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## March/April 2011

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## EDITORIAL

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Welcome to the March/April issue of HTB in which we lead with our first reports from the 18th Conference on Retroviruses and Opportunistic Infections (CROI).

We also include guidelines issued by the London HIV Consortium on prescribing antiretroviral treatment in London clinics for 2011 and basic science reviews by Richard Jefferys.

The London guidelines are likely to be controversial given the decision to prescribe Kivexa-based combinations as preferred first-line treatment for naïve patients, when it is clinically appropriate, based on the reduced cost compared to Truvada-based combinations, including Atripla.

This has given cost-based prescribing an elevated profile, though it has been a reality for many years. The higher price for raltegravir is directly related to the limited indications for when it is used. The London Consortium will include a safety audit from this change of policy which will need to demonstrate that patient safety has not been compromised by the changes.

The clinical guidelines were supported by an advisory panel that included leading doctors from all London hospitals. The changes were less radical than many people expected given the cost pressures facing all NHS departments. In this they minimise changes for people currently on stable treatment.

People currently using Atripla or Truvada-based combinations are not being asked to switch. Although some people on protease-based combinations will be asked to switch, this should be limited to cases where this has a clinical advantage. People with a complicated treatment history including drug resistance should not be asked to change currently stable protease-based combinations.

Wider public responses to these changes have so far been limited.

The London Consortium had still to post any official documents about the policy change online as we went to press. This will need to include the guidelines and the evidence base that support any changes. Please check the following link for details.

<http://www.londonspecialisedcommissioning.nhs.uk>

### HTB survey

We'd like to thank everyone who sent back the HTB reader survey distributed with the last edition. The results from the electronic version were impressive but we have less response from the printed surveys.

Please, if you still have this, send them back completed in the SAE or consider doing this online at the following link.

<https://www.surveymonkey.com/s/8QQLN6X>

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## CONFERENCE REPORTS

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### 18th Conference on Retroviruses and Opportunistic Infections (CROI)

27 February–3 March 2011, Boston

#### Introduction

This annual conference remains the most important large scientific HIV meeting and is notable for making web casts of oral presentations and lectures rapidly available. Abstracts are online in a searchable database, many of which also include the option to download the PDF poster.

We have plenty to report in this and subsequent issues of HTB, leading with the broad number of papers focusing on new drugs and biomedical interventions to reduce the risk of transmission.

<http://www.retroconference.org>

Reports in this issue include:

- New antiretrovirals: dolutegravir, entry inhibitor (BMS-663068) and tenofovir pro-drug (GS-7340)
- Immune-based treatment increases HIV-resistant CD4 cells in phase 1 study
- Antiretroviral prevention: oral PrEP, gels and treatment studies
- Further efficacy analyses from the iPrEx study
- Bone mineral density (BMD) changes in HIV-negative men using tenofovir
- Topical gels as PEP and PrEP in human and animal studies

- Maternal risk following short course HAART
- Pre-term delivery and HAART
- HAART more effective than AZT monotherapy in the Botswana PMTCT programme
- Lopinavir/r monotherapy for PMTCT
- No evidence of increased risk of MTCT with sequential pregnancies in UK and Ireland
- Recently infected women at the time of delivery have a higher rate of in-utero transmission in PEPI-Malawi
- Reduced CCL2 concentrations in cervicovaginal secretions from pregnant women
- First results from telaprevir in HIV/HCV coinfection
- HCV reinfection rates in HIV-positive gay men

## **New antiretrovirals: dolutegravir, entry inhibitor (BMS-663068) and tenofovir pro-drug (GS-7340)**

**Simon Collins, HIV i-Base**

Studies on pipeline drugs in development included early results on:

- Dolutegravir (formerly called GSK-572) from ViiV (GSK/Shionogi).
- BMS-663068, an entry inhibitor from Bristol-Myers Squibb.
- GS-7340, a new formulation of tenofovir from Gilead.

### **New integrase inhibitor: dolutegravir results in people with raltegravir resistance**

Although raltegravir generally worked well in people with multiple drug resistance, especially when supported by new drugs like darunavir/r and etravirine in the background combinations, some people still developed integrase inhibitor resistance. These were generally people with few other treatment options who are now waiting for new drugs.

Joe Eron from University of Carolina presented results from a second open-label phase 2b study of dolutegravir in people with raltegravir resistance. [1]

The dose-response rates from the initial use of a 50 mg once-daily dose of dolutegravir supported increasing the dose to 50 mg twice-daily for this second cohort of experienced patients.

Baseline demographics included median (IQR): CD4 202 cells/mm<sup>3</sup> (19–384); viral load 4.3 log copies/mL (3.9–4.8); age 47 (33–68); 75% male; duration on raltegravir 29 months (10–63). At baseline the median (range) fold change in susceptibility was >128 (0.8 to >128) to raltegravir and 2.7 (0.9 to 9.5) to dolutegravir. Baseline patterns of integrase-associated mutations were: N155H (n = 6); Y143H (n = 6); Q148+1 (n = 8); Q148+2 (n = 2); mixture (n = 1); other (n = 1).

The 50 mg twice-daily results included 24 people who added dolutegravir to their failing combination for 11 days (and dropped raltegravir if they were still taking it). To be included in the study people needed to have at least one additional drug that would be active, and this was added to dolutegravir on day 11 when the background combination was optimised, based on resistance test results.

Nearly all patients (23 out of 24) either reduced their viral load to less than 400 copies/mL or by at least 0.7 logs. The average (mean) drop in viral load at day 11 was –1.76 logs (SD 0.54) for study as a whole and –1.57 for people with integrase mutations (Q148 + others). This compared to –1.45 logs seen in the initial 50 mg once-daily study.

Safety data was available for a median 96 days (range 30–172) mainly included common grade 1 or 2 gastrointestinal events not related to dolutegravir. Grade 3 laboratory abnormalities were reported in 4 people (17%) with no discontinuations. One participant had two serious events judged unrelated to the study drug (demyelinating polyneuropathy and diabetes mellitus). No grade 4 events were reported.

The 50mg twice-daily dose has now been selected for phase 3 studies in people who have integrase inhibitor resistance to raltegravir or elvitegravir.

### **An oral entry inhibitor from BMS**

The entry inhibitor in development from Bristol-Myers Squibb called BMS-663068 (BMS-068) is a prodrug of BMS-626529, active against gp120.

Richard Nettles from BMS reported results from a randomised open-label proof of concept study using BMS-068, in 50 people who were either antiretroviral naïve (n=34) or experienced but off treatment for the previous eight weeks (n=16). Pharmacodynamic data was presented for 39 patients with an eligible IC<sub>50</sub> <0.1 μM. [2]

The study used five dose combinations using BMS 068 1200mg once-daily and either 600mg or 1200 mg twice-daily, with and without ritonavir boosting. Baseline demographics included median (range): CD4 432 cells/mm<sup>3</sup> (206–921); viral load 4.4 log copies/mL (3.3–6.1); age 42 years (20–70).

After eight days most doses had reduced viral load by 1.6 logs (ranging from –1.22 to –1.78 in the intent to treat and –1.59 to –1.77 in the pharmacodynamic analysis). CD4 cell increases ranged from +28 to +106 after 8 days. All patients with an eligible IC50 achieved viral load reductions of at least 1 log.

The pharmacokinetic slide showed ritonavir to have a relatively modest impact on boosting BMS-068 and plasma levels of BMS-529 remaining 50-fold above median protein adjusted IC<sub>90</sub> for twice-daily dosing and 9-fold above with one-daily arm (with ritonavir).

All adverse events were grade 1 or 2 and were similar in each arm (though there was not a control arm). The most frequent side effects included headache (22/50, 44%) and rash (8/50, 16%), mostly mild. There were no drug discontinuations.

Detailed results were also available in a separate poster which is available online. [3]

Drug levels suggested that ritonavir boosting may not be needed and phase 2b trials in treatment-experienced patients are planned to start later this year.

### A new version of tenofovir in early studies

First antiviral efficacy results from a new formulation tenofovir (called GS-7340) were presented by Andrew Zolopa from Stanford University and colleagues. [4]

This compound is designed to achieve higher levels of the active compound in specific tissues such as lymph nodes and target cells achieving higher intracellular levels of tenofovir diphosphate in BPMCs and higher potency compared to equivalent tenofovir doses, with lower plasma concentrations potentially reducing renal toxicity.

The double-blind active-controlled study randomised (1:1:1) 30 treatment-naïve patients (CD4 >200; viral load >15,000) to either 50 mg or 150 mg of GS-7340 or to tenofovir 300 mg. After 14 days these three groups produced time weighted viral loads changes of –0.95 (±0.32), –1.07 (±0.14) and –0.54 (±0.32) log copies/mL respectively (primary efficacy endpoint). Mean viral load levels dropped by –0.95, –1.57 and –1.74 log copies/mL in the tenofovir, 50mg and 150mg arms respectively. Blood levels were lower (C<sub>max</sub>/AUC by 94%/88% with 50 mg and by 80%/58% with 150 mg) than the tenofovir group with PBMC levels approximately 30-fold higher.

There were no study discontinuation and no grade 3 or 4 events. Side effects reported were generally mild (nausea, headache).

### C O M M E N T

**Although these are early results, the hope is that formulations that require lower doses can be coformulated more easily with other antiretroviral drugs, and that lower doses might have the potential reduce the most price of drugs used in developing countries. Although drug levels are 6-15 fold higher higher in lymph tissue, spleen and bone marrow there are no increases in plasma, liver and renal tissue. The new formulation also does not penetrate the blood brain barrier.**

**Of interest, despite the improved pharmacokinetics, data presented at CROI in 2010 included a report that GS-7340 showed no protection when used as PrEP in animal studies. [5]**

#### References

Unless mentioned otherwise, all references are to the Programme and Abstracts of the 18th Conference on Retroviruses and Opportunistic Infections, 28 February–2 March 2011, Boston.

<http://www.retroconference.org/AbstractSearch/>

Webcasts are available at the following link:

[http://www.retroconference.org/2011/data/files/webcast\\_2011.htm](http://www.retroconference.org/2011/data/files/webcast_2011.htm)

1. Eron J et al. DTG in subjects with HIV exhibiting RAL resistance: functional monotherapy results of VIKING study cohort II. 18th CROI, 27 February–3 March 2011, Boston. Abstract 151LB.  
<http://www.retroconference.org/2011/Abstracts/42541.htm>
2. Nettles R et al. Pharmacodynamics, safety, and pharmacokinetics of BMS-663068: a potentially first-in-class oral HIV attachment inhibitor. 18th CROI, 27 February–3 March 2011, Boston. Oral abstract 49.  
<http://www.retroconference.org/2011/Abstracts/41942.htm>
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<http://www.retroconference.org/2011/Abstracts/41587.htm>
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<http://www.retroconference.org/2011/Abstracts/42549.htm>
5. Garcia-Lerma G et al. Efficacy of intermittent prophylaxis with tenofovir and emtricitabine against rectal SHIV transmission in macaques and relationship to systemic and mucosal drug levels. 17th CROI 2010. Oral abstract 83.  
<http://www.retroconference.org/2010/Abstracts/37012.htm>

## Immune-based treatment increases HIV-resistant CD4 cells in phase 1 study

Simon Collins, HIV i-Base

One of the first oral presentations of the conference reported results from an immune-based treatment from Sangamo Biosciences called SB-728 presented by Jay Lalezari from Quest Clinical Research in San Francisco. [1]

The intervention in people who were successfully treated with HAART but whose CD4 count remained between 200 and 500 cells/mm<sup>3</sup> led to increases in CD4 cell counts of approximately 200 cells/mm<sup>3</sup> that were sustained for a year.

This was a small open label phase 1 study in six people. The procedure involved blood apheresis to extract CD4 cells (mean ~43 billion), genetic modification to induce resistance to HIV infection, expansion and then reinfusion several months later with a single dose infusion of either 10 or 20 billion cells. Zinc finger nuclease (ZFN)-mediated gene editing technology was used to disrupt the naturally occurring CCR5 coreceptor. ZFNs are small peptides used to introduce a double-stranded break in DNA, that when repaired adds a five base-pair insertion including two stop codes in approximately 25% of treated hematopoietic stem cells.

In this study, the modification process affected a mean 26% of cells (14 to 36%) prior to reinfusion. The percentage of CCR5 disruption in the peripheral blood 14 days after reinfusion in five participants was 6, 3, 1, 2, and 2% and this persisted for the duration of follow up. CD4 counts increased in all participants (+35 to +1038 cells/mm<sup>3</sup> at day 14). Mean follow up was 24 weeks and 4 weeks, in the low and high dose groups, respectively, with mean CD4 increases in these five people of 208, 86, 233, 911 and 210 cells/mm<sup>3</sup>. Although increased CD4 counts could be related to increased cellular transport, rectal tissue biopsies indicated that reinfused cells reached other tissue compartments. Infusion of both doses was safe and well tolerated with mild flu-like cytokine release-related side-effects immediately following the infusion, and garlic body odour related to one of the compounds used in the freezing process.

These results suggest that ZFN-modified gene disruption of CCR5 provides a feasible approach to generate a reservoir of HIV-resistant cells. Three new patients will receive 30 billion cells as a third cohort, two of whom have already received treatment.

A second presentation reported research into developing a similar disruption to CXCR4 virus that was able to shift tropism in a humanised mouse study suggesting that genetic manipulation may be able to be designed for people at all stages of HIV disease. [2]

The research was also the focus of two presentations in a symposium on the last day of the conference called Obstacles to a Cure. [3]

Paula Cannon from University of Southern California Los Angeles reported on early research in ZFN-treated autologous hematopoietic stem cells (HSC) to generate HIV resistant cells as a functional cure in mice.

Using an immune-depleted (NSG) mouse model allowed the researchers to transplant human cells grafted at day one and then analyse human cells after 2-3 months. At this time, 65% of the mouse bone cells are human origin, 80% of thymus cells, and 20-30% bone cells. The humanised mice were then infected with HIV and their viral infection was monitored over several months. While control mice showed expected CD4 declines, ZFN-treated mice maintained immune equilibrium. These differences were more striking when looking at tissue samples with severe cell depletion in bone marrow, thymus, spleen and gut mucosa in control mice (receiving untreated HSC) compared to ZFN-treated mice, who showed similar response to HIV uninfected and untreated control mice.

CCR5 expression in spleen and gut cells were only detected in the control HSC mice and not in the ZFN-HSC animals. Intriguingly, viral load curves were similar between the treated and untreated infected animals for the first six weeks, rising to >100,000 copies/mL. They remained at this level in the untreated mice but dropped to undetectable levels in both blood and tissues of the treated mice. Similar response were observed with other R5-tropic but not X4-tropic strains of HIV.

The group is now looking at additional gene deletions for CCR5 including developing responses resistant to X4 infection.

Scale up of this technology is starting with HIV-positive people diagnosed with AIDS-related lymphoma, including EBV-related lymphoma. Treatment included removing and treating HSC prior to chemotherapy and reinfusing after chemotherapy. Endpoints include immunologic and virological endpoints. This complements the SB-728 treated CD4 cells in phase 1 studies reported below.

Carl June and colleagues from University of Pennsylvania presented combined early in vivo results from the Lalezari study reported above and from patients enrolled in second phase 1 open label study being run by Pablo Tebas at University of Pennsylvania. This second study uses single dose infusions of between 5–10 billion cells in 12 people on stable antiretrovirals: 6 with CD4 >450 (6 enrolled, 4 infused, 2 on treatment interruptions, one with data from July 2009) and 6 with <500 cells/mm<sup>3</sup> (4 enrolled, 2 infused). This study also includes an 'optional' treatment interruption one month after the infusion.

Of 14 people treated, 9 have safety data. No serious events have been reported over median of 232 days (range 99–754 post infusion); 58 events were reported (48 mild, 10 moderate); 33/58 were judged related to infusion (fever, fatigue) and resolved without complications within 48 hours. No evidence was seen of genotoxicity.

All patients have an early CD4 increase post infusion of 200–300 cells/mm<sup>3</sup> by day 14, with three people have greater than 1000 cell increases, with most people dropping to, or stabilising to, an increase of around 200 from baseline after 3 months. The CD4:CD8 ratio normalised to >1.0 in most patients out to 90 days. However, in these small numbers there were a range of responses and not all patients responded as strongly.

All patients but one maintained a level of approximately 4% of modified cells that were maintained and stable out to 6 months. The patient with longest follow-up has maintained a stable level of modified cells for over 400 days and is evidence that memory

cells with stable persistence can be modified (though there are no phenotypic data on these cells yet). In vivo expansion of the modified cells was seen in 8/9 patients (mean 3-fold increase 14-30 days post infusion, but 2 people having 20–40 fold increases) with stable increases persisting for the extent of follow-up. Trafficking to other cellular tissue was demonstrated from rectal biopsy samples showing increases gene disrupted cells at least on a comparable level to that seen in blood.

The two patients who took a 12-week treatment interruption at day 28 experienced viral rebound to around 5 logs which then dropped by 1–2 logs prior to restarting treatment but larger patients numbers are needed to evaluate any consistent pattern or treatment effect.

