

## september–october 2013

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## EDITORIAL

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This issue of HTB leads with the news that the CROI website continues to be blocked. While this may seem an unusual story to bring to our front page it is central to the way that community information and activist projects such as i-Base function.

None of the community writers for HIV Treatment Bulletin have a traditional medical education or background. Our ability to report and cover the latest research is closely related to being able to have open access to recent and historical studies.

While twenty years ago when CROI held its first meetings, the data was still restricted to the conferences, the commitment to publishing conference abstracts for those unable to attend, played a ground-breaking role that most other health areas have yet to understand. Over the years, online coverage slowly expanded to include webcasts for all oral presentations with simultaneous access to slides and posters.

We think that this continued access is a very reasonable community demand and hope that HTB readers support the new CROI secretariat by insisting on full restoration of the previous website.

By contrast, the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) - now in its 53rd year - continues as a lumbering dinosaur, with little available online and abstracts only publically available for a short time, behind a difficult to navigate database. Hence, our reports from ICAAC this year are sometimes limited to abstract reviews plus articles from the US-based natap.org (who also helpfully published some of the slides).

Antiretroviral news included EU approval of cobicistat and the decision by NHS England to cover Stribild as an option for a limited number of people. Dolutegravir will be soon to face the same regulation and access process and three articles cover US approval of dolutegravir, implications for UK access and global pricing. A simple demand for dolutegravir worldwide is that it should be priced similarly to the respective cost of efavirenz. If this does not occur it is unlikely to gain widespread use – particularly in coveted (and profitable) first line markets, despite its desirable characteristics.

Additional good news is that both the UK and France will continue to support the Global Fund in the goal of further extending treatment access and the welcome news that the UK, from April 2014, will relax restrictions on HIV positive health workers.

### **BHIVA members – print copies of HTB**

Please note that BHIVA members who are reading HTB electronically who want to continue to receive the print edition, need to please resubscribe online at:

<http://i-base.info/forms/postsub.php>

Or send your name, position, organisation and full postal address details to:

[subscriptions@i-Base.org.uk](mailto:subscriptions@i-Base.org.uk)

All subscriptions - print or email - are free.

## TREATMENT ALERT

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### **CROI website still blocked**

**In the last issue of HTB we reported on the disappearance of the website for the Conference of Retroviruses and Opportunistic Infections (CROI).**

The site is all still intact and makes up an archive of 20 years of the most important HIV research. But access has been blocked because of a bureaucratic wrangle that has enabled one person to flick a switch and stop global free access to this single most important HIV information resource.

Nearly every oral presentation, plenary session and memorial lecture - at least from the last decade - was accessible with simultaneous access to slides. This was because thousands of scientists committed their findings to an open policy that should be the goal of all medical research presentation and publication.

Although CROIs use of over zealous bouncers to eject any activist - whether a doctor or advocate - who wanted to fact-check reports using a few back-up photographs of data-filled slides that flashed data for a less than a minute during crucial late-breaker sessions - has always seemed excessive - the main drive for access to information afterwards has been groundbreaking and essential.

Research does not exist in a vacuum. Good medical reports usually link to previous presentations and related studies. If those references vanish then years of reporting are undermined.

Advances in HIV, especially relating to clinical management, shifted to conference presentations rather than reliance on peer reviewed publications. This is not to suggest conference presentations replace peer reviewed literature - which continues to be essential for a thorough presentation of any study - but can shorten the time between research discoveries and application to clinical care.

Guidelines writing groups routinely rely on CROI presentations as sufficiently important to reference in clinical recommendations. Twenty-three references from the most recent US DHHS HIV guidelines, in eight of the main thirteen sections are to CROI abstracts that are now no longer freely available. [1]

Researchers commonly include CROI as a data source for meta-analyses across a broad range of clinical management topics. [2-5].

As this issue of HTB went to press, neither the community letter below, nor requests to Melissa Sordyl at Westover Management Group, have been acknowledged or replied to.

Westover Management Group recently appears to have extended its ownership of the retroconference.org domain name from Jan 2014 to Jan 2015 and if that is the case, it is difficult to understand why the domain has not been transferred to the new CROI secretariat so that the site can be restored. Whatever business disputes have occurred, these surely pale into insignificance compared to the huge importance of keeping this information available for the global community working on HIV/AIDS.

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<http://www.ncbi.nlm.nih.gov/pubmed/22496475>

### **Community advocates letter to US government partners of the Conference on Retroviruses and Opportunistic Infections**

To:

Francis S. Collins, MD, PhD, Director, National Institutes of Health

Anthony S. Fauci, MD, Director, National Institute of Allergy and Infectious Diseases

Jack Whitescarver, PhD, NIH Associate Director for AIDS Research and Director, Office of AIDS Research

Thomas R. Frieden, MD, MPH, Director, Centers for Disease Control and Prevention

August 6, 2013

Dear Sirs

We are writing to express serious concern and dismay regarding the shutting down of the website for the Conference on Retroviruses and Opportunistic Infections (CROI).

Although we appreciate that you do not have control over business disputes, both the National Institute of Allergy and Infectious Diseases and the Centers for Disease Control and Prevention are listed as scientific partners in this conference, and the financial and intellectual investments of publicly funded institutions and scientists have been vital to the success of CROI, rendering it perhaps the single most important annual HIV research conference.

CROI has also been a pioneer in making webcasts, abstracts, and posters available via the conference website; this online information is now referenced and linked to by a vast number of scientific papers and online articles.

Due to the importance of the CROI website to HIV research, we urge you to do everything in your power to intervene and resolve the current, unacceptable situation. Whether by arbitration, negotiated settlement, or other means, it is essential that the CROI website be placed back online in a way that makes original links functional.

Sincerely,

ACRIA, AIDS Action Baltimore, AIDS Foundation of Chicago, AIDS Policy Project, AIDS Project Los Angeles, AIDS Resource Center, Ohio, AIDS Treatment News, AVAC, Andrea Benzacar, Rob Camp, Community Access National Network, Julie Davids, Anna Forbes, Foundation for Integrative AIDS Research (FIAR), Nathan Geffen, Harm Reduction Coalition, HealthHIV, HIV i-Base, HIV Prevention Justice Alliance, Barbara Hughes, International Rectal Microbicide Advocates, John S. James, NASTAD, National Minority AIDS Council (NMAC), Ohio AIDS Coalition, Okaloosa AIDS Support & Informational Services (OASIS), Project Inform, Robert Reinhard, San Francisco Department of Public Health, San Francisco Hepatitis C Task Force, Treatment Action Campaign, Treatment Action Group, WORLD (Women Organized to Respond to Life-threatening Disease).

cc.

Constance A. Benson, MD, Director, CROI Foundation; Kevin M. De Cock, MD, Chair, CROI 2014

Scott M. Hammer, MD, Vice Chair, CROI 2014; Donna M. Jacobsen, IAS-USA

John Mellors, President, CROI Foundation; Julie Overbaugh, PhD, Vice Chair, CROI 2014

Melissa Sordyl, Westover Management Group, Inc./CROI LLC

## CONFERENCE REPORTS

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### **53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)**

**10-13 September 2013, Denver**

#### **Introduction**

**As HIV research is only a small part of ICAAC these reports of summaries from the meeting are largely thanks to NATAP.org.**

The conference only has limited online coverage but this includes access to a PDF file of the programme for a short time after the meeting, which includes study abstracts.

<http://icaac.org/index.php/final-program>

Many of these studies may also be presented at the EACS conference being held in Brussels in early October, and certainly again at the next CROI meeting being held in Boston in March 2014.

Articles in this issue include:

- Raltegravir safe and effective in pregnancy in small French study
- Side effects common but mostly mild in women taking higher dose protease inhibitors in pregnancy
- Good safety profile with long-acting integrase inhibitor GSK744
- TAF comparable to TDF in once-daily pill for ART-naive: 48-week results
- Dolutegravir superior to darunavir at 48 weeks in open-label ART-naive trial

### **Raltegravir safe and effective in pregnancy in small French study**

**Polly Clayden, HIV i-Base**

**Raltegravir was safe and effective in pregnancy and for exposed infants in a small French study presented at the 53rd ICAAC.**

These data were presented by Vincent Jeantils and are from an ongoing study of mother-infant pairs conducted at Jean Verdier Hospital in Bondy, France.

All HIV positive pregnant women at this centre are referred to a multidisciplinary team including infectious disease specialists, obstetricians and pediatricians. Complete blood, CD4 cell count, viral load, transaminase, creatinine, and glucose is assessed monthly.

The study, which started in 2008, included 31 pregnant women with a median age of 31 years (range 18 to 44). Two women were coinfecting with hepatitis C and three with hepatitis B.

Five (16%) women had started raltegravir-based regimens before they became pregnant and remained on them, three (10%) and 23 (74%) women started raltegravir in the second and third trimesters respectively.

Five women started raltegravir due to side effects with other antiretrovirals, 19 because of poor adherence with a previous regimen and two because of late diagnosis.

Their median CD4 count when starting raltegravir was 442 cells/mm<sup>3</sup> (range 155 to 786) and viral load 17,765 copies/mL (range 61 to 114,638). Median raltegravir duration was 71 days (range 3 to 287). Median viral load before delivery was 41 copies/mL (range 0 to 641). Six women (19%) had detectable viral load (>40 copies/mL) at delivery, ranging from 45 to 641 copies/mL.

The investigators reported no biological abnormalities were observed in the 32 infants (one set of twins). Their median gestation age at delivery was 38 weeks. Fifteen women had vaginal deliveries and the remainder had planned or emergency caesareans. Almost all women (30/31) received intravenous AZT during labour.

The median weight of the infants was 3100 g (range 2120 to 4030) and median height was 48 cms (45 to 52), with a median Apgar score of 9.6 out of 10. All infants received four weeks of antiretrovirals: 23 AZT alone, four received two and five received three-drug prophylaxis. The investigators did not observe adverse reactions to treatment in the infants and 93% have tested HIV negative at six months.

At delivery the investigators performed a pharmacokinetic evaluation of maternal and cord blood in a subset of 16 cases. The median maternal raltegravir concentration was 10 to 270 ng/mL and median cord blood concentration was 5 to 198 ng/mL. The median cord blood to maternal ratio was 3.48 (range 1 to 7.6).

The children in this study will be followed for six years, so far the longest has been five but no adverse outcomes have been reported yet.

## C O M M E N T S

**BHIVA pregnancy guidelines recommend raltegravir: as a component of a three or four drug regimen for women presenting late (>28 weeks) with viral load greater than 100,000 copies/mL or unknown, and with AZT/3TC plus a single dose of nevirapine for women presenting in labour. [2] The guidelines also do not recommend switching regimens for women who conceive on stable ART - so similar scenarios to these described could be expected in the UK.**

**In this study 61% women also received a protease inhibitor, all but one woman received intrapartum IV AZT during delivery, and all infants four weeks of prophylaxis, so isolating the effect of raltegravir is tricky but there appears to be minimal HIV transmission.**

**Raltegravir has high first and second phase viral decay, rapid placental transfer and pre-loads the neonate (giving therapeutic concentrations that are stable for several days after delivery), which make it seem a good candidate for use in pregnancy – particularly for late presenters – although we note in the BHIVA guidelines that no adequate, well controlled studies of raltegravir in pregnant women have been conducted.**

**That no birth abnormalities were observed in the 32 infants is consistent with the limited data submitted to the Antiretroviral Pregnancy Registry so far – 3 defects in 119 infants exposed to raltegravir during the first trimester, and 6 in 109 during the second or third trimesters. [3] Raltegravir is pregnancy category C.**

### References

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## Side effects common but mostly mild in women taking higher dose protease inhibitors in pregnancy

Polly Clayden, HIV i-Base

**No difference in toxicities was observed between women receiving either high dose atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r) during pregnancy in a retrospective analysis at a single centre in Chicago.**

Pharmacokinetic changes during pregnancy reduce antiretroviral drug exposure. US guidelines recommend the use of high dose protease inhibitors (PI) ATV/r and LPV/r, during later stages of pregnancy – dose adjustment is not routinely recommended in the UK.

The study was conducted to determine rates of adverse events (AEs) requiring PI discontinuation, dose reduction, or treatment of symptoms. The retrospective cohort included HIV positive pregnant women receiving high dose ATV/r or LPV/r-based ART between September 2007 and January 2013. The primary endpoint was a comparison between the groups of a composite of the AE rate, symptomatic treatment initiation related to AEs, dose reduction or discontinuation of the PI.

Overall, 65 women were included in the analysis, of these 52 received LPV/r and 13 ATV/r at doses of 600/150 mg and 400 /100 respectively.

Women were similar in both treatment groups with a median age of 29 years old, most were black (65%), and had been HIV positive for about 8 years. Time to PI dose increase was shorter for women receiving ATV/r – a median of 137 days compared to 189 in the LPV/r group,  $p < 0.05$ . The investigator noted that this was because the product labeling recommends dose adjustment during the second trimester of pregnancy.

Most women in the ATV/r group (84.6%) took tenofovir and FTC concurrently while most of those in the LPV/r group (55.8%) received 3TC/AZT.

During the study period 77% of women in the ATV/r group achieved an undetectable viral load (<48 copies/mL) compared to 84% in the LPV/r group,  $p = 0.32$ . There were 11 composite endpoints in the ATV/r group and 44 (84.6%) in the LPV/r group, both 84.6%,  $p = 0.99$ . A greater proportion of women receiving ATV/r had a laboratory abnormality, 52.6% vs 31.7%,  $p = 0.08$ . This was mostly because of hyperbilirubinaemia.

