

july-august 2016

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EDITORIAL

This summer issue of HTB contains reports from five medical conferences and rapidly changing news about PrEP in the UK.

In addition to AIDS 2016 held in Durban in July, there were important workshops before the main conference on paediatric care, cure research and TB. We also include reports from a pharmacology workshop held a month earlier.

Much of the news from AIDS 2016 was linked to HIV prevention.

Our report from the PARTNER study – together with a non-technical Q&A on the results – reached more than 40,000 people in the first week from the i-Base Facebook page, with 300 shares and translations into Spanish, Russian and Turkish. PARTNER produced a large dataset questioning whether HIV transmission effectively occurs on ART: there were zero HIV transmissions after serodifferent couples had sex more than 58,000 times without using condoms.

The reluctance to accept these results is highlighted by the contrast to responses to the PROMISE study – also reported at Durban – in which the risk of transmission from breastfeeding on ART was reported as 0.3% and 0.6% over 6 and 12 months respectively.

The NIH press release from PROMISE noted that this risk is so low that breastfeeding can now be widely recommended, even though actual transmissions occurred. In contrast, the editorial in JAMA accompanying the PARTNER results incorrectly stated “the risk is far from zero” even with no reported transmissions.

The absence of case reports in the eight years since the Swiss Statement was published contributes to the hypothesis for the PARTNER study that the true risk is zero when viral load is undetectable on ART. The challenge to researchers is still to report such cases if they in fact occur.

While the rest of the world is expanding access to PrEP, NHS England is still fighting to block this in the UK. NAT should be congratulated for winning the legal challenge, but an appeal could easily overturn this result. More importantly, the 45-day public consultation on PrEP was posted online on 10 August for you to register your own views.

SUPPLEMENTS with this issue of HTB

- **2016 pipeline report**

The i-Base/TAG pipeline report reviews the most advanced research relating to pipeline compounds for treatment, prevention, diagnostics and related strategies for HIV, TB and to a limited extent this year, hepatitis C.

The HIV chapters cover adult and paediatric care, treatment optimisation for global access, prevention advances and research into a cure. The TB chapters cover treatment and prevention.

Although principally an online publication, over 1000 printed reports and 2000 memory sticks were distributed at AIDS 2016.

- **UK guide to PrEP**

Since this new UK guide to PrEP was distributed with the May/June issue of HTB, more than 7000 of these free guides have already been ordered by UK clinics.

Please order online or using the form on the back cover.

CONFERENCE REPORTS

21st International AIDS Conference (AIDS 2016)

18–22 July 2016, Durban, South Africa

Introduction

The 21st International AIDS Conference (AIDS 2016) was held from 18–22 July 2016 in the coastal town of Durban in South Africa.

Attended by more than 18,000 delegates, this vital meeting covers all aspects of HIV research: from early basic science studies looking at mechanisms for a cure to real world practice for ensuring human rights are respected for the 35 million people living with HIV globally.

Historically, this meeting is significant for returning to Durban, sixteen years after the World AIDS Conference was first held in an African country.

Over this time, remarkable advances have been made in global healthcare but a continued theme for the conference was that this work is still only half completed. Although more than 17 million people now access HIV treatment (ART) globally, universal access is increasingly raised as the most appropriate target if the HIV epidemic is to ever be reduced.

Several other important workshops were held before the main conference, including meetings focussed on paediatrics, TB confection and HIV cure.

The AIDS 2016 programme is online as a searchable database.

<http://programme.aids2016.org/Abstract/Index>

Although the search is good at finding abstracts and when available links to posters are included on this page, further links to webcasts, and slidesets are only accessible through the online conference programme.

<http://programme.aids2016.org>

This requires searching for and then viewing the conference session in the programme where the study is presented (whether as an oral abstract, plenary talk or other type of presentation). Once the session window is opened, a column to the right of the presentation title shows links to the abstract, plus slides and webcasts if available. Webcasts can either be viewed in the session window or as separate links on YouTube.

<https://www.youtube.com/user/iasaidsconference/videos>

A disappointing number of presentations are neither available as webcasts nor supported by slides. This is not acceptable for the few presentations selected as highlights from many thousands accepted as posters.

The IAS conference should have sufficient confidence to make oral presentations conditional on consent to the presentation being available online. This is common practice for the annual CROI meetings which have a stronger scientific prestige.

Not highlighting in the programme when sessions will (or will not) be webcast is also unhelpful.

The following reports are included in this issue of HTB.

- ZERO: no linked HIV transmissions in PARTNER study after couples had sex 58,000 times without condoms
- PrEP studies at AIDS 2016: includes first preclinical data with EFdA
- Dual therapy with dolutegravir + 3TC keep viral load undetectable: 48 week results from PADDLE study
- Once-daily raltegravir at last available: 48 week results from ONCEMRK study
- Dual long-acting cabotegravir plus rilpivirine injections: 48-week results from LATTE-2
- Dolutegravir is superior to boosted atazanavir in women in the ARIA study
- PROMISE results support WHO recommendations for pregnant and breastfeeding women: more needs to be done to improve ART acceptability and adherence
- Sub-Saharan African countries moving quickly to recommend "Treat All"
- Efavirenz associated with suicide risk in analysis from START study
- CD4:CD8 ratio is more sensitive marker of risk than CD4 counts in analysis from START study
- Treatment in primary HIV infection is significantly more likely to normalise CD4:CD8 ratio
- Publications launched at AIDS 2016

AIDS 2016: TRANSMISSION & PREVENTION

ZERO: no linked HIV transmissions in PARTNER study after couples had sex 58,000 times without condoms

Simon Collins, HIV i-Base

Published to coincide with AIDS 2016, and also presented at the conference, the PARTNER study results showing the impact of HIV treatment (ART) on reducing transmission will benefit millions of people globally.

These results question whether HIV transmission is anything other than a theoretical risk when someone is taking effective ART. This reverses the common assumption that, by definition, some level of risk always exists when one partner is HIV positive.

The PARTNER study provides good evidence that undetectable viral load might be a threshold below which sexual HIV transmission does not occur. The PARTNER study is important in that it included both gay and straight couples, that it measured risk in people who were not using condoms and that it estimated absolute risks.

Previous studies have almost exclusively been conducted in heterosexual people who still reported high rates of condom use. The PARTNER study provides more than three times the amount of follow-up time from people not using condoms than all the previous studies combined. This includes 500 couple-years of follow up from people having anal sex without condoms.

Study design and methods

Between September 2010 and May 2014 the PARTNER study prospectively enrolled 1166 serodifferent couples at 75 clinical sites in 14 European countries. Entry criteria included the positive partner having an undetectable viral load on ART and that the couples were not always using condoms when they had sex.

Follow-up included routine sexual health checks (including HIV testing for the negative partner) and each participant also completed a sexual history questionnaire for each period to look at different types of risk. Couples were only included in the final analysis when the most recent viral load for the positive partners was undetectable – defined as <200 copies/mL. The primary endpoint was the rate of within-partner transmissions, determined by phylogenetic analyses for all couples in which the negative partner became positive.

Results: zero linked transmissions

Of 1166 couples enrolled, 1004 couples had at least one follow-up visit and 888 couples provided 1238 couple years of follow-up (median 1.3 years, IQR 0.8 to 2.0) per couple. This included 548 heterosexual (HT) couples and 340 gay male couples. The main reasons for data not being included in the follow-up analysis were: not yet reaching first follow-up visit (n=162), lack of HIV test (n=20), use of PEP or PrEP (n=9), no condomless sex (n=15), viral load >200 copies/mL (n=55) and lack of viral load result (n=17). There were no significant differences between couples who contributed to follow-up data compared to those who did not.

Although 11 people became HIV positive, none of these infections were phylogenetically linked transmissions. This was after at least 58,000 distinct times when couples had penetrative sex without condoms.

Baseline demographics were reported – as with all results – by categories of HIV status, gender and sexuality, with some differences between groups. This makes summarising results complex, but the median age ranged from 40 to 44 (with IQR overall ranging from 31 to 50 years). Gay men and HT women were a few years younger than HT men. Approximately 80% of the HT men were white compared to 70% of women and 90% of gay men. A higher percentage of gay men had education to college/university or higher (approximately 50% compared to 19% to 35% for heterosexuals). Although some of these differences were significant, they reflect the diversity of people living with HIV (other than there were fewer very young adults involved).

HIV positive partners had been on ART for a median of 10.6 (IQR: 4.3 to 15.6), 7.5 (IQR: 3.3 to 14.2) and 4.8 (IQR: 1.9 to 11.4) years, for HT men, HT women and gay men respectively. At baseline, couples reported having had sex without condoms for a median of 2 years (IQR 0.5 to 6.3), with differences between groups. For example, HT couples had been having sex without condoms for roughly 3 years (IQR 0.7 to 11 years) compared to 1.5 years (IQR 0.5 to 4 years) for gay couples. Approximately 23% of couples were in new/recent relationships (<6 months). Self-reported adherence to ART was similarly high at >90% in the three positive groups. Similar proportions of each group also had CD4 counts >350 cells/mm³ (85% to 91%).

Based on data from the negative partners, overall, couples reported having sex without condoms just less than once a week: a median of 37 times a year (IQR 15 to 71). Gay couples reporting condomless sex at least 22,000 times (median 41 times a year; IQR 17 to 75) and HT couples more than 36,000 times (median 35; IQR 13 to 70). These were estimates from recall and partners did not always report the same numbers. Some couples reported sex outside the main relationship: 108 gay couples (33%) and 34 HT couples (4%).

None of the 11 incident HIV infections in negative partners (10 gay and one HT) were phylogenetically linked to the positive partner. Most people (8/11) reported having sex without condoms with people outside the main relationship. All samples (n=22) were successfully sequenced for *pol* and 91% (n=20) were sequenced for *env*. None of the partner sequences clustered together and the results were consistent after using several different analyses. Additional details for these analyses are described in the online supplementary material. [2]

Interpreting the 95% confidence interval

With zero transmissions, the upper limit of the 95% confidence interval (95%CI) for the overall study was 0.3 per 100 couple years of follow up (CYFU). Each category of specific risks, given that the calculations are a factor determined by study numbers and power, had different upper 95%CI boundaries: for example, 0.88 for HT sex overall vs 0.84 for gay sex overall.

This means that the upper 95%CI for receptive anal sex for gay men (2.70 with ejaculation and 1.68 without ejaculation) needs to be interpreted as a factor of sample size: there were fewer CYFU so the upper limit is by definition higher. While this calculation is developed to define the potential range within which the true risk might lie, the 95%CI should not be interpreted as indicating a risk that has been observed in the study. To illustrate this difficulty, the higher estimated risk for HT anal sex with upper 95%CI of 12.71 and 8.14 (with and without ejaculation, respectively) are driven by fewer CYFU with this as the primary risk rather than any biological reason for this to be much higher. Of note though, more than 20% of straight couples reported anal sex.

Also of note during the study, 91 HIV positive partners reported other STIs (n=16 HT men, 16 HT women and 59 gay men) – closely matching STIs in the negative partners, also without any increased risk reported for HIV transmission.

Two non-technical Q&A resources on these results are also online from i-Base and the PARTNER study. [3, 4]

An extension of the PARTNER study is continuing to collect further data on risk for gay men. PARTNER 2 continues to follow up gay couples in the PARTNER study and to recruit additional gay couples, in order to produce a similarly powered evidence base for gay men as for HT couples, with follow up until 2019. [5]

Simon Collins is a community representative on the steering committee of the PARTNER study.

C O M M E N T

These results are simple to understand – zero transmissions from over 58,000 individual times that people had sex without condoms. They are also notable for the complexity of the analysis that was needed to prove that none of the new diagnoses were linked transmissions from within the couple.