#### C O M M E N T

**Currently this research is exciting. Up to 10% of people who respond virologically may fail to generate a similar or sufficient immunological response to HAART, and delayed initiation of HAART correlates to reduced likelihood of normalising CD4 counts (commonly referred to as >500 cells/mm<sup>3</sup>). IL-2-associated CD4 increases either failed to produce functional immune benefits or these were offset by the toxicity associated with IL-2 treatment.**

**While the publicity from this study associated the research with the case of the stem cell transplantation from a CCR5-delta32-deleted donor to a patient who has since been able to discontinue antiretroviral drugs for over three years without experiencing viral rebound, it is important to realise that these are two very different approaches.**

#### References

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1. Lalezari J et al. Successful and persistent engraftment of ZFN-M-R5-D autologous CD4 T Cells (SB-728-T) in aviremic HIV-infected subjects on HAART. 18th CROI, 27 February–2 March 2011, Boston. Oral abstract 46.  
<http://www.retroconference.org/2011/Abstracts/41074.htm>
2. Wilen C et al. Creating an HIV-resistant immune system: using CXCR4 ZFN to edit the human genome. 18th CROI, 27 February–2 March 2011, Boston. Oral abstract 47.  
<http://www.retroconference.org/2011/Abstracts/41853.htm>  
Webcast Session 11, Monday 10 am-12 noon; Auditorium. HIV: Innovative Therapeutic Approaches, ART, and Drug Resistance. Access from Tuesday 28th.  
<http://www.retroconference.org/2011/Sessions/011.htm>
3. Session 47-Symposium Obstacles to a Cure Wednesday, 4-6 pm. Webcast available online.
4. Cannon P et al. CCR5 knock-out in hematopoietic stem cells. Oral abstract 164.  
<http://www.retroconference.org/2011/Abstracts/42649.htm>
5. Tebas P et al. Disruption of CCR5 in zinc finger nuclease-treated CD4 T cells: phase I trials. Oral abstract 165.  
<http://www.retroconference.org/2011/Abstracts/42650.htm>

## Antiretroviral prevention: oral PrEP, gels and treatment studies

Simon Collins, HIV i-Base

One of the most important themes from the conference this year was the high profile given to research into medical interventions to reduce transmission.

Last year, when the iPrEx and Caprisa 004 studies showed proof of principal for oral and topical use of ARVs to reduce the risk of sexual transmission, the differences between actual and reported adherence complicated the interpretation of the potential benefits.

These and other aspects of this research were addressed in many of the studies presented at CROI. This included two separate oral sessions and a plenary talk all of which are available as webcasts. [1, 2, 3]

Despite the high potential benefit for oral PrEP to reduce infections, the idea of using an oral antiretroviral to prevent transmission seems to make some people angry, to the point of losing the science and becoming blind to the level of protection already seen.

The increasing incidence of sexual transmissions in every country directly challenges the efficacy of condoms, however effectively they can protect sexual health including from HIV.

The safety concerns include daily tenofovir having a small impact on bone mineral density, the clinical importance of which is currently unclear. This is less than the impact reported in HIV-positive people on treatment and may be mitigated by intermittent

dosing. Although intermittent dosing (once or twice weekly) would reduce cost and improve adherence this will depend on drug levels in tissue rather than blood. The use of intermittent dosing is supported by sustained drug levels in blood achieved with this strategy. However, protection comes from drug levels in the vaginal, rectal or penile tissue where HIV exposure takes place.

The risk of drug resistance from continuing to use tenofovir/FTC by people who become infected was not seen in iPrEx, but resistance data from daily dosing is very preliminary and based on frequent monitoring.

No one in this field is suggesting that oral PrEP becomes the only prevention technology, or even that it is ready for widespread use. The data do support use in specific circumstances, in high-risk individuals who include it to increase their protection.

CROI included studies looking at these issues and our reports in this issue include:

- Further efficacy analyses from the iPrEx study
- Bone mineral density (BMD) changes in HIV-negative men using tenofovir
- Topical gels as PEP and PrEP in human and animal studies

#### References

Unless mentioned otherwise, all references are to the Programme and Abstracts of the 18th Conference on Retroviruses and Opportunistic Infections, 28 February–2 March 2011, Boston.

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[http://www.retroconference.org/2011/data/files/webcast\\_2011.htm](http://www.retroconference.org/2011/data/files/webcast_2011.htm)

1.Oral abstract session: HIV Prevention: HSV2, Topical and Oral PrEP, and Circumcision, Monday 28 February 10:00 AM.

2.Oral abstract session: Advances in PrEP, Tuesday 1 March, 10.00 AM.

3.Celum C. Plenary 3/2/2011 8:30 AM Drugs for Prevention–Topical and Systemic PrEP. Wednesday 2 March 8:30 AM.

## Further efficacy analyses from the iPrEx study

### Simon Collins, HIV i-Base

Robert Grant from the Gladstone Institute of Virology and Immunology San Francisco presented follow-up results from the international iPrEx study. [1]

The initial analysis published in the NEJM in November 2010 reported a 44% reduction (36 vs 64 infections; 95%CI 15 to 63%; p=0.005) from use of daily oral tenofovir/FTC compared to placebo in 2499 young sexually active MSM at high risk of catching HIV. However, all infections in the active arm of the study were associated with undetectable (91%) or low (9%) drug levels in blood (compared to 51% of uninfected matched cases) indicating higher protection rates (~95%) with actual use. [2]

Results presented at CROI from an additional final four months of blinded randomised arms included 12 new infections in the active vs 19 in the placebo groups (p=0.002). During follow-up three months after drug/placebo discontinuation there were 4 new infections in the active arm and 2 in the placebo group (p=NS).

By all analyses, these final data retained similar significant protection rates to the initial published results. Protection was seen in all subgroups (by age, ethnicity, region, schooling, alcohol use, circumcision) but greater protection was seen in people reporting higher risks (i.e. unprotected anal intercourse, p=0.03).

Side effects were reported at similar rates in both arms and are summarised in Table 1. Differences in nausea and weight loss were seen in the first four weeks that subsequently resolved to placebo levels. No differences were seen in laboratory safety markers including phosphate, electrolytes, AST, ALT, amylase, glucose etc. While encouraging, these safety data need to be interpreted with consideration of the minimal adherence in each arm suggested by the PK sub-study.

**Table 1: Adverse events reported in iPrEx; n (%)**

	Tenofovir / FTC	placebo	P
Depression	43 (3%)	62 (5%)	0.07
Grade 3/4 events	151 (12%)	164 (13%)	p=0.51
Death	1 (<1%)	4 (<1%)	p=0.18
Serious AE	60 (5%)	67 (5%)	p=0.57
Diarrhoea	46 (4%)	56 (4%)	p=0.36
Headache	56 (4%)	41 (3%)	p=0.10
Nausea	20 (2%)	9 (<1%)	p=0.04
Weight decrease	27 (2%)	14 (1%)	p=0.04
Creatinine elevation	25 (2%)	14 (1%)	p=0.08
Confirmed Cr increase (0.4%)	5	0	p=0.06

Drug resistance was not detected in any of the cases of seroconversion that occurred during the study, but resistance to FTC was found in three people who were seronegative at baseline but later found to be recently infected by PCR viral load.

Self-reported risk reductions in behaviour changes in terms of partner reduction and increased condom use should perhaps be considered cautiously given the low correlation between reported and actual adherence.

However, the positive results reported from the study should increase the likelihood for actual adherence in the future. Of interest, despite this optimism, Dr Grant suggested that actual adherence should not be assumed, even knowing when protection is proven.

Participants in iPrEx study are being given the option to enroll in a follow-up study of open label. tenofovir/FTC.

### Bone mineral density (BMD) changes in HIV-negative men using tenofovir/FTC PrEP

Two studies were presented looking at the impact on bone mineral density during PrEP. These are important both for the opportunity to evaluate the safety of PrEP but also to look at the previously observed side effects of tenofovir separate from an additional impact of both HIV and ageing.

Albert Liu from University of California, San Francisco presented baseline (n=200) and longitudinal (n=184) results from HIV-negative men followed from 2005-2007 in a randomised tenofovir vs placebo study run in San Francisco. [3]

Demographics and baseline characteristics included: median age 40 years (range 19-60); 77% white, 7% Latino or Hispanic, 5% African American, and 5% Asian or Pacific Islander. Approximately 20% were smokers, 40% with moderate/heavy alcohol use, 15% corticosteroid use and 60% used multivitamin, calcium or vitamin D supplements. At baseline a higher proportion of men were found to have low BMD (defined as z-score > -2.0) than would have been expected (~10%; 20 vs 4.8 cases; p<0.001).

DEXA scans performed at baseline, 9 or 12 months, and 24 months showed -1.1% net decrease in mean BMD in the tenofovir vs placebo group at the femoral neck (95%CI 0.4 to 1.9%, p = 0.004) and a -0.8% net decline at the total hip (95%CI 0.3 to 1.3%, p = 0.003). At the spine (L2 to L4) there was a trend towards a -0.7% difference (95%CI -0.1 to 1.5%, p = 0.11). These results were similar after adjustment for baseline BMD, BMI, race, age, and creatinine clearance.

Declines mainly occurred during the first 12 to 15 months of treatment and were generally small. More significant losses (>3% BMD) occurred more frequently in the tenofovir group for hip and femoral neck (both p=0.02) but this was no longer significant at any location when using a >5% cut off (p=1.0, 0.13 and 0.72; for hip, neck and spine respectively).

The ten reported fractures (six in the active and four in the placebo group; p=0.75) were all trauma-related and judged unrelated to study drug.

In a second study, Kathleen Mulligan from University of California, San Francisco presented hip and spine BMD results measured every 24 weeks in approximately 500 people enrolled in a substudy of iPrEx. [4]

Participant were enrolled from sites in Peru (n=221), Thailand (n=95), the US (n=71), South Africa (n=61) and Brazil (n=55) and resulted in broader ethnicity: 18% were Caucasian, 13% black, 20% Asian, 49% mixed race; 52% were Hispanic or Latino. This was a younger population: 48% were under 25 years old and therefore likely to still be experiencing bone mass growth.

Although >60% were active (weight bearing exercise), alcohol (80%) and tobacco (43%) use was common. Mean body mass index was 23.5 (SE 0.2) kg/m<sup>2</sup>. At baseline, total age and race adjusted z-score for the group which would be expected to be 1.0 was negatively shifted to the left. Low bone mineral density (z-score < -1.0/-2.0) was seen in 36%/12% people in the spine and 18%/2% in the hip, with no difference between the active and placebo groups. Unfortunately there are limited studies of bone disease in otherwise healthy young men to verify the normative data used in bone studies, however the same data are used when evaluating low BMD related to HIV, where similar or greater rates of low BMD are commonly reported.

During the study, bone mineral density tended to increase in the placebo arm and decrease in the FTC/TDF arm, resulting in modest (-0.7 to -1.0%) but statistically significant differences between the groups by week 24 (see Table 2). These are lower than the -2 to -4% seen in HIV-positive people starting tenofovir-containing HAART. Lower patient numbers at later timepoints will require later analyses.

While these are encouraging data, it was also pointed out that it would not be expected to see differences in young healthy men, although limited drug exposure due to low treatment adherence, will also have diluted any reductions caused by tenofovir.

**Table 2: Mean (SE) percent change in bone mineral density from enrollment**

	FTC/TDF	Placebo	Difference (95%CI)	p value
<b>Total hip</b>				
week 24	-0.31 (0.13)	+0.34 (0.13)	-0.65 (-1.03 to -0.28)	0.001
week 48	-0.05 (0.22)	+0.90 (0.22)	-0.95 (-1.56 to -0.35)	0.002
week 72	+0.27 (0.28)	+0.49 (0.28)	-0.22 (-1.00 to 0.56)	0.581
<b>Spine</b>				
week 24	-0.66 (0.20)	+0.29 (0.20)	-0.95 (-1.51 to -0.39)	0.001
week 48	-0.41 (0.24)	+0.13 (0.24)	-0.54 (-1.20 to 0.12)	0.106
week 72	-0.97 (0.32)	-0.10 (0.32)	-0.87 (-1.75 to -0.01)	0.052

### Pharmacokinetic substudy: drug levels in iPrEx

The nested case-control pharmacokinetic substudy in iPrEx matched samples from 34 newly infected participants to 43 controls who remained HIV-negative. The group tested for tenofovir diphosphate and FTC-triphosphate (the active moieties of tenofovir and FTC) in blood plasma and stored PBMCs.

The results were important in demonstrating a strong correlation between presence of active drug and risk of infection/protection (present in 9% of cases vs 51% of controls,  $p < 0.001$ ). Importantly, this was able to show >95% concordance between paired plasma and PBMC samples.

In the presentation at CROI, Peter Anderson presented pharmacokinetic results that were independently associated with detectable drug levels. [5]

This included study site region (97% for US vs 50% for non-US participants,  $p < 0.0001$ ), age (73% in 25 year olds vs 44% in under 25 year olds,  $p < 0.001$ ) recent sexual activity (73% with recent high risk UAI vs 59% without UAI vs 35% no activity within 12 weeks,  $p = 0.003$ ).

The open-label phase of the iPrEx study will include real-time drug level and adherence analysis that will help increase the understanding of drug concentration associated with protection.

The drug level test used in these studies was sensitive enough to drug use within the previous two weeks if the person was already at study state levels, but this period would have been shorter for sporadic adherence.

The relationship between drug levels and degree of protection are a crucial aspect of how and whether PrEP will find a role in prevention strategies.

Intracellular drug levels following single doses of tenofovir/FTC were reported from seven HIV-negative volunteers (5 women, 2 men) in a poster from the same study group. [6]

Tenofovir-DP levels were as expected in plasma but reduced in PBMCs: they were only 15% of those expected at steady state dosing and were only 35% of the levels seen in primate studies. FTC-TP levels achieved 30% of those expected at steady state but were similar to single-dose primate studies.

The clinical results from iPrEx may not have required the optimum levels achieved at steady state from daily dosing but current analysis are unable to show this.

It would seem to be important to prioritise this aspect of protection in animal studies to further inform the likely protection in humans from weekly or twice-weekly dosing.

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## Topical gels as PEP and PrEP: animal and human studies

Simon Collins, HIV i-Base

The conference included a similarly broad range of studies looking at antiretroviral-based microbicide gels.

### Rectal use of tenofovir gel protections against ex vivo exposure

Peter Anton from the University of California presented late breaker results from a phase 1 study of rectal use of the tenofovir gel used in the Caprisa 004 study. [1]

HIV-negative participants (14 men and four women) received sequentially a single oral dose of tenofovir, single rectal dose of tenofovir gel or placebo, and seven days rectal dosing, also randomised, each separated by a two week wash out and sampling period. The study measured efficacy by ex vivo infectibility of in vivo exposed cells from rectal biopsies, and monitored plasma drug concentrations in multiple compartments and general product acceptability.

Primary endpoint was safety defined by grade  $\geq 2$  events and secondary safety by a large panel tests relating to mucosal injury that were developed for an earlier HPTN 056 rectal microbicide study.

Most side effects were grade 1 and occurred during the seven-day rectal use, more frequently with the active gel (12 vs 2 people,  $p=0.001$ ; 37 vs 6 events,  $p=0.002$ ) were gastrointestinal (GI). However, two people reported five grade 3 GI events. The only differences seen between groups in the panel of mucosal indices were decrease in two cytokines (IL1-beta and TNF-alpha) only seen at 30 minutes post dosing after the seven-day exposure.

Neither gel was particularly liked (25% tenofovir, 50% placebo) but approximately 75% in each group said they would use it if it proved to be effective.

As expected, plasma dosing achieved significantly higher levels (approximately 2 logs higher) in plasma compared to tissue, with rectal dosing not accumulating tenofovir levels in plasma.

Importantly, active drug levels of tenofovir diphosphate, 30 minutes post dosing with single rectal dose were  $>100$ -fold higher in rectal tissue compared to oral dose, achieved in 80% of samples, and were five times higher following the 7 day dosing.

Rectal biopsies taken 30 minutes post dose were infectible at baseline. Single oral dose showed no effect and single rectal dose showed a trend to an effect but after 7 day rectal dosing the tenofovir exposed cells showed significantly greater resistance to infection.

This allows the first analysis to show a strong positive correlation between tenofovir DP drug level following in vivo exposure and HIV inhibition ( $r^2=0.33$ ,  $p=0.0011$ ).

While the study concluded that although the acceptability of the gel was lower, the gel was safe in terms of tissue exposure, and topical application achieved tissue concentrations of tenofovir diphosphate that demonstrated ex vivo protection from infection.

### Oral tenofovir vs daily gel vs both

Craig Hendrix from Johns Hopkins University, Baltimore, and colleagues presented results from an open-label phase 2 study of daily oral tenofovir, daily gel and dual oral/gel in 144 sexually active HIV-negative women (aged 18-45) at four US and three African sites. This was a three-stage cross over study with each stage lasting six weeks separated by one week washout. [2]

The study looked at safety, adherence, acceptability and pharmacokinetics.

The gel resulted in levels of tenofovir diphosphate that were 100-fold higher in vaginal tissues compared to oral dosing, and dual dosing made no additional impact on tissue concentrations.

Although excellent adherence was reported ( $>90\%$  all doses reported as taken; and  $>80\%$  people taking  $>90\%$  of doses) the drug levels observed at any time point in the pharmacokinetic study showed that 35-65% of the people in all groups had drug levels below the 99% confidence interval from historical reference cohorts.

No differences in side effects overall were seen between the three regimens, though nausea, diarrhoea and headache were more common during the oral and dual stages (all  $<15\%$ ). Vaginal symptoms and reduced phosphates (general transient) were similar between stages. Nine cases of grade 3/4 hypophosphatemia occurred in 4 oral, 2 gel and 3 dual participants.

The presentation noted that although active concentration in the target site were good from the gel, and not increased by additional oral dosing, the optimum dose required for efficacy is not known and this is an important point.

