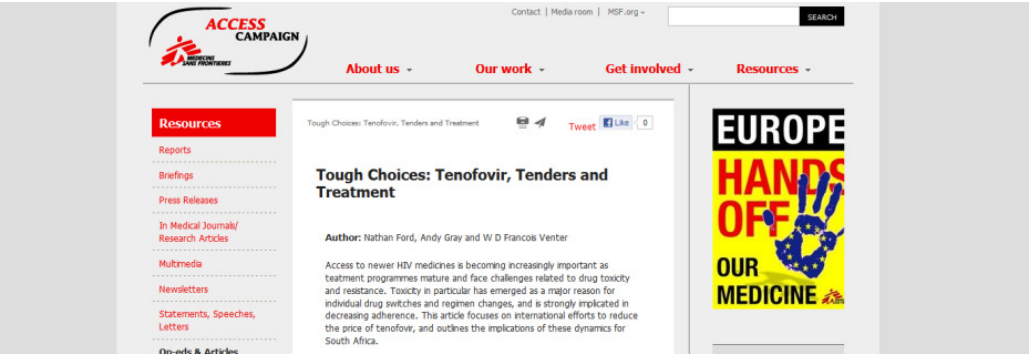
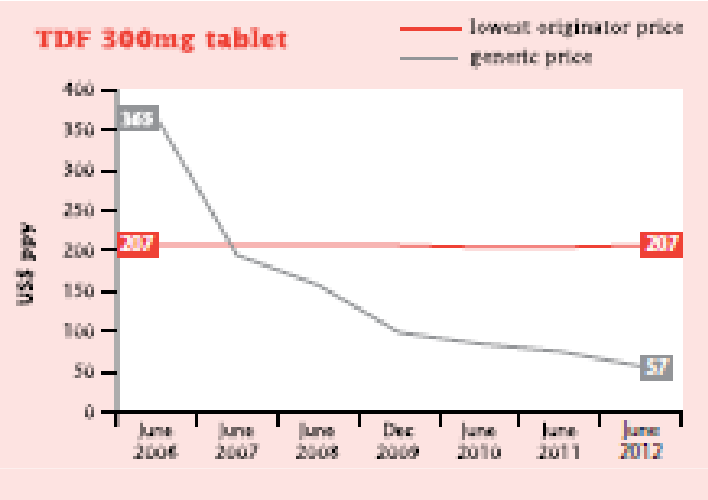
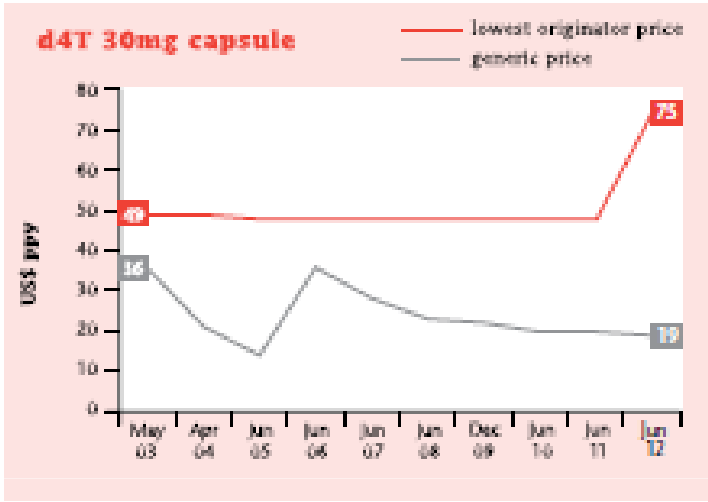
Why the 20mg stavudine trial is the MOST important clinical trial we can do right now

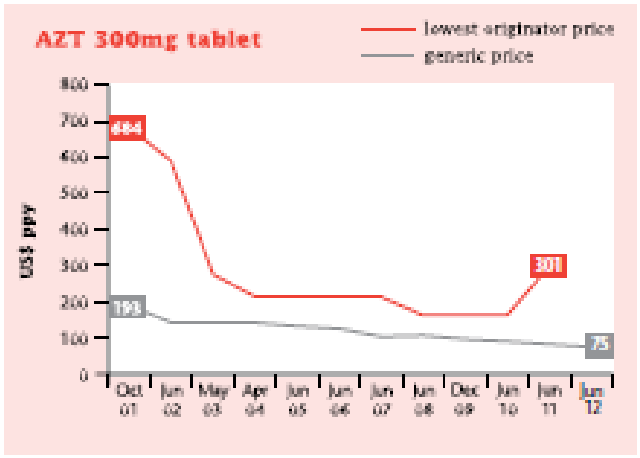
Francois Venter
Wits Reproductive Health & HIV Research Institute



- Tenofovir is an excellent drug
- BUT
- In most HIV high burden countries, cost of ARVs consume >50% of HIV budget
- Cost: d4T <<< TDF < AZT <<< ABC
- **Cost of TDF is triple that of d4T**
- Price unlikely to come down much further