The groups had similar rates of clinical interventions: symptomatic agent 31.6% vs 42.6%; dose reduction 0% vs 4.6% and antiretroviral discontinuation 7.8% vs 0.77% in the ATV/r and LPV/r groups respectively. Grades of AEs were also similar, respectively 78.9% vs 70.3% Grade 1 and 21.0% vs 29.7% Grade 2 to 4.

Antiretroviral discontinuations occurred in one woman who had constipation with ATV/r and one who had anaemia with LPV/r. The three dose reductions in the LPV/r group were related to transaminitis.

## C O M M E N T

**It would be interesting to see a comparison between side effects occurring with high and low doses of PIs in pregnancy. US guidelines recommend increasing the dose of PIs in pregnancy routinely whereas BHIVA guidelines do not – both countries report very low transmission rates.**

Ref: O'Brien C et al. Tolerability of high dose atazanavir/ritonavir versus lopinavir/ritonavir during pregnancy in HIV-infected women. 53rd ICAAC. 10-13 September 2013, Denver. Poster abstract H-1259.

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## Good safety profile with long-acting integrase inhibitor GSK744

Mark Mascolini, NATAP.org

**Analysis of eight studies involving 245 people taking oral or injected GSK1265744 confirmed that the long-acting integrase inhibitor is well tolerated and results in few serious lab abnormalities. [1]**

Injection site reactions, the most frequent adverse events, were usually grade 1.

Both oral and long-acting parenteral (LAP) formulations of GSK744 are in development. The once-daily oral agent has a half-life of about 40 hours, while half-life of the intramuscular or subcutaneous LAP formulation stretches from 30 to 40 days.

This analysis involved six short-term oral dosing studies in healthy volunteers or people with HIV and two LAP studies in volunteers. LAP injections were tested as single, monthly, or quarterly doses at 100 to 800 mg intramuscularly or 100 to 400 mg subcutaneously. There were 245 study participants, 65 of them (26.5%) women, with a median age of 32 (range 18 to 64). Twenty-nine people with a median age of 31 years (range 18 to 54) received placebo.

Six people (2.4% of 245) withdrew because of adverse events, two of them judged drug related (dizziness and a grade 1 rash). Four people (1.6%) had grade 3 or 4 adverse events, and 3 (1.2%) had serious adverse events (foot osteomyelitis, uterine fibroids, and appendicitis). No one had drug-related grade 3 or 4 adverse events or serious adverse events.

Two noninjection-related adverse events affected more than 5 study participants. Headache troubled 7% of participants, with similar rates in the GSK744 oral (7%), LAP (6%), and placebo groups (10%). Abdominal pain arose in 2% of study participants, including 2% taking oral GSK744, 2% taking the LAP formulation, and no one taking placebo.

Most people getting an intramuscular injection of GSK744 (74%) or a subcutaneous injection (96%) had an injection site reaction (ISR), compared with 25% getting intramuscular placebo and 50% getting subcutaneous placebo. ISRs affecting the highest proportions of participants were pain (73% and 86% with intramuscular and subcutaneous GSK744), erythema (19% and 79%), nodules (14% and 79%), injection site warmth (8% and 29%), induration (6% and 25%), and itching (5% and 18%). Researchers detected no consistent relationships between GSK744 dose and occurrence of any individual ISR.

Of the top three ISRs, pain lasted for medians of 5 and 6 days with intramuscular and subcutaneous injection, erythema lasted medians of 5 and 7 days, and nodules lasted medians of 22 and 47 days. No one dropped out of a study because of ISRs, all ISRs resolved, and there were no grade 3 or 4 ISRs. In a 40-person substudy, most participants rated injections "very tolerable," which was the highest rating on the scale used.

Among grade 4 lab abnormalities, 1 person each with bilirubin, creatine kinase, or triglyceride elevations. Grade 3 abnormalities included 1 bilirubin elevation, 3 creatine kinase elevations, and 4 lipase elevations. Overall, the most frequent grade 2 or worse lab abnormalities involved total cholesterol (5%), lipase (4%), bilirubin (2%), glucose (2%), and creatine kinase (2%).

Evaluation of 2540 postdose electrocardiograms (ECGs) showed that the difference in average QTcF change from baseline between the GSK744 group and the placebo group was -2.9 msec (95% confidence interval -4.96 to -0.81 msec). No one had a QTcF of 480 msec or longer or a change from baseline of 60 msec or greater. GSK744 dose was not related to change from baseline QTcF.

GSK744 has entered phase 2b clinical trials in antiretroviral-naïve adults.

### Reference

1. Lou Y, Gould E, Chen S et al. Meta-analysis of safety data from 8 clinical studies with GSK1265744, an HIV integrase inhibitor, dosed orally or as injection of long-acting parenteral nanosuspension. 53rd ICAAC. 10-13 September 2013. Denver. Abstract H-672.  
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## TAF comparable to TDF in once-daily pill for ART-naïve: 48-week results

Mark Mascolini, NATAP.org

**Tenofovir alafenamide (TAF), an investigational prodrug of tenofovir, did not accumulate in primary osteoblasts (bone-forming cells) more than in peripheral blood mononuclear cells (PBMCs) and had no cytotoxic effects in osteoblasts at concentrations that would be used in humans [1].**

The findings are in line with minimal bone mineral density (BMD) changes seen in phase 2 trials of TAF with elvitegravir, cobicistat, and emtricitabine [2, 3].

Certain antiretrovirals, particularly tenofovir disoproxil fumarate (TDF) and protease inhibitors (PIs), are linked to decreasing BMD. TAF, an oral prodrug of tenofovir, delivers more tenofovir diphosphate (TFV-DP, the active form of the drug) to PBMCs than does TDF and has greater antiviral activity than TDF in clinical studies. Because TAF also yields about 90% lower tenofovir levels in plasma than TDF, there is hope that this new agent will be less toxic in humans.

Gilead Sciences investigators conducted the studies described here with several objectives in mind: (1) to establish clinically relevant TAF concentrations in PBMCs in vitro that result in TFV-DP levels comparable to those observed in vivo, (2) to compare TFV-DP levels in primary human osteoblasts to TFV-DP levels in PBMCs with equivalent TAF exposures, and (3) to evaluate the effect of clinically relevant TAF concentrations on TFV-DP formation on primary human osteoblast growth.

More than 95% of TAF gets eliminated from plasma 2 hours after dosing. To mimic that process, the researchers pulsed TAF into PBMCs and primary human osteoblasts for 2 hours, followed by a washout. They measured TFV-DP in cells collected at multiple points after dosing. The investigators conducted PBMC loading experiments with multiple TAF concentrations to find the concentration that results in intracellular TFV-DP levels similar to those seen in vivo (677 nM). They then evaluated similar TAF concentrations in primary osteoblasts. Next, the Gilead team developed a primary osteoblast cell growth assay and evaluated TFV-DP levels after single and multiple TAF pulses. They assessed cell viability after treating primary osteoblasts with TAF for 3 days.

A 2-hour TAF pulse in PBMCs at concentrations from 124 to 370 nM yielded TFV-DP levels comparable to those seen in vivo with 25 mg of TAF, which results in a TAF maximum concentration (C<sub>max</sub>) of 484 nM. In primary osteoblasts, a single 2-hour pulse of the same TAF concentrations yielded TFV-DP levels comparable to those reached in PBMCs. Three days of daily 2-hour TAF pulses at 200 nM yielded similar TFV-DP levels.

The Gilead team saw no change in cell viability of primary osteoblasts exposed to clinically relevant TAF concentrations. The 50% cytotoxic concentration (CC<sub>50</sub>), a standard measure of cytotoxicity, was greater than 500 uM with the pulse method, which is more than 1033 times higher than TAF plasma C<sub>max</sub> (484 nM). For comparison, average CC<sub>50</sub>s for nelfinavir and lopinavir are 23.5 and 33.5 uM, or 3.4 and 1.8 times higher than their average plasma C<sub>max</sub> values (or about 34 and 18 times higher after adjustment for protein binding).

The investigators concluded that “primary osteoblasts were not preferentially loaded by TAF relative to PBMCs.” As a result, intracellular levels of TFV-DP (the active form of tenofovir) are comparable in PBMCs (about 0.677 uM) and osteoblasts (0.395 uM). Furthermore, TAF concentrations similar to those given to humans were not toxic to osteoblasts. These findings could explain the minimal changes in bone mineral density seen in clinical trials of TAF so far. [2, 3]

#### References

1. Liu Y et al. Lack of tenofovir alafenamide (TAF) effect on primary osteoblasts in vitro at clinically relevant drug concentrations. 53rd ICAAC. 10-13 September 2013, Denver. Abstract H-664.  
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## **Dolutegravir superior to darunavir at 48 weeks in open-label ART-naive trial**

**Mark Mascolini, NATAP.org**

**Dolutegravir, the integrase inhibitor that was recently licensed in the US, proved superior to darunavir/ritonavir after 48 weeks in previously untreated adults in the FLAMINGO trial. [1]**

A lower rate of dropouts due to adverse events in the dolutegravir arm and better responses in people with a pretreatment load above 100,000 copies/mL appeared to explain dolutegravir's superiority. Only two people in each treatment arm of this 484-person study had confirmed virologic failure.

These FLAMINGO results mark the second time that a randomised trial found dolutegravir superior to another recommended first-line antiretroviral. In the SINGLE trial a dolutegravir regimen was superior to an efavirenz regimen at 48 weeks, and again an adverse-event difference explained the superior outcome with dolutegravir. [2] SINGLE was a double-blind double-dummy trial, while FLAMINGO was open-label. Dolutegravir proved noninferior to raltegravir in the SPRING-2 trial. [3]

FLAMINGO is a multicenter open-label noninferiority trial that randomized 484 antiretroviral-naive adults to once-daily dolutegravir or darunavir/ritonavir plus investigator-selected tenofovir/emtricitabine or abacavir/lamivudine. No study participants had primary reverse transcriptase or protease mutations upon enrollment, and all had a viral load above 1000 copies/mL. The primary endpoint was the proportion of participants with a 48-week viral load below 50 copies/mL by snapshot analysis.

Study participants had a median age of 34, 15% were women, and 28% were nonwhite. One quarter of enrollees had a pretreatment viral load above 100,000 copies/mL, and median pretreatment CD4 count stood at a relatively high 395 cells/mm<sup>3</sup>. One third of participants started abacavir/lamivudine. Baseline characteristics differed hardly at all between treatment arms.

Of the 242 people treated in the dolutegravir arm, 18 (7%) withdrew; 3 because of an adverse event, 2 because of lack of efficacy, 6 because of loss to follow-up, and 2 because of investigator decision. Of the 242 people in the darunavir arm, 29 (12%) withdrew; 9 because of an adverse event, 2 because of lack of efficacy, 10 because of loss to follow-up, and 3 because of investigator decision.

At study week 48, the snapshot analysis determined that 90% randomised to dolutegravir and 83% randomised to darunavir/ritonavir had a viral load below 50 copies/mL. The adjusted difference of 7.1% (95% CI: 0.9% to 13.2%) established the superiority of dolutegravir to darunavir/ritonavir in previously untreated adults ( $p=0.025$ ). In a per protocol analysis, 91% randomised to dolutegravir and 84% randomised to darunavir had a viral load below 50 copies/mL at week 48 (difference 7.4%, 95% CI: 1.4% to 13.3%). Confirmed virologic failure (above 200 copies/mL) occurred in two people in each study arm, and no primary integrase, reverse transcriptase, or protease mutations arose in either arm.

The investigators proposed that the superiority of dolutegravir to darunavir reflected fewer withdrawals due to adverse events and other reasons before week 48 in the dolutegravir arm and a better dolutegravir response rate among people starting treatment with a viral load above 100,000 copies/mL. Nine people (4%) withdrew from the darunavir group because of an adverse event or death, compared with three (1%) from the dolutegravir arm. Drug-related (grade 2-4) adverse events affected 30 people in the darunavir arm (12%) and 23 in the dolutegravir arm (10%).

Among people with a pretreatment load below 100,000 copies/mL, snapshot analysis determined a 48-week sub-50-copy response rate of 88% in the dolutegravir group and 87% in the raltegravir group. Among people with a pretreatment load above 100,000 copies/mL, 48-week sub-50 response rates were 93% with dolutegravir and 70% with darunavir/ritonavir. Whether a person took abacavir/lamivudine or tenofovir/emtricitabine did not affect virologic results.

Participants randomised to dolutegravir had significantly fewer grade 2 or worse low-density lipoprotein cholesterol values (2% versus 7%,  $p<0.001$ ). Among other adverse events affecting 10% or more study participants, diarrhoea proved less frequent with dolutegravir than with darunavir/ritonavir (17% versus 29%), headache was somewhat more frequent with dolutegravir (15% versus 10%), and nausea affected similar proportion in each treatment arm (16% versus 18%). Median CD4 gain measured 210 cells/mm<sup>3</sup> in both treatment groups.

Session attendees wondered whether the open-label trial design favored dolutegravir. Perhaps people enrolled in the trial hoping to get randomised to the then-investigational integrase inhibitor. Some randomised to the already licensed darunavir may have dropped out in disappointment. But Judith Feinberg, who presented the data, said withdrawals did not occur predominantly in the early weeks of the trial, as one would expect with a disappointed-patient scenario.

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## CONFERENCE REPORTS

### 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention

30 June - 3 July 2013, Kuala Lumpur

#### Introduction

The following reports conclude our coverage from the IAS meeting held in Kuala Lumpur in July.