### Raltegravir as a topical gel in macaques

Charles Dobard and colleagues from the CDC Atlanta presented data from using a 1% raltegravir-based gel applied three hours after vaginal exposure in six macaques. [3]

The rationale for this approach is that it is easier to use an intervention after exposure than to accurately predict when protection would be needed for a pre-exposure dosing - whether this involves a 24 hour or 2 hour preexposure window. Integrase inhibitors

are a potential target for PEP/PrEP because they block later stages of the viral replication cycle, allowing an activity window 8-10 hours post exposure compared to 2 hours associated with RT inhibitors.

The gel formulation developed by this group was a clear, odourless gel that was stable for several years at room temperature. The macaques received vaginal SIV challenges twice weekly for up to 20 exposures.

Four control animals all became infected (after 10–20 viral challenges). In contrast, 5/6 macaques using the active gel remained protected through 20 exposures ( $p < 0.005$ ). Although one infection occurred, resistance did not develop while the gel was continued, although this was only for a short period. Systemic viral load in this animal was similar to control data, although levels of vaginal shedding were significantly lower.

### **Oral tenofovir/FTC protects macaques rectally exposed to FTC-resistant virus**

Protection against exposure to FTC-resistant virus was reported by Gerardo Garcia-Lerma, also from the CDC, from macaques using oral tenofovir/FTC and following rectal exposure. [4]

The rationale for this study is to determine whether tenofovir protects against the common M184V mutation as one of the more common resistant mutations reported in drug resistance surveillance studies.

Five macaques received oral tenofovir/FTC in human equivalent doses 3 days before and two hours after rectal exposure, which was administered weekly for up to 14 weeks. Five untreated animals were included as controls. None of the treated animals become infected compared to all five control animals ( $p = 0.0008$ ).

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## **Maternal risk following short course HAART**

### **Polly Clayden, HIV i-Base**

Roger Shapiro and colleagues from the Mma Bana Study, Botswana looked at maternal and infant outcomes among women receiving short course HAART for PMTCT during pregnancy and breastfeeding. [1]

In Mma Bana, pregnant women with CD4 counts  $\geq 200$  cells/mm<sup>3</sup> ( $n = 560$ ) were randomised to receive regimens of either abacavir+AZT+3TC (arm A) or LPV/r+AZT+3TC (arm B) from week 26 to 34 gestation until the infants were weaned at 6 months post partum. [2] The study also included an observational arm ( $n = 170$ ) in which women indicated for HAART according to local guidelines received lifelong NVP+AZT+3TC. Participants were followed for 24 months post partum.

Randomised women re-started HAART with NVP+AZT+3TC when indicated for treatment (at a CD4 count of 200 cells/mm<sup>3</sup> at the beginning and changed to 250 cells/mm<sup>3</sup> during the course of the study). This occurred in 9% of randomised women and 25% overall (randomised and observational) continued HAART past 6 months for treatment.

At 24 months, there were 14 (1.9%) maternal deaths: 2 during pregnancy following HAART initiation (1 arm A, 0 arm B, 1 observational), 2 from delivery to 6 months postpartum (0 arm A, 0 arm B, 2 observational), and 10 from 6 to 24 months postpartum (5 arm A, 3 arm B, 2 observational).

There were deaths across all baseline CD4 strata among randomised women (4, 2, and 3 with baseline CD4 200 to 350, >350 to 500, and >500 cells/mm<sup>3</sup>, respectively). In this group, 8 of 9 deaths were from 6 to 24 months; and 5 of these women had not re-started HAART as treatment.

There was a mean CD4 increase from baseline to 24 months in all treatment arms (15% of randomised women re-started HAART): 68 cells/mm<sup>3</sup>, 98 cells/mm<sup>3</sup>, and 283 cells/mm<sup>3</sup> in arms A, B and observational respectively. Among women with baseline CD4 >250 cells/mm<sup>3</sup>, there was a significantly higher CD4 increase in arm B vs A (86 vs 46 cells/mm<sup>3</sup>, p=0.04).

Data were available for 96% of 709 live-born infants at 24 months of follow up. The majority (97%) of infants were breastfed for a median of 5.8 months. Nine deaths occurred before breastfeeding was initiated (7 <3 days of age, 3 arm A, 2 arm B, 4 observational). There was an increase in infant mortality after weaning, only 5 (0.7%) deaths were during breastfeeding (0 arm A, 2 arm B, 3 observational), compared to 23 (3.2%) after weaning (10 arm A, 11 arm B, and 2 observational). Of these, 14 (2.0%) deaths occurred less than 3 months from weaning which accounted for 38% of all infant deaths in the study. The death rate during breastfeeding was 1.76/100 person-years compared to 5.71/100 person-years within 6 months post-weaning, p=0.02.

Eight children (1.1%) were HIV-infected at 24 months, which did not change from 6 months. HIV infection or death occurred in 6.1% of infants (6.4% arm A, 5.9% arm B, 5.8% observational)..

Causes of maternal and infant deaths are shown in Table 1.

**Table 1: Causes of maternal and infant deaths at 24 months in Mma bana**

Maternal	Infant
Arm A Extrapulmonary TB (3) Postpartum hemorrhage Bleeding disorder/hemorrhage Diarrhoea/sepsis Vulvar cancer Drowning	Diarrhoea (13) Pneumonia (5) Neonatal sepsis (5) Meconium aspiration (3) Respiratory failure/? aspiration (2) Pulmonary TB (suspected) Prematurity/respiratory distress Fever/respiratory failure
Arm B Pulmonary TB Diarrhoea/hepatic/renal failure Unknown (febrile illness, back pain)	Birth asphyxia Meningitis Hydrocephaly Car accident Unknown (weakness/lethargy)
Observational Toxoplasmosis PCP Stevens Johnson Syndrome Bowel obstruction Congestive heart failure	Unknown (no information)

The authors concluded that maternal HAART from pregnancy through 6 months of breastfeeding was associated with low overall maternal and infant mortality at 24 months. They noted that this study found similar maternal mortality/lower infant mortality than in Mashi, a previous Botswana non-HAART MTCT intervention study. Following their observation of a trend for increased maternal mortality after stopping HAART for PMTCT they suggest that 24-month mortality may be higher when stopping HAART in this situation than if it is continued.

Increased infant mortality among weaned infants has been seen previously and later weaning is now recommended by WHO but MTCT and mortality tradeoff are unstudied.

A related poster from the MTCT-Plus Initiative also looked at the impact of stopping HAART used during pregnancy for PMTCT on maternal HIV disease progression. [2] This study evaluated maternal CD4 count decline after MTCT prophylaxis.

MTCT-Plus was a multi-country HIV care programme for women, children, and families in eight African countries and Thailand.

ART-naive, HIV-positive pregnant women with CD4 count  $\geq$ 400 cells/mm<sup>3</sup> at enrollment were included in the analysis.

The majority of the women evaluated received single-dose nevirapine (sdNVP) or short-course ARV prophylaxis with AZT or AZT+3TC. HAART (AZT+3TC+NVP or nelfinavir) was initiated during pregnancy in programmes in Thailand and Kenya. All regimens were stopped shortly after delivery with a median duration of 10 weeks.

Of 1563 women, 172 (10.9%) initiated HAART, 689 (43.5%) sdNVP, 532 (33.6%) short-course ARV prophylaxis, and 190 (12%) women received no documented prophylaxis.

At baseline, women were a median of 27 (IQR 23-30) years of age with a median CD4 count of 469 (IQR 361-613) cells/mm<sup>3</sup>. The median follow up time was 26.1 (IQR 14.5-40.7) months. Overall, 11.6% of women with enrollment CD4 >250 cells/mm<sup>3</sup> declined to <200 cells/mm<sup>3</sup>.

Among women who initiated prophylaxis with CD4 >400 cells/mm<sup>3</sup>, the cumulative probability to reach endpoint of CD4 count <350 cells/mm<sup>3</sup> at 24 months was 28.0% (95% CI 24.6, 31.6), overall. The proportions by intervention were: 36.3% (95% CI: 27.4, 47.2), 21.5% (95% CI: 16.4, 27.9), and 27.8% (95% CI: 23.0, 33.2) in the HAART, AZT or AZT/3TC, and sd-NVP groups respectively.

Almost half (47.8% [95% CI 41.2-54.8%]) of the women with baseline CD4 counts of 400-499 cells/mm<sup>3</sup> declined to <350 cells/mm<sup>3</sup> during follow up, compared to 18.3% (95% CI, 14.9-22.3%) of those with higher baseline CD4 counts,  $p < 0.001$ .

HAART was significantly associated with CD4 decline compared to short course AZT or AZT/3TC, AHR 2.2 (95% CI 1.5-3.3),  $p < 0.0001$ . Of note, in this analysis, both undocumented intervention and s/d NVP were also associated but to a lesser extent than HAART,  $p = 0.02$  and  $p = 0.001$  for short course and s/d NVP respectively. The only other association observed was with age 25-35 years.

Of women receiving HAART, 60.3% (CI 43.5-77.5%) with baseline CD4 counts of 400-499 cells/mm<sup>3</sup> declined to <350 cells/mm<sup>3</sup> during follow up compared to 48.4% (95% CI 34.8 – 64.2) with baseline CD4 >500 cells/mm<sup>3</sup>.

The authors wrote their findings suggest that women exposed to HAART as MTCT prophylaxis were twice as likely to have CD4 decline below the threshold of treatment eligibility at 24 months after delivery, than women receiving other PMTCT interventions. They propose that women with baseline CD4 <500 cells/mm<sup>3</sup> would benefit from lifelong treatment. They urge caution in interpreting their findings though, as women in this observational cohort received a relatively short duration of HAART during pregnancy only.

#### C O M M E N T

As the Botswana investigators note, significantly increased infant mortality, as in their study, associated with early weaning has been reported elsewhere. Later weaning protected by maternal HAART or infant prophylaxis is now recommended by WHO, although the risk/benefit of breastfeeding beyond 6 months is a bit of an evidence free zone.

With respect to maternal health and mortality these reports raise important issues. Following the results of the Strategies for Management of Anti-Retroviral Therapy, or SMART study (and a smaller west African study Trivican) in 2006 - which showed that stopping HAART doubled the risk of morbidity and mortality compared to continuing – there was concern about the consequences for women receiving HAART in pregnancy and stopping. [3] This is a population where (at least in richer countries) giving short course HAART for PMTCT is standard of care.

At enrolment, SMART participants were receiving HAART (for a median of 6 years) and had a CD4 count of >350 cells/mm<sup>3</sup>. They were randomised to continue or stop and those that stopped re-start when they reached CD4 <250 cells/mm<sup>3</sup>. Although the duration of HAART received by a pregnant woman is shorter than the that received by the majority of people in SMART – in these studies about 10 weeks and 8 months in MTCT-Plus and Mma Bana respectively – the hazard ratio for OI or death from any cause in SMART was 1.6 for the subgroup that received HAART 0 to <3 years before stopping (albeit looking at small numbers).

However, data from WITS looking at progression after stopping showed, among pregnant women with CD4 >350 cells/mm<sup>3</sup> starting HAART for PMTCT, changes in CD4 and viral load were similar at one year post partum whether women stopped or continued therapy after delivery. [4] None of the WITS women progressed to AIDS or death during the first year post partum.

Although the causes of death were not SMART events in the Botswana study and numbers are very small, these and MTCT-Plus results if shown in other studies may mean that it is not safe for women to stop HAART for PMTCT whatever their baseline CD4.

These presentations make the results of the PROMISE study important, as it will give randomised, data to definitively answer the question. If there really is a big difference between stopping and not stopping, then this part of PROMISE may be able to end early as there will be a DSMB monitoring during the course of the study there are stopping rules at each interim evaluation.

Also, in Mma Bana, 6 of 9 (67%) maternal deaths among those randomised occurred in the Arm A triple nucleoside group. Six of 8 (75%) mother-to-child transmissions were in Arm A and those infants were 3 times more likely to be infected than Arm B. Again, numbers are tiny, neither outcome was statistically significant and triple nucleosides are not standard of care, but there may be a difference by regimen between this strategy and PI or NNRTI based HAART. It is likely though that LPV/r-based regimens will remain the standard of care for women in this situation particularly as it is more available and cheaper in Africa and has more safety data.

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## Pre-term delivery and HAART

Polly Clayden, HIV i-Base

A poster discussion session at CROI 2011 looked at HAART during pregnancy and pre-term delivery. [1]

Discussant Claire Thorne, from the MRC Centre of Epidemiology for Child Health and the Institute of Child Health, began with a quick overview of the inconsistent findings on this “controversial topic” to date.

Pre-term delivery is defined as birth before 37 weeks of gestation. Recent WHO estimates suggest about one in ten infants are born prematurely. The rate varies across the world with the lowest in Europe and highest in Africa. Pre-term infants account for 75% of perinatal mortality and 85% of all pre-term births occur in Africa and Asia. Dr Thorne noted that why this happens is still not completely understood.

An association between HAART and pre-term delivery was first observed in Europe in 2000. Since then several (mainly European) studies have reported similar findings and other (mainly American) reports have not found an association. Dr Thorne stressed that issues of populations and methods are critical to the interpretation of these diverse findings.

While the benefits to mothers and PMTCT from HAART are unequivocal, pre-term infants have higher morbidity and mortality risks than those carried to full term. Approximately 80% of pre-term infants of women receiving HAART are born between 32 and 36 weeks, when these risks are relatively low at least in industrialised countries. However striking inequalities exist in the chance of survival of pre-term infants between these settings and those with more limited resources.

This session included cohort data from France, Spain and Botswana and from a randomised trial in Botswana.

Jeanne Sibude showed findings from the National ANRS French Perinatal Cohort. [2] This study investigated trends in pre-term delivery between 1990 and 2009 among all singleton pregnancies included in the cohort (n=13957). Risk factors were identified in a subgroup of women (n=2631) for which more detailed data were collected between 2005 and 2009.

The investigators performed multivariate analyses adjusted for maternal age, intravenous drug use, BMI, smoking, assisted conception, HCV coinfection, timing of initiation of ART and baseline viral load

They observed a steady rise in pre-term delivery by time period reflecting changes in routine management: 9.2% in 1990 to 1993 (no ART during pregnancy) and 9.6% in 1994 to 1996, (AZT monotherapy for 90% of women), to 12.4% during 1997 to 1999 (double NRTI treatment for the majority and HAART for selected women), and 14.3% in 2005 to 2009 (HAART),  $p < 0.01$ . This exceeded the background rate in France of 4.3% in 1995 and 5.9% in 2005.

Between 1990 and 2009 the risk of pre-term delivery overall was higher for HAART and double NRTI treatment than for AZT monotherapy, AOR 1.69 (95% CI 1.38- 2.07) and 1.24 (95% CI 0.96-1.6) respectively,  $p < 0.001$ .

Among the subgroup of women initiating HAART during pregnancy in 2005-2009 pre-term delivery rates were similar between women already receiving HAART at conception and those initiating HAART in pregnancy, respectively 14.2% and 13.6%,  $p = 0.6$ .

Pre-term delivery was also associated with maternal age, IV drug use, smoking, BMI, marital status and late access to care.

Most women received a RTV-boosted PI. There was a higher risk of pre-term delivery among women receiving a boosted, compared to a non-boosted PI (very few women received NNRTI-based regimen in this cohort), 14.4 vs 9.1%, AOR 2.03 (95% 1.06-3.89),  $p = 0.03$ .

Women initiating HAART with a boosted PI during pregnancy were more likely to be hospitalised for any cause, particularly premature labour, metabolic or vascular disease and infections, compared to those receiving a non-boosted PI,  $p < 0.001$ . The investigators suggested this might be due to “increased toxicity at the end of pregnancy”.

María Isabel González-Tomé presented data from the Spanish Cohort for the Study of HIV MTCT. [3] This was a prospective cohort study of 803 children in 7 Spanish hospitals. MTCT interventions were: none, AZT monotherapy, double NRTI, HAART with PI and HAART without PI. Risk factors were evaluated for pre-term delivery and low birth weight  $< 2500$  grams.

This study found 175 (21%) pre-term deliveries and 200 (25%) infants with low birth weight.

Older age, HCV coinfection, prenatal care and no antiretroviral treatment during pregnancy were associated with pre-term delivery in univariate analysis.

In multivariate analysis, only illegal drug use was associated with pre-term delivery, OR 2.9 (95% CI 2.2-4.0),  $p = 0.0001$  and CD4  $> 250$  cells/mm<sup>3</sup> was protective, OR 0.4 (95% CI 0.2-0.65),  $p = 0.0001$ .

In this cohort, unlike the other presentations, HAART with or without PI was not significantly associated with pre-term delivery or low birth weight.

The first presentation from Botswana was by Natasha Parekh from the Harvard School of Public Health who showed data from 16,203 deliveries from October 2007 to March 2010. [4] Data were taken from obstetric records of women with live births at 26 weeks or longer gestational age across 6 hospitals. Out of 15,326 women in this cohort with HIV status recorded, 4,343 were HIV-positive.

The investigators evaluated rates of pre-term delivery, very pre-term delivery ( $< 32$  weeks) and very small for gestational age ( $< 3rd$

percentile on Botswana-specific weight-for-age curves). They then looked at risk factors for very pre-term delivery and very small for gestational age among all women and HIV-positive women.

They found a prevalence very pre-term delivery of 4.3% and respective rate of neonatal death of 26%, OR 49 (95% CI 38-64) and a prevalence of very small for gestational age of 3.7% with a respective rate of neonatal death of 8%, OR 5.2 (95% 3.8-7.1).

