is a live vaccine, the initial series of trials will take place in HIV low-incidence settings.

MTBVAC contains MTB attenuated by the deletion of two virulence genes: phoP

and fadD26. Analyses of clinical isolates from an *M. bovis* XDR strain (B strain) responsible for an MDR-TB outbreak in Spain in the early 1990s suggest that phoP plays an important role in regulating mycobacterial lipids that contribute to MTB virulence.[15,16] Preclinical studies indicate that MTBVAC is safe in immune-compromised mice and protects guinea pigs and nonhuman primates against MTB infection. Notably, vaccination with MTBVAC in mice resulted in greater differentiation of CD4 T-cells into effector and memory T-cells compared with BCG.[17] This finding suggests that MTBVAC has the potential to confer longer-lasting immunity than BCG.

VIRAL VECTOR VACCINE CANDIDATES

Viral vector vaccines use weakened, nonreplicating viruses to transport MTB DNA into human cells, where the DNA is transcribed into proteins that provoke an immune response. The three viral vector candidates in human trials represent the most advanced branch of the pipeline, with two of these undergoing multiple phase II trials and the third recently completing an initial phase I study. Each intends to boost the effects of earlier vaccination with BCG under a prime-boost strategy.

MVA85A/AERAS-485

The most significant news from the TB vaccines world in the past year came from the disappointing results of the phase IIb trial of vaccine candidate MVA85A/AERAS-485 in BCG-primed infants. This marked the first efficacy trial of an engineered TB vaccine since the Chengalpattu, India, trial of BCG in 1968. Developed by the Oxford-Emergent Tuberculosis Consortium with support from Aeras, MVA85A is a recombinant strain of modified vaccinia virus Ankara (MVA) that expresses MTB antigen Ag85A. MVA85A aims to boost earlier vaccination with BCG, as most BCG-vaccinated individuals carry immunologic memory of the Ag85A antigen.

The phase IIb trial randomized 2,794 BCG-vaccinated, HIV-negative infants ages four to six months to receive either MVA85A or placebo (*Candida* skin test antigen). The primary study endpoint was safety with two secondary efficacy outcomes: protection against TB disease and prevention of MTB infection. Although admirably safe, MVA85A did not protect infants against either TB disease or MTB infection. The study team reported 39 cases of incident TB in the placebo group compared with 32 cases in the vaccine group, for an overall estimated vaccine efficacy of 17.3 percent. For the MTB infection endpoint, 171 infants in the placebo group and 178 infants in the MVA85A group became infected with MTB during the study, yielding an estimated efficacy against infection of –3.8 percent. The differences

between vaccine and placebo groups with respect to either secondary efficacy endpoint were not statistically significant.[18]

Although disappointing, results from the MVA85A trial may inform the development of other candidates in the pipeline. MVA85A stimulated CD4 T cells to produce the cytokines IFNγ, TNFα, and IL-2 in vaccinated infants, but only at modest levels that did not add protection to BCG. This response was lower than that predicted by animal studies, highlighting the incomplete window into efficacy offered by current animal models. Analyses of a sample bank collected during the trial may also help to identify correlates of risk of TB disease.[19]

Helen McShane, professor of vaccinology at Oxford University and lead developer of MVA85A, raised the possibility that MVA85A may afford greater protection to adolescents and adults. Adults vaccinated with BCG have demonstrated stronger responses to Ag85A compared with infants.[20] A second phase IIb trial of MVA85A among BCG-vaccinated adults living with HIV in South Africa and Senegal should help to answer this question; it is continuing to enroll participants.[21]

Crucell Ad35/AERAS-402

More disappointing news surrounds Crucell Ad35/AERAS-402, another viral vector vaccine candidate that entered phase IIb trials, one enrolling BCG-vaccinated infants and the other enrolling BCG-vaccinated, HIV-positive adults. Crucell Ad35 uses human adenovirus 35 expressing three MTB antigens: Ag85A, Ag85B, and TB10.4. Immunogenicity data from earlier phase I trials indicated that Crucell Ad35 elicited a robust CD8 T-cell response, but only a modest response from CD4 T cells and their associated cytokines.[22] After reviewing preliminary data, each trial was revised from a phase IIb proof-of-concept study to a smaller phase II study, with safety and immunogenicity as the primary endpoints and without enrollment of the larger study population needed to evaluate efficacy. Without the efficacy groups, the trial will now enroll 500 participants instead of the 4,000 specified by the original protocol.[23] This recategorization has dimmed the prospects of Crucell Ad35, and reflects low immunogenicity response rates to the vaccine in the early, blinded data.