Many of the key oral presentations are available as webcasts, but unfortunately not all. Online coverage as we went to press is patchy and it is disappointing that many important sessions may not be posted online. Similarly, although many slide presentations are available, many are not.

However, all abstracts are online through the link to the Programme At a Glance online database for the meeting and contact details for many researchers are also available.

<http://pag.ias2013.org/PAGHome.aspx>

The year the conference has also posted webcasts from the press conferences on YouTube, including for the late-breaker sessions.

<http://www.youtube.com/user/iasconference>

The following reports are included in this issue of HTB.

- High prices for antiretrovirals in middle-income countries outside Africa
- Comparable efficacy and pregnancy outcomes with boosted atazanavir and lopinavir at standard doses
- PrEP gives little extra benefit in attempted conception if male partner is on ART



## High prices for antiretrovirals in middle-income countries outside Africa

Polly Clayden, HIV i-Base

**Middle-income countries outside of Africa are paying, on average, four times more for antiretrovirals than African countries with similar Gross National Incomes (GNI) according to an analysis presented at IAS 2013.**

There have been substantial reductions in the prices for antiretrovirals in the lowest income countries –defined by a GNI less than US\$1025/person-year – but these low prices are not consistent in middle-income countries with large HIV epidemics. There is no established mechanism for fair pricing in these countries and several key antiretrovirals are still on patent.

Andrew Hill from Liverpool University presented findings from an analysis of pricing of six key single agents and dual combinations used routinely in first and second line treatment, on behalf of colleagues from Thailand, South Africa and the UK.

The investigators looked at prices for nevirapine (NVP), efavirenz (EFV), tenofovir (TDF), AZT/3TC, TDF/FTC and lopinavir/ritonavir (LPV/r). Antiretroviral prices used in national programmes (2010-2012) were extracted from the WHO Global Price Reporting Mechanism (GPRM) database.

They then compared treatment costs – with both branded and generic antiretrovirals – with per capita annual GNI using the World Bank database.

The 20 countries were classified as:

**Low income** (GNI less than US\$1025/person): Ethiopia, Malawi, Uganda, Tanzania, Kenya, Cambodia.

**Low-middle income** (GNI US\$1026-\$4035): Nigeria, Vietnam, India, Philippines, Indonesia, Ukraine.

**Upper-middle income** (GNI US\$4036-\$12,475): Namibia, South Africa, Botswana, Thailand, China, Malaysia, Brazil, Russia.

Dr Hill suggested that a gradual price rise as income increases might be expected but this analysis revealed huge disparities in prices between African and non-African upper-middle income countries not clearly correlated with rising GNI.

Overall median treatment costs were mostly uniformly low in low and low-middle income countries and prices remained stable in African countries as GNI increased. Antiretroviral drug prices in upper-middle income countries outside of Africa were significantly higher than African countries with similar GNIs (See Table 1). The highest prices of any country analysed were in Malaysia, which has a lower GNI than Russia or Brazil.

**Table 1: Median cost of treatment (US\$ per person per year and range) in higher-middle income countries by location**

Formulation	African countries	Non-African countries	Cost Ratio
EFV (600 mg OD)	60 (51-69)	241 (57-784)	4.0
NVP (200 mg BID)	30 (29-35)	97 (32-162)	3.2
TDF (300 mg OD)	107 (79-135)	477 (262-715)	4.5
TDF/FTC (300/200 mg OD)	122 (102-143)	468 (157-779)	3.8
AZT/3TC (300/150 mg BID)	98 (97-113)	562 (372-752)	5.7
LPV/r (400/100 mg OD)	425 (397-490)	1000 (793-3794)	2.4

Ref: Hill A et al. Is the pricing of antiretrovirals equitable? Analysis of antiretroviral drug prices in 20 low- and middle-income countries. 7th IAS Conference on HIV Pathogenesis Treatment and Prevention, 30 June – 3 July 2013, Kuala Lumpur, Malaysia. Oral abstract WELBDO.

The investigators will repeat the analysis dividing the costs by originator and generic suppliers. They will look at patent restrictions on some antiretrovirals that might be causing higher prices in some middle-income countries.

Dr Hill remarked there was “no rhyme or reason to prices”. He concluded: “We need a new system of fair pricing for antiretrovirals for all middle-income countries with large HIV epidemics”.

### C O M M E N T

**Non-African countries can get forgotten in mechanisms to aid fair pricing and rarely has an analysis shown this so starkly.**

**Aggressive intellectual property rules proposed in a free trade pact under negotiation by the US and 11 Asia-Pacific countries - the Trans Pacific Partnership - could prevent equitable access to affordable medicines further by extending patent protection for originators and restricting generic production. This could make promising new pipeline drugs like dolutegravir completely out of reach for many people with HIV.**

Ref: Hill A et al. Is the pricing of antiretrovirals equitable? Analysis of antiretroviral drug prices in 20 low- and middle-income countries. 7th IAS Conference on HIV Pathogenesis Treatment and Prevention, 30 June – 3 July 2013, Kuala Lumpur, Malaysia. Oral abstract WELBDO.

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## Comparable efficacy and pregnancy outcomes with boosted atazanavir and lopinavir at standard doses

Polly Clayden, HIV i-Base

**Retrospective data collected from nine London centres and presented at IAS 2013 suggests atazanavir/ritonavir (ATV/r) and lopinavir/ritonavir (LPV/r) at standard doses are comparable in efficacy and pregnancy outcomes.**

In the UK and Ireland uptake of ART is high and rates of vertical transmission are low. HIV positive pregnant women frequently use protease inhibitors (PIs) despite concerns about pre-term delivery (for which data are conflicting) and altered pharmacokinetics.

The two PIs most commonly prescribed in this situation are ATV/r and LPV/r. Melissa Perry showed findings from a case note review conducted between September 2007 and August 2012 to look at which, if either, is preferred for pregnant women.

The investigators compared infant outcomes: pre-term delivery, transmission, birth weight, need for phototherapy and birth defects. Tolerability and virological response were compared in the women.

The analysis included 493 pregnancies. Women were a median age of 33 years, 81% were black African, 97% acquired HIV through heterosexual exposure, only 0.6% from injection drug use, 4% were coinfecting with hepatitis B and 1% hepatitis C.

ATV/r use increased and LPV/r use decreased over the study period; overall 187 women received ATV/r and 306 LPV/r. Tenofovir/FTC was the most common RTI backbone for women receiving ATV/r (70%) and AZT/3TC for those receiving LPV/r (62%) – again reflecting changes in standard of care. The majority – 88% and 92% for ATV/r and LPV/r respectively – received the standard PI dose.

There were similar proportions of pre-term (< 37 weeks) deliveries in both treatment groups: 13% with ATV/r (n=19) vs 14% with LPV/r (n=40). Background population rate is 8% in UK and Ireland. There were also no differences in outcomes between women who conceived on antiretroviral treatment compared to those who received it post conception (See Table1).

**Table 1: Timing of ART in pregnancy**

Timing of ART	Atazanavir/r	Lopinavir/r	Total
Pre-conception	95	82	177
Post-conception	92	224	316
Total	187	306	493

There were two transmissions: ATV/r 1 (0.7%) vs LPV/r 1 (0.4%), giving an overall rate of 0.5%.

The percentage of infants requiring phototherapy was low: ATV/r 2 (2%) vs LPV/r 2 (1%) and not seen more frequently in the ATV/r group (but very small numbers to make any comparison).

Birth defects were consistent with that reported to the Antiretroviral Pregnancy Register and occurred in 3 (3%) and 2 (2%) of infants exposed to ATV/r and LPV/r respectively at conception.

Low birth weight (<2500 g) occurred in 15% of infants in both treatment groups.

Two (2%) and 5 (5%) women receiving ATV/r pre- and post conception discontinued their PI due to tolerability, compared to 5 (6%) and 24 (11%) respectively for those receiving LPV/r. Although none of the comparisons were significant, Dr Perry pointed out that 55% of the 11% discontinuations in the post-conception LPV/r group were related to nausea and vomiting.

Women started ATV/r and LPV/r at a median of 20 and 22 weeks gestation. The majority of women had undetectable viral load (<50 copies/mL) at delivery: ATV/r 85% vs LPV/r 81%, p=0.61. Median time to undetectable: ATV/r 56 days vs LPV/r 43 days, p=0.52. This was despite the majority of women who received ATV/r receiving it at the standard dose with concomitant tenofovir.

This is the first study comparing pregnancy outcomes between these two PIs. Although it is limited as it is small and retrospective the findings are encouraging. Both regimens were successful in preventing vertical transmission. There were no differences in rates of pre-term delivery, outcomes, tolerability or virological suppression.

The pre-term delivery rate reported in this study is comparable to some studies and more favourable than others.

### C O M M E N T

**As the numbers of women in this analysis were small, the difference in side effects between LPV/r and ATV/r was not significant but the increase in discontinuations among women receiving LPV/r due to nausea and vomiting is worth emphasis and likely to become so with a larger sample size.**

**As with non-pregnant adults the use of LPV/r is declining and ATV/r increasing over time. It is reassuring that – despite the majority of women who received ATV/r receiving it at the standard dose with concomitant tenofovir – there was good viral suppression and a low transmission rate as with the women in the US cohort with increased doses of PIs described above.**

Ref: Perry M et al. Lopinavir and atazanavir in pregnancy: comparable infant outcomes, virological efficacy and preterm delivery rates. 7th IAS Conference on HIV Pathogenesis Treatment and Prevention, 30 June – 3 July 2013, Kuala Lumpur, Malaysia. Oral Abstract TUAC0101.

## **PrEP gives little extra benefit in attempted conception if male partner is on ART**

**Polly Clayden, HIV i-Base**

**PrEP offers little extra benefit to successful and safe conception for couple with an HIV negative woman and HIV positive man if he is receiving ART, they limit unprotected sex to ovulation, and STIs are treated – according to modelling data presented at IAS 2013.**

The model also suggests that younger age of the negative woman reduces the risk of transmission by decreasing the number of unprotected sex acts required for her to conceive.

Researchers from Los Angeles developed the model to estimate the annual probability of a woman remaining HIV negative, conceiving via unprotected sex with an HIV positive man and delivering a child according to various clinical scenarios. Raphael Landovitz showed data from the model in an oral presentation.

The aim of the study was to evaluate the additive benefit of PrEP for successful conception, without HIV transmission in this setting and explore the relative benefits of ART and PrEP, alone and in combination. It also evaluated the impact of maternal age on annual successful conception and non-transmission of HIV.

The primary outcome is an HIV negative woman remaining negative and successfully conceiving and developing a child.

Inputs included: transmissibility, the man receiving ART, the woman receiving PrEP, number of sex acts, female fertility by age and assuming STIs are treated. The sampling method and ranges for each parameter were chosen based a review of the relevant literature including data from HPTN-052 and Partners PrEP.

The model simulated two scenarios:

1. **Optimal** – unprotected sex limited to ovulation (0 to 12 acts per month – sampled about 3)
2. **Suboptimal** – unprotected sex acts not limited to ovulation (0 to 60 acts per month – sampled about 15).

In both scenarios this revealed that the HIV positive man being on ART has the greatest influence on HIV transmission.

With an optimal scenario the annual probability of a woman remaining HIV negative and delivering a child was: 27.6% with no ART or PrEP; 29.5% with PrEP; 30.6% with ART and 30.7% with treatment and PrEP. All pairwise comparisons were highly significant ( $p < 0.0001$ ) except for ART vs ART and PrEP, which was non-significant.

A suboptimal scenario gave these annual probabilities: 17.0% with no ART or PrEP; 24.1% with PrEP; 29.3% with ART and 30.3% with treatment and PrEP. In this scenario, all pairwise comparisons were also highly significant.

Comparing results from each annual probability calculation in optimal and suboptimal scenarios was highly significant for all comparisons.

In the optimal scenario, age is the most important factor for an HIV negative woman delivering a child. In the suboptimal scenario, for women <40 years, ART is the next most important factor.

Dr Landovitz summarised, based the inputs to this model, PrEP provides little added benefit if all the following are true: the HIV positive man is receiving ART; unprotected sex is limited to the period of ovulation and STIs are diagnosed and treated in both partners.

He noted that in the optimised scenario, there is little absolute difference between all four strategies, but in the suboptimal scenario, ART for the HIV positive man drives the differences between strategies. The model also highlights that younger maternal age is associated with the desired outcome.

He stressed that all model results are limited by inputs, and are no substitute for clinical decision-making on an individual basis. But the data are reassuring that people can achieve the desired results without adding PrEP if they are able to optimise the other modifiable risk factors and they have access to ART.

The model was developed by clinicians as a tool to help couples understand the risks of HIV transmission during conception, and to allow couples and health workers to better understand the role of maternal and the benefit of PrEP for conception.

Ref: The benefits of pre-exposure prophylaxis as an adjunctive method of HIV-1 prevention during attempted conception between HIV-1-uninfected women and HIV-1-infected male partners: a modelling approach. 7th IAS Conference on HIV Pathogenesis Treatment and Prevention, 30 June – 3 July 2013, Kuala Lumpur, Malaysia. Oral Abstract TUAC0104.