In multivariate analysis, very preterm delivery was associated with history of poor obstetric outcome (including stillbirth, preterm delivery, or low birth weight), AOR 2.12 (95% CI 1.54-2.93), hypertension in pregnancy AOR (1.75, 95% CI 1.17-2.63), and maternal HIV infection AOR 1.65 (95% CI 1.26-2.17). Very small for gestational age was also associated with a history of poor obstetric outcome AOR 1.77 (95%CI 1.23-2.53), hypertension in pregnancy AOR 3.44, (95%CI 2.40-4.93), and maternal HIV infection AOR 1.90 (95%CI 1.41-2.55).

Initiating HAART before conception was associated with very small for gestational age, AOR 1.75, (95% CI 1.21-2.52), but not with very pre-term delivery, AOR 0.78, (95% CI 0.49-1.26). Among HIV-positive women. HAART initiation before conception was also associated with hypertension in pregnancy, AOR 1.34 (95% CI 1.00-1.77).

Kathleen Powis presented the only data from a randomised controlled trial in the second presentation from Botswana. [5]

This study analysed 530 women (267 receiving PI-based and 263 triple NRTI HAART) in the randomised treatment arms of Mma Bana who received a median of 11.3 weeks (IQR 8.3-12.9 weeks) of HAART in pregnancy.

The investigators found higher rates of pre-term delivery in the women receiving a PI compared to those receiving triple NRTI treatment, 21.4% vs 11.8%,  $p=0.003$ . This was regardless of duration of HAART in pregnancy.

In multivariate analysis, PI-based HAART in the third trimester of pregnancy was associated with a two-fold increase in pre-term delivery AOR 2.03 (95% CI 1.26-3.27).

The investigators noted a lower maternal weight gain in the women receiving PI-based treatment compared to triple NRTI but this had no association with the likelihood of pre-term delivery.

They found a 2-fold higher rate of hospitalisation (22.7 vs 12.7%,  $p=0.02$ ) and 5-fold higher rate of mortality (6.8 vs 1.4%,  $p=0.002$ ) in the first 6-months of life among infants born pre-term but they did not observe a difference by maternal treatment regimen.

#### C O M M E N T

**Much discussion following the presentations focused on the difficulties of accurately determining pre-term delivery, which has contributed to uncertainty, particularly with observational data. PI-based HAART does appear to show increased likelihood of pre-term delivery from the “controversial” data to date.**

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## HAART more effective than AZT monotherapy in the Botswana PMTCT programme

### Polly Clayden, HIV i-Base

There are limited data from programmes in resource-limited settings describing the effectiveness of HAART compared to AZT monotherapy for PMTCT.

Scott Dryden-Peterson and colleagues from Botswana showed findings from a prospective, observational study of infants, born to HIV-positive mothers, enrolled on the maternity wards of one urban and one rural hospital between February 2009 and April 2010.

The investigators followed the infants from birth to 6 months and compared transmission rates between infants born to mothers receiving either HAART or an AZT based PMTCT strategy. Infants were tested for HIV (DNA PCR) at 1 month of age.

In Botswana, in accordance with national guidelines, the PMTCT programme provided HAART for women with CD4 <250 cells/mm<sup>3</sup> and AZT monotherapy from 28 weeks gestation for women with CD4 ≥250 cells/mm<sup>3</sup> (with single-dose NVP if <4 weeks AZT received). Infants were given single dose NVP+ one month AZT.

A total of 423 mothers agreed to participate and had received either HAART or AZT. Out of 428 infants, 258 were born to mothers receiving HAART and 170 to those receiving AZT (with or without single dose NVP).

Mothers receiving HAART had a longer duration of antiretrovirals prior to delivery, median 12 weeks (IQR 7.1-17.7) compared to median 10.4 weeks (IQR 7.8-12.1) for those receiving AZT, p=0.001.

The median CD4 count was lower for women receiving HAART compared to AZT, respectively 262 vs 430 cells/mm<sup>3</sup>, p<0.001.

There were no significant differences in infant prophylaxis, infant feeding or prematurity between the two groups.

Overall 10 infants (2.5%) were HIV-infected, 9/158 (5.7%) in the AZT group and 1/249 (0.4%) in the HAART group, p=0.001. When the investigators restricted the AZT group to mothers with CD4 >350 cells/mm<sup>3</sup>, as recommended in WHO guidelines, their findings were similar, p=0.007. They noted that half the infections occurred among mothers with >350 cells/mm<sup>3</sup>.

In multivariate analysis, the adjusted risk ratio for AZT compared to HAART was RR 15(95% CI 2.1-109), p=0.008.

The investigators acknowledged that they were unable to determine HIV status for 21 (4.9%) infants, including 9 who died prior to testing. Also, they were unable to determine efficacy in protection during breastfeeding as few women opted to do so in this programme.

However they wrote: "Strategies to provide HAART for all pregnant women, as currently underway in Botswana, could nearly eliminate MTCT."

#### C O M M E N T

**PROMISE will also more definitively address the AZT vs HAART debate for women who do not presently require therapy for their own health. In the Kesho Bora study with randomised comparison of women with similar CD4 200-500 cells/mm<sup>3</sup>, the transmission rate in women who received AZT vs those who received HAART was not significantly different. [2]**

**However real life is not always like a trial and notably in this analysis women with lower CD4 counts receiving HAART had better transmission rates than healthier women with AZT. That PMTCT strategies are complicated from an operational point of view has been a big concern among implementers.**

**If the differences between the groups are as great as appear to be in the retrospective analysis in the Botswana report, again PROMISE will then end early as there will be interim DSMB reviews of the data.**

#### References

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## Lopinavir/r monotherapy for PMTCT

Polly Clayden, HIV i-Base

In an oral late breaker, Roland Tubiana presented findings from a French multisite PMTCT study - PRIMEVA (NCT00424814) – designed to evaluate the use of lopinavir/r (LPV/r) monotherapy in pregnancy for women not needing treatment for their own health.

This was an open label, phase II/III trial. Untreated women with CD4 ≥350 cells/mm<sup>3</sup> and viral load <30,000 copies/mL were randomised 2:1 to receive either LPV/r monotherapy (n=69) or LPV/r + AZT + 3TC (n=36), from 26 weeks gestation until delivery.

The primary endpoint of the trial was >75% women with viral load <200 copies/mL at week 8 of treatment. Secondary endpoints included viral load at delivery and comparative analysis of safety outcomes during pregnancy and until 24 months in children.

The baseline characteristics were similar between arms; women had a median CD4 count of 525 cells/mm<sup>3</sup> and viral load of 2952 copies/mL.

Intent-to-treat analysis of the monotherapy arm revealed a viral load <200 copies/mL at week 8 in 61/69 women (88.4%, 95% CI 78.4-94.9). This was similar to that observed in the control arm (94.4%, 95% CI 81.3-99.3) p=0.18.

The proportions of women with viral load <200 copies/mL at delivery was similar between the LPV/r and control arms, 91.3% (95% CI, 82.0-96.7) vs 97.2% (95% CI, 85.5-99.9), p=0.41. But when the investigators looked at viral load <50 copies/mL at the same

time point, a greater proportion of women in the control arm achieved this, 79.7% (95% CI 63.3-88.4) vs 97.2% (95.5-99.9) in the LPV/r and control arms respectively,  $p=0.01$ .

Similar proportions of cesarean section delivery (49.5%) and pre-term delivery (10.5%) were observed in both arms. Changes of ART due to tolerability were significantly less frequent in the monotherapy arm compared to control, respectively 1.4% vs 11.1%,  $p=0.046$ .

There was one case of transmission in the control and none in the monotherapy arm.

Evaluation of the infants is ongoing.

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## No evidence of increased risk of MTCT with sequential pregnancies in UK and Ireland

Polly Clayden, HIV i-Base

Many HIV-positive women in the UK and Ireland have more than one pregnancy after their diagnosis. In 2009 40% of pregnancies in this population were sequential. The majority of these women will have received mother to child transmission (MTCT) interventions in previous pregnancies.

Clare French and colleagues from the MRC Centre of Epidemiology for Child Health and UCL Institute for Child Health looked at whether sequential pregnancies are associated with increased MTCT risk.

Pregnancies in diagnosed HIV-positive women in the UK and Ireland are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC).

The investigators analysed NSHPC data on live singleton births from 2000 to 2010. They compared the risk of detectable maternal viral load at delivery and of MTCT in sequential pregnancies with the risk in first reported index pregnancies. This included those in women with only one pregnancy. They conducted multivariate analyses using logistic regression.

During this period there were 10,154 pregnancies, of which 2099 (20.7%) were sequential. Of the sequential pregnancies, 1795 were 2nd; 274 were 3rd; and 30 were 4th or 5th.

The investigators found that 100% of sequential pregnancies ( $n=2099$ ) were diagnosed prior to pregnancy, compared with less than half (43.5%) of index pregnancies ( $n=8055$ ),  $p<0.001$ . They noted that sequential pregnancies were more common in the more recent period evaluated (5.5% in 2000-2003 vs 66.4% in 2008-2010) and were more likely to have vaginal deliveries. Women were also more likely to be receiving HAART at conception for subsequent pregnancies,  $p<0.001$ .

In multivariate analysis adjusted for year of delivery and treatment duration, the likelihood of having a detectable viral load at delivery did not differ significantly between index and subsequent pregnancies,  $p=0.77$ . Infant HIV infection status was available for >80% of births and there was no significant difference in mother to child transmission in a multivariate model adjusted for year of delivery, treatment duration and mode of delivery.

The investigators wrote: "As the number of sequential pregnancies increases, and the treatment and management histories of women consequently become more complex, it is important that the situation be carefully monitored."

### C O M M E N T

#### Good news.

#### Reference

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## Recently infected women at the time of delivery have a higher rate of in-utero transmission in PEPI-Malawi

Polly Clayden, HIV i-Base

HIV incidence infection in pregnancy is common in women in sub-Saharan Africa.

Investigators from the PEPI-Malawi trial recently developed a multi-assay algorithm (MAA) to determine incidence. They used the assay to identify women in the trial who were likely to have been recently infected with HIV at the time of delivery. They then evaluated whether those women were at increased risk of in utero mother-to-child transmission of HIV (MTCT).

Susan Eshleman and colleagues showed findings from this evaluation as a poster at CROI 2011.

PEPI-Malawi compared three infant regimens for prevention of post-natal MTCT.

The investigators obtained plasma samples from 2561 women at time of delivery. The samples were tested using the BED-Capture EIA (BED) and an avidity assay (a modified version of the BioRad HIV-1/HIV-2+0 ELISA).

For their MAA they used the following criteria to identify recently infected women:

BED<1.0 OD-n + avidity < 80% + CD4 cell count >200 cells/mm<sup>3</sup> + HIV viral load >400 copies/mL

They identified 73 (2.9%) women as recently infected using the MAA.

All but 9 women with non-recent infection had a BED result >1.0 and/or an avidity result >80%; 4 women with non-recent infection had a CD4 count <200 cells/mm<sup>3</sup>; and 5 had a viral load <400 copies/mL.

Of 54 women known to have non-recent HIV infection (median time since previous positive HIV test, 4.29 years, range 2.3 to 6.1 years), none were misclassified as recently infected. Nor were 9 women already receiving HAART at the time of delivery.

The recently infected group were younger, had lower parity and higher median CD4 cell count at delivery than the non recent group (all p<0.0001).

The risk of in utero MTCT was significantly higher among women identified as recently infected compared to non-recent< 17.8% vs 6.7%, p= 0.001.

In a multivariate analysis, increased risk of in utero transmission was independently associated with: recent infection AOR 2.49 (95% CI 1.30-4.78), p=0.006; viral load (per log<sub>10</sub> increase, AOR 2.01 (95% CI 1.60-2.51), p<0.0001; and age (per 10-year increase, AOR 0.66 (95% CI 0.43-0.93), p=0.02). There was no association with CD4 count, infant gender, early presentation or infant regimen.

The investigators concluded that their results suggest recent maternal HIV acquisition is strongly associated with in utero HIV transmission independent of viral load at delivery.

### C O M M E N T

**This is the first randomised trial data to show the association between recent infection and in utero transmission.**

#### Reference

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## Reduced CCL22 concentrations in cervicovaginal secretions from pregnant women

Polly Clayden, HIV i-Base

Pregnant women are at greater risk both of HIV acquisition and transmission to their negative partners than non-pregnant women. This is independent to behavioural factors and is likely to have biological causes.

Jan Walters and colleagues from University of California, University of Southern California and Children's Hospital Los Angeles hypothesised that pregnancy may cause shifts of the cervicovaginal cytokine profile that may increase the risk of infection.

Using a multiplex assay, the investigators compared concentrations of 39 immunodulatory factors in cervicovaginal lavage from 21 pregnant and 24 non-pregnant HIV negative women attending ob/gyn clinic. They measured cervical ectopy (an independent risk for HIV transmission) by planimetry. They used the same multiplex assay to determine plasma CCL22 concentrations.

They found 26/39 (66%) measured immunomodulatory factors were detectable in at least half of the tested samples. Concentrations of CCL22 were 3-fold lower in cervicovaginal lavage in pregnant women than non-pregnant women (geometric mean 30 pg/mL vs 90 pg/mL, p=0.001).

They observed a strong negative correlation of the cervicovaginal lavage CCL22 concentration with gestational age (Spearman's rank correlation coefficient  $-0.49$ ,  $p=0.0006$ . Non-pregnant women were assigned a gestational age of zero.

No other tested factors were associated in adjusted analysis.

The investigators concluded that pregnancy appears to result in reduced concentrations of the HIV suppressive cytokine CCL22 in cervicovaginal secretions, which could contribute to the increased susceptibility to HIV during pregnancy. They suggested that their hypothesis should be tested in prospective studies.

#### Reference

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## First results from telaprevir in HIV/HCV coinfection

### Simon Collins, HIV i-Base

The most important study relating to hepatitis C coinfection was the late-breaker presentation of interim results from the first study using the HCV NS3/4A serine protease inhibitor telaprevir in people with HIV/HCV coinfection.

Community pressure led to earlier studies of the newest HCV drugs in people with coinfection than would have occurred otherwise, so the results are keenly awaited. Even though PEG-interferon and ribavirin are still required, there is hope that new treatments will improve response rates, especially in people with HCV genotype-1, and reduce duration of treatment. Telaprevir has already shown impressive responses in HCV mono-infection in both naïve and experienced patients.

Mark Sulkowski from Johns Hopkins School of Medicine, Baltimore presented initial results from a phase 2a study of coinfecting patients with HCV genotype 1a/b, where some people were on HAART (part B, CD4 >300, viral load <50) and others were not (part A, CD4 >500 and viral load <100,000). Limited data about interactions between telaprevir and antiretrovirals limited choice of HAART to tenofovir/FTC plus either efavirenz or atazanavir/ritonavir. People using efavirenz used a higher telaprevir dose. [1]

In this 48-week study all participants used pegylated IFN- $\alpha$ 2a (180 mg/week) plus ribavirin throughout. Ribavirin was dosed at 800mg/day in the US and but five patients at European sites used weight-based dosing (1000 mg/day if under 75 kg and 1200 mg/day if >75 kg). The randomisation in each group was to telaprevir 750 mg every 8 hours vs placebo for the first 12 weeks of the study.

Interim results were presented for 59/60 people who have so far enrolled (n=13 in part A ; n=46 in part B), with 12-week results available for 41 people. In part B roughly half the group used efavirenz and half used atazanavir/r.

The study also included detailed stopping rules at weeks 4, 8, 12, 24 and 36 for non-response or subsequent rebound based on HCV viraemia in order to limit the risk of developing resistance to telaprevir.

Baseline characteristics included: 88% male, 69% white, mean age 46 years, 68% genotype 1a, 83% baseline HCV RNA >800,000 IU/mL with 10% participants having advanced liver fibrosis based on biopsy.

Results were presented showing HCV viral suppression, at weeks 4 and 12. See Table 1. At week 4, by intent-to-treat analysis, approximately 70% (26/37) vs 5% (1/22) of people in the telaprevir vs placebo groups had undetectable HCV viral load. At week 12 these response rates were 68% (25/37) vs 14% (3/22) respectively.

**Table 1: Interim results using pegIFN + ribavirin plus telaprevir (TVR) or placebo (PCB) in HIV/HCV coinfecting patients**

N (%)	Part A: no ART		Part B: EFV/TDF/FTC		Part B: ATV/r + TDF + FTC/3TC		Total	
	TVR n = 7	PCB n = 6	TVR n = 16	PCB n = 8	TVR n = 14	PCB n = 8	TVR n = 37	PCB n = 22
Undetectable HCV RNA* at wk 4	5 (71)	0 (0)	12 (75)	1 (12)	9 (64)	0 (0)	26 (70)	0 (0)
Undetectable HCV RNA* at wk 12 <sup>#</sup>	5 (71)	1 (17)	12 (75)	1 (12)	8 (57)	1 (12)	25 (68)	3 (14)
Undetectable HCV RNA* at wks 4 and 12 <sup>#</sup>	3 (43)	0 (0)	10 (62)	0 (0)	6 (43)	0 (0)	19 (49)	0 (0)

\*determined by Roche Taqman v2, LLOQ of 25 IU/mL. <sup>#</sup>41 patients have reached week 12

Reponses in the HAART and no-HAART groups were similar and median trough levels of telaprevir were similar in the three groups. Variability in antiretroviral trough levels of efavirenz, atazanavir and tenofovir were similar to placebo.

Three people in each of the telaprevir and placebo groups were stopped early for failure to meet minimum viral responses or viral breakthrough.

HIV viral load remained stable for patients on HAART but reduced by approximately one log in the no-HAART group due to the anti-HIV action of interferon that has been previously reported.