Ad5Ag85A

Like MVA85A, vaccine candidate Ad5Ag85A aims to boost BCG by overexpressing the MTB antigen 85A. Ad5Ag85A is a recombinant, replication-deficient adenovirus serotype 5 vaccine vector and was recently evaluated in a phase I trial that enrolled 24 HIV-negative adults: 12 previously vaccinated with BCG and 12 who were BCG-naive.[24] The study reported a few mild adverse reactions at the injection

site, all resolved within 24 hours, and no vaccine-related serious adverse events. The vaccine showed greater immunogenicity in the study group primed with BCG, activating cytokine production in both CD4 and CD8 T cells. Volunteers in the BCG-naive group also responded to the vaccine, although at a slower rate.

McMaster University, where the vaccine was conceptualized, plans to conduct a phase I trial evaluating aerosol delivery of Ad5Ag85A.[25] Some concerns surround the appropriateness of using the Ad5 vector to deliver vaccine in HIV-positive adults given a safety signal that emerged from the STEP trial evaluating a potential HIV vaccine built on the Ad5 platform. In the STEP trial, uncircumcised vaccine recipients with preexisting Ad5 antibodies showed an increased risk of HIV acquisition, although the mechanism of this reaction remains unknown.[26]

McMaster University is now developing Ad5Ag85A with support from CanSino, a Chinese biotechnology company based in Tianjin.

ADJUVANTED SUBUNIT VACCINE CANDIDATES

The prime-boost strategy also includes several adjuvanted subunit vaccine candidates that contain fusions of different MTB protein antigens in combination with an adjuvant. Vaccines based on purified antigens are less immunogenic than live attenuated or inactivated whole-cell vaccines and thus benefit from adjuvants (pharmacological agents that boost the body's immune response to antigens). Adjuvanted subunit vaccines represent the most well-populated segment of the pipeline, with five candidates in clinical development.

M72 + AS01

The most advanced adjuvanted subunit vaccine, M72 + AS01, is completing several phase IIa studies in preparation for a multisite phase IIb trial in Africa. M72 + AS01 contains a fusion protein of MTB antigens 32A and 39A in the adjuvant AS01. It remains one of just a few vaccines with backing from a major pharmaceutical company, GlaxoSmithKline (GSK), with additional support provided from Aeras.

Phase I/IIa trials suggest that M72 + AS01 has an acceptable safety profile and stimulates both CD8 and CD4 T-cell responses. The CD4 T-cell response has emerged as particularly interesting. In a phase IIa trial among 45 MTB-infected and -uninfected adults in South Africa, M72 + AS01 triggered T cells outside of the typical Th1 and Th17 responses seen in other vaccine candidates. These novel T-cell populations appeared to include Treg cells, which may mediate the inflammation caused by Th1 and Th17 cytokines. T-cell counts after administration

of M72 + AS01 were also higher in MTB-infected participants than in individuals uninfected with MTB, suggesting that vaccination with M72 + AS01 may boost T-cell populations primed by natural MTB infection. This finding stands in contrast to a small adult trial of MVA85A, which showed no significant difference in magnitude of Ag85A-specific T cells across MTB-infected and -uninfected study participants after vaccination.[27]

The three ongoing or recently completed phase IIa studies aim to evaluate the safety and immunogenicity of M72 + AS01 in diverse patient populations: infants in Gambia; HIV-positive adults in Chennai, India; and adults with TB disease in Taiwan and Estonia.[28] The phase IIb study will be the largest adult trial of a novel TB vaccine, aiming to enroll 4,500 HIV-negative adult volunteers in TB endemic communities in sub-Saharan Africa. The primary endpoint will examine protective efficacy of two doses of M72 + AS01 against pulmonary TB disease. Secondary endpoints will include safety and immunogenicity, as well as an exploratory endpoint assessing the vaccine's effectiveness at preventing MTB infection.[29]

Hybrid 1, Hybrid 56, and Hybrid 4 + IC31

The Statens Serum Institut (SSI) in Denmark is choosing between several adjuvanted subunit vaccines to advance into phase II efficacy trials.