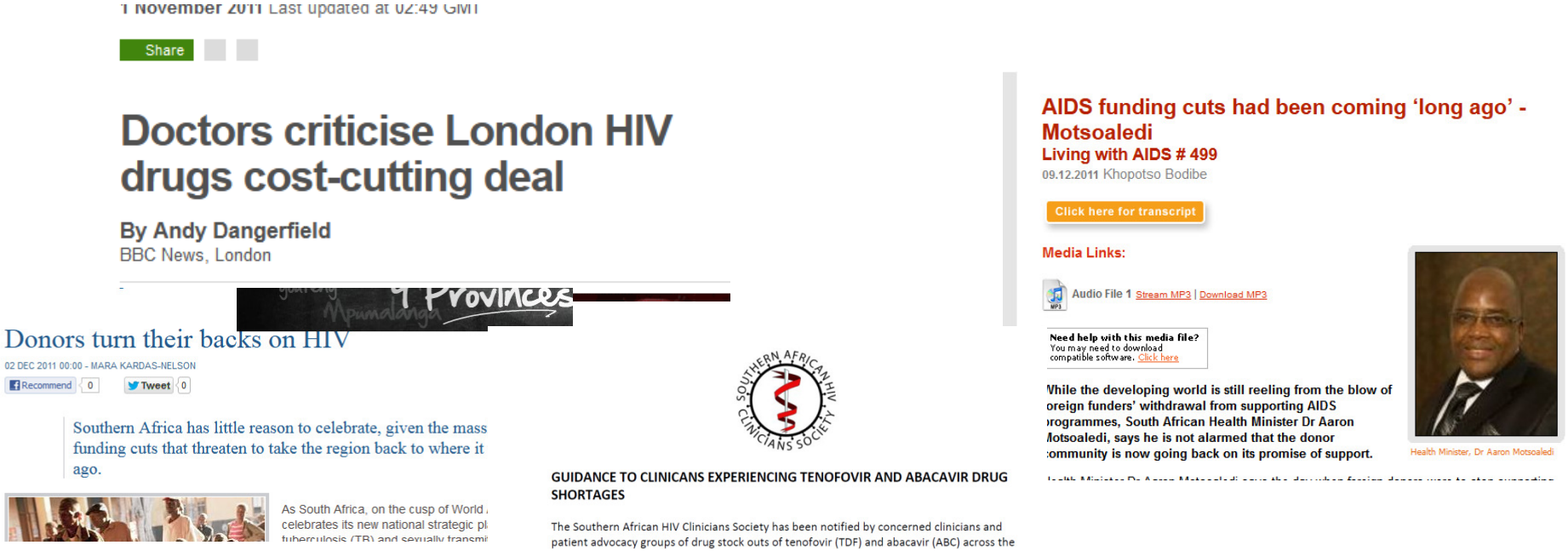
UNTANGLING THE WEB OF

ANTIRETROVIRAL PRICE REDUCTIONS

15th Edition – July 2012

Cold reality

- Decreased donor funding, economic recession – ART programmes curtailed, rationed; $16 billion vs $24 billion needed in 2015
- Supply line failures throughout the world



1 November 2011 Last updated at 02:49 GMT

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Doctors criticise London HIV drugs cost-cutting deal

By Andy Dangerfield
BBC News, London

Provinces

Donors turn their backs on HIV

02 DEC 2011 00:00 - MARA KARDAS-NELSON

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Southern Africa has little reason to celebrate, given the mass funding cuts that threaten to take the region back to where it ago.

As South Africa, on the cusp of World celebrates its new national strategic pl tuberculosis (TB) and sexually transmi

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

GUIDANCE TO CLINICANS EXPERIENCING TENOFOVIR AND ABACAVIR DRUG SHORTAGES

The Southern African HIV Clinicians Society has been notified by concerned clinicians and patient advocacy groups of drug stock outs of tenofovir (TDF) and abacavir (ABC) across the

AIDS funding cuts had been coming 'long ago' - Motsoaledi

Living with AIDS # 499

09.12.2011 Khopotso Bodibe

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While the developing world is still reeling from the blow of oreign funders' withdrawal from supporting AIDS rogrammes, South African Health Minister Dr Aaron Motsoaledi, says he is not alarmed that the donor community is now going back on its promise of support.