Most patients experienced side effects, as would be expected from interferon/ribavirin treatment. Side effects reported more often in the telaprevir arm compared to placebo included nausea (35 vs 15%), pruritis (35 vs 5%), dizziness (32 vs 5%), anorexia and vomiting (both 19 vs 9%) and moderate rash (11 vs <1%). Severe rash was not seen.

There were 3 grade 3/4 events, all in the telaprevir arm: 2 bacterial infections and one case of anaemia. The two discontinuations of all drugs were for anaemia and jaundice (both in the atazanavir and telaprevir arm).

Based on this limited interim analysis, these very early responses in small groups of people with coinfection appear to show similar efficacy for people with coinfection compared to HCV mono-infection, with an indication that treatment can be used with HAART.

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#### Webcast

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## HCV reinfection rates in HIV-positive gay men

Simon Collins, HIV i-Base

Several research groups that highlighted the increased rates of sexual HCV transmission in HIV-positive gay men have also included reports of reinfection with HCV after achieving successful HCV treatment.

In a cohort of 62 HIV-positive men from the Netherlands, Thomas and colleagues compared HCV genetic samples obtained during initial acute HCV infection to the last available sample (median time 2.1 years; IQR 0.5–3.8). Of the 58 patient with successful samples expanded in the NS5B gene, HCV genotype switches were found in 10 people: genotype 1a to 4d (n=4), 4d to 1a (n=3), 1a to 3a (n=1), 3a to 1a (n=1) and 4a to 4d (n=1). [1]

HVR1 sequences (which allow for clade comparison within genotypes) were successfully expanded in 37/48 people without a genotype switch and showed that reinfection with the same genotype occurred in two people (one with genotype-1a and one genotype-4d).

The researchers concluded that “reinfection occurred frequently in this group of patients: in 12 of 58 (21%) a different virus was detected at the end of follow-up than the initial virus”. The study also suggested that partial immunity against re-infection with the same genotype might exist in HIV-positive people.

In a second poster from the same group, Femke Lambers and colleagues looked at rate of HCV reinfection in HIV-positive men in Amsterdam who had achieved sustained virological responses (SVR) to HCV treatment. Of 26 people who became PCR-negative, maintained for two months, six were reinfected. One person was excluded from the analysis because his genotype was unknown. Total follow-up time in these 25 people was 35.5 years; median follow-up 1.1 years (IQR 0.4 to 1.9). The median time between test intervals was 2.9 months (IQR 1.6 to 4.1).

This led to an incidence of HCV reinfection in this group of 16.9 /100 person-years (95%CI 6.9 to 35.2), which is approximately 10-fold higher than HCV infection rates in HIV-positive men who have not previously been infected with HCV.

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## ANTIRETROVIRALS

### London HIV Consortium issues new guidelines for ARV prescribing

Simon Collins, HIV i-Base

The London HIV Consortium, the pan-London commissioning group for HIV services, has just outlined the results of the tender process for purchasing HIV drugs for the next two years. This is part of an ongoing process to manage the HIV budget within government-imposed restrictions on NHS budgets. Over two years the group is faced with having to make savings of approximately £10 million to manage the same service on a budget that has not increased in line with inflation.

This will change the way that some HIV drugs will be prescribed in London. Although there are circumstances where the choice of

when to use each drug has changed, all drugs will still be available for different situations.

Initially the changes mostly affect the choice of treatment for people who are starting treatment. Most people who are currently on stable treatment will not be asked to change treatment. However, some people on stable treatment will be asked to switch one or more of their current drugs.

The main changes are:

- More people starting treatment will start with a combination of two pills rather than one pill once a day.
- Some people on current treatment will be asked to change to a similar alternative treatment.

This policy for broadly influencing prescription practice has been part of London drug commissioning for many years.

The details of these changes are explained below.

Cost is the principal reason behind the changes. Widespread cuts across the NHS include nearly all services. HIV is no different to any other service in this respect. Prescribing the most cost effective treatment first will help protect other aspects of HIV services. HIV treatment is also very individual. Treatment will continue to be individualised for each person's circumstances.

### **Outline of 2011 process**

This year the Consortium changed the process of purchasing drugs. This required drug manufacturing companies to tender bids for the costs of their drugs for a range of clinical settings, for example for first-line therapy or for first treatment failure etc. This process has taken several months. It has involved input from doctors from the leading HIV hospitals, pharmacists and community advocates.

The tender included the option for a sliding scale of costs if larger quantities are used.

The principles for this process are important:

- No drug will be excluded from being prescribed. The range of individual patient responses makes it likely that in some circumstances there will be a clinical need for some people to use different combinations to those recommended.
- The guidelines for use of treatment are supported by evidence. The decisions were not determined just by the cost of a drug. The decision on accepting a drug tender are dependent on them being effective and reducing the risk of side effects. The cheapest drugs were not selected if they were not as effective or had greater side effects. This process will not result in widespread use of less effective drugs simply because they are priced cheaply. However, where two options are broadly similar but have a significant difference in costs, the less expensive drug will be preferred.
- These measures are being taken due to financial constraints being imposed throughout the NHS. If HIV care does not respond by providing the cost-effective treatments, then cuts are more likely to be made in other HIV services: reduced clinic time, fewer doctors and nurses, shorter appointments and reduced monitoring.

All manufacturers had the opportunity to modify aspects of their bids to standardise them with other aspects of the tender process, especially in relation to the staggered price related to the volume of drugs purchased.

These budget estimates are dependent on reaching projected target volumes for each drug, including maintaining current drugs levels for some existing drugs. In order to reach or maintain these targets over the year, every London clinic will be working to the same guidelines. Although a clinic can prescribed outside these guidelines the drug costs for those patients will not be reimbursed by the London HIV Consortium.

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### **C O M M E N T**

**HIV care is faced with the challenge of being managed and maintained under the financial constraints being imposed on the NHS. This has to be done without jeopardising patient care and these guidelines have the potential to improve patient care in many cases.**

**An audit will track the outcomes from key treatment changes, initially at three-monthly intervals, to confirm that safety and efficacy is maintained.**

**These recommendations broadly fall within the BHIVA guidelines (though these have not been significantly revised since 2008), which include the importance of cost effectiveness when clinical data support several therapeutic choices.**

**HIV care remains one of the most cost-effective medical interventions. These proposed changes minimise disruptions to patient care, maintain access to high quality drugs and retain flexibility for individualised care.**

**Although this tender is for two years the clinical guidelines will be reviewed and changed if new research raises concerns about the clinical use of any of the preferred drugs.**

## What this means in practice

The recommendations for people starting treatment and people already on treatment and are summarised below.

### 1. Treatment-naïve patients

Preferred option:

- a) Efavirenz or nevirapine plus coformulated abacavir/3TC (Kivexa)

When there are clinical reasons not to use any of these drugs, alternatives can of course be used. This includes drug resistance, concern for side effects, shift work, pregnancy, high viral load (over 100,000 for abacavir) or high risk of heart disease (a greater than 10% risk over ten years, again for abacavir). If abacavir/3TC is not appropriate tenofovir/FTC is recommended.

Alternatives:

- a) Atazanavir/r is recommended as the first choice if efavirenz or nevirapine are not appropriate.
- b) Tenofovir/FTC is recommended when abacavir/3TC is not appropriate.
- c) Other drugs can be used when there is a clinical need. For example, alternative protease inhibitors can be used whenever these are clinically more appropriate.

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### C O M M E N T

**This main change for people starting treatment is that there will be more people using two pills a day rather than one. First-line treatment will still use once-daily combinations and number of daily doses is probably more important than daily pill count. All the recommended combinations are already widely used.**

In practice this should not be a significant problem for most people. Most people prefer one drug to two, but there are few studies that show it makes a difference to adherence or to clinical results. While the ease of use of single-pill formulations are popular, there are little data suggesting that one vs two pills daily has a poorer clinical outcome.

When there are clinical reasons to use alternatives, these will still be used. Common reasons not to use abacavir/3TC includes a higher risk of heart disease and a viral load >100,000 copies/mL when starting treatment (based on ACTG 5202). For a few people this might also include higher lipids as tenofovir/FTC has a better lipid profile than abacavir/3TC.

Atazanavir/r is already a widely used, once-daily protease inhibitor that is generally easy to tolerate and easy to modify in case of side effects. This has the potential to improve combinations, for example for people currently taking twice-daily protease inhibitors. Switching to alternatives, including back to the original treatment is possible at all stages if this is needed.

The commissioners already influence drug prescribing. Currently there are financial incentives for clinics to start at least 85% of new patients on NNRTI-based combinations using CQUINs (DoH Commissioning for Quality and Innovations). For 2011/12 clinics that do not broadly follow the new guidelines, threatening to derail the pan-London approach, will having their drug budget withheld entirely.

### 2. People currently on stable treatment

- a) Some people using protease inhibitor-based treatment that does not include atazanavir will be recommended to switch to using atazanavir-based combinations unless there is a clinical reason to stay on their current treatment. These reasons could include previous side effects and drug resistance. Only the protease component of the combination is being recommended to switch.

- b) People currently on NNRTI-based stable treatment are not being asked to switch. People currently using Atripla will not be asked to change from Truvada (tenofovir/FTC) to Kivexa (abacavir/3TC), although they do have this option. This decision may be reviewed in the future, but is unlikely to change in the short-term. This is dependent on clinics across London following the general guidelines for new and existing patients.

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### C O M M E N T

**The protease inhibitor switch may improve treatment for many people as this may include reduced doses and lower pill counts with some changes.**

The staggered approach to switching people who are stable on their current treatment is dependent on clinics across London following the general guidelines for new and existing patients.

These guidelines might also prompt a review to switch patients on older treatments that are not recognised as first choice options in BHIVA guidelines.

### 3. Use of raltegravir

Raltegravir will still be used predominantly by people with documented triple-class resistance. It can also be used in a limited number of other situations where there is a clinical need. This includes cases where a rapid reduction of viral load is important (for example HIV diagnosis in late pregnancy) or to avoid drug interactions (for example with chemotherapy). The higher cost of raltegravir compared to other first-line and second-line drugs is the reason behind this more restricted access.

Raltegravir can be prescribed by any doctor outside of these guidelines but the cost of the treatment will have to be paid by the hospital rather than by the London Consortium.

#### C O M M E N T

**Raltegravir was initially developed as a treatment for people with drug resistance. It was also priced higher as a life-saving drug rather than a treatment for standard therapy. Although the cost for raltegravir has come down it is still more expensive than alternative switching options. It is disappointing that the cost of raltegravir currently limits prescribing at any treatment stage as the potential advantages of raltegravir over protease inhibitors include reduced side effects such as less impact on lipids (cholesterol and triglycerides). The disadvantages of raltegravir include fewer long-term data as it is a newer drug, needing to use twice-daily dosing, and that previous drug resistance limits the ability to switch easily from a protease inhibitor to raltegravir. Several studies have shown an increased risk of treatment failure compared to staying on a protease inhibitor.**

#### Additional background

HIV-positive people will be able to discuss these proposals with their doctor. As with all treatment decisions, discussing options with the medical team is always recommended.

For many years, antiretroviral drugs have been bought on a pan-London basis by the London HIV Consortium as part of a way to deliver equity of care for HIV-positive people in all boroughs, independently of which London clinic they attend. Each year this group negotiates the price of each drug with each company.

While the process of drug pricing has a low profile amongst most people who use treatment, it is very complicated. The cost of a drug rarely is the same as its list price. This has led to many improvements in HIV care including greater prescribing consistency and access and use of the newest drugs. This group is focussed on the quality of care as it is on costs, and it has developed a range of services that have improved patient care.

For example, the same London HIV Consortium are responsible for establishing the New-Fill service to correct facial fat loss in NHS clinics in London. It has also helped maintain routine services by saving costs with other initiatives such as expanding home delivery of drugs (this saves VAT costs that are otherwise charged on hospital prescribed medicines).

By ring-fencing high cost drugs for people with most extensive drug resistance, this ensured equity of access to the most extensive treatment for people whose virus was most difficult to treat.

Simon Collins is a member of the London HIV Consortium Drug and Treatment Sub-Committee.

HIV i-Base receiving no funding from the London HIV Commissioners.

#### References and links

The London Consortium Drug Group included lead clinicians from London clinics, HIV-specialist pharmacists, community advocates, HIV-positive people and health commissioners. Document from the group will be posted online.

<http://www.londonspecialisedcommissioning.nhs.uk/>

A slide set summary of the recommendations in PDF and the Powerpoint files are available from the i-Base website.

<http://www.i-Base.info/changes-to-hiv-drug-prescribing-in-london>

## EMA issue restricted indication for d4T (stavudine)

### European Medicines Agency (EMA)

The European Medicines Agency has completed a review of Zerit as part of the procedure for the renewal of the medicine's marketing authorisation.

The Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended that the marketing authorisation for Zerit should be renewed but that the use of the medicine should be severely restricted in both adults and children.

In this context:

- Prescribers are reminded of the severe side effects seen with Zerit and should only use the medicine when other appropriate treatments are not available;

- Patients being treated with Zerit should be assessed frequently and switched to appropriate alternatives as soon as possible;
- Prescribers should consult the updated prescribing information and the communication letter that will be sent to them for more information;
- Patients should continue reporting any possible side effects to their doctor and should contact their doctor or pharmacist with any questions they have concerning their treatment.

Source: European Medicines Agency (EMA) (21.02.2011)

Reference: Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 14-17 February 2011

A questions and answers document referring to this matter can be found in the following link:

[http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500102227](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500102227)

## Changes to starting dose of saquinavir in naïve patients

Following the Dear Healthcare Professional communication in July 2010 regarding the association of saquinavir (Invirase) with arrhythmogenic risk due to prolongation of the QT and PR intervals, the European Medicines Agency have reviewed the consolidated pharmacokinetic and safety data for saquinavir. It is now recommended that for treatment-naïve patients initiating treatment with saquinavir/ritonavir, the starting dose of saquinavir is 500 mg (1 x 500 mg film-coated tablet) two times daily with ritonavir 100mg two times daily in combination with other antiretroviral agents for the first 7 days of treatment. After 7 days, the recommended dose of saquinavir is 1000 mg two times daily with ritonavir 100mg two times daily in combination with other antiretroviral agents.

The latest Summary of Product Characteristics for Invirase 500 mg film-coated tablets can be accessed through the electronic medicines compendium website:

<http://www.medicines.org.uk>

Source: Notification of the revised recommendation for the starting dose of Invirase 500 mg film-coated tablets in treatment-naïve patients.

Further information: Roche UK Medical Information on 0800 3281629 or Roche Ireland on (01) 469 0700.

## FDA approve nevirapine XR

On 25 March 2011, the FDA approved an extended release formulation of nevirapine XR (Viramune-XR) 400 mg extended release tablet.

The approval is based on one principal clinical trial (1100.1486) that demonstrated prolonged suppression of HIV-1 RNA through 48-weeks, and a supportive trial (1100.1526).

Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, nevirapine should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm<sup>3</sup> or in adult males with CD4+ cell counts greater than 400 cells/mm<sup>3</sup> unless the benefit outweighs the risk

The 14-day lead-in period with immediate-release nevirapine 200 mg daily dosing must be strictly followed; it has been demonstrated to reduce the frequency of rash.

If rash persists beyond the 14-day lead-in period with immediate-release nevirapine, do not begin dosing with nevirapine XR. The lead-in dosing with 200 mg once-daily should not be continued beyond 28 days, at which point an alternative regimen should be sought.

### C O M M E N T

**Filing in Europe for nevirapine XR has already taken place with a decision from the EMA expected in the third quarter of 2011**

Source: FDA list serve

The complete product label will be posted at:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

## FDA safety updates to antiretroviral labels

**The following summaries cover revisions to the US drug labels that were recently approved by the US Food and Drug Administration (FDA). Please check the full update for details.**

Revised labels are posted to the FDA website:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

### Lopinavir/r oral solution

On 24 February 2011, FDA approved changes to the Kaletra (lopinavir/ritonavir) Oral Solution product label related to toxicity in preterm neonates secondary to adverse events related lopinavir and/or the inactive ingredients propylene glycol and ethanol.

This label change was made after review of 10 postmarketing cases with life-threatening events reported in neonates (babies less than 4 weeks old) that received Kaletra oral solution. Postmarketing life-threatening cases included cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, central nervous system depression, and respiratory complications. Of the 10 cases, there was one death due to cardiogenic shock related to a large overdose of Kaletra oral solution.

Reduced metabolism by the liver and reduced kidney function in newborns can lead to an accumulation of lopinavir (the active ingredient), as well as alcohol and propylene glycol. Preterm babies may be at increased risk for health problems because they cannot metabolise propylene glycol; this could lead to accumulation and adverse events such as serious heart, kidney, or breathing problems.

The *Dosage and Administration* section 2.2 and the *Overdosage* section 10 were revised and a new *Warning and Precautions* was included to describe the toxicity in preterm neonates.

Please refer to the full label for details.

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Source: FDA listserve (24 Feb 2011).

Reference: Kaletra (lopinavir/ritonavir) oral solution label changes related to toxicity in preterm neonates.

<http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm244639.htm>

### Atazanavir use during pregnancy

On 4 February 2011, FDA approved new labeling for atazanavir (Reyataz) to include dosing recommendations for treatment of HIV-1 infection during pregnancy and postpartum period.

The major revisions to the package insert are summarised below. Other, minor changes to the package insert and patient package insert were made for consistency.