Together, this provides the strongest estimate of actual risk of HIV transmission when an HIV positive person has undetectable viral load – and that this risk is effectively zero. While no study cannot exclude the possibility that the true risk might lie within the upper limit of the 95%CI – even if the true value is actually zero due to some as yet unproven mechanism – the 95%CI can never be zero, just become increasingly close. Neither the presence of STIs nor likely viral load blips between tests had any impact in enabling transmission.

The results provide a dataset to question whether transmission with an undetectable viral load is actually possible. They should help normalise HIV and challenge stigma and discrimination.

The results challenge criminalisation laws that in many countries, including the US, continue to imprison hundreds of people based on assumptions of risk that these results disprove, even when condoms are used and viral load is undetectable.

Activist Sean Strub, from the SERO project (www.seroproject.com) said: “Hundreds of people living with HIV in the US have been charged with criminal offences for the perceived or potential risk of HIV exposure or transmission. Some are serving or have served long prison sentences for spitting, scratching or biting and others for not being able to prove they had disclosed their HIV positive status before having sexual contact (even in the absence of any risk of HIV transmission).

HIV criminalisation has created a viral underclass in the law, further burdening a disenfranchised community, putting a disproportionate share of the shared responsibility for preventing sexually-transmitted infections on one party, and discouraging people at risk from getting tested for HIV.”

The results will also have a positive impact on quality of life of both HIV positive and HIV negative individuals who are in serodifferent relationships, irrespective of their choice to use condoms.

The ongoing PARTNER 2 study is continuing to follow-up gay couples and is still enrolling new couples to achieve a similar statistical power for anal sex compared to vaginal sex. For further details of sites please see the PARTNER2 website. [3]

This study generated such interest that within a few days of the i-Base reports being posted, Facebook links had been shared more than 300 times, with a reach of 40,000 people.

Several other HIV organisations translated the articles and versions in Spanish, Russian and Turkish were soon online, with edited versions being distributed in many other countries including South Africa and the US. [6, 7, 8, 9, 10]

This unprecedented level of interest for an i-Base report reflects the importance of these results to people living with HIV.

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PrEP studies at AIDS 2016: includes first preclinical data with EFdA

Simon Collins, HIV i-Base

PrEP was a major theme at the conference with probably more oral presentations and posters than any other subject.

Oral PrEP works. So there was limited new scientific data with the overwhelming majority of studies relating to implementation issues.

A few of the studies with new scientific data are summarised below.

IPERGAY – continued efficacy with longer follow-up

Follow-up of 336 participants in the open label phase of the French/Canadian IPERGAY study (median 18 months, with >500 patient years of follow up) continued to show protection from event-based dosing for PrEP. The single infection was in someone who had not been taking PrEP for several months and who had no detectable drugs levels at diagnosis. [1]

Results from this open label phase were similar to the double-blind phase in terms of partner numbers, frequency of sex and STI rates (which remained high at approximately 40%). One key exception was that when condoms were used less frequently, this was compensated for by higher PrEP use. Also, that participants reported improved pleasure from sex and reduced fear. [2]

A median of 18 pills were taken by participants each month (IQR: 11 to 25), indicating that the overall results related to someone taking approximately 4 pills a week. Modelling data (from the iPrEX study) suggested this level of dosing would provide greater than 95% protection for men.

The single new HIV infection was a man in a stable relationship with a single partner who started ART three days after diagnosis.

The only outstanding scientific questions about the use of oral PrEP using tenofovir DF plus FTC principally relates to the amount of flexibility for timing of event-based dosing, the optimal time for the pre-dose, and whether this strategy provides similar levels of protection for people who have sex less than once a week.

PrEP used by sero-different couples as a bridge to ART

Similarly impressive results were also presented from the Partners Demonstration Project which was an open label study that provided PrEP to the HIV negative partners of HIV positive people as a bridge until the later started ART. [3]

This study enrolled more than 1000 heterosexual couples in four sites (two in Kenya and two in Uganda). In about two-thirds (67%) of the couples the positive partners were women. Random drug level testing suggested high adherence with tenofovir detected in >80% of negative partners that were sampled. During the two years of the study, ART was started by 92% of the positive partners.

Only five incident infections were reported (IR 0.3, 95% CI 0.1-0.7) despite modelling suggesting that more than 60 incident HIV infections would be expected (IR 5.1 per 100 person years, 95% CI 3.9-6.4). These figures showed that PrEP and ART led to reduction in relative risk of 94% (95% CI 85-98, p< 0.001).

Maraviroc for oral PrEP?

Results from a phase 2 study using maraviroc as oral PrEP in women at risk of HIV were presented in as an oral abstract. [4]

This study is a similar design to a study in men presented at CROI in 2016, which although five transmissions were reported, none were in people with detectable drugs. This four-arm randomised study is important for including active drugs for all participants: maraviroc (MVC), MVC + FTC, MVC + tenofovir DF (TDF) or TDF/FTC. All doses were once-daily with matched placebo.

In the women's study, tolerability was also generally good and comparable between arms, and adherence measured by presence of active drugs levels was about 60%.

No new infections were reported, though, similar to the study in men, the study was not powered to show PrEP efficacy.

Long acting PrEP

Several oral presentations looked at long acting (LA) injectable formulations of rilpivirine and cabotegravir, that were both being studied for use as PrEP (although only cabotegravir studies are continuing).

A delay between the single-dose and multiple-dose clinical studies enabled researchers to look at the long pharmacokinetic tail. Rilpivirine was detectable at sub-therapeutic levels in 7/7 plasma samples collected a mean of 541 days after a single dose exposure to rilpivirine LA. Drug was detectable in vaginal fluid but not in vaginal or rectal tissue. [5]

A qualitative study on acceptability of LA PrEP injections with cabotegravir reported mostly good acceptability. [6]

Slight reprieve for dapivirine

Several new analyses from the MTN-020/ASPIRE study suggested that the dapivirine vaginal ring might have higher efficacy as PrEP (perhaps with risk reduction of 75% [95% CI: 18 to 92], $p=0.01$) compared to placebo for the highest adherent group. [7]

These analyses used complex ways to correlate adherence with risk and were with small numbers of infections, but results are certainly higher than the initial presentations suggested earlier this year at CROI 2016.

Further work in an open label extension will focus on why adherence to using the ring was so low overall.

Data in mice for EFdA with potential for yearly slow release implant

Looking further into the future, early data from using the investigational NRTI EFdA, flew under the radar of most PrEP reports.

This small study reported PrEP efficacy against oral and vaginal exposure in humanised BLT mice (bone marrow, liver, thymus).

Although this is early pre-clinical data, the results are important because EdFA is being developed as a slow-release (and removable) implant formulation, that has the potential to provide therapeutic drug levels from a once-yearly implant. [8]

C O M M E N T

While PrEP is fast-becoming a new focus for HIV prevention globally, the UK is increasingly isolated for its failure to provide PrEP, even with the recent announcement of EU approval. [9]

Participants in the UK PROUD study, who helped generate data to support broad use are now faced with the imminent prospect of no further access to PrEP. This is one of many shameful UK health disasters.

The poster with early data supporting a potential role for EFdA as PrEP is perhaps a highlight from the conference.

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AIDS 2016: ANTIRETROVIRALS

Dual therapy with dolutegravir + 3TC keep viral load undetectable: 48 week results from PADDLE study

Simon Collins, HV i-Base

Updated results from the PADDLE study were a highlight of AIDS 2016 and were presented as an oral late-breaker on the last day. [1]

This was a small (n=20) single-arm open label study in treatment-naïve participants that was notable for reporting at the EACS 2015 conference that rapid viral suppression to <50 copies by week 8 that was maintained to 24 weeks. Although median baseline viral load was low (24,000 copies/mL [IQR: 12,000 to 37,000]), four people were >100,000 copies/mL. [2]

The results at week 48 were similar, with suppression maintained to <50 copies/mL throughout in 18/20 participants.

Low level detectable viral load was reported at week 36 in one participant (at 246 copies/mL) who resuppressed without a change in treatment (even though the study protocol recommended changing).

One participant committed suicide linked to “severe stress and emotional trauma” that was not judged related to the study medications.

C O M M E N T

These results are encouraging for the likelihood of this being a durable option, however small the dataset.

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Once-daily raltegravir at last available: 48 week results from ONCEMRK study

Simon Collins, HIV i-Base

After many years of research, Merck now have a once-daily formulation of raltegravir - though it requires two tablets and a higher milligram daily dose.

In addition to developing the new raltegravir formulation, non-inferiority needed to be shown in a randomised, double-blind placebo controlled phase 3 study, rather than relying on pharmacokinetic bioequivalence studies. The original raltegravir 400 mg twice-daily version was compared to the new 2 x 600 mg once-daily formulation, with background NRTIs tenofovir DF + FTC for all participants.

Results of this study were presented as a late-breaker oral abstract at AIDS 2016 by Pedro Cahn from Fundación Huesped, Buenos Aires.

Of the 802 participants randomised 2:1 to the once- vs twice-daily formulations, 797 received study drug and 732 (92%) completed follow-up to week 48.

Baseline characteristics overall included a study population that was 85% male, 59% white and mean age 36. Mean CD4 and viral load were 415 cells/mm³ and 4.6 log copies/mL respectively, with 28% having viral load >100,000 copies/mL.

At the primary endpoint at week 48, viral suppression to <40 copies/mL was reported by 88% of each arm with no significant differences related to efficacy or tolerability between arms. The once-daily formulation has slightly fewer serious side effects (5.8% vs 9.4%; difference -3.6% [95%CI -8.0 to +0.2]) and discontinuations due to side effects (0.8% vs 2.3%; difference -1.5 [95%CI -4.1 to +0.1]), though neither difference was statistically significant.

Viral failure during the study (defined as non-suppression by week 24 or more than one consecutive blip >40 copies/mL) was reported in 7% of each group. Of these, approximately half resuppressed by week 48 without changing treatment: 20/26 vs 8/18 in the once-vs twice-daily arms groups respectively.

Of the 5/14 with drug resistance in the once-daily arm, 4/5 (0.9%) had resistance to raltegravir. Of the 3 people tested in the twice-daily arm, 2/3 had no resistance and 1/3 failed testing.

The study will continue until week 96 for secondary endpoint analyses.

C O M M E N T

Although raltegravir was the first integrase inhibitor to be approved – the results of more than a decade of commitment to this new class – the higher price compared to existing combinations meant that many people who could have benefitted were not able to access this drug.

As newer integrase inhibitors became available, the twice-daily formulation meant that even after lowering the price, raltegravir had a limited market.

In the meantime, some doctors reported switching the twice-daily 400 mg formulation to 800 mg once-daily after viral load was suppressed to <50 copies/mL. While these reports were largely positive this off-label use had limited uptake.

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Dual long-acting cabotegravir plus rilpivirine injections: 48-week results from LATTE-2

Simon Collins, HIV i-Base

Results from the first proof-of-principle for injection only antiretroviral treatment (ART) was presented as an oral late breaker by David Margolis from ViiV Healthcare.

This phase 2 study required an induction period using oral drugs and compared monthly and two-monthly intramuscular injections to a control group that remained on oral drugs throughout.

There was an open-label phase 2b study in 301 treatment-naïve participants, randomised 2:2:1 to 4-weekly (4W) or 8-weekly (8W) injections or to oral ART (cabotegravir plus abacavir/3TC).

The 20-week induction phase used cabotegravir (30 mg once-daily) plus abacavir/3TC once-daily, adding in oral rilpivirine (25 mg once-daily) for the last four weeks. After induction, 91% (n=286) of participants continued into the randomised phase because their viral load was <50 copies/mL. The primary analysis at week 32 of the main study (ie starting after the induction period) was presented at CROI 2016 earlier this year - and these data were used to select the 4-weekly dose for phase 3 studies. [2]

At week 32, viral suppression to <50 copies/mL was achieved in 94%, 95% and 91% of the 4W, 8W and oral arms respectively, which met pre-specified criteria for showing each intramuscular injection (IM) arm was not worse than the oral treatment group. Virologic non-response rates were slightly lower in the 4W arm (<1% v 4% in the other arms) with lower non-virologic reasons for discontinuation in the 8W arm (vs 5% in each of the other two arms).