Health Minister, Dr Aaron Motsoaledi

Imagine you are the health minister of a cash-strapped country

- Malawi: almost everyone is on d4T; ½ million in SA
- MSF: 11/23 countries reached ART coverage of >60%, six 1/3 of coverage (July 2012)
- 2 choices:
- Treat as many as possible (Kivexa vs Truvada in the UK)
- Or use ‘best treatment’ at expense of universal access (ADAP programmes in the US)

Precedent

- AZT – original daily dose 1500mg, now 600mg
- Darunavir/rit 1200/200mg - now 800/100mg
- Current dose reduction studies – AZT, efavirenz, others
- Other drugs restricted by cost: Liposomal ampho B vs conventional ampho B

Reasons we shouldn't test d4T 20mg? (1)

- Twice daily vs once daily – yes, but not a deal breaker
  (excellent results with BD dosing, case of raltegravir)
- Doesn't cover hep B – yes, screen at $15
- Resistance compromises 2nd line options – very questionable
- Expensive study, could be used to pay for TDF – cost of 8 weeks of TDF just for South Africa, standard cost of this kind of study, lots of other 'me-to' studies not opposed
- New drugs are coming, potential savings may be out-dated when the study ends – no, unlikely to be affordable or available to us in next 10 years

Reasons we shouldn't test it? (2)

- The poor tolerability of d4T limits therapeutic durability – yes, but we're testing a new dose, - with diligent preclinical and clinical monitoring - this may change
- d4T's side effects detract from d4T's savings on cost - yes, but we're testing a new dose, this may change

Reasons we shouldn't test it? (3)

- Won't tell us long term toxicity – yes
- Currently 2 year study (standard), DEXA 6 monthly for 2 years will give us a good idea of early lipoatrophy, advocate for longer follow-on
- Hopefully: "Safe for 2 years, probably longer" and we do the follow-on; but even 2 years would be a gain

Reason we SHOULD test it

- d4T is useful in the acute situation in unstable patients
- Occasionally only available drug - (anaemic patients with renal failure)
- Drug stock out ‘go to’ option
- Paediatrics

Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa

Megan Palmer[a], Matthew Chersich[b,c], Harry Moultrie[e], Louise Kuhn[d], Lee Fairlie[e] and Tammy Meyers[a,e]

Introduction: Stavudine is a commonly used drug in paediatric antiretroviral treatment

2 issues here

- **Is this trial ethical?**
- Is this trial undermining a critical and on-going campaign to access tenofovir?

Is this trial (WRHI 001) ethical?

- Standard research format – non-inferiority
- Toxicity monitoring, design extensively consulted
- 3 different IRBs approved it, 3 regulators
- Consent, GCP, experience of investigators, DSMB oversight, community advisory board, extensive monitoring – all in place

Ethical?

- Participants are protected as much as possible
- “It would never be allowed to happen in the developed world” – unclear why not

So what is this debate about?

- Is d4T likely to be used in the future as 30mg BD? Almost certainly, and possibly in even greater volumes
- Is there a public health priority here? Clearly

2 issues here

- Is this trial ethical?
- **Is this trial undermining a critical and on-going campaign to access tenofovir?**

Scenarios: next 10 years

- Funding – universal access – could be funded, may not be
- Trial – may be successful, may not be (or stopped)

Scenario 1: Universal access (1)

- Funding sufficient for universal access, everyone goes on TDF
- Study successful – expensive, but we have excellent data on TDF toxicity in developing countries, and **when we get forced to use d4T, we use it at the safest dose**

Scenario 1: Universal access (2)

- Funding sufficient for universal access, everyone goes on TDF
- Study NOT successful (stopped/fails) – limited data on TDF toxicity in developing countries, **when we get forced to use d4T, we use toxic dose**

Scenario 2: Funding fails (1)

- Donor obligations unable to keep up with load/distracted by other priorities
- Study successful – d4T non-inferior to TDF
- **Countries that can't afford TDF have an option, for at least 2 years; and we have an alternative where we do use TDF**

Scenario 2: Funding fails (2)

- Donor obligations unable to keep up with load/distracted by other priorities
- Study NOT successful – d4T inferior to TDF (toxic or not suppressive)
- **Poorer countries face dreadful rationing choice: treat with a safe drug, or treat many with a toxic one**

- “It is unclear why the Gates Foundation considers this study to be a priority and it seems an aberration in an otherwise carefully considered strategy for supporting research into the optimisation of ART for resource limited settings”
- Its not just the Gates Foundation
- Its unclear to me (and many others) why this is being opposed

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Editorial

Dose reduction of antiretrovirals: a feasible and testable approach to expand HIV treatment in developing countries

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keywords antiretrovirals, efavirenz, darunavir, lopinavir/ritonavir, stavudine, drug cost

to work.

It is urgent to implement reasonably large, well-powered non-inferiority trials comparing lower doses and the currently used ones, and we think that it would be in the best interest even of drug companies and regulatory agencies to propose and fund such trials, as it is ultimately more convenient to access a wider patient population. These trials should also consider economic data, in order to analyse real life based models, and would also allow to

In summary

- Universal access needs some guarantees and fall-backs
- The study is ethical, participant safety acceptable
- The public health/cost argument: d4T is very likely going to be used
- We need to get dose right (for adults and children)

- **The 20mg stavudine trial is the <u>MOST</u> important clinical trial we can do right now**