Hybrid 1 + IC31 is beginning a phase IIa trial with backing from SSI, TBVI, and the European & Developing Countries Clinical Trials Partnership (EDCTP). Hybrid 1 + IC31 contains antigens Ag85B and ESAT6 in IC31, an adjuvant developed by Intercell. Phase I data indicate that Hybrid 1 + IC31 elicits a robust CD4 T-cell response as measured by IFNγ production. SSI also supported the Hybrid 1 candidate paired with the adjuvant CAF01 in a separate phase I trial. CAF01 will remain a backup adjuvant for Hybrid 1, with no plans for further evaluation. Selection between the IC31 and CAF01 adjuvants mainly reflects timing; CAF01 was not ready for testing in humans until much later than IC31.[30]

Although Hybrid 1 + IC31 remains under investigation in two studies, it will likely be phased out in favor of Hybrid 56 + IC31. Else Agger of SSI said that "Hybrid 56 + IC31 will stand on the shoulders of Hybrid 1 + IC31." The Hybrid 56 + IC31 vaccine contains antigens expressed during both active TB disease (85B and ESAT6) and latency (Rv2660). The first phase I trial of this candidate began in South Africa in 2011 and completed enrollment in November 2012. Hybrid 56 + IC31 appears safe and well-tolerated, and a second phase I, or possible phase IIa, safety and dose-finding study will begin in May 2013 pending favorable immunogenicity results from the first trial. The phase I/IIa trial will take place in South Africa and one additional African site among MTB-

uninfected and latently infected adults.[31] Hybrid 56 + IC31 appears more stable than Hybrid 1 + IC31 in pharmaceutical evaluations. Animal models also suggest that Hybrid 56 demonstrates a higher ESAT6 response than Hybrid 1 and has better vaccine efficacy during late-stage MTB infection, although the mechanisms of these reactions remain unclear.[32]

A separate fusion protein candidate, Hybrid 4 + IC31/AERAS-404, also uses adjuvant IC31 and is being developed by Aeras and Sanofi Pasteur following initial support from SSI. Hybrid 4 + IC31 fuses the antigens Ag85B and TB10.4. The TB10.4 antigen is expressed in both MTB and BCG, unlike the ESAT6 antigen used in Hybrid 1 + IC31 and Hybrid 56 + IC31, which is not present in BCG. ESAT6's role as a common diagnostic reagent in several commercial tests for TB has encouraged researchers to reserve it for diagnostic use by replacing it with an antigen in the same gene family: TB10.4.[33,34] Hybrid 4 + IC31 has completed four phase I studies in adults, including a study in 70 volunteers to assess how it performs as a booster to BCG in preparation for future phase II studies in infants.[35] A phase I/IIa safety and immunogenicity study in infants is expected to start in June 2013 at multiple sites in South Africa.[36]

ID93 + GLA-SE

ID93 + GLA-SE is an adjuvanted subunit vaccine in phase I trials that includes a latency antigen. ID93 + GLA-SE combines four MTB antigens, three expressed in active TB disease (Rv2608, Rv3619, Rv3620) and one expressed during latency (Rv1813). Testing in animals suggests that GLA-SE enhances both Th1 and Th2 immune responses.[37] Lead developers for ID93 + GLA-SE include Aeras and the Infectious Disease Research Institute in Seattle.

A phase I study evaluating ID93 + GLA-SE's safety among BCG-naive adults is currently under way in the United States with a second study among BCG-primed adults planned in South Africa. The trial in the U.S. will enroll four cohorts in escalating doses of both adjuvant and antigen; each cohort will receive three immunizations spaced one month apart. The fourth cohort began enrollment in March 2013, and the investigators have reported no adverse events to date.[38]

In addition to these phase I trials, preclinical studies in mice and nonhuman primates are assessing whether ID93 + GLA-SE can serve as a therapeutic vaccine administered in conjunction with standard antimicrobial treatment. When given with isoniazid and rifampicin, ID93 + GLA-SE elicited a stronger Th1 immune response, shortened the length of chemotherapy, and extended survival time in mice and monkeys. Future preclinical work will evaluate ID93 + GLA-SE as a therapeutic adjunct against MDR-TB strains and paired with first-line drug regimens.[39]

WHOLE-CELL OR FRAGMENTED MYCOBACTERIA VACCINE CANDIDATES

Whole-cell mycobacteria vaccines represent an older branch of the pipeline, as two of these candidates had entered clinical trials by the early 1990s. Vaccines of this type contain inactivated, replication-deficient whole-cell or fragmented mycobacteria. Each of the whole-cell vaccine candidates discussed below may serve as therapeutic vaccines that would synergize with chemotherapy in order to improve treatment for either active TB disease or LTBI. In addition to their immunotherapeutic potential, each is also being studied under a more traditional prime-boost vaccination strategy.