By week 48, the percentage with <50 copies/mL dropped slightly to 91%, 92% and 89% of the 4W, 8W and oral arms respectively. Virologic non-response was greater in the 8W vs 4W arms (7% vs <1%) but this led to few discontinuations (<1% vs 0). Discontinuations due to side effects or death was lower in the 8W group (0 vs 5%).

Tolerability at 48 weeks – mainly linked to injection site reactions (ISRs) – was similar to the 32 week results. Slightly higher rates of ISRs in the 8W group levels out to approximately 30% of participants by week 48. Of these, 82% were mild and 17% were moderate: 90% resolved within 7 days. The most common symptoms were pain (67%, nodules (7%) and swelling (6%). Only 2/230 participants (<1%) discontinued due to ISRs.

Other side effects generally occurred at low levels and were similar between injection groups: fever 5% vs 3% vs 0; fatigue 4% vs 2% vs 1%; flu-like symptoms 2% vs 3% vs 0; in the 4W, 8W and oral arms respectively, with headache reported by 2% in all arms.

Virological failure only occurred in two people in the 8W arm and 1 person in the oral group. Mutations associated with drug resistance to integrase inhibitors (Q148R) were only reported in one person in the 8W group.

In a patient survey, participants reported higher rates of satisfaction with injections compared to oral drugs and higher preference for continuing with current combination.

C O M M E N T

Even with the potential obstacles and disadvantages of intramuscular injections with very long half-lives, the option to not take daily pills has always been seen as exciting by many people – even now once-daily single pill formulations are available.

Injectable long-acting ART is steadily getting closer, with phase 3 studies now planned using 4-weekly injections.

Long-acting cabotegravir injections are also being studied at PrEP in a phase 2b/3 study in HIV negative men and transgender women, compared to a control arm of daily oral tenofovir/FTC. [3]

A poster at AIDS 2016 from a phase 2 study of cabotegravir LA PrEP reported preference over daily oral PrEP. [4]

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Dolutegravir is superior to boosted atazanavir in women in the ARIA study

Polly Clayden, HIV i-Base

Dolutegravir-based ART was superior to a boosted atazanavir-based regimen in treatment naive women at 48 weeks, according to data from the ARIA study presented at AIDS2016.

The ARIA study was performed to provide additional data on women receiving the dolutegravir (DTG)-based fixed dose combination (FDC) in which it is co-formulated with abacavir (ABC) and lamivudine (3TC). [1] The FDC is marketed by ViiV Healthcare as Triumeq and was first approved in August 2014 in the US. [2] The study is multi-national, multi-site, open label, randomised, non-inferiority, phase 3b. It is ongoing and enrollment was from September 2013 to September 2014

Catherine Orrell from the University of Cape Town presented 48-week data, on behalf of the ARIA investigators, in an oral late breaker. [3]

Eligible women were: ART-naive, HLA-B*5701 negative, with viral load 500 copies/mL or more and hepatitis B negative. They were randomised 1:1 to 48 weeks of treatment with DTG/ABC/3TC or atazanavir/ritonavir plus tenofovir DF/emtricitabine (ATV/r + TDF/FTC) once daily, and stratified by viral load less than or above 100, 000 copies/mL and CD4 count less than or above 350 cells/mm³.

Women who became pregnant during the course of the study were withdrawn and offered entry into a DTG/ABC/3TC pregnancy study. [4]

The primary endpoint was the proportion of women with viral load <50 copies/mL at week 48 using the FDA Snapshot algorithm (-12% non-inferiority margin).

A total of 495 women were randomised and treated: 248 and 247 in the DTG/ABC/3TC and ATV/r + TDF/FTC arms respectively. The women were a median age of 37 years; approximately 43% were of African origin, 45% were white and 22% were Asian. About half of the participants had CD4 <350 cells/mm³ and about 28% had viral load >100,000 copies/mL. Participants were well matched for demographic and baseline characteristics. Of the women in the DTG/ABC/3TC arm, 83% (n=206) completed week 48, compared with 78% (192) in the ATV/r + TDF/FTC arm.

Five women in the DTG/ABC/3TC arm (2%) and eight in the ATV/r + TDF/FTC arm (3%) became pregnant and withdrew from the study.

In ITT analysis, DTG/ABC/3TC was superior to ATV/r + FTC/TDF at 48 weeks: 82% vs 71% of participants had viral load <50 copies/mL respectively, adjusted difference 10.5% (95% CI: 3.1% to 17.8%), p=0.005.

Differences in response were driven by Snapshot virologic non-response (6% vs 14%) and fewer discontinuations due to adverse events or death (4% vs 7%) in the DTG/ABC/3TC arm.

No participant receiving DTG/ABC/3TC developed INSTI or ABC/3TC resistance. DTG/ABC/3TC had a favourable safety profile to ATV/r + TDF/FTC and a similar overall profile for DTG to that reported in previous studies.

C O M M E N T

The participants in the registrational studies (typically for such studies) were approximately 80% men (and few non-white participants), so this clinical trial evaluating DTG in women is welcome. More important still is data on pregnant women – which is essential to DTG's recommendation in the WHO guidelines without restriction.

As noted above, five (2%) ARIA participants in the DTG/ABC/3TC FDC arm and eight (3%) in the ATV/r + TDF/FTC arm were discontinued from the randomised phase of the study due to pregnancy.

Of these pregnant women, four in each treatment group had undetectable viral load at the time of discontinuation. Two additional women became pregnant in the DTG/ABC/3TC FDC treatment group during the continuation phase of the study.

Of the seven women who became pregnant in the DTG/ABC/3TC arm (including during the continuation phase), three resulted in a normal infant with no apparent congenital anomaly, two women elected to terminate the pregnancy, one woman experienced an anembryonic pregnancy, and the outcome of one pregnancy was unknown. [5]

Other studies looking at DTG in pregnancy are described in Fit for Purpose 2016. [6]

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AIDS 2016: PREGNANCY & PMTCT

PROMISE results support WHO recommendations for pregnant and breastfeeding women: more needs to be done to improve ART acceptability and adherence

Polly Clayden, HIV i-Base

Continued antiretroviral treatment was safe in women with higher CD4 counts after delivery and associated with improved maternal health – but virologic failure rates were high – according to data from the PROMISE study, presented at AIDS2016.

The study also revealed that acceptance of ART was low in this population and women needed time to consider starting treatment. And it found that ART during breastfeeding essentially eliminates vertical transmission by breast milk.

PROMISE (Promoting Maternal-Infant Survival Everywhere) is a multi-country, multicomponent study, that began in 2010 and included 5398 asymptomatic HIV positive pregnant women who were not eligible for antiretroviral treatment (ART) at the time of enrollment. The study included breast feeding (BF) and formula feeding (FF) women, depending on local guidelines. Participants were randomly assigned different antiretroviral strategies to look at vertical transmission during pregnancy and post-partum, infant safety, and maternal health.

Research questions include:

- **Antepartum (1077BF/FF)** Among HIV positive women who do not meet criteria for starting ART for their own health, what is the best intervention to prevent in utero and intrapartum HIV transmission to infants? Maternal ART vs a single drug prophylaxis regimen.
- **Postpartum (1077BF)** Among HIV positive women who do not meet criteria for starting ART for their own health, what is the best intervention to prevent transmission of HIV to infants during breastfeeding? Maternal ART vs single drug infant prophylaxis.
- **Maternal health** What is the best intervention to preserve maternal health after delivery? Stopping vs continuing ART.

The first part of the study (finally) provided randomised controlled trial (RCT) data to show that taking three drug ART in pregnancy was more effective in preventing vertical transmission than taking one drug during pregnancy, another in labour and two after delivery. [1, 2, 3]

These findings were reported on 4 November 2014 during a scheduled interim review of PROMISE by an independent data and safety monitoring board (DSMB). The US National Institutes of Health issued a press release explaining the results on 17 November 2014. [4]

Standard of care also changed during the course of the study: as PROMISE was ongoing, the START study showed ART in people with CD4 500 cells/mm³ or more reduces the risk of HIV disease progression. [5] PROMISE participants were informed of these results by the study group and women not receiving ART were strongly recommended to start immediately for their own health.

World Health Organization (WHO) guideline subsequently changed to recommend “Treat All” reflecting the START results. [6]

Several analyses from PROMISE were presented at AIDS 2016 – this commentary summarises results from studies looking at stopping or continuing ART postpartum, ART acceptability among women with higher CD4 counts and transmission during breastfeeding. The results broadly support the recommendations in the WHO guidelines – including lifelong ART for all pregnant and breastfeeding women – but also show that work needs to be done to improve adherence support and acceptability of ART among asymptomatic women.

Continuing ART postpartum benefits maternal health

In 2008/2009 when PROMISE was designed the health benefits of postpartum ART for women with high CD4 counts had not been evaluated in RCT. Judith Currier presented results from the component of PROMISE (1077HS) designed to assess the risks and benefits of continuing vs stopping ART among non-breastfeeding women after delivery. [7] She showed these findings in an oral late breaker presentation on behalf of the study team.

HIV positive, non-breastfeeding, postpartum women with no indication for ART based on local guidelines, and who had received ART during pregnancy for at least four weeks in the main study, were randomised to continue or stop ART within 42 days of delivery. Women were followed for 84 weeks after the last enrollment. Those who stopped were restarted when their CD4 count dropped below 350 cells/mm³ or otherwise clinically indicated.

ART was provided by the study. The majority of participants received a regimen of lopinavir/ritonavir (LPV/r) plus tenofovir

DF and emtricitabine (TDF/FTC). Atazanavir/ritonavir and, in some settings, rilpivirine and raltegravir were also available. Overall 90% of women were on PI-based ART.

The primary composite endpoint included: death, time to AIDS event (WHO stage 4), and serious non-AIDS events (cardiovascular, renal or hepatic). The primary safety endpoint was time to first targeted grade 2, 3 or 4 event. Key secondary endpoints were: a composite of HIV/AIDS related or WHO 2/3 events; or time to WHO 2/3 events.

The planned study sample size of 2000 participants provided 90% power to detect a 50% reduction from an annual primary event rate of 2.07% (calculated from other clinical trials). But in November 2014 the DSMB approved stopping enrollment at 1630 participants due to longer than expected time to enrol (the longer follow up was expected to make up for smaller sample size). All analyses were intent to treat.

Participants were informed of the START results and all offered ART in June 2015.

There were 1652 participants enrolled from 52 sites across eight countries: Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand and the US between January 2010 and November 2014. The majority were from Brazil (31%), Botswana (28%) and Thailand (18%).

Of the total, 827 and 825 women continued and stopped ART for a median of 2.31 vs 2.35 years; 79 (9.6%) vs 70 (8.5%) respectively discontinued the study. Adherence to randomly assigned treatment was generally good: 15% of women stopped ART in the continue arm and 12% restarted ART before the study threshold in the stop arm.

Median age was 28 years and 28% were black African, 16% Thai (16%) and 15% white. Median CD4 count at study entry was 696 cells/mm³, median ART exposure before delivery was 19 weeks and 91% had entry viral load <1000 copies/mL. During follow up 31% of the stop arm started ART at a median CD4 of 372 cells/mm³.

For the primary efficacy outcome events were very rare and not significantly different between arms. The events included: two cases of cervical cancer, and two deaths (one homicide and one unknown); and two cases of extrapulmonary TB, one toxoplasmosis and four deaths (one hepatic encephalopathy and one unknown), in the continue and stop arms respectively. The rate of safety endpoints was higher in the continue arm compared to the stop arm but this was not statistically significant.