#### Dosing during pregnancy and the postpartum period

- Reyataz should not be administered without ritonavir
- Reyataz should only be administered to pregnant women with HIV-1 strains susceptible to atazanavir
- For pregnant patients, no dose adjustment is required for Reyataz with the following exceptions:

For treatment-experienced pregnant women during the second or third trimester, when Reyataz is coadministered with either an H2-receptor antagonist or tenofovir, Reyataz 400 mg with ritonavir 100 mg once daily is recommended. There are insufficient data to recommend a Reyataz dose for use with both an H2-receptor antagonist and tenofovir in treatment-experienced pregnant women.

No dose adjustment is required for postpartum patients. However, patients should be closely monitored for adverse events because atazanavir exposures could be higher during the first 2 months after delivery [See *Use in Specific Populations (8.1)* and *Clinical Pharmacology (12.3)*.]

#### Risk summary

Atazanavir has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that atazanavir does not increase the risk of major birth defects overall compared to the background rate. Nevertheless, because the studies in humans cannot rule out the possibility of harm, Reyataz should be used during pregnancy only if clearly needed.

Cases of lactic acidosis syndrome sometimes fatal and symptomatic hyperlactatemia have occurred in pregnant women using Reyataz in combination with nucleoside analogues. Nucleoside analogues are associated with an increased risk of lactic acidosis syndrome.

Hyperbilirubinemia occurs frequently in patients who take Reyataz, including pregnant women. All infants, including neonates exposed to Reyataz in-utero, should be monitored for the development of severe hyperbilirubinemia during the first few days of life.

#### Antiretroviral pregnancy registry data

As of January 2010, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 635 exposures to atazanavir-containing regimens (425 exposed in the first trimester and 160 and 50 exposed in second and third trimester, respectively). Birth defects occurred in 9 of 393 (2.3%) live births (first trimester exposure) and 5 of 212 (2.4%) live births (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between atazanavir and overall birth defects observed in the APR.

#### Clinical pharmacology in pregnancy

The pharmacokinetic data from HIV-infected pregnant women receiving atazanavir/ritonavir were included in Table 17 of the package insert.

Below is a summary of the data contained in the table. Limited data were available during 2nd trimester (n=5); whereas during the 3rd trimester and postpartum period 20 and 34 subjects, respectively were available.

- In the 2nd trimester the C<sub>max</sub>, AUC and C<sub>min</sub> values were 3078.85 ng/mL, 27657.1 ng·h/mL and 538.70 ng/mL, respectively.
- In the 3rd trimester the C<sub>max</sub>, AUC and C<sub>min</sub> values were 3281.46 ng/mL 34251.5 ng·h/mL and 668.48 ng/mL, respectively.
- During postpartum the C<sub>max</sub>, AUC and C<sub>min</sub> values were 5721.21 ng/mL, 61990.4 ng·h/mL and 1462.59 ng/mL, respectively.
- Atazanavir peak concentrations and AUCs were found to be approximately 28–43% higher during the postpartum period (4–12 weeks) than those observed historically in HIV-infected, non-pregnant patients. Atazanavir plasma trough concentrations were approximately 2.2-fold higher during the postpartum period when compared to those observed historically in HIV-infected, non-pregnant patients.

Please refer to the full label for details.

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Source: FDA listserve (04 Feb 2011).

Reference: Reyataz (atazanavir) label revised, adding dosing recommendations for pregnancy and postpartum period.

<http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm242383.htm>

### Nelfinavir interaction with warfarin

On 24 February 2011, FDA updated the nelfinavir (Viracept) label to include drug-drug interaction information between nelfinavir and warfarin.

Table 11 (Established and Other Potentially Significant Drug Interactions) of the *Precautions* section of the label was changed to add the following:

Coadministration of warfarin and nelfinavir may affect concentrations of warfarin. It is recommended that the INR (international normalised ratio) be monitored carefully during treatment with nelfinavir, especially when commencing therapy.

Please refer to the full label for details.

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Source: FDA listserve (24 Feb 2011).

Reference: Viracept (nelfinavir) Label change reflects drug-drug interaction information with warfarin

<http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm244619.htm>

## TREATMENT ACCESS

### FDA approval of generic ARVs

Since the last issue of HTB, the US Food and Drug Administration (FDA) has granted tentative approval for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
FTC (emtricitabine) 200 mg capsules	Cipla, India	29 March 2011
tenofovir/3TC 300 mg/300 mg FDC tablet	Cipla, India	04 March 2011
abacavir scored tablets for oral suspension, 60 mg	Cipla, India	04 March 2011
AZT 100 mg dispersible tablets (paediatric)	Matrix, India	23 February 2011
abacavir oral Solution, 20 mg/mL	Cipla, India	16 February 2011

FDC = Fixed Dose Combination.

“Tentative Approval” means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States. Tentative approval does, however make the product eligible for consideration for purchase under the PEPFAR program for use outside the United States.

Fixed Dose Combinations are reviewed for PEPFAR under the FDA guidance titled “Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously approved Antiretrovirals for the Treatment of HIV”. This document was developed to clarify what regulatory requirements apply to such applications, what issues might be of concern, and how these issues should be addressed. The guidance is intended to encourage sponsors to submit applications for combination and co-packaged products, and to facilitate submission of such applications to FDA.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf>

Effective patent dates are listed in the agency’s publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:

<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

An updated list of generic tentative approvals is available on the FDA website:

<http://www.fda.gov/oia/pepfar.htm>

Source: FDA list serve:

<http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

## Treatment access news

News summaries by Charlotte Walker and Polly Clayden.

### Global Fund reports rise in people on treatment

#### GFO Observer

By December 2010, programmes supported by the Global Fund were providing antiretroviral (ARV) treatment to 3.0 million people living with HIV, an increase of 20% compared to December 2009, according to data provided by the Fund. Global Fund-supported programmes were also providing directly observed therapy short course (DOTS) to 7.7 million people with TB, an increase of 28%; and had distributed 160 million insecticide-treated mosquito bed nets, an increase of 53%. In 2010 alone, 56 million bed nets were distributed. The number of malaria cases treated rose to 170 million in 2010 from 108 million in 2009, an increase of 77%.

As a result, the Global Fund says, more than 6.5 million lives have been saved. Each day, 4,400 deaths are averted.

Since the Global Fund started in 2002, programmes supported by the Fund have provided one million pregnant women with a complete course of antiretrovirals to prevent transmission of HIV from mothers to their children. In addition, 5.0 million basic care and support services have been provided to AIDS orphans and vulnerable children; 150 million sessions of HIV counselling and testing have been provided; and 2.7 billion condoms have been distributed.

The Global Fund says that it now provides one-fifth of international resources to fight AIDS, as well as 63% of international funding to fight tuberculosis and 60% of international funding to fight malaria.

Source: GFO Issue 142: 17 March 2011.

<http://www.aidspan.org/gfo>

## UK increases funding to the Global Fund

In February 2011 the UK Department for International Development (DfID) launched a report of their Multilateral Aid Review (MAR) which claimed the Global Fund to fight AIDS TB and Malaria (GFATM) to be 'very good value for money'.

Andrew Mitchell, the Secretary of State for International Development, has pledged that those organisations in the 'very good' bracket will get increased funding although the amount of funding that will be made available is still to be decided.

In 2010 The UK contributed \$313, 565,165.

### C O M M E N T

**In the last HTB we included an article from Global Fund Observer (?) reporting corruption within Global Fund. This had stopped funds to several African countries and had led to Germany pulling out of future funding commitments. However, this DfID report is leading a turn-around in the Global Fund's credibility.**

**The Global Fund, and indeed DfID, like to promote the GFATM's major success as "providing AIDS treatment to 3 million people". While this is good news and represents about half those on treatment it is important to remember that coverage far from meets need and 14.6 million remain in need of treatment now.**

References:

The DfID Multilateral Aid Review: Taking forward the findings of the UK MAR Report  
[http://www.dfid.gov.uk/Documents/MAR/Taking\\_forward.pdf](http://www.dfid.gov.uk/Documents/MAR/Taking_forward.pdf)

The Gloab Fund press release about the UK MAR:  
[http://www.theglobalfund.org/en/pressreleases/?pr=pr\\_110301](http://www.theglobalfund.org/en/pressreleases/?pr=pr_110301)

The Global Fund pledges and contributions spreadsheet:  
<http://www.theglobalfund.org/en/resources/?lang=en>

Treatment access statistics:  
<http://www.avert.org/universal-access.htm>

## UK government development priorities and HIV

In February 2011 DfID also published their Bilateral Aid Review (BAR) Country Summary report, which outlines what the UK will fund at individual country level and their key priority areas. The UK government have agreed to fund HIV programmes through large multilateral organisations such as the Global Fund but they have pulled out of funding HIV-related programmes at country level, at least until 2015.

This is not in line with a report launched by the House of Commons on World AIDS Day 2010, outlining the "Progress on the Implementation of DfID's HIV Strategy". One of the key recommendations in this paper stated: "Although we welcome the increase in access to anti-retroviral treatment, which has been achieved, it is a serious concern to us that the global commitment to provide universal access to treatment by 2010 will not be met. We urge DfID to expand its programmes to increase access to anti-retroviral treatment".

Progress has been made over the last 10 years with regards to provision of HIV services in developing countries and DfID have played a crucial role in this progress so far.

### C O M M E N T

**If DfID are to reduce their funding of HIV programmes to Global fund contributions only and not prioritise HIV at country level, it is difficult to see how they are taking the recommendations from the WAD paper forward.**

**Previous efforts need to be scaled up and built upon rather than scaled down and forgotten. HIV is intrinsically linked to other key DfID priority areas such as Malaria, TB, Maternal and Child Health, Wealth Creation and Poverty Reduction. Now there is evidence that treatment not only saves the lives of those already HIV-positive but can also reduce transmission of HIV, we should be concentrating UK resources to providing essential HIV services to those who need it.**

**It is important to act now, to lobby our MPs, write letters, ask questions and speak to local councilors about the importance of the UK's continued leadership on HIV at international, national and regional level.**

References:

DfID's Bilateral Aid Review (BAR) Country Summary report:  
<http://www.dfid.gov.uk/Documents/MAR/BAR-MAR-country-summaries-web.pdf>

House of Commons report on 'Progress on the Implementation of DfID's HIV Strategy':  
<http://www.publications.parliament.uk/pa/cm200910/cmselect/cmintdev/49/49i.pdf>

## Update on the Patent Pool

The Medicines Patent Pool was established in September 2010 by UNITAID and is now independent. It was created to make it simpler for generic manufacturers to produce low cost, effective HIV drugs. Both the US and UK governments support this initiative.

Since its launch it has made progress. Recently the project announced that Gilead, Roche, Sequoia and ViiV (Pfizer/GSK) have agreed to enter into negotiations regarding the licensing of their HIV drugs. This is a major step forward.

Prior to this, most companies took the position that allowing their medicines to be produced by specific generic manufacturers was sufficient to discharge their responsibility towards universal global access to treatment.

Whilst getting these companies to collaborate is a significant achievement, there is still much to be done.

Campaigners will now be focusing their lobbying on companies refusing to engage with the patent pool. This includes Abbott Laboratories, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck & Co. and Johnson & Johnson

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### C O M M E N T

In early April, students from the UK organisation STOP AIDS began protests at Johnson and Johnson HQ and at pharmacies across London as the start of a campaign to get the company to change its mind and start negotiations with the patent pool.

Johnson & Johnson's refusal to enter into talks is problematic as the US NIH has already reached agreement with the patent pool for the rights they own on darunavir. Johnson and Johnson own the remainder of the patent rights, so they will be blocking generic production of darunavir through the patent pool if they do not reconsider.

For this initiative to work it is critical that all the manufacturers of currently needed drugs are involved. Otherwise it is likely that treatment strategies will be driven less by medical priorities and more by which companies are prepared to negotiate the best deals.

References:

More information can be found at the following website:  
<http://www.medicinespatentpool.org/LICENSING/Company-Engagement>

ViiV Press Release:  
<http://www.viivhealthcare.com/media-room/press-releases/2010-07-16.aspx>

Details of the STOP AIDS campaign:  
<http://www.stopaidscampaign.org/poolparty>

## TRIPS agreement flexibilities provide opportunities for improved access to ARVs

On 15 March 2011, UNAIDS released a Policy Briefing highlighting the ways in which governments, particularly in developing countries, can use the TRIPS Agreement flexibilities and the subsequent Doha Declaration on the TRIPS Agreement and Public Health to overcome the changes to patent law which will come into effect in developing countries from 1st January 2016. By signing up to the TRIPS agreement, countries are losing their flexibility to authorise patents of varying lengths and are forced to patent all intellectual property rights.

The TRIPS Agreement flexibilities can be used to mitigate the impact on the production of generic drugs such as ARVs. They include:

- Compulsory licenses – these are mechanisms whereby governments or other public authorities can authorise the use of patent-protected inventions without the consent of the patent-holder, who will receive compensation royalties. Compulsory licenses can be granted based upon various grounds of interest such as public health as determined by the WTO Member themselves.
- Parallel imports – due to various market factors, companies are sometimes able to produce patented medicines at cheaper prices in certain countries. Developing countries can then buy the drugs at lower prices and import them rather than buying from domestic markets and having to pay high prices. Legally a patent can only control the price of sale within the country of manufacture. This means an intermediary could buy patented drugs in one country at a cheaper rate, import them to another country at a slightly higher price whilst still undercutting the domestic manufacturer. This is called 'parallel importing'.
- Bolar provision/regular exception - this is a mechanism whereby a patented product can be used without authorisation to obtain the generic marketing approval prior to patent expiry. This enables generic products to enter the market immediately after patent expiry.

- Exemptions for least developed countries – in November 2005 the WTO TRIPS Council extended the time at which least developed countries are mandated to comply with the TRIPS Agreement to 1st January 2016. This is subject to further extension upon request (Article 66.1 TRIPS Agreement)

The Doha Agreement states that the TRIPS Agreement “does not and should not prevent Members from taking measures to protect public health. Accordingly while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members’ right to protect public health and, in particular, to promote access to medicines for all.”

Several countries have begun to use the flexibilities outlined above to ensure access to cheaper generic ARVs. In 2006-2007 Thailand issued a compulsory license for efavirenz and lopinavir/ritonavir. This resulted in a tripling of the number of people using lopinavir/ritonavir despite outrage by multinational drug companies.

To enable countries which are already WTO Members to make use of the opportunities provided by TRIPS flexibilities, it is a pre-condition that they must first amend their national patent laws to incorporate the flexibilities. In 2007 a UNDP study showed that only 6 countries had incorporated the flexibilities into their legislation. A more recent study by WIPO on 142 countries revealed a vast disparity in the levels of inclusion of the TRIPS Agreement flexibilities both between countries and with regards to the different types of flexibility. For example of 112 countries with the information available, only 36 (32%) had laws allowing for with regards to parallel imports. Without these national legislative amendments, the TRIPS Agreement flexibilities will not be available for use, which in turn limits the opportunities for access to cheaper ARVs.

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## **Driving a decade of change: HIV/AIDS, patents and access to medicines for all**

**Ellen ‘t Hoen et al.**

An overview on global antiretroviral access since 2000 based on priced reductions driven by generic drugs, the threat from patent restrictions and the new Patent Pool initiative is available online from the IAS website.

*From the abstract summary:*

“Global trade rules agreed upon in 1994 required many developing countries to begin offering patents on medicines for the first time. Government and civil society reaction to expected increases in drug prices precipitated a series of events challenging these rules, culminating in the 2001 World Trade Organization’s Doha Declaration on the Agreement on Trade-Related Aspects of Intellectual Property Rights and Public Health. The Declaration affirmed that patent rules should be interpreted and implemented to protect public health and to promote access to medicines for all. Since Doha, more than 60 low- and middle-income countries have procured generic versions of patented medicines on a large scale.”

“Despite these changes, however, a “treatment timebomb” awaits. First, increasing numbers of people need access to newer antiretrovirals, but treatment costs are rising since new ARVs are likely to be more widely patented in developing countries. Second, policy space to produce or import generic versions of patented medicines is shrinking in some developing countries. Third, funding for medicines is falling far short of needs. Expanded use of the existing flexibilities in patent law and new models to address the second wave of the access to medicines crisis are required.”

Reference

Ellen ‘t Hoen et al. Journal of the International AIDS Society 2011, 14:15doi:10.1186/1758-2652-14-15.  
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## PRENANCY & WOMEN'S HEALTH

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### Lower incidence of pregnancy in HIV-positive compared to HIV-negative women in the Women's Interagency HIV Study

Polly Clayden, HIV i-Base

Data are scant describing the relationship between HIV and conception.

The Women's Interagency HIV Study (WIHS) is a multicentre US cohort of 3766 women with and without HIV. WIHS participants are broadly representative of HIV-positive women in the US. They are mostly African American and half live below the poverty line.

An analysis published ahead of print in AIDS, looked at the incidence of pregnancy and time to conception among women in this cohort between 2002 and 2009.

Women were eligible if they were 45 years or below, sexually active with male partners, or reported a pregnancy outcome within the past year, and never reported hysterectomy, tubal ligation or oophorectomy.

Overall, 1412 women were at risk from becoming pregnant during this time period. Of these, 941 (67%) were HIV-positive, and the remaining 471 (33%) were HIV-negative. During follow up, 456 women reported 766 pregnancies; 404 (53%) were among the HIV-positive women, and 362 (47%) the HIV-negative women. Interestingly, 192 pregnancies occurred at the same visit that hormonal contraception was reported.

The investigators found an overall incidence of pregnancy in this group of 1.2 (95% CI 1.1-1.3) per 100 person years.

After adjusting for age, parity, alcohol consumption, exchanging sex, number of male sex partners and contraception use in the past six months, being HIV-positive was associated with a 40% reduction in the rate of pregnancy, incidence rate ratio (IRR), 0.60 (95% CI 0.46-0.78). Also, it took 73% longer for HIV-positive women to get pregnant compared to HIV-negative women, relative time, 1.3 years (95% CI 1.35-2.36).