RUTI

Vaccine candidate RUTI consists of fragmented MTB and is being developed by Archivel Farma, a Spanish biotechnology company, as a therapeutic vaccine to shorten treatment of both LTBI and active TB disease. In May 2011, RUTI completed a phase II trial in HIV-positive and HIV-negative people with LTBI. Results of the trial indicate that RUTI elicits an immune response by activating MTB antigens ESAT6 and Ag85B. Archivel Farma is currently looking for a financial partner for a planned phase III trial that will test a single dose of RUTI under two scenarios: first, as an adjunct to chemotherapy to prevent active TB disease in people with LTBI; and second, to prevent relapse episodes in active TB patients by administering the vaccine in the continuation phase of treatment.[40]

Preclinical studies have also assessed RUTI's prophylactic effect in mice and guinea pigs. These findings raise two possibilities for RUTI's development as a preventive vaccine: first, that RUTI might be administered to recently infected people who have negative TB skin tests but are contacts of index cases; and second, that RUTI might boost BCG under a more conventional prime-boost strategy.[41,42]

Dar-901

After a hiatus, the whole-cell mycobacteria vaccine SRL172 studied in the earlier phase III DarDar trial returns to the pipeline as Dar-901. Developed by the Geisel School of Medicine at Dartmouth University, Dar-901 consists of inactivated, whole-cell *Mycobacterium vaccae*. A new manufacturing method developed by Aeras represents the primary difference between Dar-901 and SRL172. The *M. vaccae* used in Dar-901 is broth-grown, a more scalable production method than the agar-grown *M. vaccae* used in the DarDar trial.

Dar-901 has completed preclinical testing in animals and will begin a phase I trial in the United States in late 2013 assessing the safety of three doses of vaccine in BCG-vaccinated, HIV-positive adults.[43]

Earlier work on this candidate culminated in the phase III DarDar trial that evaluated the protective effect of SRL172 against disseminated TB disease in HIV-positive, BCG-primed adults in Dar es Salaam, Tanzania. This trial stopped early due to slow accrual of disseminated TB cases following improved HIV interventions in the study population.[44]

In contrast to the DarDar study, the Dar-901 study will use definite, culture-confirmed TB disease as the primary endpoint rather than disseminated TB. If successful in phase I, further phase IIa studies will evaluate Dar-901 among both HIV-positive and -negative adults in Tanzania.[45]

Mycobacterium vaccae

AnHui Longcom, a Chinese pharmaceutical company, is studying *M. vaccae* as an adjunct to standard antimicrobial therapy. The company already holds a license from the Chinese State Food and Drug Administration to distribute *M. vaccae* as a therapy-shortening adjunct for pulmonary TB. A phase IIb trial among people with MTB infection in Nanjing recently ended, and the company plans to begin a phase III trial soon.[46] A 2003 Cochrane Collaboration review found no evidence that *M. vaccae* immunotherapy benefits patients with pulmonary TB as measured by either mortality or treatment duration, a conclusion that calls into question AnHui Longcom's decision to conduct additional efficacy trials.[47] None of the clinical trials conducted by AnHui Longcom since the Cochrane review has been published in English-language, peer-reviewed journals.

Mycobacterium indicus pranii

A more unconventional path charts the development of *Mycobacterium indicus pranii* (MIP; also called *Mycobacterium w*), a fast-growing, nonpathogenic mycobacterium first developed as a vaccine against leprosy. MIP shares B- and T-cell epitopes (the specific part of an antigen that the cells recognize) with both *Mycobacterium leprae* and MTB, an observation that led the Indian Department of Biotechnology (DBT) to study its potential as a TB vaccine by revisiting data from the original leprosy trials.

Instead of launching a new clinical trial, the government of India nested a retrospective, observational analysis of MIP's protective effect against TB disease among the 28,948 people enrolled in the phase III trial of MIP against leprosy. After resurveying this population 10 years after the initial trial, investigators found

fewer cases of TB disease among those vaccinated with MIP compared with the unvaccinated control group.[48] However, the retrospective nature of this study left investigators unable to calculate measures of vaccine efficacy or establish a causal link between MIP vaccination and lower risk of developing pulmonary TB.