WHO Stage 2 and 3 events were almost halved (44% reduction) with continued ART. The key events were: 16 herpes zoster and four bacterial infections; and six pulmonary TB, 43 herpes zoster, four thrombocytopenia, 10 oral candidiasis and 11 bacterial infections, in the continue and stop arms respectively. See Table 1.

Table 1: PROMISE 1077HS endpoints

Endpoint (time to first event)	Continue ART		Stop ART		Hazard ratio (95% CI)	p-value
	n	rate/100 py	n	rate/100 py		
Primary efficacy outcome	4	0.21	6	0.31	0.68 (0.19 to 2.40)	0.54
Primary safety endpoint	260	18.4 (15.7 to 21.4)	232	15.4 (13.1 to 18.2)		0.08
Secondary endpoints						
Composite endpoint	57	3.09	99	5.49	0.56 (0.41 to 0.78)	<0.001
WHO 2/3 events	39	2.02	80	4.36	0.47 (0.32 to 0.68)	<0.001

Toxicity rates were higher in the continue arm but the difference was not statistically significant.

Among participants randomised to continue ART, 189/827 (23%) had virologic failure at or after 24 weeks of treatment. Of the 155 (82%) with resistance testing, 103 (66%) failed with no evidence of resistance to their current regimen (suggesting non-adherence). Of the 52 with evidence of resistance: 22 had resistance to one of the drugs in the failing regimen; 14/25 (11%) failing a PI regimen and 8/27 (30%) failing an NNRTI regimen.

Low acceptance of ART among women with higher CD4 counts: they need more time to consider

Following the START results, in June 2015, all women not receiving ART at that time were recommended to start for their own health.

In a second oral late breaker, Lynda Stranix-Chibanda showed PROMISE participants' response to these recommendations and their reasons to accept or decline ART. [8]

The study used a mixed methods approach to collect responses from participants receiving the START information. Study staff contacted participants to return to the clinic and gave START results. This was done using a structured script, the language was chosen by the participant and the staff assessed comprehension. Information included that about the trial aims, study location and results.

Participants also attended a counselling session to discuss the implication of START for them as individuals. Those not receiving ART discussed the offer of starting with the study staff and decided whether or not to accept during that session.

Women selected their primary reason for accepting or rejecting the offer from a set of options. The results were recorded and categorised by the study staff.

All 1483 women not on ART were advised to start: 984 women (66%) accepted the offer but 499 (34%) declined. Acceptance rates varied by country, quite broadly, with a mean of 66% (Brazil) and range of 100% (Peru) to 37% (Tanzania). Reasons for accepting or declining ART after initial counselling session are shown in Table 2.

Table 2: Reasons for accepting or declining ART in PROMISE

Reason	1077BF/FF	1077HS
<i>For accepting ART</i>		
Concerned about health	46%	43%
Understands treatment is now recommended	35%	36%
Concerned about CD4 count	16%	13%
Other reason	2%	7%
<i>For declining ART</i>		
Wants more time to consider	44%	33%
Feels well/knows CD4 count is high	13%	28%
Concerned about HIV disclosure	9%	3%
Concerned about commitment to life-long ART	9%	7%
Concerned about potential side effects	8%	8%
Other reason	7%	14%
Knows not indicated in current guidelines	6%	0%
Too busy with childcare or other responsibilities	2%	5%
Concerned about adherence	1%	5%

Dr Stranix-Chibanda explained that a number of women were not willing to start ART after a single counselling session. This was despite exposure to considerable ART education and HIV monitoring within a well-resourced trial setting.

Women particularly needed time to consider starting ART and the researchers noted that the women continued to be offered ART through to study exit and the proportion remaining off ART decreases with each visit.

Breastfeeding

Finally, data were shown from the PROMISE 1077BF study, designed to compare transmission rates with maternal ART vs infant nevirapine (NVP) during extended breast feeding until 18 months post-delivery (the first randomised trial to do so). Taha Taha and colleagues showed these findings in a late breaker poster.

This postpartum component of PROMISE was conducted in 14 sites in: Indian, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe.

The study enrolled 2431 mothers and their HIV uninfected infants between June 2011 and October 2014. They were randomised at 6–14 days postpartum to maternal ART plus six weeks of daily infant NVP (n=1220) or daily infant NVP (n=1211). Women were asymptomatic with a median CD4 count 686 cells/mm³ and 97% WHO stage I). They were a median age of 26 years. Infants had a median gestational age of 39 weeks and birthweight of 2.9 kg.

Baseline characteristics were similar across study arms. The median duration of breastfeeding was 15 months was also similar across study arms (p=0.85).

Rates of HIV transmission during breastfeeding were very low and did not differ significantly between arms at 12 months postpartum these rates were 0.5% with maternal ART and 0.6% with infant nevirapine. Rates of infant survival were high (98.9%) and did not differ significantly between arms (p=0.72).

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Sub-Saharan African countries moving quickly to recommend “Treat All”

Polly Clayden, HIV i-Base

There is broad support for universal treatment of people with HIV among fast track countries, and many are committed to adopting “Treat All” policies by the end of this year, say researchers from the World Health Organisation (WHO). But challenges to full implementation remain.

Meg Doherty and colleagues from WHO HIV/Hepatitis department showed findings from a survey of country level adoption of Treat All policies recommended in the 2016 Consolidated Antiretroviral Guidelines, as a poster presentation at AIDS2016.

“Progress towards the ending the AIDS epidemic by 2030 depends on adoption and implementation of global guidelines to optimally treat all people living with HIV and knowing how best to deliver interventions, they wrote.

WHO has implemented a country intelligence database since 2013 to better follow policy and practice trends at country level.

The researchers showed data for 144 low- and middle-income countries (LMIC) and 35 fast track countries, to July 2016. They found that 24% of all LMIC and 40% of fast track countries have adopted Treat All. A further 31% of LMIC and 40% of fast track countries plan to do so by the end of 2016. They noted that only 6% of all LMIC had adopted Treat All one year ago.

They expect that by the end of 2016 more than half LMIC and 80% of fast track countries will have adopted Treat All. But they also note that implementation is just getting started and most countries have not yet put Treat All policies into practice.

Option B+ is almost universally adopted but is not yet fully implemented. By the end of the year the researchers predict 58% of LMIC and fast track countries will have adopted Treat All for children.

The majority (90%) of LMIC adopted efavirenz plus TDF and 3TC (or FTC) as the preferred first-line regimen. Almost half of LMIC (47%) have fully implemented routine viral load; 26% have partially implemented it.

The researchers wrote: “With the 2016 Consolidated ARV Guidelines, WHO has rapidly updated global guidance to reflect new science regarding the benefit of early HIV treatment. There is broad support for universal treatment among fast track countries and many are committed to adopting Treat All policies by the end of 2016”.

But implementation comes with challenges. And that the uptake of recommendations on task shifting, integration and decentralisation are lagging. They add that differentiated service models might be part of the solution as programmes expand.

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AIDS 2016: SIDE EFFECTS

Efavirenz associated with suicide risk in analysis from START study

Simon Collins, HIV i-Base

Suicide-related side effects are an important concern with efavirenz. Given how widely efavirenz continues to be used the main safety concern is whether current prescribing practice is sufficiently accurate to minimise these risks.

Earlier studies have reported that the risk is significantly higher than with other ARVs but also that doctors are careful to use alternative options for people who have a history of anxiety, depression or other psychiatric symptoms. [1, 2]

An oral presentation at AIDS 2016 provided information on both actual risk and prescriber awareness from a new analysis from the large international START study. [3]

START randomised more than 4600 treatment naive individuals with CD4 counts >500 cells/mm³ to either immediate ART or deferred ART (until the CD4 counts dropped to 350 cells/mm³). Importantly, before randomisation doctors were asked to pre-specify the choice of ART for all participants, irrespective of which group they would later join.

This design enabled the START researchers to identify appropriate control groups for participants who were either judged to be at risk or not at risk from suicide-related side effects in a way that could highlight the impact of efavirenz and also the underlying risk independent of ART.

START enrolled a largely young healthy group in early HIV infection. Baseline demographics have already been reported. [4, 5] Additionally, 270/4685 (5.8%) participants had a prior psychiatric diagnoses.

Efavirenz was pre-specified for 3516 participants (75%). This was less often in those with psychiatric diagnosis (40%) than without (77%). Although characteristics were similar between participants for whom efavirenz was pre-specified or not, prior psychiatric disease was less frequent (3.1% vs 13.9%) in the those pre-specified to use efavirenz, as was current use of psychiatric treatment (4.0% vs 15.1%). Also significant, was the higher use of efavirenz in low- and middle-income vs high-income countries (65% vs 35%).

In the study overall, there was no difference in suicidal behaviour between the early vs deferred arms (27 vs 24 events; HR 1.15 (0.66 to 1.99), p=0.63). Of the 52 events, 30 were suicide attempts and 16 events where people wanted to commit suicide. There were single cases of self harm and self harm ideation. The three people who died from suicide were all in the deferred arm and this occurred after starting treatment.

The majority of events occurred in those with a previous psychiatric history. The rate was 10-fold higher in people in whom efavirenz was prespecified and 3-fold higher in those pre-specified to use other ART, in people with a previous diagnosis (see Table 1). This, together with the higher rate of events in people pre-specified to use other ART (overall rates 1.28 vs 0.63 per 100 PY) show a generally high awareness not to prescribe efavirenz in people at highest risk.

Table 1: Suicide-related events by prespecified efavirenz use and psychiatric history

	Psychiatric history	No psychiatric history
EFV pre-specified	7 2.0 /100PY	22 0.2 /100PY
Other ART	8 1.7 /100PY	14 0.5 /100PY

A subgroup analysis that censored participants in the deferred group at the start of ART was then able to look more specifically at the role of efavirenz in people not thought to be at risk (ie who had been assigned to use efavirenz) and also at the roll of psychiatric-related events in people not exposed to efavirenz.

In this analysis there were 17 vs 3 events in the immediate vs deferred group assigned to receive efavirenz (HR 4.16; 95%CI 1.2 to 14.4), $p=0.02$ showing that in people without a psychiatric history, efavirenz was significantly related to a risk of suicide-related events.

Similarly, in the people whose medical history might be associated with suicide-related events irrespective of ART, there were 9 vs 8 events (HR 1.04; 95%CI 0.4 to 2.7, $p=0.93$) for non-efavirenz versus their ART-naïve controls - indicating that other ART had no impact on people judged to be at high risk due to past history.

Both these analyses were protected by randomisation and therefore likely to provide high quality evidence. Also importantly, the interaction between these two groups was also statistically significant ($p=0.05$ for difference in HRs), see Table 2.

In multivariate analysis, the factors that were significantly associated with risk of suicide-related events were: previous psychiatric diagnosis (HR 12.8; 95%CI 4.7 to 34.9, $p<0.001$), heavy alcohol use (HR 6.1; 95%CI 1.9 to 19.6, $p = 0.003$) and ever having used recreational drugs (HR 2.9; 95%CI 1.0 to 7.9, $p=0.04$).

Table 2: Suicidal and harming events by randomisation group

	n	Immediate ART		Deferred ART		HR	95%CI	p	p
		Events	Rate	Events	Rate				
Intention to treat (ITT) analysis									
EFV pre-specified	3516	18	0.34	11	0.21	1.42	0.6 to 1.9	0.37	0.23
EFV not pre-specified	1169	9	0.53	13	0.72	0.74	0.3 to 1.8	0.5	
Censoring deferred arm participants at ART initiation									
EFV pre-specified *	3516	17	0.35	3	0.08	4.16	1.2 to 14.4	0.02	0.05
EFV not pre-specified **	1137	9	0.59	8	0.69	1.04	0.4 to 2.7	0.93	

* 6/17 vs 0/3 were in people with psychiatric history.