## ANTIRETROVIRALS

### **Cobicistat approved as pharmacokinetic (PK) booster for atazanavir and darunavir in EU prior to the US**

**Simon Collins, HIV i-Base**

**On 25 September 2013, Gilead announced that its pharmacokinetic booster cobicistat had been approved in Europe with an indication to boost once-daily use of either atazanavir (300 mg) or darunavir (800 mg), in combination with other ARVs in a combination. [1]**

Approval is based on results from a Phase 3 study (study 114) in which cobicistat was non-inferior compared to ritonavir at boosting atazanavir over 48 weeks. All patients also used tenofovir and FTC. Additional PK studies showed cobicistat and ritonavir produce a similar boosting effect on darunavir drug levels.

As with ritonavir, cobicistat has the potential to interact with a wide range of other drugs.

Cobicistat is a selective inhibitor of the cytochrome 450 3A4 liver enzyme responsible for metabolising atazanavir and darunavir which, similar to ritonavir, results in higher drug levels and slower clearance of the boosted drug. Cobicistat is also a CYP3A substrate, a weak CYP2D6 inhibitor and is metabolised, to a minor extent, by CYP2D6. The transporters that cobicistat inhibits include p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3.

Until full prescribing information is available on the EMA website, please see the Gilead press statement for further details. [1]

In Study 114, cobicistat was well tolerated and most adverse events were mild to moderate. The most common adverse reactions (incidence greater than or equal to 10 percent, all grades) were jaundice, ocular icterus and nausea.

Based on the information in the SPC for Stribild, Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance (see section 4.8). Patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3 mg/dL) from baseline should be closely monitored for renal safety.

Cobicistat is dosed at 150 mg once-daily.

Cobicistat is marketed under the brand name Tybost.

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2. Gilead press statement. Gilead receives complete response letters from U.S. Food and Drug Administration for elvitegravir and cobicistat. (29 April 2013). <http://www.gilead.com/news/press-releases>

### **NHS England approves four-in-one Stribild (Quad) for limited use**

**Simon Collins, HIV i-Base**

**On 11 September, NHS England issued a policy statement for a single tablet, four-in-one HIV combination treatment called Stribild (also known as Quad). [1]**

This is important as Stribild is the first HIV treatment to be reviewed under the new NHS structure for commissioning HIV care.

The commissioning position, effective from August 2013, states the following scenarios in which it will be routinely funded:

- In ARV experienced patients with no prior history of virological failure or drug resistance, and who require a switch from their current regimen where there is a clinical advantage of Stribild over alternative switch options and where the use of the individual components is not contraindicated. OR
- In ARV-naïve patients with high viral loads who are not suitable for NNRTIs (or others on NNRTI who need to switch for reasons unrelated to resistance). AND
- Where the decision to prescribe Stribild has been taken after review in a Multidisciplinary HIV specialist treatment meeting and that this will be subject to clinical and commissioner audit. AND
- Where Stribild prescribing is no greater than 5% of the patients in a clinical cohort on treatment.

The combination was approved by the US FDA in December 2012 and by the EMA in May 2013. [2, 3]

The four drugs in Stribild are an integrase inhibitor (elvitegravir 150 mg) a pharmacokinetic booster (cobicistat 150 mg), FTC (emtricitabine 200 mg) and tenofovir DF (300 mg).

Stribild needs to be taken once-daily with food. It should not be started in patients with estimated creatinine clearance below 70 mL per minute.

For further details please refer to the full prescribing information and patient information leaflets on the EMA website. [4]

C O M M E N T

**As the first new ARV to receive EU approval under the current NHS restructuring, this is broadly good news for HIV positive people.**

**It shows that a new treatment can be reviewed and available relatively soon after European approval. It also recognises that new drugs have more limited data and therefore the requirement for a case review, by a team with experience of complex cases, is also probably good.**

**It is likely that these recommendations were closely related to the negotiated price that is referred to in the document but not given. The UK list monthly price for Stribild is £1034.72 (ex-VAT) so the discounted price is likely to be significantly lower - though the lack of transparency over actual drug costs is perhaps not in patient interests.**

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## Dolutegravir approved in the US

Simon Collins, HIV i-Base

**On 12 August 2013, the FDA approved dolutegravir (50 mg tablets), a new integrase inhibitor to be used in combination with other antiretroviral drugs. [1, 2]**

The indication for use in adults and children aged 12 years and older weighing at least 40 kg (approx. 88 lbs). Approval is based on results from four phase 3 studies whose results have already been reported in HIV Treatment Bulletin (HTB). [3]

- SPRING-2: dolutegravir (once-daily) vs raltegravir (twice-daily) with investigator chosen dual NRTIs (abacavir/3TC or tenofovir/FTC)
- SINGLE: dolutegravir plus abacavir/3TC vs efavirenz/tenofovir/FTC (Atripla) in treatment naïve patients
- SAILING: dolutegravir (once-daily) vs raltegravir (twice-daily) with investigator chosen background regimen in treatment-experienced but integrase-naïve patients on currently failing combinations; and
- VIKING-3: dolutegravir (once-daily) with investigator chosen background regimen in treatment-experienced patients with resistance to raltegravir or elvitegravir.

The indication for children older than 12 years is based on a 24-week open-label study in integrase-naïve patients.

Dolutegravir is dosed 50 mg once-daily for naïve and integrase-naïve patients and at 50 mg twice-daily for patients who are integrase-experienced. Twice-daily dosing is also required for naïve and experienced patients when coadministered with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin to overcome UGT1A/CYP3A inducing by these drugs.

Dolutegravir should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.

Side effects include hypersensitivity reactions and worsening liver enzymes in patients with HIV and hepatitis B and/or hepatitis C coinfection.

Dolutegravir can be taken with or without food.

For prescribing details see the full product information. [4]

Dolutegravir is marketed by Viiv Healthcare and has the tradename Tivicay.

C O M M E N T

**US approval of this long-awaited new integrase inhibitor is welcomed and it is clearly supported by good efficacy and tolerability results. At a low milligram dose it also has the potential to be coformulated with other ARVs and a Fixed Dose Combination (FDC) with abacavir/3TC is already underway.**

**Although dolutegravir is active against HIV that is resistant to raltegravir or elvitegravir, even using twice-daily dose it is not able to overcome extensive integrase inhibitor resistance. The prescribing information notes that poor virologic response was observed in subjects treated with 50 mg twice daily with Q148 mutations plus two or more additional integrase-associated mutations including L74/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. [4, 5]**

**Also, although indication is to take with or without food, drug levels are increased when taken with a meal, especially if this has a higher fat content (AUC increased by 33%, 41%, and 66% when administered with low-, moderate-, or high-fat meals, respectively, compared with fasting). [6]**

**Given the need for a twice daily dose in integrase inhibitor experienced patients to increase drug exposure it would be interesting to know whether taking it with food to maximise the PK levels in patients with existing integrase inhibitor mutations would affect outcomes.**

**As with all new drugs, how widely dolutegravir will be used, is likely to depend on pricing (see article below).**

**Dolutegravir was submitted to the European regulatory agency at the same time as to the FDA and a decision is expected later this year. [7]**

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## **ViiV goes for gold: US premium pricing may make dolutegravir redundant in the UK**

**Simon Collins, HIV i-Base**

**On 12 August 2013, the FDA approved dolutegravir in the US. i-Base reported the news with an article linked to previous clinical trial results that noted not only the potential advantages but also some of the cautions. [1]**

One of the concerns was how the price, which didn't accompany the original company press statement, would be critical for whether dolutegravir finds a significant market.

While pricing is complex, the first indications of where ViiV have set their new drug are not encouraging. Unfortunately, dolutegravir has been priced as a second- rather than first-line option, with a US Wholesale Acquisition Cost (WAC) price of \$1175 per month for 30 tablets (\$39 per day, \$14,105 per year). When used by someone with integrase inhibitor resistance the dose increases to 50 mg twice a day, presumably doubling the cost. [2]

The once-daily dose is higher than currently approved integrase inhibitors raltegravir and boosted elvitegravir (at \$12,976 and \$13,428 annual WAC, respectively, see Table 1). In the US market this will make a dolutegravir-based combination approximately 25% higher than the most widely prescribed first-line fixed dose combination (FDC) Atripla (efavirenz/tenofovir/FTC), but comparable to protease inhibitors. [3]

The WAC is useful for comparison to other HIV drugs. It reflects the price wholesalers are asked to pay for a drug, but discounts are usually negotiated, and the WAC is set by the manufacturer with no input from the FDA. It is the catalogue price before rebates and discounts are given for volume purchasing (and before retail markups and discounts are calculated). This is different to the average wholesale price (AWP) referred to in the US DHHS guidelines. [4] AWP's are largely benchmarks used by public and private payers and are calculated by third-party institutions. The AWP can be 20-30% higher than the WAC.

The price is in contrast to the public statements of GSK CEO Andrew Witty who had stressed that pharmaceutical companies are benefitting from modern technology to reduce the costs of drug development and that these savings should be passed on to "customers". He has also stated that bringing a drug to market costs closer to \$300 million rather than the more frequently asserted \$1 billion and that this is as "one of the great myths of the industry". [5] GSK are the major shareholder of ViiV Healthcare (85% vs 15% with Pfizer).

It is difficult to see how this is good news for anyone. The only way dolutegravir is likely to become widely used in the UK - and many other European countries with national healthcare systems - is if the discounted price matches current first-line therapy such as Atripla. Setting a price in the US that is higher than both currently approved integrase inhibitors (raltegravir and elvitegravir) is the best way of ensuring that they do not reach patients who need them. Shareholders, in whose name the rationale for high pricing is often deferred to, should be furious. By focusing on a high drug price, they are following the approach taken by Gilead when the FDC Stribild was approved last year. [6] ViiV risk slashing their potential market even before the medicine reaches the pharmacy.

The potential to use dolutegravir in resource-limited settings, where it is likely to offer advantages over standard-of-care for first-line and second-line treatment, is even more connected to its price. The dramatically reduced cost of ARVs in resource-limited settings is already considerably lower. For example, annual costs are US \$130 for an FDC with tenofovir/3TC/efavirenz and US \$306 for a combination of atazanavir/ritonavir plus separate tenofovir/FTC. [7]

The target price for dolutegravir to become a first-line option in resource-limited settings is approximately US \$60-70 per year. This is the challenge that ViiV, working with other major organisations that are driving global access to HIV treatment, needs to meet. This low milligram dose, together with a generic formulation and sufficiently large orders, could make this achievable.

**Table 1: WAC prices for commonly used ARVs and combinations**

Drug/combination	Annual WAC price (\$US) [3]	Reference date
Single drugs		
dolutegravir	14,105	August 2013
raltegravir	12,976	March 2012
elvitegravir/c *	13,428	August 2012
efavirenz	7,859	January 2013
rilpivirine	17,078	January 2013
atazanavir/ritonavir	16,238	January 2013
Dual nucleosides		
tenofovir/FTC	14,681	January 2013
abacavir/3TC	12,394	February 2012
Combinations		
dolutegravir + tenofovir/FTC	28,786	
dolutegravir + abacavir/3TC	26,549	
raltegravir + tenofovir/FTC	27,570	
raltegravir + abacavir/3TC	25,370	
elvitegravir/cobicistat + tenofovir/FTC	28,109	
efavirenz/tenofovir/FTC (Atripla)	22,540	
rilpivirine/tenofovir/FTC (Eviplera/Complera)	23,238	
atazanavir/ritonavir + tenofovir/FTC	30,949	

\* WAC for Stribild minus WAC of tenofovir/FTC, for price comparison only as not currently available as separate formulation.

**C O M M E N T**

**By not pricing dolutegravir as a first-line option, ViiV have missed the opportunity to radically change the way HIV drugs are prescribed. Unless subsequent negotiations and discounts change this, dolutegravir is unlikely to be widely used in the UK. Drug development is futile if better drugs do not reach their potential to improve the lives of people who they were designed to benefit. Premium pricing is no longer a model for drug pricing.**

**As a guide for comparison, dolutegravir costs more than ten times the cost of gold; at \$0.78 compared to \$0.043 per milligram. It is hardly compensation to realise that by weight, dolutegravir pricing might be considered modest compared to Janssen's rilpivirine, which at more than \$47 for a 25 mg daily dose is just short of \$2 per mg. These are uncomfortable comparisons given the demand for life-saving medicines. [8]**

**The company says that it is not able to discuss pricing in the UK until after dolutegravir receives approval by the European Medicines Agency, and a decision is expected later this year. However, Marc Meachem, Head of External Affairs at ViiV Healthcare in the US, said that prices are set individually in each country and that European prices are not connected to charges made in the US. He explained that the US price included two assistance programmes for people who either have no health insurance when dolutegravir will be provided free or who are on low income when insurance contribution (out-of-pocket) charges are subsidised.**

**However, he also confirmed that integrase inhibitor-experienced patients who required the twice-daily dose will be charged double prices. This seems particularly unfair given how few people are currently in this situation and how this will disproportionately affect those people who are most in need of life-saving options.**

**ViiV is already in negotiations with a generic manufacturer, in which the company will provide dolutegravir under a royalty-free agreement. Until further details are available it is difficult to comment on the impact this will have in resource-limited settings, as ViiV is unlikely to have any control over the price that the generic company charges.**

Thanks to Polly Clayden and Tim Horn for additional comments.

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## From sky high to CHAI\* - what needs to be done about dolutegravir pricing?

**Polly Clayden HIV i-Base and Mark Harrington, TAG**

With a low 50 mg once-daily dose, good efficacy, minimal toxicity, pregnancy category B, and the potential to be low cost and co-formulated, dolutegravir is an attractive contender for use in low- and middle-income countries.