Consequently, investigators at the DBT are now working in reverse order by returning to animal studies to assess MIP's immunogenicity against MTB. Preclinical investigations are assessing both live and killed formulations of MIP, as well as a novel aerosol route of delivery.[49] Immunogenicity data from these studies indicate that MIP stimulates strong Th1 and Th17 immune responses through both CD8 and CD4 T-cell cytokines.[50]

The Drug Controller of India has already licensed MIP for use in humans; the product has been evaluated in three recently completed phase III trials sponsored by the DBT and Cadila Pharmaceuticals. These trials evaluated a killed formulation of MIP as an adjunct to first-line antimicrobial therapy among category I TB patients, category II TB patients, and individuals with tuberculous pericarditis, respectively.[i] Results have yet to be published.

Where are we going? Recommendations on getting to zero with vaccines

A vaccine that successfully acts against pulmonary TB would offer a powerful, and possibly essential, tool for reaching zero tuberculosis deaths, new infections, and suffering. Mathematical modeling commissioned by Aeras suggests that a 60 percent–effective vaccine given to adolescents could avert 71 percent (67 million) of the TB cases and 60 percent (8 million) of the TB deaths projected to occur between 2014 and 2050.[51] However, researchers must clear several hurdles on the road to an efficacious TB vaccine, beginning with unanswered questions of TB immunology. The following recommendations outline priority areas for research and discovery.

1. **Prioritize the science behind biomarker discovery.** Biomarkers of protective immunity against TB are urgently needed to reduce the cost, time, and uncertainty of advancing candidates through the pipeline. Discovery of potential biomarkers will not refashion the clinical pipeline overnight. Even with biomarkers, phase III trials will still be required to determine vaccine efficacy, and markers of protective immunity themselves will require clinical

i In India, category I refers to drug-susceptible TB patients receiving standard first-line anti-TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide). Category II refers to patients who did not complete category I treatment but are not confirmed DR-TB cases. Under category II, patients receive a regimen that includes first-line anti-TB drugs with the addition of streptomycin.

validation. Yet, validated biomarkers would allow researchers to look for efficacy earlier and improve the selection of candidates for expensive late-phase trials. Launching numerous efficacy trials without a clearer picture of protective immunity risks inducing research fatigue among host countries, donors, policy makers, and TB-affected communities. The cost these endeavors pose to health systems and communities cannot be overstated. Stefan Kaufmann has estimated that even in areas with high TB incidence, phase III trials may need to include 20,000 people per study arm to obtain statistically significant findings.[52]

Ultimately, biomarkers are tools whose discovery will follow scientific research unveiling the dynamics of how the human immune system responds to MTB at different stages of infection and disease. The field's focus on these tools should not jump ahead of the advances in microbiology, immunology, and other disciplines that will make this search possible. Just as no single biomarker will produce an efficacious vaccine, no strategy pursued in isolation will uncover correlates of immunity. The research areas described below may offer complementary insights into biomarker discovery.

(a) Correlates of risk. One method seeks to identify correlates of risk for TB disease through observational cohort studies. Willem Hanekom of the South African TB Vaccine Initiative is following two prospective cohorts to identify biomarkers distinguishing MTB-infected adolescents and infants who develop active TB disease from those who do not. Preliminary analyses of blood samples from the adolescent cohort have identified more than 1,200 genes differentially expressed between adolescents who control MTB infection and those who develop active disease. Genes regulating myeloid cell inflammation appear to play an important role.[53,54]

(b) Human challenge model. Development of a human mycobacterial challenge model may also illuminate correlates of risk and protective immunity. The most obvious route to a human challenge model for TB remains untenable, since exposing people to virulent MTB poses grave ethical concerns. Helen McShane is leading several studies to develop a human mycobacterial challenge model that uses intradermal BCG vaccination as a surrogate for aerosol MTB infection.[55,56]

(c) Host/pathogen interaction. The information conveyed by biomarkers will likely be contextual, defined by both the stage of MTB infection or TB disease under study and the scientific questions asked by vaccine researchers. Given the importance of context, several questions related to the interaction of host and pathogen deserve increased attention.

First, the immunologic life cycle of MTB is poorly understood, and although 90 percent of infected individuals resist active disease, the mechanisms of this resistance remain opaque.

Second, our window into the cellular immune response required to overcome active TB disease is too narrow. Induction of Th1 cytokines appears necessary but not sufficient for conferring protective immunity. The role of humoral immunity through B cells and antibodies also remains unclear.

Third, our assumptions based on markers observed in animal studies have not translated into human studies. No animal model has been validated with human disease, and few models have tested candidate vaccines against the range of MTB strains observed in the field.