** 5/9 vs 2/8 were in people with psychiatric history.

Simon Collins is a community representative on the START group working on this analysis.

C O M M E N T

The good news from START is that even with widespread use of efavirenz, especially in people who either started immediate treatment there were few serious reports of suicide-related behaviour and only three suicides.

Even with few events - a good thing - efavirenz was still associated with a significantly higher risk of suicide related complications, especially in those with a history of depression or other psychiatric conditions.

These results support the continue screening of patients for such history before starting efavirenz.

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AIDS 2016: TREATMENT STRATEGIES

CD4:CD8 ratio is more sensitive marker of risk than CD4 counts in analysis from START study

Simon Collins, HIV i-Base

An analysis from the START study reported that the CD4:CD8 ratio was a better predictor of risk compared to the CD4 count in people with strong immune function.

These START results showed that early antiretroviral treatment (ART) is protective against the primary endpoints of serious HIV- and non-HIV-related events that still occurred at high CD4 counts. Understanding whether there are more sensitive markers than the CD4 count could both help identify people at higher risk and have the potential to change the way HIV is routinely monitored now that ART is increasingly started at high CD4 counts.

START randomised more the 4600 treatment naive participants with CD4 counts above 500 to either immediate ART or deferring until the CD4 count reached 350. This analysis looked at hazard ratios (HR) for individual biomarkers and combinations including CD4, CD8, CD4%, CD8%, CD4:CD8 ratio and HIV viral load, with and without adjustment of other baseline variables (including age, gender, country etc).

In the 138 people with serious events over three years, the absolute CD4 count had no association with risk of a serious event in the early ART group (HR per 100 cells higher 0.98; 95%CI: 0.88 to 1.11, $p = 0.78$) and only a moderate association in the group with deferred ART (HR 0.87; 95%CI: 0.79 to 0.97, $p=0.011$).

However, CD8, CD8%, CD4:CD8 ratio and viral load were strong predictors irrespective of treatment group: HR 1.07 (CI: 1.04, 1.09, $p<0.001$) per 100 CD8 cells higher and 0.85 (CI: 0.80, 0.90, $p<0.001$) per 20% higher CD4:CD8 ratio. The effect of CD8 count and CD4:CD8 ratio remained strong after adjusting for viral load ($p<0.001$ and $p<0.002$, respectively).

Further analyses showed that although reduction in viral load explained most of the reduced risk of serious events, this was also to a lesser extent linked to an increase in CD4:CD8 ratio.

C O M M E N T

The finding that CD8 and CD4:CD8 ratio were better predictors of serious events is an important result for monitoring people at high CD4 counts.

This warrants review by guidelines that have already moved to reducing immunological monitoring with CD4 counts in people who are assumed to be at low risk.

Reference

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<http://programme.aids2016.org/Abstract/Abstract/7083>

Treatment in primary HIV infection is significantly more likely to normalise CD4:CD8 ratio

Simon Collins, HIV i-Base

Starting ART in primary compared to chronic HIV infection had a significantly higher chance of getting a CD4:CD8 ratio >1.0 in a retrospective study in which individuals were their own controls.

This was a retrospective analysis by Alexander Pasternak from University of Amsterdam and colleagues of 48 people who started a temporary period of ART in primary infection (PHI) – for either 24 or 60 weeks – and who after a median time of 2.4 years off-ART, subsequently restarted treatment again during chronic HIV infection (CHI).

As would be expected, the median CD4 count was higher at baseline for the PHI compared to CHI periods: 505 (IQR: 303 to 713) vs 310 (245 to 418) cells/mm³ respectively ($p< 0.0001$).

However, there was no difference in the dynamics of CD4 recovery between the PHI and CHI follow-up periods with median CD4 increases of 210 cells/mm³ at week-60 for both groups (although the PHI response reached higher absolute CD4 levels).

- 2. Stigma, discrimination, violence and human rights.** The urgent needs of trans people: to be protected from violence, discrimination and other forms of human-rights violation.
- 3. Services.** Detailed descriptions of gender-affirming health services and HIV-related and other essential health interventions. These include primary care, cross-sex hormone therapy, surgical procedures and service integration. HIV-related services include condom and lubricant programming, harm reduction services for substance use and safe injection, pre- and post-exposure prophylaxis, voluntary HIV testing, antiretroviral therapy, sexual and reproductive health, and mental and psychosocial health.

The chapter also addresses HIV and hormonal therapy.

- 4. Service delivery.** Trans-competent clinical approaches, social and behavioural interventions, approaches to HIV prevention, community-led service delivery, safe spaces (drop-in centres), and the use of information and communication technologies.
- 5. Programme management.** Practical guidance on planning, starting, scaling up, managing and monitoring both large multi-site programmes and more localised organisations.

<http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/implementing-comprehensive-hiv-and-sti-programmes-with-transgend.html>

https://www.unfpa.org/sites/default/files/pub-pdf/TRANSIT_report_UNFPA.pdf (PDF)

[.thelancet.com/journals/lanhiv/issue/vol3no7/PIIS2352-3018\(16\)X0007-0](http://www.thelancet.com/journals/lanhiv/issue/vol3no7/PIIS2352-3018(16)X0007-0)

Untangling the web of ARV price reductions

Médecins Sans Frontières (MSF)/Doctors Without Borders

The 18th edition of the MSF HIV drug pricing report is the single most important reference for pricing and access to generic HIV drugs globally.

This update is the clearest report for tracking the importance of generic competition, primarily from India.

Since the last edition, the lowest available price for a WHO-recommended first-line one-pill-a-day ART (tenofovir/emtricitabine/efavirenz) had dropped by 26% from \$136 to US\$100 per person per year. For second-line ART, the lowest available price has dropped 11% from \$322 to \$286 (zidovudine/lamivudine + atazanavir/ritonavir).

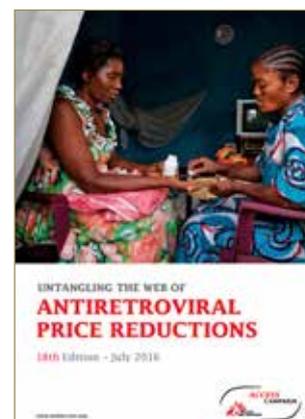
Newer drugs remain more expensive but are the only options for third-line ART. The lowest annual price for raltegravir + darunavir/ritonavir + etravirine is \$1,859, reduced by only 7% from \$2,006 in 2014. This is 18 times the price of first-line therapy, and six times the price of second-line combinations.

The report also highlights the growing concern for access to ART in middle-income countries who pay much higher prices due to patents.

MSF. Untangling the web of antiretroviral price reductions (18th edition).

<http://www.doctorswithoutborders.org/article/msf-report-shows-price-newer-hiv-medicines-18-times-more-expensive-first-line-treatment>

https://www.doctorswithoutborders.org/sites/usa/files/antiretroviral_price_reductions.pdf (PDF)



Making viral load routine

Médecins Sans Frontières (MSF)/ Doctors Without Borders

Based on a survey from ten ART sites and seven viral load testing labs this MSF report aims to share practical lessons from the field with Ministries of Health and implementing partners.

The two-part report covers the strategies required within the clinic (for clinicians, counsellors and patients) and the realities of both setting up and keeping a viral load testing laboratory functional in low-income settings.

It emphasises that national viral load scale up plans must link both programmatic and laboratory planning if viral load tests are to become a routine part of HIV care.

<http://www.msfacecess.org/content/report-making-viral-load-routine>

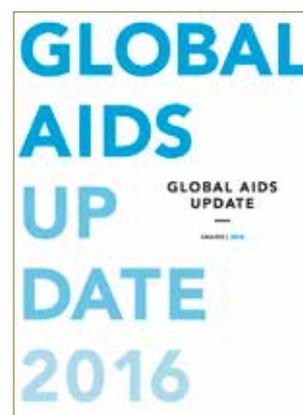
UNAIDS: global AIDS update

UNAIDS

Summary 12-page report from UNAIDS on the plans to end AIDS by 2030 and the progress towards the 90:90:90 targets for 2020.

<http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016>

http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf (PDF)



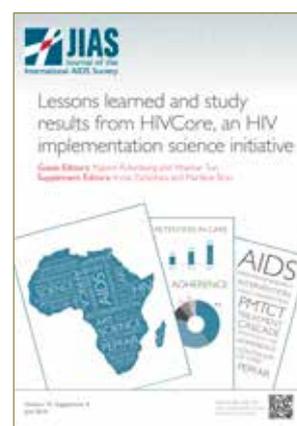
Implementation science in Africa: JIAS special issue

The Journal of the International AIDS Society launched a special issue on implementation: “Lessons learned and study results from HIVCore, an HIV implementation science initiative”.

HIVCore is a five-year US NIAID-funded project focused on operations and implementation research. This report includes ten articles based on these issues in several African countries

<http://jiasociety.org/index.php/jias/issue/view/1482>

<http://jiasociety.org/index.php/jias/article/download/21261/pdf> (PDF)



HIV and related infections in prisoners

The Lancet

An excellent special issue of The Lancet produced for AIDS 2016 includes articles by key researchers on HIV care for prisoners.

Prisoners experience high rates of HIV, TB and viral hepatitis and often have little or no access to HIV treatment, prevention, and care.

As with previous special editions, access to all content is provided free.

<http://www.thelancet.com/series/aids-2016>

Lancet HIV: focus on prevention

Although the full contents of this AIDS 2016 edition of the Lancet HIV were not free, most of the key articles are open access.

[http://www.thelancet.com/journals/lanhiv/issue/vol3no7/PIIS2352-3018\(16\)X0007-0](http://www.thelancet.com/journals/lanhiv/issue/vol3no7/PIIS2352-3018(16)X0007-0)

i-Base/TAG pipeline report 2016

HIV i-Base and TAG

This annual publication from i-Base and TAG reviews the most advanced research relating to pipeline compounds for treatment, prevention, diagnostics and related strategies for HIV, TB and to a limited extent this year, hepatitis C.

The HIV chapters cover adult and paediatric care, treatment optimisation for global access, prevention advances and research into a cure. The TB chapters cover treatment and prevention.

Over 1000 printed reports and 2000 memory sticks with PDF publications were distributed at AIDS 2016.

<http://i-base.info/2016-pipeline-report>

<http://i-base.info/htb/wp-content/uploads/2016/07/2016-Pipeline-Report.pdf> (PDF)



CONFERENCE REPORTS

8th international workshop on HIV paediatrics

15–16 July 2016. Durban, South Africa.

Introduction

The 8th International Workshop on HIV paediatrics was held from 15 - 16 July in Durban.

The slides of the presentations given during the meeting and the webcasts of these presentations, are published online when consent has been provided.

<http://www.infectiousdiseasesonline.com/event/workshop/8th-int-workshop-hiv-pediatrics>

<http://www.infectiousdiseasesonline.com/8th-pediatrics-presentation>

The report in this issue of HTB is:

- No increased resistance with once daily dosing of abacavir and 3TC than twice daily dosing in the ARROW trial

No increased resistance with once daily dosing of abacavir and 3TC than twice daily dosing in the ARROW trial

Polly Clayden, HIV i-Base

Once daily dosing of abacavir (ABC) and lamivudine (3TC) was non-inferior to twice daily dosing in development of viral resistance in the ARROW trial, according to data presented at the 8th International Workshop on HIV Paediatrics.

The ARROW trial – conducted in Uganda and Zimbabwe – showed that once daily dosing of ABC and 3TC was bioequivalent with twice daily dosing and gave similar treatment outcomes at 96 weeks.

In a resistance sub study, the ARROW investigators compared the development of viral resistance in children randomised to once vs twice daily dosing over the course of the trial.