Swiftly after the FDA approved dolutegravir its US price was announced – an eye-watering US\$14,105 per patient per year. [1,2] Few outside the originator company considered this a pricing victory and several groups declared it to be quite the reverse. [3, 4, 5]

Meanwhile discussions among those set on optimising treatment for poor countries have marked the drug as a potential replacement for efavirenz first line – which would need it to be available at a similar price. The step from US\$14,105 to US\$48 is quite a steep one and much will need to be done to achieve this. [6,7]

This article borrows shamelessly from a previous one – Seven Ways to Speed up the Pipeline [8] – in which we explore some of these issues in more depth.

### **CHAI**

The Clinton Health Access Initiative (CHAI) supports national governments to access HIV treatment and offers reduced prices for first and second line antiretrovirals to members of its procurement consortium, which includes over 70 countries. [9]

CHAI produces an ARV Ceiling Price List and many of the listed products are made available through voluntary licensing agreements between the originator and generic companies.

The ceiling price for efavirenz is currently US\$48 and a fixed dose combination of this plus tenofovir is US\$130.

Middle income countries outside Africa who are not eligible for this and/or other price reduction mechanisms can pay, on average, four times more for antiretrovirals than African countries with similar Gross National Income (see article in this issue of HTB). [10]

### **Not-for-profit price from the originator**

The originator manufacturer ViiV Healthcare has said it will provide dolutegravir (branded Tivicay) at a not-for-profit price to eligible customers in its access programme ie to least developed countries, low-income countries and sub-Saharan Africa, following registration and marketing approval of the product and on request.

The price at which the drug will be available has not yet been announced and will be based on production costs, transport and volume.

Uptake will be determined by a number of factors including World Health Organisation (WHO) treatment guidelines; national treatment guidelines; stringent regulatory authorities and national regulatory approval processes.

ViiV plans to calculate and communicate the not-for-profit price “at the earliest opportunity”.

As there has been no announcement yet from the company, with a back-of-an-envelope calculation, considering that the not-for-profit price of raltegravir, with a high daily dose – 400 mg twice daily (16 times dolutegravir 50 mg once daily) – but with similar active product ingredients (API) is approx US\$675 per patient per year, adding inactive ingredients, packaging and shipping, perhaps we could optimistically expect a price of about US\$200.

### **Real world research**

Dolutegravir showed superiority to efavirenz at 48 weeks in naïve patients in phase III trials, mainly driven by fewer side effects. [11] Efavirenz fulfils many desirable characteristics for an ideal antiretroviral but the discontinuation rate for central nervous system side effects is about 25% in settings where people have options. It looks like this could be mitigated somewhat with a lower (400 mg) dose as shown in ENCORE 2. [12] But tolerability might be increasingly unacceptable as eligibility criteria for ART continue to broaden and more asymptomatic people are starting treatment, which is why possible alternatives to efavirenz need to be considered.

The data from the comparisons with efavirenz and from studies comparing dolutegravir to raltegravir and in people with resistance to other integrase inhibitors [13, 14] were used to gain FDA approval of a broad indication for dolutegravir. The indication for children older than 12 years is based on a 24-week open-label study in integrase-naïve patients.



Although some of the trials have now almost two years worth of data, how it would perform in a real world, low- or middle-income setting still poses questions. A Médecins Sans Frontières (MSF) paper published in 2008 stressed that populations in these settings include significantly larger proportions of women of childbearing age, children, and people with tuberculosis (TB), malaria, and other co-infections – but research is conducted in order to provide information to register drugs for rich countries. [15] The authors considered four drugs that had been recently approved or were in the pipeline at the time of publication. They looked at dose selection, comparability and compatibility with other antiretrovirals, and use in specific populations – none had enough information to make help decisions about treatment in low- and middle-income countries. The registrational trials for dolutegravir mostly had about 80% men and few non-white participants and hardly anyone co-infected (a few hepatitis B but none with TB or malaria).

ViiV seem to have been better than most with their development programme – dolutegravir has been studied in several treatment scenarios and regimens (although in a fairly homogenous population) and there is some information from PK studies about interactions with oral contraceptives, methadone and rifampicin [16, 17] but more information from the company and independent investigator-led studies is essential to address important gaps and this work needs to be done in a coordinated way.

Treating HIV/TB co-infection simply is a downside to dolutegravir – 50 mg twice-daily dosing will be required when it is co-administered with rifampicin to overcome UGT1A/CYP3A induction by this drug, which is used in standard first line TB treatment.

ViiV is planning a trial in TB co-infected people as well as a study of dolutegravir in women. The company is also looking at women who become pregnant on trials with dolutegravir.

A phase 3 investigator-led study comparing 400 mg efavirenz plus FTC/TDF to dolutegravir plus abacavir/3TC in naive patients, with sites in several African countries, is in the planning stage. [18] This study has few exclusion criteria, includes people with TB co-infection and aims to be as close as possible to real life. Adding a third arm with dolutegravir plus TDF/3TC would be interesting.

The study will look at another potential role for dolutegravir currently under discussion – in second line, not as a replacement for boosted atazanavir or lopinavir with two RTIs, but with boosted darunavir. This regimen has the potential to be a once-daily co-formulated second line option with no cross-resistance to the current recommended first line.

People starting in the efavirenz arm will switch to this second line and those in the dolutegravir one to darunavir/r plus TDF/FTC.

Results from this study are important and donors need to step up.

### Generic formulations and licensing

ViiV has said it will authorise FDA to cross-reference their data for generic production.

An article from Fierce Pharma quotes Marc Meachem that ViiV has “wrapped up a deal allowing a generic company to make a low-cost version of Tivicay, subject to regulatory approvals. That version would be intended for the globe’s poorest countries and countries in sub-Saharan Africa.” [19]

There has been no announcement so far from the company as to which generic manufacturers and when. It is also unclear whether it will negotiate the licences through its own voluntary licensing mechanism set up in 2010 – which includes about 67 sub Saharan and low income countries – or license dolutegravir to the Medicines Patent Pool (MPP) for which discussions are underway for adults, and there has been a promise for children along the lines of that in place for abacavir. [20] Voluntary licences for only 67 countries will probably not be acceptable for the MPP so negotiations might take a bit of time but both parties have said to expect news by the end of the year. One of the advantages of the MPP is that terms are in the public domain and we won’t have to continue to guess.

If dolutegravir is only recommended second line – perhaps co-formulated with darunavir/r – this will not be sufficient volume to produce a flurry of healthy generic competition and in turn a suitably low price.

### Regulatory approval

In Seven Ways to Speed up the Pipeline we wrote: “Regulatory delay has posed as much of an obstacle to timely access to antiretrovirals in developing countries as has patent protection, yet it has attracted none of the advocacy attention”.

Tables 1 and 2 show the respective delays from approval by the FDA to that by South Africa’s Medicines Control Council (MCC) and between FDA approval for the US market and tentative approval (TA) for low-income countries.

**Table 1: Regulatory delay by the MCC compared to US FDA [21]**

ARV single or combination	FDA US approval	MCC approval	Delay (years)
AZT	1987	1992	5
3TC	1995	1996	1
LPV/r	2000	2002+	2+
TDF	2001	2007	6
ATV	2003	2007	4
FTC	2003	2007	4
FTC/TDF	2004	2007	3
EFV/FTC/TDF	2006	2010	4

\*Aluvia (Abbott lopinavir/ritonavir co-formulation produced for developing countries in a different colour to Kaletra) was registered by the MCC in 2008.

Source: Clayden and Harrington. Seven Ways to Speed up the Pipeline. 2013.

**Table 2: FDA delay from US to tentative antiretroviral approval [22, 23]**

	FDA US approval	FDA TA approval	Delay (years)	From 2004*
AZT	1987	2005	18	1
3TC	1995	2005	10	1
LPV/r	2000	2009	9	5
TDF	2001	2007	6	3
ATV	2003	2008	5	4
FTC	2003	2008	5	4
FTC/TDF	2004	2009	5	5
EFV/FTC/TDF	2006	2009	3	-

\* Tentative approval began in 2004.

Source: Clayden and Harrington. Seven Ways to Speed up the Pipeline. 2013.

We noted that, in the past, license agreements were negotiated several years after products were already approved in rich countries and more recently, with newer antiretrovirals, agreements have been signed a year or two before FDA approval, and ViiV is already negotiating licenses for dolutegravir.

For TA, the FDA Guidance for Industry Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV 2006 includes a list of regimens and components for which the agency is satisfied that safety and efficacy have been established (and demonstrated in product labelling or peer reviewed literature). [24]

It suggests FDC or co-packaged products for combinations on this list could be developed without conducting new clinical trials. It is important for the list to be updated to include acceptable dolutegravir regimens and FDCs that can be approved without further trials, to guide generic manufacturers.

Many developing countries rely on WHO prequalification – the scheme has helped countries to build regulatory capacity as it engages their regulators in the process and offers training in evaluation.

There is an agreement with the FDA that tentatively approved antiretrovirals are also prequalified. Although generally considered to be useful, WHO PQ is horribly slow, taking about two years to prequalify a drug. [25, 26]

ViiV needs to ensure that originator dolutegravir is pre-qualified as soon as possible and support generic tentative approval.

As far as national agencies are concerned, the company plans submissions in stages targeting the highest burden countries first. This part of the process will be highly dependent on national regulatory capacity, which is lacking in most countries with large HIV epidemics. [27]

### **Inclusion in WHO and National Guidelines**

Recommending new antiretrovirals in the WHO guidelines poses a classic chicken and egg conundrum and boosted darunavir is an example from the most recent guideline update [28, 29]. Despite being generally considered to be a better tolerated PI (with better virological response in some studies) than boosted lopinavir, darunavir was only included as a footnote for second line treatment due to the lack of availability of a heat stable, co-formulated generic version. Meanwhile generic manufacturers are reluctant to make the investment to produce one, without a strong signal from WHO.

Whether dolutegravir is included first or second line in subsequent guideline updates, the recommendation from WHO needs to be clear. Any change in recommendations and introduction of new generic products will hopefully lead to changes in national guidelines and will require massive support, from organisations such as UNITAID and CHAI, to make the transition.

Although manufacturing costs of dolutegravir are estimated to be low – about \$US30 [30] – only a first line recommendation would mean that a generic version could be produced in sufficient volume to make a tempting profit if it were pegged at a similar price to efavirenz.

### **Pricing in middle income countries**

MSF greeted the news of the FDA approval with concern that “...ViiV’s business strategy will result in dolutegravir being priced out of reach in countries excluded from ViiV’s licensing deals” [31] – ie those outside the 67 countries in its access programme. MSF encourages the company to make a licence agreement with the MPP, but this will need to include “all low- and middle-income countries and have no restrictions on where the drug can be manufactured or active pharmaceutical ingredients can be sourced”.

The pricing analysis of middle-income countries outside Africa – ineligible for access prices and other discounts – summarised above shows they can pay, on average, four times more for antiretrovirals than African countries with similar incomes.

ViiV needs to take all the necessary steps to make sure dolutegravir will be affordable and available for all those who could benefit from it.

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## Pharmacokinetics of etravirine with once-daily and twice-daily dosing

Simon Collins, HIV i-Base

**A pharmacokinetics and pharmacodynamic analysis from a randomised study of etravirine in treatment-naive patients was published in the May/June edition of Clinical HIV Trials supporting once-daily dosing. [1]**

This was an analysis from a double blind 48-week SENSE trial in 157 treatment-naive patients randomised to either etravirine (4 x 100 mg tablets once-daily with a meal) or efavirenz (600 mg once-daily), plus two NRTIs (tenofovir/FTC - 60%; abacavir/3TC - 26%; and AZT/3TC -14%). The study was designed to compare tolerability of etravirine to efavirenz, with a primary endpoint of CNS events at 12 weeks. Main results from this study – at 12 weeks and 48 weeks – were published in 2011. [2, 3]

Baseline characteristics included 81% male, 85% Caucasian, and median CD4 and viral load at baseline of 302 cells/mm<sup>3</sup> and 4.8 log copies/mL (34% were >100,000 copies/mL) respectively.

This secondary analysis looked at the relationship between efficacy, safety and AUC and trough plasma concentrations of etravirine, also in relation to previous PK studies. No significant relationship was observed for either PK parameter and sex, age, body weight or HCV status. Exposure levels were similar to other once-daily studies and higher than 200 mg twice-daily with darunavir/ritonavir plus tenofovir/FTC, see Table 1.

**Table 1: Etravirine PK in SENSE and other studies**

Trial	ETR dose	AUC <sub>24h</sub> (ng•h/mL)	C <sub>0h</sub> (ng/mL)
SENSE trial (n=71)	400 mg QD	12,447 (8,261–15,652)	330 (188–472)
HIV 2032 (n=21)	400 mg QD	10,412 (3,364–18,650)	233 (58–480) **
Monetra (n=24)	400 mg QD	Not done	422 (264–655)
DUET (n=575)	200 mg BD	9,044 (916–119,680)	298 (2–4,852) **

Note: AUC<sub>24h</sub> = area under the curve over the dosing interval; C<sub>0h</sub> = trough concentration; ETR = etravirine; IQR = interquartile range. \*\* Geometric mean and 95% confidence intervals.

No relationship was reported between any side effects and AUC levels. Data on C<sub>max</sub> was not presented.

Similarly, no relationship was reported for viral load reductions at week 48 (approximately –3.0 for middle quartiles and –3.3 log copies/mL in the lowest and upper quartile) and etravirine trough concentration (<188, 188–329, 330–471 and >471 ng/mL for quartiles 1–4, respectively).