2. **Pursue innovation within clinical trials.** Clinical trials should synergize with advances in basic science through an iterative process of research and discovery. In *Tuberculosis Vaccines: a Strategic Blueprint for the Next Decade*, Aeras and TBVI outlined stage-gate criteria for advancing vaccines from one stage of the pipeline to another. These criteria evaluate candidates in nine categories, ranging from safety to regulatory strategy.[57] Yet the immunogenicity and efficacy criteria appear underdeveloped compared with those for the other categories, perhaps reflecting the distance untraveled in basic science. Refining the immunogenicity criteria would endow the stage gates with greater utility for advancing only the most promising candidates.

   To enable this refinement, clinical trials should collect serum and cell samples that can be retrospectively analyzed to search for biosignatures distinguishing participants who demonstrate different outcomes or vaccine response. Sample-bank analyses should be back-translated to move preclinical models closer to mirroring human TB infection and disease. This potential could be maximized by linking samples collected by different trials to larger biobanks, or by making these data publicly available to other research teams. The diversity of TB disease across human populations means that analyses limited by geography may elide key insights into the variability of host/pathogen interaction. The establishment of integrated biobanks faces serious logistical challenges stemming from protocol differences across trials. The harmonization of trials would enable clinical research to better support basic science.

   Researchers should map innovative pathways within the current strategies that define the clinical pipeline. Over a dozen vaccine candidates have entered clinical trials since the turn of the century, yet each has charted parallel, nonintersecting research trajectories. Combining different candidates might offer one way to capture the respective strengths of different vaccines under development through a twist on the dominant prime-boost strategy.

At the Third Global Forum on TB Vaccines, Helen McShane raised the possibility of combining MVA85A and Crucell Ad35, as these candidates target distinct MTB antigens and elicit CD4 and CD8 T-cell responses, respectively. The prospect of combination trials raises an important regulatory question: will vaccines used in combination need to retrace all of the steps stretching from preclinical to clinical trials together if they have completed these stages individually?

The role of BCG in such an approach also deserves attention. Instead of maintaining BCG as the prime inoculation, should vaccination with BCG be seen as the background on top of which researchers prime and boost with a combination of different vaccines?

3. **Increase funding for TB vaccine research, including basic science.** In 2011, donors spent $95.4 million on TB vaccine R&D, a sum that represents only 25 percent of the annual investment of US$380 million called for in the Stop TB Partnership's *Global Plan to Stop TB 2011–2015*.[58] Additional funding alone will not produce an effective vaccine; money must be strategically placed to solve intractable issues slowing TB vaccine R&D. The National Institute of Allergy and Infectious Diseases has committed US$10 million to fund Tuberculosis Research Units investigating the biology of MTB infection and TB disease. This offers one example of targeting funding toward research with the potential to identify biomarkers.

Conclusion

Despite well-populated clinical and preclinical pipelines, the TB vaccine community faces a curious catch-22: without known correlates of protective immunity, many believe that efficacy trials offer the only route for evaluating whether candidate vaccines prevent TB disease. But trials that demonstrate no statistically significant protective efficacy against TB cannot illuminate the correlates of immunity that would revolutionize the field. Markers of protective immunity are not an end in themselves, but instead offer a suite of tools, discovery of which will depend on major advances in microbiology and immunology. Extricating ourselves from this quandary will require pairing a renewed dedication to basic science with a willingness to challenge the assumptions underlying current models.

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Table 2. A guide to the MTB antigen universe: MTB antigens used in vaccines under clinical development

Antigen gene name (protein name)	Stage of expression	Present in which vaccine candidates
Rv3804 (Ag85A)	Active disease	MVA85A, Crucell Ad35, Ad5Ag85A
Rv1886 (Ag85B)	Active disease	Hybrid 4 + IC31, Hybrid 56 + IC31, Crucell Ad35
Rv3875 (ESAT6)	Active disease	Hybrid 1 + IC31, Hybrid 56 + IC31
Rv0288 (TB10.4)	Active disease	Hybrid 4 + IC31, Hybrid 1 + IC31, Crucell Ad35
Rv1196 (Mtb39A)	Active disease	M72 + AS01
Rv0125 (Mtb32A)	Active disease	M72 + AS01
Rv2608	Active disease	ID93 + GLA-SE
Rv3619	Active disease	ID93 + GLA-SE
Rv3620	Active disease	ID93 + GLA-SE
Rv1813	Latent infection	ID93 + GLA-SE
Rv2660	Latent infection	Hybrid 56 + IC31

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