A total of 669 participants receiving twice daily ABC and 3TC containing regimens, for at least 36 weeks, were randomly assigned to continue with twice daily dosing or switch to once daily. Viral load was tested retrospectively using stored plasma samples at 0, 48 and 96 weeks post randomisation. Samples with >1000 copies/mL were genotyped at the Joint Clinical Research Centre, Kampala, Uganda.

Participants were a median age 5.5 years (range 1.8–16.9). They had previously received twice daily ABC and 3TC based ART for a median of 1.8 years: 48% with nevirapine; 18% with efavirenz and 34% with AZT.

HIV genotypes were: 49% subtype A; 25% subtype C (including all Zimbabwean participants) and 20% subtype A.

The investigators reported no difference between once daily vs twice daily ABC and 3TC in viral suppression at various time points (0, 48 and 96 weeks) and viral load thresholds (<80, <400 and <1000 copies/mL), all p-values non-significant.

There was no difference between once daily and twice daily in drug resistance mutations post baseline ($p=0.15$). The investigators found, overall 33%, 23% and 28% of participants had the L74V mutation at weeks 0, 48 and 96, respectively. At the same time points 42%, 28% and 34% had Y115F; and 6%, 6% and 5% had K65R. Only one participant receiving once daily triple NRTIs had Q151M at weeks 48 and 96. The investigators noted that thymidine analogue mutations were rare.

There was also no difference in intermediate/high level resistance to NRTIs between once daily and twice daily ABC and 3TC based regimens ($p=0.15$).

Among the subgroup of participants receiving an NNRTI plus ABC and 3TC regimen (WHO current recommendation) intermediate/high level resistance at 0, 48 and 96 weeks after randomisation was respectively: 15%, 16% and 8% for tenofovir DF and 0%, 4% and 2% for AZT, compared to 75%, 84% and 79% for ABC.

The investigators concluded that both tenofovir DF and AZT are second-line NRTI options for children failing ABC and 3TC based first-line ART.

Ref: Musime V et al. Viral drug resistance in African children taking once- versus twice-daily abacavir and lamivudine in the ARROW trial. 8th international workshop on HIV paediatrics. 15–16 July 2016. Durban, South Africa.

CONFERENCE REPORTS

TB 2016

16–17 July 2016. Durban, South Africa.

Introduction

The International AIDS Society (IAS) organised a two-day conference dedicated to this infectious disease immediately before AIDS 2016 in Durban, South Africa.

<http://www.tb2016.org>

This meeting incorporates the biannual SA TB Conference.

Reports in this issue are:

- Universal treatment of multi-drug resistant TB is possible within current budgets with generic production
- Shortened nine-month MDR-TB treatment works well in children and adolescents
- Levofloxacin: safety and tolerability in HIV positive and negative children treated for MDR-TB

Universal treatment of multi-drug resistant TB is possible within current budgets with generic production

Polly Clayden, HIV i-Base

Generic production could make novel multi-drug resistant tuberculosis (MDR-TB) regimens available for US \$53–507 per treatment course according to data presented at TB2016. [1]

High drug prices contribute to slow progress with scaling up treatment of MDR-TB with novel regimens worldwide. Dzintars Gotham and colleagues from Imperial College London, Howard University, Washington and St Stephens Centre, London showed that competitive generic production could make universal coverage possible within current budgets.

This group have previously used similar methodology to look at cost of generic production of HIV and HCV treatment – they first presented data from the MDR-TB treatment production costs evaluation last year at EACS. [2]

For moxifloxacin, linezolid and clofazimine, the investigators estimated prices by obtaining the costs of active pharmaceutical ingredients (API) from Indian export data. For bedaquiline, delamanid and pretomanid (newer drugs so no comprehensive export data) they estimated the costs using those of synthetic processes and raw materials. To estimate generic prices, the investigators combined API per kilogram costs with dosage, manufacturing costs (including excipients, cost of tableting and packaging) and a 10–50% mark up.

They collected current drug prices from the Global Drug Facility (GDF) website, where these were available. For delamanid they used the recently announced price from the originator. As the price for pretomanid is yet to be announced, the investigators conservatively assumed pricing at their highest generic estimate.

The analysis revealed that novel regimens could be available for US \$53–507 per treatment with generic production. In 2014, US \$173 million were spent on second-line TB drugs through the GDF. Assuming this budget, the investigators calculated that estimated drug prices would allow the purchase of: 86–170% more STREAM B treatments (at least 202,000 more treatment courses); 401–679% more STREAM C (at least 386,000 more treatment courses); 406–689% STREAM D (at least 529 more treatment courses); 1362–3007% more MDR-END (at least 319 more treatment courses); 23–164% more PaMZ (at least 282, 000 more treatment courses). See Table 1.

Table 1: Treatment courses that could be bought with a budget of US \$173 million

Regimen	Current lowest cost	Estimated generic cost	Current number of treatment courses afforded	Estimated number of treatment courses afforded
STREAM arm B*, 9 months (moxifloxacin, clofazimine, ethambutol, pyrazinamide, isoniazid, prothionamide, kanamycin)	\$734	\$272–395	236, 000	438, 000–636, 000
STREAM arm C, 9 months (levofloxacin, clofazimine, ethambutol, pyrazinamide, isoniazid, prothionamide, bedaquiline)	\$1,799	\$231–359	96, 000	483, 000–749, 000
STREAM arm D, 6 months (levofloxacin, clofazimine, pyrazinamide, isoniazid, kanamycin, bedaquiline)	\$1,325	\$168–262	131, 000	660, 000–1,030, 000
MDR-END, 20 months (delamanid, linezolid, levofloxacin, pyrazinamide)	\$7,408	\$ 238–507	23, 000	342, 000–726, 000
PaMZ 6 months (pretomanid, moxifloxacin, pyrazinamide)	\$140	\$53–114	1, 236,000	1, 518, 000–3, 264, 000

*Newly recommended WHO shortened 9-month regimen

The investigators concluded that at existing prices current budgets are not sufficient to afford universal treatment of MDR-TB with novel regimes. But generic production could make novel regimens available for US \$173 million – the amount spent on second-line drugs at current prices procured by the GDF in 2014.

C O M M E N T

Earlier findings from this excellent analysis were presented in October at EACS. But unlike that from HIV and HCV communities, so far the reaction from those working on TB has been lukewarm.

The annual incidence of MDR-TB is only 480,000, so there will not be the potential economies of scale seen with generic drugs to treat adult HIV and HCV.

Optimising treatment of paediatric HIV might be more analogous – where the number of priority drugs, formulations and regimens have had to be vastly pruned (and still needs more pruning) – to make sufficient volumes possible and procurement simpler.

References

1. Gotham D et al. Affordability of comprehensive MDR-TB treatment with novel regimens, at current prices versus estimated competitive generic prices. TB2016. 16–17 July 2016. Durban, South Africa. Poster abstract P42.
2. Gotham D et al. Target prices for novel treatments for drug-resistant tuberculosis. 15th European AIDS Conference (EACS). 21-24 October 2015. Barcelona, Spain. Oral abstract 351.

Shortened nine-month MDR-TB treatment works well in children and adolescents

Polly Clayden, HIV i-Base

The nine-month Bangladesh regimen for treatment of multidrug-resistant tuberculosis (MDR-TB) was successful in 83% of children and adolescents in an observational trial conducted in francophone Africa, presented at TB2016. [1]

Preliminary results presented previously at the 46th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union) in 2015 showed the regimen to be successful in 82% of adults participating in the study. It was coordinated by The Union and from January 2013 to March 2015 recruited participants in: Benin, Burkina Faso, Burundi, Cameroon, Ivory Coast, Niger, Central African Republic, Democratic Republic of Congo and Rwanda. [2,3]

The regimen was: four months of kanamycin, moxifloxacin, prothionamide, isoniazid, clofazimine, ethambutol, and pyrazinamide (4 Km Mfx Pto H Cfz E Z), and then five months of moxifloxacin, clofazimine, ethambutol and pyrazinamide (5 Mfx Cfz E Z). Treatment was directly observed throughout the study.

Bassirou Souleymane from Action Damien Niger showed the findings from the Bangladesh regimen for children and adolescents study in an oral presentation.

The investigators collected data on all participants aged less than 18 years who were diagnosed with rifampicin-resistant TB and treated with the regimen during the inclusion period of the study.

Forty-eight children and adolescents were started on treatment with the Bangladesh regimen: 23 (48%) girls, 5 (10%) aged 0–9 years, 9 (19%) HIV positive, and 30 (63%) previously treated for TB.

Treatment was successful in 83% of participants (56% cured, 27% treatment completed), and there was no significant difference by age (85% in 15–17 vs 80% in 0–15 year-olds). There were more deaths among participants with HIV than those without (22% vs 5%), but treatment success was similar according to HIV status among surviving participants (100% vs 92%).

Adverse events were reported in 62% of the participants, none of which was severe. Of 24 participants assessed after treatment ended, 21 were alive with confirmed treatment success, two had died and one had recurrence.

The investigators concluded that treatment with the nine-month Bangladesh regimen appeared to be excellent in children and adolescents irrespective of HIV status with very limited side effects. They encourage countries to adopt the shortened MDR-TB treatment regimen in this population.

References

1. Bakayoko-Yeo-Tenena A et al. Treatment of multidrug-resistant tuberculosis (MDR-TB) in children and adolescents with a 9-month regimen in Africa. TB2016. 16–17 July 2016. Durban, South Africa. Oral abstract 220. Code P38.
2. Clayden P. Promising first results with a 9-month regimen for multidrug resistant tuberculosis in French-speaking African countries. HTB. 1 February 2016.
<http://i-base.info/htb/29604>
3. Kuaban C et al. First results with a 9-month regimen for multidrug-resistant tuberculosis (MDR-TB) in francophone Africa. 46th World Health Conference on Lung Health of the International Union Against Tuberculosis and lung Disease. 2 – 6 December 2015, Cape Town. LB CDC.
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Levofloxacin: safety and tolerability in HIV positive and negative children treated for MDR-TB

Polly Clayden, HIV i-Base

Levofloxacin was safe and well tolerated in children with and without HIV in long-term use. The data provide additional support for its inclusion in paediatric TB treatment and prevention regimens. [1]

These findings were presented as a poster at TB2016 authored by South African investigators from: Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town; Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch University, Cape Town; and Western Cape Government Department of Health, Brewelskloof Hospital, Worcester.

Levofloxacin is a fluoroquinolone and a key component of MDR-TB treatment in children. The drug is also included in two phase 3 trials of preventive therapy in MDR-TB exposed adults and children. The most notable side effects of fluoroquinolones include: arthropathy, neuropsychiatric symptoms and QT interval prolongation. There have been persistent concerns about the safety of fluoroquinolones in children because of arthropathy in juvenile animals. Prospective data on levofloxacin in children is scarce, particularly on its long-term use.

The data were from a prospective, observational, cohort study conducted in Western Cape, South Africa. Children with MDR-TB in this cohort are routinely treated with a 6–7 drug regimen. The regimens include: a fluoroquinolone, a second-line injectable, ethionamide, terizidone, high-dose isoniazid, ethambutol, pyrazinamide, and occasionally other drugs such as PAS. At the beginning of the study levofloxacin was dosed at 10–15 mg/kg once daily and later at 15–20 mg/kg once daily.

There were 70 participants in the study with a median age of 2.1 years (range 0.4–7.3). Of these: 44% were 0–2; 50% were 2–5; and 6% were 6–15 years of age. Approximately half the group were girls; 17% were HIV-infected; and 23% and 35% respectively were underweight or short for their age. The children were followed for a total of 68.5 person years; median time 11.6 months (IQR 9.2–14.7).