As would be expected, older age was also independently associated with a reduction in the incidence rate of pregnancy and the relative time to pregnancy was 30% longer in this group. Women with at least two sex partners in the past six months had a 28% lower pregnancy rate and 64% lower time to pregnancy compared to those with only one (this was despite reporting lower baseline prevalence of contraception, 25 vs 75%,  $p < 0.001$ ). Women with at least three previous births conceived the fastest and had an incidence rate of pregnancy that was more than 12 times higher than those with no prior births.

Importantly, among the HIV-positive women, women with a CD4 count of 350 cells/mm<sup>3</sup> or more had a significantly faster time to first pregnancy than those with lower CD4 counts,  $p < 0.0073$ .

#### Reference

Lin BS et al. Relative time to pregnancy among HIV-infected and uninfected women in the Women's Interagency HIV Study, 2002-2009. AIDS. 2011 Mar 13; 25(5):707-711  
<http://journals.lww.com/aidsonline/toc/2011/03130>

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## PAEDIATRIC CARE

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### Long-term outcomes for infants starting lopinavir/ritonavir at less than 6 months

Polly Clayden, HIV i-Base

World Health Organisation (WHO) and national guidelines recommend universal treatment with antiretrovirals for all HIV-infected infants.

Guidelines also recommend using protease inhibitor-based treatment for children exposed to single dose nevirapine through PMTCT.

Initiation of therapy is recommended as soon as possible but there are limited data to guide treatment of very young infants.

Ellen Chadwick and colleagues from IMPAACT P1030 showed data in AIDS, published ahead of print in February 2011, from a study designed to look at the pharmacokinetics (PK) and safety of the liquid formulation of lopinavir/ritonavir (LPV/r) in HIV-infected infants starting treatment between 2 weeks and 6 months of age.

This was a prospective, open label, phase I/II study of 31 children from 17 centres in the US and Brazil treated with a high dose (300mg LPV/75mg RTV/m<sup>2</sup> twice daily). Children were enrolled into two age groups: 14 days to 6 weeks and 6 weeks to <6 months. Children were followed until 48 weeks after the last child was enrolled.

The median duration of follow up was 123 (range 4-252) weeks. Ten (32%) children permanently discontinued the study including four before 12 months of age. Two discontinued after viral rebound to >50,000 copies/mL (weeks 43 and 176); three after parents refusal to attend study visits and/or give medication (weeks 2, 42 and 145), three had non-treatment related conditions (CMV resulting in death at week 8; failure to thrive due to severe food allergy at week 70 and severe iron-deficiency anaemia at week 120) and two because their research sites closed (weeks 73 and 120).

Intensive PK sampling was performed at in 26 children at 12 months of age, pre-dose and 2, 4, 8 and 12 hours after an observed dose. Of these, 20 children had evaluable results.

The investigators found, the median AUC of the two groups was comparable at 12 months of age (99.1 ug h/mL [IQR 82.4-124.5] vs 112 ug h/mL [IQR 95.0-148.8],  $p=0.93$ ). They also found a significant positive correlation of LPV trough concentration and age,  $p<0.0001$ .

By ITT analysis, at week 48, 22/31 (71%) children had a viral load <400 copies/mL; 6/10 in group 1 and 16/21 in group 2. Of these 11/15 (73%) on study treatment at 48 weeks had a viral load <50 copies/mL. Overall 29/31 (94%) children achieved a viral load <400 copies/mL while on study treatment and 19/29 (66%) children remained undetectable until the end of the study at a median of 123 (range 42-252) weeks. The children who sustained viral suppression had a higher percentage of predose time points at which concentrations exceeded the LPV target of 1 ug/mL (92 vs 71%),  $p=0.002$ .

The median baseline CD4 percentage was 35% (range 11-59%). There was a median increase of 4% (95% CI - 4 to 13%),  $p=0.12$ , among the 24 children with data available at 48 weeks and 23 (96%) had CD4 percentage >25%. Among the 19 children with follow up through 96 weeks there was a median increase of 8% (95% CI -2 to 13%),  $p=0.15$ .

The investigators noted that low LPV levels occurred at two weeks of therapy, with the lowest in infants <6 weeks of age. In this very young age group the median AUC was approximately half that seen in the older children >6 months of age. But these values were comparable between the two groups by 12 months of age and comparable to adults. They also noted that the LPV dose of 300mg/m<sup>2</sup> is higher than the currently recommended dose for children >6 months of age.

#### Reference

Chadwick EG et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS*, 25(6):767-776 (13 March 2011).  
<http://journals.lww.com/aidsonline/toc/2011/03130>

## Effects of antiretroviral exposure through PMTCT strategies on infants in Botswana

Polly Clayden, HIV i-Base

The effects of in antiretroviral (ARV) exposure through PMTCT on HIV-uninfected infants are poorly understood, particularly in resource-limited settings.

Two papers published in JAIDS report findings from sub-studies of the Mashi and Mma Bana randomised controlled PMTCT trials, both conducted in Botswana. [1, 2]

We have covered both these trials extensively in HTB, including early findings from these analyses reported at CROI 2010. [3]

### Increased severe anaemia risk with HAART

Scott Dryden-Peterson and colleagues conducted a post hoc analysis of pooled data from the trials. Infants were grouped by three ARV exposure categories: infants exposed to maternal HAART in utero and during breastfeeding and one month post natal AZT (HAART-BF); infants exposed to maternal AZT in utero and 6 months postnatal AZT during breastfeeding (AZT-BF); and infants exposed to AZT in utero and formula feeding (AZT-FF).

Overall, the investigators analysed data from 1719 infants (691 HAART-BF, 503 AZT-BF and 525 AZT-FF).

They observed severe incident anaemia (grade 3 or 4) in 118 (7.4%) infants from birth through 6 months of age. This occurred in 82 (12.5%) infants in the HAART-BF group, 25 (5.3%) in the AZT-BF and 11 (2.5%) in the AZT-FF groups. Severe anaemia was more frequent in the HAART-BF, group compared to infants in either of the other two groups: OR 2.53 (95% CI 1.59-4.04) and OR 5.96 (95% CI 3.14-11.3) vs AZT-BF and AZT-FF respectively, both  $p<0.001$ .

They noted that different frequency of assessment between the groups (AZT-BF group had haemoglobin measured monthly) could create potential bias. There was little evidence of this though, as they did not detect significant differences in the rate of treatment-modifying anaemia between birth, 1, 3-4 or 6-7 month visits among the study groups,  $p=0.15$ .

In multivariate analysis, besides HAART-BF exposure, which remained the strongest risk factor: gestational age, per week OR 0.89 (95% CI, 0.82-0.96)  $p=0.005$ ; male sex OR 1.53 (95% CI 1.03-2.27) and low maternal income <\$100 a month OR 2.04 (1.12-3.71)  $p=0.02$ , were all associated with severe incident anaemia. The investigators did not find an association with maternal BMI, CD4, viral load or haemoglobin. Nor was there an association with maternal HAART regimen or duration of antenatal HAART. Infants

who were small for their gestational age were not at greater risk of severe anaemia.

The majority of episodes of severe anaemia were resolved with multivitamin and iron supplements or stopping AZT but 11 infants from the HAART-BF group needed transfusion. Six infants died (1 HAART-BF, 2 AZT-BF and 3 AZT-FF), three of the infants had severe anaemia reported as cause of death. Two infants were lost to follow up before their severe anaemia was resolved.

Microcytosis and hypochromia occurred in 21.2% and 29.3% of incident anaemias with measurements available. Estimated haemoglobin iron at birth was lower for HAART-BF infants than the other two groups ( $p < 0.001$ ).

The investigators suggested these findings deserve further investigation and emphasised the established benefits of maternal HAART. They wrote: "Mitigating strategies such as iron supplementation to HIV-exposed breastfed infants or alternative antiretrovirals should be evaluated to maximise the benefits of maternal HAART while minimising potential risks."

### **Lower weight HAART-exposed infants catch up by 6 months**

Kathleen Powis and colleagues from the same group looked at the effects of in utero ARV exposure on longitudinal growth through 6 months of age in 619 HAART-exposed and 440 AZT-exposed uninfected infants from the two trials.

This was a retrospective analysis of infants carried to 37 weeks gestation or greater.

The investigators used WHO's Child Growth Standards to calculate z-scores for an infant's weight for age (WAZ), length for age (LAZ) and weight for length (WLZ).

They reported mean birth weights of 3.01kg and 3.15kg for HAART- and AZT-exposed infants respectively,  $p < 0.001$ . HAART-exposed infants had lower values for all three z-scores at birth, all  $p < 0.001$ .

HAART-exposed infants had greater improvement compared to AZT-exposed infants in WAZ from birth through 2 months,  $p = 0.03$ , but the investigators observed no difference in WAZ between the two exposure groups from 3 through 6 months,  $p = 0.26$ .

Similarly, LAZ increased more in the HAART-exposed infants through 2 months,  $p = 0.002$ , but this difference did not remain significant at 3 to 6 months,  $p = 0.08$ .

HAART-exposed infants also had a more rapid increase in WLZ through 2 months than AZT-exposed infants,  $p < 0.001$ . Between 3 and 6 months, the WLZ z-score in HAART-exposed infants declined while the AZT group had small increase. The difference in growth patterns between the two groups was significant,  $p = 0.04$ .

There was no difference in wasting or stunting between groups, which occurred in about 6% and 5% of infants overall respectively.

The investigators wrote: "This analysis is the first to provide reassurance that lower birth weight associated with in utero HAART exposure does not persist during early infancy. It also highlights the importance of early and routinely scheduled health care for HAART-exposed HIV-uninfected infants."

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1. Dryden-Peterson S et al. Increased risk of severe infant anaemia following exposure to maternal HAART, Botswana. *J Acquir Immune Defic Syndr*. Volume 56. Number 5. 15 April 2011.
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<http://i-base.info/htb/10238>

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## **DRUG INTERACTIONS**

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Recent updates to the Liverpool University drug interaction website.

### **No interaction between raltegravir and oral contraceptives**

#### **HIV-druginteractions.org**

A placebo-controlled, randomised, two-period crossover study in 19 healthy HIV-seronegative women was conducted to assess the effect of raltegravir (400 mg twice daily) on the pharmacokinetics of an oral contraceptive containing ethinylestradiol and norgestimate.

The geometric mean ratio (GMR) and 90% confidence interval (CI) for ethinylestradiol when co-administered with raltegravir relative to alone was 0.98 (0.93–1.04) for AUC and 1.06 (0.98–1.14) for C<sub>max</sub>. The GMR (90% CI) for norelgestromin (an active metabolite of norgestimate) when co-administered with raltegravir relative to alone was 1.14 (1.08–1.21) for AUC and 1.29 (1.23–1.37) for C<sub>max</sub>. There were no discontinuations due to a study drug-related adverse experience, nor any serious clinical or laboratory adverse experience.

Raltegravir had no clinically important effect on ethinylestradiol or norgestimate pharmacokinetics and no dose adjustment is required for oral contraceptives containing this combination when co-administered with raltegravir.

Source: [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org) (24 March 2011).

Ref: Anderson MS et al. Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women. *Br J Clin Pharmacol*, 2011, 71(4): 616-620.

<http://www.ncbi.nlm.nih.gov/pubmed/21395656>

## Case report: extreme bradycardia with lopinavir/ritonavir and metoprolol and lacidipine

### HIV-druginteractions.org

This case describes a patient stable on lacidipine, ramipril, levothyroxine, rosuvastatin, metoprolol and acetylsalicylic acid who developed extreme bradycardia (20-25 bpm) and hypotension (50/20 mmHg) 48 hours after starting HIV post-exposure prophylaxis (tenofovir, emtricitabine, lopinavir/ritonavir).

An electrocardiogram showed complete atrioventricular block (AV). The patient recovered a regular sinus rhythm after treatment with isoprenaline. Results of all diagnostic tests, including cardiac enzymes, complete blood cell count, electrolytes and tomography were normal. Lopinavir/ritonavir, lacidipine, ramipril and metoprolol were discontinued. Raltegravir was prescribed on day 4. Lacidipine, ramipril were re-instated on day 7 and metoprolol on day 9.

Blood concentrations were analysed approximately 12 h after the last dose of tenofovir/emtricitabine and 20 h after the last dose of lopinavir/ritonavir. Lopinavir, ritonavir, tenofovir and emtricitabine plasma concentrations were 8.40 mg/L, 0.29 mg/L, 0.059 mg/L and 0.12 mg/L, respectively. The lopinavir plasma concentration was higher than usual (3 to 7 mg/L); but the measurement was done only 3 days after treatment initiation while 2 weeks are required to see the maximal enzyme inducing effects of ritonavir. Tenofovir and emtricitabine plasma concentrations were in the normal range. Genetic analysis showed the patient to be an intermediate metaboliser for CYP2D6, a normal metaboliser for CYP3A4 and a low expressor of P-gp.

The authors propose that the AV block and the hypotension were primarily associated with co-administration of the lopinavir/ritonavir combination with metoprolol and lacidipine for the following reasons. First, the patient was asymptomatic while he started antiretroviral therapy. Second, discontinuation of lopinavir/ritonavir, lacidipine, ramipril and metoprolol, restored normal rhythm. Third, the re-introduction of lacidipine, ramipril and metoprolol without lopinavir/ritonavir induced no bradyarrhythmia.

Metoprolol undergoes  $\alpha$ -hydroxylation and O-demethylation by several CYPs (predominantly 2D6 but also 3A4). As the patient was an intermediate metaboliser for CYP2D6, the contribution of CYP3A4 to the total clearance of metoprolol could be increased. Hence inhibition of CYP3A4 by low dose ritonavir might have contributed to an increased metoprolol exposure. Lacidipine (a dihydropyridine calcium antagonist) is a CYP3A4 substrate. Co-administration of ritonavir with lacidipine, whose bioavailability is less than 50%, may increase exposure to lacidipine by inhibiting CYP3A4 and P-gp, resulting in hypotension.

This case raises several important points - HIV PEP has a strong potential for drug-drug interactions in patients with comorbidities requiring long term medications; these potential interactions have to be identified as they may lead to early near-fatal complications.

Source: [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org) (30 March 2011).

Ref: Puech R et al. Extreme bradycardia due to multiple drug-drug interactions in a patient with HIV post-exposure prophylaxis containing lopinavir-ritonavir. *Br J Clin Pharmacol*, 2011, 71(4): 621-623.

<http://www.ncbi.nlm.nih.gov/pubmed/21395657>

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## BHIVA NEWS

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### **CROI feedback workshops online**

An online webcast of the post-CROI BHIVA workshop held in London are now online. This is an excellent opportunity to see a review of this years conference summarized and discussed by leading UK doctors.

<http://www.bhiva.org/CROI2011London.aspx>

### **BASHH/BHIVA PEPSE guidelines for comment**

Draft UK national guideline on HIV PEPSE 2011 are available for consultation until 5th June 2011.

#### **UK GUIDELINE FOR THE USE OF POST-EXPOSURE PROPHYLAXIS FOR HIV FOLLOWING SEXUAL EXPOSURE**

Clinical Effectiveness Group, British Association for Sexual Health and HIV

Scope and Purpose:

The main objective is to ensure the appropriate use of post-exposure prophylaxis (PEP) following potential sexual exposure (PEPSE) to HIV as a potential method of preventing HIV infection.

This guideline offers recommendations on the potential use of PEPSE, the circumstances in which it may be recommended, the treatment regimens which may be recommended and the appropriate use of subsequent diagnostic tests to measure individual outcome. These guidelines are intended to be complementary to the existing DH/EAGA guidance on PEP.

It is aimed primarily at clinicians and policy-makers in sexual health, primary and emergency care within the United Kingdom who should consider the development of appropriate local pathways. It is likely that this guideline will be used by voluntary sector agencies in providing information for individuals who may potentially be exposed to HIV during sexual activity.

Comments should be sent to the CEG guideline lead Dr Keith Radcliffe, marked 'PEPSE':

[keith.w.radcliffe@hobtpct.nhs.uk](mailto:keith.w.radcliffe@hobtpct.nhs.uk)

<http://www.bashh.org/guidelines>

### **UK national guideline on safer sex advice**

The new UK National Guideline on Safer Sex Advice are online until 31 May 2011 for comments.

<http://www.bhiva.org/SaferSexAdviceConsultation.aspx>.

The objective of this document is to provide guidance for practitioners in Level 3 Genitourinary medicine (GUM) services (Level 5 in Scotland) on safer sex advice provided in sexually transmitted infection (STI) and HIV management consultations. The guideline consists of:

- Recommendations on the format and delivery of brief behaviour change interventions deliverable in GUM clinics
- Recommendations on the content of safer sex advice given to individuals at continued risk of STI
- Additional advice to be provided for those living with HIV, or from groups with higher rates of HIV incidence.

Much of the guidance is applicable in other sexual health and general practice settings, including HIV care services. The evidence base for the recommendations will be summarised in an accompanying on-line document. Issues relating to implementation of behaviour change interventions in clinics, such as designing service structures and care pathways or the competencies required in different multidisciplinary staff groups, are addressed in British Psychological Society Good Practice Guidelines.

The Clinical Effectiveness Group of BASHH and BHIVA is grateful for all comments, which will be reviewed before publication.

## BASIC SCIENCE

Updates on basic science from Richard Jeffery's excellent web blog.