Etravirine has a half-life of 30–40 hours and earlier studies have reported that although trough levels are 25% lower with 400 mg once-daily compared to 200 mg twice-daily dosing, this remains more than 50-fold higher than the protein adjusted IC<sub>50</sub> for wild-type HIV (4 ng/mL). [4, 5, 6]

An earlier switch study in treatment-experienced patients reported 3/24 experiencing virological failure although 2 of these 3 were reported to have had etravirine resistance at baseline. [4]

### C O M M E N T

**Several studies have already reported on once-daily etravirine but given the half-life of etravirine is 30–40 hours it is unclear why etravirine was developed as a twice-daily drug.**

**In this study it is difficult to compare data from once-daily dosing to historical twice-daily studies in combination with darunavir/r which would also have lowered etravirine levels.**

**Many HIV drugs were approved based on conservative dosing that was later modified to fewer daily doses or reduced dosing - as with AZT, 3TC, d4T, abacavir, nevirapine and efavirenz - but this is dependent on the impact the new dose has on drug levels and supportive evidence in clinical studies. These changes often came long after the initial approval, missing the opportunity of many years of simplified treatment. Raltegravir was a recent exception - perhaps because non-inferiority to twice daily dosing wasn't seen because once-daily was used as initial treatment rather than a switch dosing once viral load was suppressed.**

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## TREATMENT ACCESS

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### **UK pledges £1 billion for Global Fund**

#### **Stop AIDS press release**

**UK support to the Global Fund to Fight AIDS, TB and Malaria could get an additional 735,000 people onto lifesaving HIV treatment across the developing world by 2016, following an announcement which campaigners say has set the world the challenge of raising its ambition towards finally defeating AIDS – as well as TB and malaria.**

The pledge of £1 billion over the next three years equates to a doubling of the UK contribution to the Global Fund, a collaboration between northern and southern governments, the private sector, NGOs and people affected by the three diseases, which has saved nearly 9 million lives in a decade. However, the £1 billion pledge will only be delivered in full if the Global Fund achieves its overall replenishment target of \$15bn.

The commitment from the UK throws down the gauntlet to other donor countries, like Germany, Australia and Japan to dramatically increase their contributions so the Global Fund can secure the \$15bn it says could tip the balance in the three epidemics.

The ambition of the UK commitment matches that shown by the Obama administration, which has pledged \$1.65 billion for 2014 alone. If the total generated is less than \$15 billion, the UK says it will give 10% of the total number pledged.

STOPAIDS spokesperson Diarmaid McDonald said: “STOPAIDS have been working for many years, with many others to secure this commitment and we see it as an incredible statement of ambition from the government – one which the world will celebrate. The UK’s leadership in international development gives the nation the opportunity to achieve some truly historic things, and this lifesaving commitment to the Global Fund is just that – historic.

“By building on the successes we’ve had to date, scaling up the latest, smartest interventions, we have an opportunity to tip the balance in the AIDS, TB and malaria epidemics, saving the lives of millions. But that opportunity won’t last forever – delay and the numbers affected will creep up and the ambition to control the epidemics will be put back out of reach. The Global Fund must secure \$15bn from the world to seize this chance.

“By tying their £1bn commitment to the overall total raised, the UK have firmly put the spotlight on other donors. Whilst we hope that the commitment to giving 10% of the total is a floor rather than a ceiling, the responsibility is now on the leaders of Germany, Australia and Japan to act. The UK has shown it has the ambition to seize the opportunity we have to bring AIDS under control – the rest of the world must rise to the challenge.”

Source: STOPAIDS campaign press release. UK pledge raises world’s ambition on AIDS, (24 September 2013).  
[http://stopaids.org.uk/uk\\_pledge/](http://stopaids.org.uk/uk_pledge/)

### **France pledges \$1.4 billion for Global Fund**

#### **Global Fund Observer**

**France has announced that it will contribute €1.08 billion (\$1.4 billion) to the Global Fund for the Fourth Replenishment period (2014–2016).**

That works out to about \$467 million a year. This approximately the same as the amount France pledged for the Third Replenishment (2011–2013).

There had been fears that France would lower its contribution. However, in recent months, France tried to dispel these fears.

France has been the largest European contributor to the Global Fund. Globally, France is second only to the US, which pledged about \$4.0 billion for the Third Replenishment.

It is expected that up to 5% of France’s pledge will be earmarked for capacity-building activities in Francophone countries aimed at improving the effectiveness and health impact of Global Fund grants. France started this practice in 2011.

Source: Global Fund Observer. France Pledges \$1.4 Billion for Global Fund’s Fourth Replenishment. GFO Issue 122. (16 July 2013).  
[http://www.aidspace.org/node/1838#comment\\_section](http://www.aidspace.org/node/1838#comment_section)

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## UNAIDS reports new HIV infections are reduced by one-third compared to 2001

### UNAIDS report

**A new report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) shows dramatic acceleration towards reaching 2015 global targets on HIV. [1, 2]**

- New HIV infections among adults and children were estimated at 2.3 million in 2012, a 33% reduction since 2001.
- New HIV infections among children have been reduced to 260 000 in 2012, a reduction of 52% since 2001.
- AIDS-related deaths have also dropped by 30% since the peak in 2005 as access to antiretroviral treatment expands.
- By the end of 2012, 9.7 million people in low- and middle-income countries were accessing ART, an increase of nearly 20% in just one year.

In 2011, UN Member States agreed to a 2015 target of reaching 15 million people with HIV treatment. However, as countries scaled up their treatment coverage and as new evidence emerged showing the HIV prevention benefits of antiretroviral therapy, the World Health Organization set new HIV treatment guidelines, expanding the total number of people estimated to be in need of treatment by more than 10 million.

“Not only can we meet the 2015 target of 15 million people on HIV treatment—we must also go beyond and have the vision and commitment to ensure no one is left behind,” said Michel Sidibé, Executive Director of UNAIDS.

Significant results have also been achieved towards meeting the needs of tuberculosis (TB) patients living with HIV, as TB-related deaths among people living with HIV have declined by 36% since 2004.

Despite a flattening in donor funding for HIV, which has remained around the same as 2008 levels, domestic spending on HIV has increased, accounting for 53% of global HIV resources in 2012. The total global resources available for HIV in 2012 was estimated at US\$ 18.9 billion, US\$ 3-5 billion short of the US\$ 22-24 billion estimated to be needed annually by 2015.

As well as outlining new global HIV estimates, the 2013 UNAIDS “Report on the global AIDS epidemic” reviews progress on ten specific targets which were set by United Nations Member States in the 2011 UN Political Declaration on HIV and AIDS.

The report finds that progress has been slow in ensuring the respect of human rights, securing access to HIV services for people most at risk of HIV infection, particularly people who use drugs, and in preventing violence against women and girls—a key factor in vulnerability to HIV. Gender inequality, punitive laws and discriminatory actions are continuing to hamper national responses to HIV and concerted efforts are needed to address these persistent obstacles to the scale up of HIV services for people most in need.

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## GUIDELINES

### **Southern African treatment guidelines retain CD4 threshold of 350 for starting ART**

#### **Southern African HIV Clinicians Society (SAHCS)**

**The following statement from the SAHCS is important given the recent focus on the evidence supporting the clinical benefits of earlier treatment, especially following the WHO guidelines increasing the CD4 threshold to 500 cells/mm<sup>3</sup>. [1]**

#### **SAHCS statement on WHO consolidated guidelines**

The Society notes the WHO's new guideline threshold of 500 cells/mm<sup>3</sup> for the initiation of antiretroviral therapy in asymptomatic, non-pregnant adults.

This is not the same as the Society's guideline of 350 cells/mm<sup>3</sup>. [2]

There is no additional new data to support changing our own guideline, but we acknowledge the WHO recommendation may cause confusion. Several on-going clinical trials will complete within the next few years. These will help inform when to start, both from an individual patient and public health perspective. We therefore suggest clinicians consider the following when making treatment decisions.

There are clear individual benefits (reduced mortality and tuberculosis) for starting ART in any patient with a CD4 below 350 cells/mm<sup>3</sup> based on the findings of a randomised controlled trial. There is sufficient evidence to suggest any patient regardless of CD4 count who has chronic active hepatitis B, tuberculosis or any other significant clinical condition (as described in our 2012 adult ART guidelines) will benefit from ART initiation above the 350 threshold. There is also clear benefit associated with using ART above this threshold for preventing MTCT, and for

treating the positive partner in a serodiscordant sexual partnership to prevent transmission to the HIV-negative sexual partner.

The data for individual benefit above 350 cells/mm<sup>3</sup> is based almost entirely on observational cohorts, which have inherent biases, and these data are from developed countries. Even where benefit is shown, this is relatively small.

Complications of earlier treatment include more drug toxicity and potential for resistance due to longer periods on ART, as well as vulnerability to ART interruptions in a climate of international and local drug stock outs.

Epidemiological data suggesting broader ART coverage has a beneficial impact on reducing HIV incidence in communities is compelling but unproven, and should not influence decision making at an individual level unless such an approach was adopted as a large scale public health strategy.

We believe initiating treatment above 350 cells/mm<sup>3</sup> is a highly individualised decision that should take into account the patient's clinical condition, their wishes and their motivation, after a careful explanation of the risks, possible benefits and financial burden that may result if self-funding.

Source

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## SIDE EFFECTS

### **Longitudinal changes in weight, lean body mass and bone mineral density in first-line combinations: ACTG 5205 substudy**

**Matt Sharp, HIV I-Base**

**As treatment guidelines shift and more people initiate ART for life-long therapy, it is critical to understand various regimens impact on the body. A new analysis reports the impact of different regimens on lean body mass and bone mineral density after starting treatment.**

The large ACTG 5202 study randomised 1857 ART naïve individuals starting therapy to tenofovir/FTC or abacavir/3TC with either efavirenz (EFV) or atazanavir/ritonavir (ATV/r) and included a metabolic substudy, which has a new analysis published in 13 August 2013 edition of AIDS. [1] Previous metabolic analyses have focused on BMD, peripheral fat and visceral fat. [2, 3]

This paper was a post-hoc analysis to compare weight and lean body mass (LBM) between pooled and randomised NRTI components from baseline to week 96. Whole body dual energy absorptiometry (DXA) and hip and lumbar spine measurements at 24, 48 and 96 weeks and every 48 weeks until the end of follow-up, and single-slice CT scans at baseline and week 96 were administered. LBM was defined as fat-free, bone-free mass defined by DXA. Initially, an intent-to-treat analysis was performed but after the DSMB recommended unblinding the NRTI component of the study due to virologic failures with ABC/3TC, a second as-treated analysis was done.

This substudy (A5224s) included results from 269 participants from 37 ACTG trial sites in the US and Puerto Rico. Baseline demographics included mean (+/- SD) age 37 (+/-10), weight 78.0 kg (15.5); median (IQR) BMI 24.9 kg/m<sup>2</sup> (21.8 – 28.2). Mean CD4 count was 236 cells/mm<sup>3</sup> (+/- 185) and median (IQR) viral load was 4.6 log copies/mL (4.2–4.9). The majority of participants were men (85%) with 15% women. All participants regardless of their ART regimen gained a mean average of 4.8 kg at week 96 (p<0.001) although those in the ATV/r arm gained statistically significant greater weight than those in the EFV arm regardless of analysis. BMI also increased in all participants by a mean 1.5 kg/m<sup>2</sup> at week 96 and this was greater in the ATV/r arm (by 0.88 kg/m<sup>2</sup> in the ITT analysis) compared to the EFV arm. Change in LBM increased significantly in all treatment arms by a mean of 1.4 kg at week 96. Interestingly, those who screened with at least 100,000 HIV-RNA copies/mL and were randomised to receive ATV/r had significantly greater mean gain in LBM, compared to EFV. Overall, lower CD4 count and higher viral load at baseline levels were both associated with greater gain in total body mass, BMI and LBM at week 96 after adjusting for treatment arm, suggesting a return to health effect.

When looking at hip and lumbar spine BMD in a multivariate linear regression analyses, ABC/3TC was associated with less percentage hip BMD between baseline and week 96 (mean change 1.35; 95% CI 0.18, 2.35; p=0.02) The regimen was also associated with less percentage loss in lumbar spine mean percentage BMD from week 0 to 96. (mean change: 2.00; 95% CI 0.66, 3.33; p=0.004) Compared to EFV, ATV/r was associated with greater mean percentage loss in lumbar spine. (mean change: -1.46; -2.82; -0.10; p=0.035)

As expected, lower baseline CD4 count, lower baseline weight, higher HIV RNA, less increase in LBM over 96 weeks, and higher increase in CD4 count over 96 weeks, and history of fracture were associated with loss in BMD in both measurements.

According to the authors, this is the first study to look longitudinally at changes in LBM, assessment of body and visceral fat, and LBM on the change of bone mineral density after initiation of current first-line therapy, and they also suggested that weight, BMI and LBM changes may mediate some of the change in BMD. Limitations include that long-term follow up was not of duration to adequately assess bone endpoints and that the study population was relatively young.