The investigators reported that overall most adverse events were grade 1 or 2; the most frequent were vomiting (24 events in 19 children; 0.351 events/person-year) and ALT elevation (27 events in 22 children; 0.394 events/person-year). There were no arthritis events and only three grade 1 arthralgia events in three children (event rate 0.044 events/person-year).

Among grade 1 or 2 adverse events attributed to levofloxacin, vomiting (16 events in 14 children; 0.234 events/person year) and ALT elevation (18 events in 16 children; 0.263 events person year) remained the most reported.

There were three grade 3 and five grade 4 adverse events; seven were ALT elevation (none were attributed to levofloxacin) and one grade 3 headache, possibly related to levofloxacin. No adverse events led to permanent discontinuation of levofloxacin.

The investigators concluded that levofloxacin was safe and well tolerated and can be an option in TB treatment and preventative regimens. But they noted that making an assessment of adverse events associated with levofloxacin in multidrug regimens was hard – many adverse events were likely due to other second-line TB drugs. It is also likely that the event rates they reported overestimate those actually due to levofloxacin.

They suggested that mild arthralgia might be underestimated in young children but serious arthropathy is unlikely to have been missed. Neuropsychological events also might be underestimated. The investigators will report on QT prolongation elsewhere.

C O M M E N T

There are limited data on the use of second-line TB drugs in children. Second-line drugs are more toxic than those used in first-line treatment and adverse events are hard to monitor in children. Paediatric formulations are not usually available and doses using divided and/or crushed tablets are uncertain.

Pharmacokinetic data on which to base optimal dosing have been mostly absent until quite recently – thanks to the work of the Stellenbosch group who performed this levofloxacin evaluation. TB drugs are also frequently used with antiretrovirals in children with HIV and TB.

The data above are from a large ongoing study designed to characterise the pharmacokinetics and toxicity of second-line TB drugs for treatment and prevention of drug resistant TB in HIV positive and negative children, by age and HIV status.

We have previously reported findings from this excellent initiative as they have been presented. [2, 3, 4, 5]

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CONFERENCE REPORTS

2016 Towards an HIV Cure Symposium

16–17 July 2016, Durban, South Africa

Introduction

The 5th Annual IAS Towards an HIV Cure Symposium was held in Durban on 16 & 17 July 2016.

This is an abstract-driven conference selected from studies to be presented at AIDS 2016 meeting directly afterwards.

The symposium was co-chaired by Prof. Françoise Barré-Sinoussi, Dr. Steven Deeks and Prof. Sharon Lewin.

The programme and slide presentations from this workshop are already online.

<http://www.iasociety.org/HIV-programmes/Towards-an-HIV-Cure/Events/2016-Symposium>

Detailed reports on cure research from this meeting and at AIDS 2016 will be included in the next issue of HTB.

CONFERENCE REPORTS

17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

8–10 June 2016, Washington DC, USA

Introduction

The 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, was held from 8 - 10 June 2016 in Washington DC.

The slides of the presentations given during the meeting and the webcasts of these presentations, are published online when consent has been provided:

<http://www.infectiousdiseasesonline.com/event/workshop/international-workshop-clinical-pharmacology-hiv-hepatitis-therapy-2016>

The abstract book is also available in PDF format online:

http://regist2.virology-education.com/Abstractbook/2016_6.pdf

Natap.org has also published extensive reports from the workshop, many including full slide sets:

<http://www.natap.org/2016/Pharm/Pharm.htm>

Reports in this issue of HTB are:

- Modelling data might support use of low dose 400 mg efavirenz in pregnancy
- Pharmacokinetics of antiretrovirals comparable to that in non-pregnant women from three weeks after delivery

Modelling data might support use of low dose 400 mg efavirenz in pregnancy

Polly Clayden, HIV i-Base

Simulated exposure following 400 mg efavirenz once daily during third trimester of pregnancy, indicates that the lower dose might be adequate in this population, according to data presented at the 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy.

Efavirenz (EFV) 400 mg once daily is non-inferior to EFV 600 mg in adults and recommended by World Health Organisation as part of an alternative first-line regimen. [1] The pharmacokinetics (PK) of antiretrovirals can alter during pregnancy, leading to reduced drug exposure and the risk of virological failure and vertical transmission.

To date (and despite a lot of discussion) it remains unknown whether the 400 mg dose is adequate during pregnancy. And CYP2B6 polymorphisms influencing EFV clearance make this question a bit complicated.

Stein Schalkwijk from the PANNA Network, based at Radboud University Medical Centre, Nijmegen, alongside investigators from The Netherlands, South Africa, Thailand and the US IMPAACT 1026s group developed a physiologically-based population PK model to describe the PK of EFV in HIV positive pregnant and non-pregnant women. [2] They included published data, pooled from nine EFV pregnancy PK studies, and used the model to simulate EFV exposure following 400 mg EFV QD during third trimester of pregnancy.

Data from 249 women (1697 samples) were included in the model. Median non-pregnant weight was 59 kg (IQR 52-68). Median gestational age 35 (range 25-39) weeks. Among 41 (16%) women with genotype available: eight were categorised as slow metabolisers; 22 intermediate; and 11 fast metabolisers.

After controlling for pregnancy-induced changes in protein-binding and plasma liver flow, the investigators found that pregnancy had no effect on intrinsic clearance.

For 400 mg, the simulated median C₁₂ in pregnancy were: 3.22 (IQR 2.23–4.57), 1.26 (IQR 0.92–1.75), and 0.82 (IQR 0.58–1.20) mg/L for slow, intermediate and fast metabolisers, respectively, compared to 4.37 (IQR 3.17–6.07), 1.74 (IQR 1.24–2.32), and 1.17 (0.84–1.64) mg/L for non-pregnant women.

In slow, intermediate and fast metabolising pregnant women 1%, 30% and 61% had C₁₂ below 1.0 mg/L, respectively, compared to 1%, 14%, and 38% in non-pregnant women.

The investigators reported that the frequencies of C₁₂ below 0.7 mg/L were: 38% in pregnancy and 15% for non-pregnant fast metabolising women. But despite this increase in below target fast metabolising pregnant women, the

predicted unbound concentrations were unchanged by pregnancy. Simulated EFV unbound concentrations showed 18% of C₁₂ in fast metabolising pregnant women below the protein-binding-adjusted threshold of 0.7 mg/L, compared with 15% in non-pregnant women.

The investigators concluded that although pregnancy decreases total EFV C₁₂, EFV unbound is predicted to be unchanged. Although this finding needs confirmation in human studies, it suggests that a dose reduction to 400 mg might be feasible.

C O M M E N T

A PK study of EFV 400 mg in pregnant women is underway at the St Stephen's Centre, Chelsea and Westminster Hospital, London. [3]

This study is recruiting women who are stable on EFV 600 mg once daily for more than 12 weeks and willing to take EFV 400 mg once daily at gestational age of 28 weeks (plus or minus three weeks).

The study should finally provide the evidence to guide global recommendations for this optimised EFV dose in pregnant women.

Reference

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<http://www.who.int/hiv/pub/arv/arv-2016/en/>
2. Schalkwijk S et al. Is pregnancy a barrier to the proposed lower dose of efavirenz? 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. 8–10 June 2016, Washington DC, USA. Poster abstract P_26.
3. US National Institutes of Health. SSAT063- Pharmacokinetics of efavirenz 400 mg once daily during pregnancy in HIV-1 infected women.
<https://clinicaltrials.gov/ct2/show/NCT02499874>

Pharmacokinetics of antiretrovirals comparable to that in non-pregnant women from three weeks after delivery

Polly Clayden, HIV i-Base

When looking at pregnancy induced pharmacokinetic changes, timing of the postpartum control curve from three weeks after delivery was comparable to non-pregnant women, according to investigators from the PANNA study.

Pregnancy may induce changes in the pharmacokinetics (PK) of antiretrovirals, which could lead to sub-therapeutic levels. PANNA is a European clinical pharmacology network that investigates the PK of new antiretrovirals in HIV positive pregnant women.

The PANNA protocol includes taking PK curves in the third trimester of pregnancy (at approximately 33- weeks gestational age) and postpartum (at least two weeks after delivery). The postpartum curve is used as the intrapatient control curve for the non-pregnant woman.

The PANNA investigators found that sometimes, the postpartum curves are performed before the preferred period with a minimum of two weeks. They also noted that the choice of 2–6 weeks postpartum – although widely used in PK studies – has not been validated. So they assessed this timing and the effect of pregnancy on the PK of several antiretroviral agents in a study presented by Angela Colbers from PANNA at 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy.

Women with paired PK for the antiretrovirals for which lower exposure in pregnancy was observed were included in the analysis: emtricitabine, tenofovir DF, atazanavir/ritonavir, darunavir/ritonavir, raltegravir and maraviroc.

The investigators calculated relative ratios for AUC and C_{max} for each participant and antiretroviral agent. They divided the ratio of the AUC in the third trimester/postpartum for each participant and antiretroviral agent by the geometric mean ratio of the third trimester/ postpartum in the study population for that antiretroviral agent.

There were 157 paired PK parameters, from 62 participants, generated in the PANNA study, included in the analysis. Median age at delivery was 32 years (range 19–45); 60% were black, 39% white and 1% of other ethnicity. Weight at postpartum PK sampling was 71 kg (range 43–126), and weight at third trimester PK sampling was 76 kg (range 48–139).

The investigators reported they observed no statistically significant difference for AUC ($p=0.337$) or C_{max} ($p=0.227$) relative to reference from week 3 postpartum onward (>week 8 pooled).

They concluded that no time effect was observed for postpartum curves taken at least 3-weeks post- delivery, and these curves were comparable to non-pregnant population means. They added that dose reductions (after dose increase in pregnancy) should be considered from two weeks post-delivery onwards.

Reference

Colbers A et al. Timing of the postpartum curve in pharmacokinetic studies in pregnancy should not be too early. 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. 8–10 June 2016, Washington DC, USA. Oral abstract O_3.

http://regist2.virology-education.com/2016/17HIVHEPPK/04_Colbers.pdf (slides)

TREATMENT GUIDELINES

BHIVA antiretroviral guidelines – 2016 update

Simon Collins, HIV i-Base

In August 2016, BHIVA published the interim update to the 2015 BHIVA antiretroviral guidelines.

Changes include interim consensus opinion by the panel on newly approved HIV drugs, with the full GRADE analyses planned for the full guideline update in 2017.

- Tenofovir alafenamide/emtricitabine (TDF/FTC) is now included with tenofovir DF/emtricitabine (TDF/FTC) as a preferred NRTI backbone for first-line therapy. In the absence of bone, renal or other concerns, both dual formulations are equally recommended. However the guidelines note that highest benefits from using TAF will be in people with higher risk for bone and renal complications, noting the generic TDF is likely to shortly be available.
- As a substrate of p-glycoprotein (pgp), there are potential drug-drug interactions for TAF that do not apply to TDF [SPC]. Co-administration of pgp inducers (including some anticonvulsants, rifamycins and St John's wort) with tenofovir may result in lower tenofovir concentrations and loss of efficacy. Rifampicin and other rifamycins induce P-glycoprotein and are therefore expected to decrease the absorption of TAF [23]; TAF is therefore not recommended.
- Previous references to tenofovir now specify TDF or TAF.
- Use of TDF or TAF without either 3TC or FTC is included as an option when genotypic resistance tests show HIV or HBV resistance to 3TC/FTC. This reference is not clear as presumably drug resistance to only one of these viruses would still maintain sensitivity to the other.
- Many previous references to ritonavir-boosted atazanavir or darunavir protease inhibitor therapy (PI/r) now include also cobicistat (PI/c)
- Updates to the chronic kidney disease and bone disease sections of special populations.
- Small changes to managing virological failure.

All changes to the updated guideline are highlighted in yellow.