C O M M E N T

**The is a complex study to interpret and differences between groups even when statistically significant may not have a clinical relevance, especially without considering individual results and lifestyle factors. The authors also note the large number of analyses that were performed without appropriate adjustment increasing the probability of Type-1 errors.**

**However, the dataset is still important for highlighting the broad directions of changes when starting treatment with combinations that are still commonly used.**

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## HIV DRUG RESISTANCE

### **Persistence of transmitted drug resistance mutations suggests source partners may be treatment-naïve**

**Matt Sharp, HIV i-Base**

**A recent analysis from the UK HIV drug resistance database on the persistence of transmitted drug resistance (TDR) over time suggests that poor adherence by people on ART is unlikely to be linked to most cases of TDR.**

The results may also help interpret individual resistance tests in the context of TDR. [1, 2]

The study, published online on the 31 July 2013 in the *Journal of Infectious Diseases*, estimated the persistence of transmitted drug resistant virus in 313 treatment naïve patients who had at least one drug-related mutation in their first resistance test (from 1997 - 2009) and at least one subsequent resistance test result prior to starting treatment. Recent infection could only be confirmed for the 15% of patients who had a previous HIV negative test result in the previous 18 months.

Previous studies looking at the loss and persistence of transmitted mutated virus have generally been small and this is the first large study to provide estimates of what occurs to viral mutations over time.

Population sequencing genotype testing (sensitive to variants present at >15% of the viral populations) was used and longitudinal samples were compared to check that samples were from the same patient and to exclude potential cases of HIV reinfection.

The researchers used an analysis model that ensured an accurate rate at which mutations became undetectable, enabling them to estimate the average rate loss of mutations as soon as they were identified in treatment-naïve patients during chronic infection. Patient characteristics included CD4 count, viral subtype, number of mutations at the first test, and whether the mutation was pure or mixed.

A total of 717 mutations were detected in the first tests, with 1, 2, 3 and 4 or more mutations present in 59%, 19%, 7% and 15% of patients, respectively. Similarly, the percentage of patients with resistance to one, two or three ARV classes was 68%, 27% and 6%, respectively. By drug class, 65%, 38% and 24% of people had resistance to NRTIs, NNRTIs and PIs respectively.

Out of the 717 TDR mutations detected during the first test, 21% were a mixture (92 wild type, 37 with a non-TDR mutation alone, and 18 mixed). Most people (89%) only had one additional resistance test prior to starting treatment.

The overall rate of loss of TDR mutations was 18 (95% CI: 14-23) per 100 person-years of follow-up (PYFU) but there was a wide variability for individual mutations. Within drug classes, NRTIs showed the most variation in persistence. M184 was rapidly lost at 71 per 100 PYFU (95% CI: 34-149; median time to loss 1.0 years (95%CI 0.5 - 2.0 years); M41L was highly persistent with a rate of loss of only 8 per 100 PYFU (95% CI: 4-15; median time to loss 8.6 years (95%CI 4.6 - 16.0 years), and was similar to other TAMs (D67N, L210W and K219Q/N). However, K70R was lost more quickly.

Although there was a rapid transition of T215F and T215Y to one of the T215 revertants, these were then highly stable, with a rate of loss of only 5 mutations per 100 PYFU (95% CI 3-11; median time to loss 13.0 years (95%CI 6.6-25.7 years).

There was no statistical difference in the rate of loss with NNRTI variants (median time to loss 2.7 (95% CI: 1.8-4.1) years), with K103N being the most common with a rate loss of 18 per 100 PYFU (95% CI: 10-34; median time to loss: 3.7 (95% CI: 2.0-6.8) years). L90M was the most common PI variant, with a rate loss of 12 per 100 PYFU (95% CI 5-31; median time to loss: 5.8 (95% CI 2.2-15.3) years). There was little variation among the rate loss with the other PI mutations.



In the multivariate analysis there was no effect on the rate of TDR mutations when looking at CD4 count ( $p=0.5$ ) or viral load ( $p=0.2$ ), at the initial test, recent infection ( $p=0.3$ ) or number of mutations detected at the first test ( $p=1.0$ ). There was a statistically significant rate of loss higher loss with non-subtype B compared to subtype-B. (adj. HR 2.8; 95% CI 1.26-6.3,  $p=0.01$ ). TDR mixtures were also associated with a significant higher rate of loss.

The authors concluded that the long persistence of certain mutations suggests that treatment-naïve patients (potentially undiagnosed) could be the route for most TDR and that baseline genotype tests should be continued in chronically infected patients. Also, due to the high variability in TDR mutations the detection of one or more mutations may signal that undetected viral mutants may have been archived in latent cells. Systematic testing will also provide more detail on the existence of TDR in the population.

#### C O M M E N T

**The finding that certain mutations are stable and not replaced by wild-type virus suggests that most cases of TDR may come from treatment naïve patients rather than from poorly adherent people on treatment, especially given the high rates of viral suppression once HIV is treated.**

**This is the first time that data have supported this explanation and these results deserve further investigation.**

**This finding is also important as the UK HIV MSM epidemic may be largely driven by undiagnosed people - in either acute or chronic infection - and this resistance analysis included a high proportion of MSM (70%). [3]**

**The high variability in the time to loss for many mutations limits the use of this data for estimating the time of infection in individual cases but in detection of M184V or Y181C appears supportive of relatively recent HIV infection.**

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## TUBERCULOSIS

### **Activists call EU failure to approve delamanid for MDR tuberculosis due to limited data both “myopic and disappointing”**

**New York HIV activist group TAG issued the following press statement following the EU CHMP decision against approval for delamanid. [1]**

#### **TAG press statement**

Treatment Action Group (TAG) is disappointed by the failure of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to recommend marketing approval for delamanid, a new drug in development for multidrug-resistant tuberculosis (MDR-TB). The drug, one of the first new compounds to fight tuberculosis (TB) in over 40 years, has demonstrated safety and clinical benefit against multidrug-resistant TB (MDR-TB) in clinical trials to date.

The decision by the CHMP was based on the duration of treatment (two months) in the phase IIb randomised controlled trial (Trial 204). It considered that the trial was too short to establish the effectiveness of delamanid in treating TB when added to other anti-TB medicines. Without new treatment options such as delamanid, treatment for people who have the disease will remain intolerable, toxic, lengthy, and ineffective, and patients – of which the European Union and its neighboring countries have many – will continue to die.

“The EMA’s refusal to recommend the approval of a new drug that has more evidence of safety and efficacy than nearly all existing drugs for MDR-TB is both myopic and deeply disappointing,” said Mark Harrington, executive director of Treatment Action Group. “The EMA appears to be willing to delay wide availability and access to a drug with considerable evidence of clinical benefit – including a possible survival advantage – and proven ability to shorten time to TB culture conversion. The EMA is failing to respond to the drug-resistant TB crisis – which affects Europe more than any other region in the world – with appropriate twenty-first-century regulatory approaches.”

Delamanid, a new drug to fight TB, is currently enrolling patients in its phase 3 clinical trial, after phase 2 studies indicated improved efficacy and survival: in a comparison of patients taking a background regimen of MDR-TB drugs, those who also took delamanid for six months were 35 percent more likely to be cured than those who took the drug for two months or less, and about seven times less likely to die after 24 months of follow-up. Yet, because the six-month data were from an open-label (rather than a randomised) trial, the EMA is preventing this likely lifesaving drug from being available in European Union member countries. If Otsuka, delamanid’s sponsor, appeals to the EMA and is unsuccessful, delamanid could languish an additional three years before EMA approval. Otsuka is also waiting to hear a response regarding its filing with the Japanese regulatory authority.

Treatment Action Group is baffled at how a sophisticated agency such as the EMA can make such an egregious error by not approving delamanid. Regulatory flexibility in the face of the global emergency of drug-resistant TB is urgently needed. This decision is another indication that regulators worldwide, with the exception of the U.S. Food and Drug Administration (FDA), are completely unprepared for responding appropriately to global health threats such as drug-resistant TB, and that they are not ready to deal with innovation in the TB field. The EMA has now set a terrible example for developing countries, which face enormous drug-resistant TB problems.

“MDR-TB patients need access to better treatments now,” said Wim Vandeveld, chair of the Global TB Community Advisory Board and member of the European AIDS Treatment Group. “While Otsuka waits for regulatory approval, it must also make the drug available immediately for patients in urgent need under compassionate use mechanisms that allow for pre-approval access.”

Treatment Action Group urges Otsuka to roll out compassionate use programmes and expanded access studies in high-burden countries as soon as possible to ensure that treatment is available for those people who may have run out of treatment options. Compassionate use allows the patients access to the drug through pre-approval access programmes.

More evidence is needed to confirm delamanid’s safety and efficacy, but phase III trial results are expected within three years. In that period of time, 1.5 million people will be diagnosed with drug-resistant TB, and many of them will die, while others, poorly treated or untreated, will continue to transmit the airborne disease. Bedaquiline, another novel drug for MDR-TB, received accelerated approval by the FDA in December 2012 based on its phase II trial results, but enrollment in its sponsor, Janssen’s, phase III trial, has yet to begin. Most other drugs currently used to treat drug-resistant TB have not been rigorously tested in clinical trials for TB.

“The EMA’s failure to license delamanid increases the likelihood that bedaquiline will be used as a single new agent in failing DR-TB regimens, enhancing the risk of the emergence of resistance, and delaying the chance to use these two promising new drugs together in people at the greatest risk of disease progression and death,” commented TAG’s Harrington. “We urge them to reconsider their dangerous decision.”

The EMA explained their decision online: “The CHMP’s main concern was that the benefits of delamanid in the treatment of multi-drug resistant tuberculosis had not been sufficiently shown. The CHMP considered that the duration of treatment in the main study (two months) was too short to establish the effectiveness of delamanid in treating tuberculosis when added to other anti-tuberculosis medicines. As delamanid was to be used for at least six months the data from two months’ treatment could not be used to predict the effectiveness of delamanid when given for six months. In addition, the results of the extension and follow-up studies could not be used to support the longer term use of delamanid as the studies included only those patients who had agreed to take part and who might therefore not be representative of the patients as a whole. Finally, the CHMP was of the view that it was not possible from the data submitted to determine the most appropriate dosing for delamanid. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Delamanid did not outweigh its risks and recommended that it be refused marketing authorisation.” [2]

#### References

1. TAG press statement. Treatment Action Group criticises European refusal of new drug to fight tuberculosis, (24 July 2013).
2. EMA. Delamanid opinion: What were the CHMP’s main concerns that led to the refusal? EMA website, (25 July 2013).  
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## BASIC SCIENCE AND CURE RESEARCH

### **Circulating memory T follicular helper cells correlate with the development of broadly neutralising antibody responses against HIV**

**Richard Jefferys, TAG**

**A study published on 12th September 2013 by the journal *Immunity* ties together two emerging areas of HIV vaccine research. [1]**

In recent years, scientists have discovered that a small proportion of chronically infected individuals develop antibody responses capable of broadly neutralising a diverse array HIV isolates. These antibody responses typically take years to develop, and are not present at sufficient titres to offer noticeable benefit to the infected individuals they are isolated from, but there is reason to believe that if they could be induced by a vaccine they could protect uninfected people against HIV acquisition.

A potential complement to this line of investigation has been the discovery of T follicular helper cells (Tfh), a specialised CD4 T cell subset that plays a critical role in providing help to B cells, thereby facilitating antibody production. Researchers have posited that Tfh may have an important role in the generation of broadly neutralizing antibodies against HIV, but direct evidence has been lacking.

In the *Immunity* paper, Michela Locci and colleagues report that there is a circulating population of Tfh that can be identified using a combination of surface markers, and that in a large cohort of HIV positive individuals the frequency of these cells correlated with the development of broadly neutralising antibodies against HIV. The data suggest that inducing this type of Tfh response should be a goal for vaccines aiming to create neutralising antibodies against HIV (or potentially any other pathogen).

In a helpful example of kismet, the September 13th issue of the journal *Science* featured an article by Jon Cohen describing progress in discovering broadly neutralising antibodies to HIV, [2] along with a review on the same topic [3] and a podcast interview with the senior author of the review, Michel Nussenzweig [4].

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## PREVENTION AND TRANSMISSION

### HIV self testing to become legal in the UK from April 2014

Simon Collins, HIV i-Base

**On 15 August, the UK Chief Medical Officer Professor Dame Sally Davies announced that from April 2014 the rules banning HIV self testing kits will be lifted, although tests will need to comply with new regulations. [1]**

This is likely to be the result of a lobbying campaigns, principally by the Terrence Higgins Trust and National AIDS Trust, as a strategy to make testing easier to access, in the hope that this will reduce current rates of late diagnosis.

Whether this approach is successful has yet to be determined, given concerns that both taking an HIV test and learning the results requires a level of support that at the minimum should involve at least one other person. Even in the context of face-to-face HIV testing, some people do not remain within the health care setting and are lost to follow up for many years until they become symptomatic. It is difficult to understand how home testing will tackle this issue, even though a positive result with a home test kit includes “advice” to get a follow-up confirmatory test at an NHS clinic.

Clear information about how to interpret the result and what to do afterwards will be included with the kit.

Current rules prevent companies from selling HIV self-testing kits in England. Once these rules are lifted, all kits will be subject to strict regulatory control by the Medicines and Healthcare Regulatory Authority before they are authorised for sale.

BHIVA Chair, Dr David Asboe, welcomed the availability of regulated HIV self-testing kits, while noting two important caveats: “First, home tests can record negative results when a person first catches HIV at a time when they are usually highly infectious. False reassurance at this time could increase the risk of HIV transmission. Second, home tests also have significant rates of false positive results. It is therefore vital that home tests are not used as a substitute for the expanded testing currently available in healthcare and other settings, and that the transfer into high quality, specialist care of someone who tests positive is monitored.”

The statement, in a press release from BHIVA, also stated: “Psychological support and medical care are critically important. Furthermore, it is crucial that we evaluate the effectiveness of this policy in reducing undiagnosed infections without unwanted effects on behaviour, psychological wellbeing, and uptake of broader sexual health services.” [2]

#### References

1. Department of Health. Modernisation of HIV rules to better protect public. (15 August 2013).  
<https://www.gov.uk/government/news/modernisation-of-hiv-rules-to-better-protect-public>
2. BHIVA press release. British HIV Association (BHIVA) response to Department of Health announcement ‘Modernisation of HIV rules to better protect public’. (15 August 2013).  
<http://www.bhiva.org/BHIVA-response-to-DH-announcement.aspx>

### Agreement to develop long-acting rilpivirine as PrEP

**On 25 September 2013, Janssen announced that it had signed a license agreement with international nonprofit health organisation PATH for early stage research to develop a long acting depot formulation of rilpivirine as a potential pre-exposure prophylaxis (PrEP) against HIV. [1]**

PATH is planning to collaborate with partners including the HIV Prevention Trials Network for future research for these initial phase 2 studies, and this initiative is funded by the Bill & Melinda Gates Foundation. [2]

Rilpivirine is an NNRTI currently licensed as an oral drug in ARV treatment-naïve adults with a viral load less than or equal to 100,000 copies/mL and is coformulated with tenofovir/FTC in the fixed dose combination Eviplera (Eduvant in the US).

#### Reference

1. Janssen press statement. Janssen R&D Ireland announces agreement with PATH for early development of rilpivirine in long-acting formulation for potential prophylactic intervention, (25 September 2013).
2. PATH press release. New partnership advances drug formulation that could help prevent HIV infection, (25 September 2013).  
<http://www.path.org/news/press-room/647>

## Use of ART at baseline by “treatment naïve” patients in HPTN-052

Matt Sharp, HIV i-Base

**A recent analysis of people who had undetectable viral load at baseline in the HPTN-052 study found detectable ARV drug levels and most of those randomised to the deferred treatment arm continued to use treatment.**

Luckily, these numbers are small enough not to affect the main study results, but this raises an interesting challenge for future researchers.

HPTN 052 randomised HIV positive partners in sero-different couples to either starting treatment while their CD4 count was between 350 and 550 cells/mm<sup>3</sup> or to defer treatment until it reached 250 and the study has been widely reported due to the impact that treatment had on reducing sexual HIV transmission. Participants self-reported no use of ART upon enrolling in the trial. However, blood samples at enrolment were subsequently tested in a subset of participants and showed that ART drugs were commonly detected.

The results of this retrospective sub-group analysis were reported by Jessica Fogel from Johns Hopkins University and colleagues in the 1st August 2013 edition of the Journal of Infectious Diseases. [1]

The large phase 3 HPTN 052 was conducted in Africa, Asia and the Americas. The results were widely publicised for showing a 96% reduction of HIV transmission. [2].

However, an interim review by the Data and Safety Monitoring Board (DSMB) for the study noticed that some of the HIV positive partners already had an undetectable viral load when they entered the study. This raised concerns that some participants were already taking ART, and others in the delayed treatment arm perhaps continued their treatment. Since then, this post-hoc analysis retrospectively analysed enrolment blood samples from 209 HIV positive partners for 16 most commonly used ARVs, based on viral load at baseline: all those with suppressed <400 copies/mL (n=96); or low 401 and 1,000 copies/mL (n=48); and a random group with high viral load >1,000 copies/mL (n=65). Follow up sampling was also conducted.

Almost half the suppressed group (45/96, 47%) had a least one ARV detected (d4T, AZT, 3TC, nevirapine), with minimal use in the other groups (only 2/48 in the low viral load group and 1/65 with high viral load). These cases were distributed from five different countries. Demographic and clinical factors associated with ART detection were country of origin and lower CD4 count. No association was seen in regards to age, race, gender, reported ART use for pMTCT, or self reported condom use. None of the 48 participants transmitted HIV to their partners. Follow-up testing was performed from enrollment samples to determine whether ART was still used off-study after enrolment.

Roughly half of the people with detectable drug levels were randomised to the deferred treatment arm of the main study, and they appear to have continued using treatment (based on results from the 16 people with follow up samples).

Off-study ART use did not appear to impact the study-administered ART response. In those in the early ART initiated arm of the trial, off-study ART use was not associated with viral suppression or treatment failure. In the delayed ART arm, viral suppression in the first year of the study despite off-study ART was more common among those who had ART detected at enrolment. In most cases those participants continued to use off-study ART after enrolment did this without the knowledge of the research staff.

Self-reporting of prior ART use can therefore be a limitation of similar transmission studies. However, the reasons for not disclosing would be important to know. Some HIV positive people may have wanted to enter a trial in order to have help with disclosure to their partner from counselors.

In addition, 51 of the 96 people with undetectable viral loads are likely to be elite controllers and would presumably be at low risk for transmitting HIV. In addition to the value of monitoring for drug use at baseline, this raises the question of whether a minimum viral load should be an entry criteria for future studies of PrEP, which would also overcome this problem.

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## OTHER NEWS

### UK to lift ban on HIV positive health workers who are on ART with undetectable viral load

Simon Collins, HIV i-Base

**On 15 August 2013, the UK Department of Health announced important changes in the regulations that previously restricted HIV positive people from working in some healthcare jobs, specifically some dental and surgical procedures. [1]**

The announcement included information that: “Strict rules on treatment, monitoring and testing will be in place to safeguard patients”.

The press statement noted that: “... the change will bring the UK in line with most other Western countries. Under the new system, patients will have more chance – around one in five million – of being struck by lightning than being infected with HIV by a healthcare worker.”

The changes have the potential to reduce this risk further if it prompts healthcare workers to be tested.

Each case will be decided individually and will only be considered if an HIV positive healthcare worker has an undetectable viral load on ART and is being routinely monitored.

The policy will be in place from April 2014. Public Health England will now put in place a programme to register and monitor healthcare workers who have HIV and ensure they are able to perform certain procedures when appropriate.

The statement noted that: "There is no record of any patient ever being infected through this route in the UK" and went on to list the only four documented cases reported worldwide:

- A dentist in Florida (USA), who transmitted HIV to six patients (reported in 1992).
- An orthopaedic surgeon in France who transmitted HIV to one patient during a hip operation (reported in 1999).
- An obstetrician and gynaecologist in Spain who transmitted HIV to one patient during a Caesarean section (reported in 2003).
- An additional case of HIV transmission by a nurse in France, where the route of transmission is still unclear (reported in 2000).

In a statement from BHIVA, chair Dr David Asboe, said "BHIVA welcomes the relaxation of the ban on healthcare workers infected with HIV working on certain dental and surgery procedures. This reflects increased confidence in the effectiveness of antiretroviral treatment in reducing viral levels and resulting infectiousness." [2]

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1. Department of Health. Modernisation of HIV rules to better protect public. (15 August 2013).  
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2. BHIVA press release. British HIV Association (BHIVA) response to Department of Health announcement 'Modernisation of HIV rules to better protect public'. (15 August 2013).  
<http://www.bhiva.org/BHIVA-response-to-DH-announcement.aspx>

## ON THE WEB

### *Online journals*

## **CID supplement on HCV and injecting drug users: free online issue**

**A supplement from Clinical Infectious Diseases include a diverse range of articles on this important subject. Full text access is available free online.**

### **Prevention and management of hepatitis C virus infection among people who inject drugs: moving the agenda forward**

Clinical Infectious Diseases Vol. 57, suppl 2 - 15 August 2013.

[http://cid.oxfordjournals.org/content/57/suppl\\_2?etoc](http://cid.oxfordjournals.org/content/57/suppl_2?etoc)

Contents include:

- **Prevention and management of hepatitis C virus infection among people who inject drugs: moving the agenda forward** - Jason Grebely.
- **Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention** - Kimberly Page.
- **Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy** - Natasha K.
- **Hepatitis C virus vaccines among people who inject drugs** - Andrea Cox and David Thomas.
- **Understanding barriers to hepatitis C virus care and stigmatisation from a social perspective** - Carla Treloar, Jake Rance, and Markus Backmund.
- **Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all** - Philip Bruggmann and Alain H. Litwin.
- **Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: ETHOS study** - Maryam Alavi.
- **Enhancing assessment and treatment of hepatitis C in the custodial setting** - Jeffrey J. Post, Amber Arain, and Andrew R. Lloyd.
- **Peer support models for people with a history of injecting drug use undertaking assessment and treatment for hepatitis C virus infection** - Sione Crawford and Nicky Bath.
- **Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis** - Esther J. Aspinall.

- **Directly observed pegylated interferon plus self-administered ribavirin for the treatment of hepatitis C virus infection in people actively using drugs: a randomized controlled trial** - Robert J. Hillsden.
- **Psychoeducation improves hepatitis C virus treatment during opioid substitution therapy: a controlled, Prospective multicenter Trial** - Jens Reimer.
- **Hepatitis C virus reinfection following treatment among people who use drugs** - Bart P. Grady, Janke Schinkel, Xiomara V. Thomas, and Olav Dalgard.
- **Management of mental health problems prior to and during treatment of hepatitis C virus infection in patients with drug addiction** - Martin Schaefer, Rahul Sarkar, and Crisanto Diez-Quevedo.
- **Management of hepatitis C virus/HIV coinfection among people who use drugs in the era of Direct-Acting Antiviral-based therapy** - Lynn E. Taylor, Tracy Swan, and Gail V. Matthews.
- **Drug-drug interactions in the treatment of HCV among people who inject drugs** - Stefan Mauss and Hartwig Klinker
- **Recommendations for the management of hepatitis C virus infection among people who inject drugs** - Geert Robaeyns,

## FUTURE MEETINGS

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### Conference listing 2013-2014

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.

#### 14th European AIDS Conference (EACS)

16-19 October 2013, Belgium

<http://www.eacs-conference2013.com/index.php?id=40>

#### 15th International Workshop on Co-morbidities & Adverse Drug Reactions in HIV

15-17 October 2013, Belgium

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

#### 4th International Workshop on HIV and Ageing

30 - 31 October 2013, Baltimore

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

#### 6th Annual BHIVA Conference for the Management of HIV / Hepatitis Co-infection

13 November 2013, London

<http://www.bhiva.org>

#### BHIVA Autumn Conference including CHIVA Parallel Sessions

14-15 November 2013, London

<http://www.bhiva.org>

#### 4th International Workshop on HIV & Women - From Adolescence through Menopause

13 - 14 January 2014, Washington, DC.

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

#### 1st International workshop on the Optimal Use of DAAs in Liver Transplanted Patients

23 April 2014, Amsterdam

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

#### Conference on Retroviruses and Opportunistic Infections (CROI) 2014

3-6 March 2014, Boston

<http://www.croi2014.org/>

### **20th IAS World AIDS Conference**

20-25 July 2014, Melbourne, Australia

<http://www.aids2014.org>

### **12th International Congress on Drug Therapy in HIV Infection**

2-6 November 2014, Glasgow

<http://www.hiv11.com>

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## **PUBLICATIONS & SERVICES FROM i-BASE**

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

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

RSS news feed is available for HIV Treatment Bulletin for web and PDA.

An average of 200,000 pages from individual ISP accounts contact the website each month, with over 6000 hits a day.

### *Non-technical treatment guides*

#### **i-Base treatment guides**

i-Base produce six booklets that comprehensively cover five 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>

- Introduction to combination therapy (April 2013)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (October 2013)

### *Publications and reports*

#### **HIV Treatment Bulletin (HTB)**

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published every two months in print, PDF and online editions.

#### **HTB South**

A quarterly bulletin based on HTB but with additional articles relevant to Southern Africa. HTB South is distributed in print format by the Southern African HIV Clinicians Society ([www.sahivsoc.org](http://www.sahivsoc.org)) to over 20,000 doctors and healthcare workers. It is also available as a PDF file and is posted online to the i-Base website.

#### **HTB Turkey**

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB..

#### **HTB West Balkans**

HIV Bilten is an edition of HTB in Bosnian, Montenegrin, Croatian and Serbian, for the West Balkans, produced by Q Club.

## Why we must provide HIV treatment information

Text from activists from 25 countries and 50 colour photographs by Wolfgang Tillmans.

### *Translations of i-Base publications*

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages. Information to support this is available on the i-Base website.

<http://i-base.info/category/translations>

### *Advocacy resources*

#### **UK CAB: reports and presentations**

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 580 members from over 120 organisations.

<http://www.ukcab.net>

### *Phoneline and information services*

#### **Online Q&A service**

An online question and answer service that now has over 3000 questions and comments online. Questions can be answered privately, or with permission, can be answered online.

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

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• Introduction to Combination Therapy (April 2013)  
1  5  10  25  50  Other \_\_\_\_\_

• Guide to Changing Treatment and Drug Resistance (February 2013)  
1  5  10  25  50  Other \_\_\_\_\_

• HIV and your Quality of Life: Side Effects and other Complications (July 2012)  
1  5  10  25  50  Other \_\_\_\_\_

• Guide To HIV and hepatitis C coinfection (Out of print, new edition due 2013)  
1  5  10  25  50  Other \_\_\_\_\_

• Clinical Trials: a community guide to HIV research (March 2009)  
1  5  10  25  50  Other \_\_\_\_\_

**Treatment guides in other languages are available as PDF files on the website**

• **Phoneline support material** (please specify quantity of each)

A3 posters \_\_\_\_\_ A5 leaflets \_\_\_\_\_ A6 postcards \_\_\_\_\_ Small cards \_\_\_\_\_

Please fax this form back, post to the above address, or email a request to HIV i-Base:

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