Reference

BHIVA. Guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)

<http://www.bhiva.org/HIV-1-treatment-guidelines.aspx>

<http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf> (PDF)

HIV PREVENTION

PROUD study closes leaving participants without access to PrEP

Simon Collins, HIV i-Base

On 29 July 2016, the PROUD study website announced that the study will close without being able to continue to provide participants with oral PrEP. [1]

The press release blames NHS England for cancelling the previous commissioning process and the lack of government action to take an executive decision that PrEP – as with current PEP - could be commissioned nationally, rather than by local authorities.

A derisory offer of £2M to further research PrEP has not been adequately resourced or planned early enough to cover participants in PROUD, but more importantly, fails to allow access to PrEP for anyone until at least 2017.

Although Public Health England (PHE) is working to design another study – the scientific rationale for further research is difficult to see, PROUD proved PrEP was so effective in people at high risk of HIV that the study had to finish early.

The manufacturer of the version of PrEP used in PROUD, tenofovir DF/FTC (marketed as Truvada) have failed to extend further access to PrEP – and also failed to offer NHS England an affordable price reduction, even though the patent for tenofovir DF is due to expire in 2017.

The press release from PROUD emphasises that it is legal in the UK to purchase generic versions of PrEP online for personal use.

Links for information on how to do this are on the following websites:

<http://www.iwantprepnw.co.uk>

<http://prepster.info>

<http://i-base.info/uk-guide-to-prep>

C O M M E N T

This is a shameful situation for UK public health and research to withdraw effective PrEP from gay men and trans women.

While countries throughout the world are setting up programmes to include oral PrEP as a key strategy to reduce ongoing HIV infections, based on study results that include PROUD, the UK trails behind. Worse than this, NHS England sends a message that the sexual health of gay men is such a low priority that even people at highest risk are being abandoned.

On 22 July 2016, the EU finally agreed to approve PrEP for use in Europe. [2]

Although the legal challenge by the National AIDS Trust was successful in forcing NHS England to reopen the commissioning process – and the open consultation is now online – this decision is being appealed. See later reports in HTB for details.

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EMA overcomes its own prejudice to approve PrEP in Europe: four years too late

Simon Collins, HIV i-Base

On 22 July 2016, the European Medicines Agency (EMA) overcame their own organisational blocks and finally recommended granting authorisation for TDF/FTC to be used as PrEP in the European Union (EU).

This has taken four years since the FDA approved PrEP in the US. The delay is directly due to inappropriate actions from the agency for which no-one has yet formally taken responsibility.

The recommendation for approval (by the Committee for Medicinal Products for Human Use – CHMP) is based on the same clinical evidence that was used to approve PrEP in the US in July 2012 – iPrEX and the Partners PrEP study.

Following US approval, instead of allowing a similar application for EU access, the EMA took it upon itself to decide that PrEP was not for Europe – despite community pressure to enable access. Instead, a committee, acting without authority or transparency, decided to block access to the latest prevention options to people in the EU.

Their rationale was an erroneous belief that there would be little demand for PrEP and a misguided concern that people using PrEP might use fewer condoms – the outcome that PrEP is specifically designed to protect against.

These concerns are not the remit for a scientific agency charged with evaluating efficacy and safety of medicines. To refute this, the EMA should provide examples of when statins, fibrates or other medicines for cardiovascular health have been withheld due to the committee concerns that people might continue to smoke cigarettes, enjoy pastries or exercise slightly less than recommended guidelines.

In this case the EMA took inappropriate moral – rather than scientific – decisions to block access to the most advanced option for protection against HIV infection.

In doing this they disproportionately affected marginalised populations including gay men, people who inject drugs, sex workers and migrant communities.

C O M M E N T

Recommendations by the CHMP need to be formally adopted by the EU, after which, as with all medicines, each member country negotiates access, price and reimbursement.

France announced an early access programme for PrEP in November 2015.

The EMA delays played a role in the tens of thousands of new HIV infections that occurred since 2012 – and yet no-one from the EMA has acknowledged this lack of transparency in the approval process or taken personal responsibility for these decisions.

Reference

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002578.jsp&mid=WC0b01ac058004d5c1
2. PrEP to be available free in France from January 2016, HTB December 2015.
<http://i-base.info/htb/29311>

NAT legal challenge forces NHS England to reopen process for PrEP: 45-day public consultation now online

Simon Collins, HIV i-Base

On 2 August 2016, a legal challenge was successful in achieving a judgement that forced NHS England to reopen the process to commission PrEP. [1]

The legal action was taken by National AIDS Trust (NAT) – a community HIV policy campaign group – in response to a decision by NHS England in March 2016 to abandon an 18 month prespecified process for PrEP to be evaluated for use by the NHS. [2]

Deborah Gold, Chief Executive of NAT, said: “This is fantastic news. It is vindication for the many people who were let down when NHS England absolved itself of responsibility for PrEP. The judgment has confirmed our view - that it is perfectly lawful for NHS England to commission PrEP. Now NHS England must do just that. Over 4,000 people are getting HIV every year in the UK - we desperately need further prevention options to add to condom use. PrEP works. It saves money and it will make an enormous difference to the lives of men and women across the country who are at risk of acquiring HIV. The delay to commissioning PrEP is both unethical and expensive.”

In his judgement Mr Justice Green wrote: “No one doubts that preventative medicine makes powerful sense. But one governmental body says it has no power to provide the service and the local authorities say that they have no money. The Claimant is caught between the two and the potential victims of this disagreement are those who will contract HIV/AIDS but who would not were the preventative policy to be fully implemented.” He went on to conclude that NHS England does have the power to commission PrEP.

Unfortunately, but not unpredictably, NHS England has announced that they will appeal the decision, in an attempt to further extend a bureaucratic delay for access to one of the most effective options to protect against HIV.

NHS England is criticised for online response to court judgement

An announcement on the NHS website [3] was quickly and widely criticised for pitting one patient group against another. [4, 5]

Firstly the announcement started with a factually incorrect and incomplete statement in bold that “PrEP is a measure to prevent HIV transmission, particularly for men who have high risk condomless sex with multiple male partners.” Secondly it went to great lengths to stress that any decision to fund PrEP would result in restricted or blocked access to new drugs for other indications. Thirdly it referred to an estimated budget of £20 million while noting in other places that financial costs were linked to a different part of the commissioning process.

The weekly newsletter from the Patients Association criticised the statement for implying “that other services would have to be sacrificed in order to fund PrEP”. Katherine Murphy, Chief Executive of the Patients Association said: “We are deeply concerned about this divisive narrative around PrEP, care for HIV positive patients, and commissioning structures within the NHS. It is important to note that NHS England’s highest cost estimate for PrEP is £20m a year.”

“Two points are worth making to provide a vitally needed perspective. Firstly, this constitutes 0.02% of NHS England’s annual budget. Secondly, this figure is insignificant compared with the £483m that NHS England were spending on HIV treatment in 2013. This is not to suggest that PrEP would negate the need for HIV treatment but ‘prevention-is-better-than-cure’ has long been a guiding principle for NHS commissioning; it is not entirely clear why this logic is not

being employed for the care of patients with HIV.” The article continued: “To pit one patient against another patient is unacceptable and compromises the reputation and core values of the NHS.” [4]

C O M M E N T

NHS England should clearly accept responsibility for this mess and not try to shuffle it back on to people who are quite reasonable expecting services appropriate for their health.

The 45-day public consultation on PrEP was published online on 10 August 2016. [5]

References

1. NAT. Historic win for NAT as the High Court overturns NHS England refusal to consider PrEP. (2 August 2016). http://www.nat.org.uk/Media-and-Blog/Press-Releases/2016/August/Historic_win_NAT_PrEP_judicial_review.aspx
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3. NHS England. August update on the commissioning and provision of Pre Exposure Prophylaxis (PREP) for HIV prevention. (2 August 2016). <https://www.england.nhs.uk/2016/08/august-update-on-the-commissioning-and-provision-of-pre-exposure-prophylaxis-prep-for-hiv-prevention>
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Two large PrEP studies using two-month infusion of antibodies to prevent HIV infection: oral PrEP included for all participants

Simon Collins, HIV i-Base

Two large international studies have just been launched using a new strategy to prevent HIV transmission. [1]

Rather than using oral HIV drugs for PrEP – either with daily or event-driven dosing – these studies use a monoclonal broadly neutralising antibody (mAb) called VRC01 to boost immune responses to the virus. VRC01 is given as an infusion every two months.

Also important – and essential for other future PrEP research – these studies include the opportunity for all participants to also receive oral PrEP, recognising that this is currently best standard of care. [2]

Broadly neutralising HIV mAbs, including VRC01 have the potential to be used for treatment and prevention. New antibodies that will be even more active are expected in the next few years.

However, as with most HIV drugs, several different antibodies are likely to be needed in combination. VRC01, for example, misses 13% of viruses, though the implications of this for PrEP are unclear.

The current studies are being jointly run by two US publicly-funded research networks – HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN). The two studies – HVTN 703/HPTN 081 and HVTN 704/HPTN 085 – have a similar design with three arms. Several thousand people will be randomised to either one of two active groups receiving 30 mg/kg or 10 mg/kg infusions or to a control group that receives a placebo saline solution.

HVTN 704/HPTN 085 will take place at 24 sites in Brazil, Peru and the United States, and will enrol 2,700 men and transgender people who have sex with men. This study is now enrolling. HVTN 703/HPTN 081 will enrol 1,500 women at 15 sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania and Zimbabwe. This study is due to start shortly, within the next two months.

Both studies are collectively called AMP. [3]

An excellent overview of using mAbs for HIV treatment and prevention was given at the CROI 2016 conference in February and is available online as a free webcast. [4]

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FUTURE MEETINGS

Conference listing 2016/2017

The following listing covers some of the most important upcoming HIV-related meetings and workshops. Registration details, including for community and community press are included on the relevant websites.

18th International Workshop on Comorbidities

12 – 13 September, New York

<http://www.intmedpress.com/comorbidities>

20th Annual UK Resistance and Antiviral Therapy Meeting

15 September 2016, London

<http://www.mediscript.ltd.uk>

7th International Workshop on HIV & Aging

26 - 27 September 2016, Washington DC, USA

<http://www.virology-education.com>

7th BHIVA Conference for the Management of HIV/Hepatitis Co-infection

12 October 2016, London

<http://www.bhiva.org>

BHIVA Autumn Conference 2016

13–14 October 2016, London

<http://www.bhiva.org>

HIV Research for Prevention Conference (HIVR4P) 2016

17-21 October 2016, Chicago

<http://www.hivr4p.org>

European HIV Clinical Forum: Integrase Inhibitors

22 October 2016, Glasgow

<http://hiv-forum.com>

Congress on HIV Therapy (Glasgow 2016)

23-26 October 2016

<http://hivglasgow.org>

24th Conference on Retroviruses and Opportunistic Infections (CROI 2017)

13-16 February 2017

<http://www.croiconference.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

All i-Base publications are available online, including editions of the treatment guides.

<http://www.i-Base.info>

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

<http://www.i-base.info/qa>

Three new pocket guides: ART, pregnancy and side effects

A new series of pocket-size concertina folding leaflets that is designed to be a very simple and direct introduction to HIV treatment.



The first three pocket leaflets are:

- Side effects and Quality of Life
- HIV and pregnancy
- ART (included with the Sept/Oct HTB)

We hope this is especially useful as a low literacy resource.

The leaflet uses simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

i-Base treatment guides

i-Base produces six booklets that comprehensively cover important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

<http://www.i-base.info/guides>

- NEW: Guide to PrEP in the UK (June 2016)
- Introduction to ART (January 2016)
- HIV testing and risks of sexual transmission (June 2016)
- HIV and quality of life: side effects & complications (June 2016)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)

Order publications and subscribe by post, fax or online

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<http://i-base.info/order>

htb(e)

HIV TREATMENT BULLETIN (e)

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<http://www.i-Base.info>

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