### Continuing debate over the role of microbial translocation in HIV infection

**Richard Jefferys, TAG**

Several years ago, researchers led by Jason Brenchley and Daniel Douek at the National Institute of Allergy & Infectious Diseases published data suggesting an important role for microbial translocation in HIV pathogenesis. [1]

Microbial translocation is the leaking of normally friendly commensal bacteria from the gut – where they are usually contained – into the systemic circulation. Brenchley and colleagues proposed that this phenomenon contributes to immune activation in people with HIV, and thus plays a causative role in the progression of the disease.

Several subsequent studies have confirmed an association between markers of microbial translocation found in the bloodstream (e.g. the bacterial component LPS and bacterial DNA) and immune deficiency in people with HIV, including people with poor immune reconstitution on antiretroviral therapy (ART). [2]

However, these results have not ruled out the possibility that microbial translocation occurs as a result of HIV-induced immune deficiency, rather than playing a key role in causing it.

To try and gain a better understanding of the importance of microbial translocation in the pathogenesis of HIV infection, Daniel Douek has collaborated with researchers from the INSIGHT network to analyse samples from the Strategic Management of AntiRetroviral Therapy (SMART) trial. [3]

This trial randomised 5,472 people with HIV to either continuous or intermittent, CD4-guided ART, and the results showed that intermittent ART was associated with a doubling of the risk of illness and death compared to continuous treatment. [4]

During the study, 85 participants died, 142 developed major cardiovascular disease events, and 100 developed AIDS-defining events. Of these participants, 74, 120, and 81, respectively, had samples available.

Douek and colleagues used a case control study design to evaluate whether any of a suite of different markers of microbial translocation showed associations with these clinical outcomes. The same case control study design has previously been used to analyse the data from SMART, revealing a highly significant association between levels of inflammatory biomarkers and mortality. [5]

The biological markers assessed in the new study were: intestinal fatty acid binding protein (a marker of damage to cells of the gut wall called enterocytes), the bacterial product lipopolysaccharide (LPS), bacterial DNA (16S rDNA), anti-LPS antibodies (endotoxin core IgM antibody or EndoCAb) and soluble CD14 (sCD14). CD14 is a molecule expressed on monocytes that is known to be shed as a result of stimulation by LPS.

The only marker that showed a correlation with a clinical outcome was sCD14; higher levels were significantly associated with an increased risk of mortality. Levels of sCD14 also correlated with the inflammatory biomarkers that have previously been associated with mortality risk in SMART. The study authors offer a variety of possible reasons why other markers of microbial translocation were not associated with clinical outcomes, and argue strongly that elevated levels of sCD14 represent a consequence of microbial translocation (even though the other markers did not correlate with sCD14). There are, however, alternate possibilities that might explain elevated sCD14 levels that are not discussed in the paper. Specifically, alpha interferon has been reported to increase levels of sCD14, and levels of this cytokine are increased in HIV infection. [6]

Furthermore, a study published last year that looked for evidence of monocyte stimulation by LPS in HIV found that the gene expression patterns of these cells were more consistent with stimulation by alpha interferon, not LPS. [7]

So while Douek and colleagues write: "these observations are consistent with a model in which HIV infection causes ongoing damage to the gut mucosa, leading to increased microbial translocation, increased systemic inflammation, and increased mortality," this interpretation of the data seems debatable, as the elevated levels of sCD14 may not necessarily be explained solely by microbial translocation.

Coincidentally, the current issue of the Journal of Infectious Diseases includes a letter from several researchers (Andrew Redd, Ronald Gray and Thomas Quinn) highlighting the uncertainty regarding whether microbial translocation is a cause or consequence of HIV pathogenesis. They argue that the current evidence favors the view that "increased microbial translocation and LPS levels are a consequence of advanced HIV-1 disease and AIDS." The letter closes by stressing the need for additional longitudinal studies to fully resolve the issue. [9]

Source: TAG Basic Science Blog (08 Feb 2011).

<http://tagbasicscienceproject.typepad.com>

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## Jostling latent HIV from slumber

Richard Jefferys, TAG

A study in the new issue of the *Journal of Immunology* suggests that triggering a cell surface molecule called toll-like receptor 8 (TLR8) may be a means to activating latent HIV infection. [1]

Erika Schlaepfer and Roberto Speck report that, in vitro, targeting TLR8 with the drug resiquimod (aka R-848) prompted HIV activity in latently infected cells of myeloid-monocytic origin (which include monocytes, macrophages, dendritic cells, microglial cells, and hematopoietic stem cells) and also had an activating effect on HIV in latently infected CD4 T cells, by causing production of the cytokine TNF-alpha. The researchers took a very preliminary look at whether individuals on HAART might be able to respond to such an approach, and found that--solely based on TNF-alpha production--their monocytes reacted to TLR8 stimulation comparably to those from HIV negative controls.

The conclusion from the findings is that "TLR8 agonists, in combination with HAART, are intriguing compounds for purging HIV from its latent reservoirs and sanctuary sites." Schlaepfer and Speck caution, however, that "we believe that compounds, and, in particular, TLR8 agonists, acting on the latent reservoir should be given in cycles, because a longer-term administration of any such compound might be too toxic."

Resiquimod has been studied in humans with hepatitis C infection and appeared quite potent in terms of inducing alpha interferon production (and associated side effects). [2]

The manufacturer, 3M, does not appear to be developing it further but has recently offered it to the pharmaceutical industry for license. [3]

Development of a TLR7 agonist as a hepatitis C treatment was stopped in 2007 due to toxicology studies showing "intense immune stimulation in animals."

Source: TAG Basic Science Blog (23 Mar 2011).

<http://tagbasicsscienceproject.typepad.com>

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## Dubious analysis of a therapeutic tat vaccine trial

Richard Jefferys, TAG

Toward the end of last year, a group of Italian researchers led by Barbara Ensoli published some limited data from an ongoing trial of a therapeutic HIV vaccine [1], and issued a press release to draw attention to the paper. [2]

The resulting press coverage was generally favorable. Somewhat lost in the discussion of the results was the fact that they were obtained in an “ad hoc exploratory interim analysis,” which is generally considered to be a dubious and unreliable way to analyse trial data. The vaccine candidate contains the Tat protein from HIV-1, and Ensoli’s group has been developing it for many years now. The question of whether the approach has any potential has been controversial [3]; a macaque study suggesting protection against SHIV was not confirmed [4] and there have also been reports of disputes about the vaccine’s development among the Italian research community. [5]

In light of this background, trumpeting the results of an ad hoc exploratory interim analysis via press release seems an imprudent strategy for the researchers to pursue.

The trial described in the paper is not placebo controlled, which adds to the challenge of trying to interpret the results. Because there is no control arm, comparisons in the paper are made between vaccine recipients and HIV positive individuals enrolled in “a parallel prospective observational study at the same sites.” Most of the immunological analyses reported in the paper involve small subsets of the 87 participants, but it is not clear how these subsets were selected. The primary aim of the trial is to compare the immunogenicity (ability to induce anti-Tat immune responses) of two different doses and two different dosing schedules of the vaccine. The secondary aim is monitor safety. The trial protocol, which is included in the supporting information for the paper, does not make reference to the conduct of ad hoc exploratory interim analyses or their publication.

Amidst this sea of caveats, the researchers report that the higher vaccine dose was more immunogenic but no significant differences were apparent between the 3-dose and 5-dose immunisation schedules. The vaccine was also found to be generally safe and well tolerated. From these top-line results, the paper descends into murky sub-analyses suggesting that the vaccine may have decreased CD8 T cell activation, both increased and decreased in CD4 T cell activation (depending on the marker), increased regulatory CD4 T cells, increased CD4 T cells and B cells, decreased CD8 T cells and natural killer cells, and altered representation of different memory T cell subsets. None of the reported analyses are statistically corrected for the multiple comparisons being performed.

Although the suggestion that therapeutic vaccination might reduce immune activation in HIV is not unprecedented, there is a discomfiting gap between the murkiness of the methodology and the breezily conclusive title of the paper: “Therapeutic Immunisation with HIV-1 Tat Reduces Immune Activation and Loss of Regulatory T-Cells and Improves Immune Function in Subjects on HAART.” The only way to show whether the vaccine can achieve these outcomes is with a randomised placebo-controlled study. [6]

Source: TAG Basic Science Blog (24 Jan 2011).  
<http://tagbasicscienceproject.typepad.com>

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## Studies on the loss of naïve T cells

Richard Jefferys, TAG

A recent post covered a review by Beth Jamieson and Tammy Rickabaugh describing the parallel effects of HIV infection and aging on the pool of naïve T cells in humans. [1]

Three recent papers address different aspects of naïve T cell loss, including the first study to document a decrease in this population in people with chronic hepatitis C infection.

In PLoS One, Beth Jamieson's group reports on a study of naïve CD4 T cell levels in younger (20-32 years) and older (39-58 years) individuals with untreated HIV infection, compared to age-matched HIV-negative controls. [2]

The researchers use a cell surface marker named CD31 to discriminate between naïve CD4 T cells that have recently been produced by the thymus (CD31+) and those that have proliferated in the circulation (CD31-). Consistent with previous studies, HIV infection had a strong effect on naïve CD4 T cell levels that was additive to that seen in aging; the absolute number of CD31+ naïve CD4 T cells in the younger individuals mirrored those measured in HIV-negative controls who were 17-28 years older. While both HIV infection and aging were associated with declines in CD31+ naïve CD4 T cell numbers, loss of CD31- naïve CD4 T cells was only observed HIV infection; in this case the effect was independent of aging as the absolute loss was similar in both the younger and older HIV-positive participants. In a separate longitudinal analysis of the effects of antiretroviral therapy, CD31+ naïve CD4 T cells achieved levels comparable to age-matched controls after two years of treatment. However, CD31- naïve CD4 T cell levels remained significantly reduced.

The researchers also evaluate telomere lengths in both naïve CD4 T cell subsets, finding them to be reduced both as a result of HIV infection and aging; as was seen for CD31+ naïve CD4 T cell numbers, the effects were additive. Jamieson and colleagues conclude by suggesting that their results likely explain why disease progression occurs more rapidly among HIV-positive individuals over the age of 50, because this older population already has reduced numbers of naïve CD4 T cells, making the impact of HIV infection more severe. They also note that incomplete recovery of naïve CD4 T cells may play a role in increasing the risk of aging-associated diseases in people with HIV.

One commonly cited causative mechanism of naïve T cell depletion in HIV is the persistent activation of these cells, which leads to their differentiation into memory cells. Another contributing factor is lymphoid tissue fibrosis (a type of scarring damage associated with immune activation & inflammation). Naïve T cells continually recirculate through lymphoid tissue and depend on signals received in that environment for their survival.

A recent study by Ming Zeng and colleagues delves into this link between lymphoid tissue fibrosis and naïve T cell loss in both SIV and HIV infection. [3]

The researchers find that fibroblastic reticular cells (FRC)--which form the pathways along which T cells travel in lymph nodes--are the major source of IL-7, a cytokine essential for naïve T cell survival. Fibrotic damage (measured by the accumulation of collagen) is shown to disrupt the FRC network and therefore impede the ability of T cells to access IL-7, causing an increase in T cell apoptosis. Both naïve CD4 and CD8 T cells are affected. Additional studies reveal that the loss of T cells in turn exacerbates the damage to FRCs by reducing the production of a cytokine called lymphotoxin- $\epsilon_2$ , which is vital for maintaining FRC networks. The results suggest that there is a vicious cycle in which fibrosis damages FRCs, which causes T cell loss, which then further exacerbates FRC loss.

Continuing their investigative work, Zeng et al look for a source of collagen and find that production of the cytokine TGF-beta by regulatory T cells is increased in HIV, and TGF-beta induces collagen production by fibroblasts. In lab experiments, the antifibrotic drug pirfenidone blocks TGF-beta signaling and reduces collagen production, leading the researchers to conclude that this drug may deserve consideration as an adjunctive therapy for promoting immune reconstitution in HIV.

Lastly, a study published in the 1st March issue of the Journal of Infectious Diseases demonstrates that another persistent chronic infection, hepatitis C, can accelerate naïve CD4 T cell loss. The authors conclude that their findings provide an explanation for the reduced response to vaccinations observed in people with chronic HCV. [4]

Source: TAG basic science blog (17 Mar 2011)  
<http://tagbasicscienceproject.typepad.com>

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## **Intensifying treatment does not reduce HIV reservoirs, but gut immune responses may have a role to play**

**Richard Jefferys, TAG**

A study led by Hiroyu Hatano from Steve Deeks's group at UCSF reports that adding the integrase inhibitor raltegravir (Isentress) to a standard antiretroviral (ART) regimen failed to reduce residual HIV replication, or the HIV reservoir, in a group of individuals with suboptimal CD4 count increases despite prolonged HIV suppression. The intensification approach also did not significantly increase CD4 T cell counts or reduce levels of immune activation, which the authors note adds to the evidence that low-level HIV replication is unlikely to be a major cause of suboptimal CD4 T cell gains in people on ART. [1, 2]

Interestingly, a secondary analysis--conducted in collaboration with Barbara Shacklett's laboratory at UC Davis--revealed a novel association between the magnitude of HIV Gag-specific CD8 T cell responses in gut-associated lymphoid tissue (GALT) and the size of the HIV reservoir (as measured by proviral DNA in peripheral blood mononuclear cells). Hatano and colleagues caution that the findings are preliminary and require confirmation by larger studies, but also write: "approaches aimed at expanding HIV-specific CD4+ and CD8+ T cell responses in the gut mucosa may accelerate clearance of the viral reservoir. The next logical step would be to pursue therapeutic vaccine studies using HIV vaccines that elicit strong mucosal T cell responses in HAART-treated patients."

Coincidentally, a paper that appeared online today in the journal *Blood* describes an approach to augmenting HIV-specific CD8 T cell immunity in GALT. [3]

The researchers sampled HIV-specific CD8 T cells from individuals on ART, expanded them in the laboratory, and then re-infused them. Persistence up to 84 days was documented, as well as trafficking to GALT. Many of the cells displayed a "central memory" phenotype, which is believed to be important due to the ability of these cells to self-renew and proliferate robustly upon encountering antigen. Although the infusion approach has practical limitations, the study authors suggest that their results imply that vaccination strategies aiming to boost systemic and GALT HIV-specific CD8 T cell responses are worth pursuing.

Source: TAG basic science blog (21 Mar 2011)

[http://tagbasicscienceproject.typepad.com/tags\\_basic\\_science\\_vaccin/2011/03/intensifying-treatment-does-not-reduce-hiv-reservoirs-but-gut-immune-responses-may-have-a-role-to-pl.html](http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2011/03/intensifying-treatment-does-not-reduce-hiv-reservoirs-but-gut-immune-responses-may-have-a-role-to-pl.html)

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## **OTHER NEWS**

### **Global scientific strategy towards an HIV cure**

#### **IAS press release**

On 28 February 2011, more than 30 scientists gathered for a one-day meeting prior to the 18th Conference on Retroviruses and Opportunistic Infections (CROI) to launch an international working group on HIV reservoirs and strategies to control them.

Under the auspices of the International AIDS Society, the scientists will guide the development of a global scientific strategy 'Towards an HIV Cure'. The strategy aims at building a global consensus on the state of the HIV reservoirs field and defining scientific priorities that must be addressed by future research to tackle HIV persistency in patients undergoing antiretroviral therapy, the key hurdle impeding any alternative to long-term therapy. This global scientific strategy will help mobilise and focus resources to fund the most promising strategies towards either eradication or a functional cure, and stimulate international research collaborations.

The international scientific working group will be co-chaired by Professor Françoise Barré-Sinoussi, International AIDS Society (IAS) President-elect and 2008 Nobel Laureate for Medicine, and Professor Steve Deeks, University of California, San Francisco (UCSF) and Positive Health Program (AIDS Program) at San Francisco General Hospital. The working group will work closely with an advisory board composed of leading advocates and major research stakeholders in HIV cure, including representatives of people living with HIV, funders and clinicians from high prevalence settings. The advisory group will be co-chaired by Pr. Françoise Barré-Sinoussi and Dr. Jack Whitescarver, Director of the Office of AIDS Research at the National Institutes of Health.

This initiative comes on the back of the successful workshop 'Towards a cure: HIV Reservoirs and strategies to Control Them' held in conjunction with the 18th International AIDS Conference (AIDS 2010) in Vienna in July 2010. [1]

Source: IAS press release. Scientists unite to develop global scientific strategy towards an HIV cure. (28 February 2011).

Reference:

1. 'Towards a cure': HIV reservoirs and strategies to control them. 16–17 July 2010, Vienna. Powerpoint presentations and abstracts along with rapporteur summaries are posted online.

<http://www.iasociety.org/Default.aspx?pageId=349>

## Online European clinical trials registry

### EU press release

Public online register gives access to information on clinical trials

The EU Clinical Trials Register ([www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)) was launched on 23 March 2011 by the European Medicines Agency. The online register gives for the first time public access to information on interventional clinical trials for medicines authorised in the 27 EU Member States and Iceland, Liechtenstein and Norway. The database also allows the public to search for information on clinical trials authorised to be carried out outside the EU if these trials are part of a paediatric investigation plan.

The information contained in the EU Clinical Trials Register is extracted from EudraCT, the EU clinical trials database. It is provided by the sponsor of the clinical trial, and is a component of its application to a national medicines regulatory authority for authorisation to conduct a trial. The information from the sponsor is loaded into the EudraCT database by the national medicines regulatory authority. The authority adds to this information the authorisation of the clinical trial and the opinion from the relevant ethics committee. Information on third country trials that are listed in a Paediatric Investigation Plan (PIP) is provided by the PIP addressee directly, via the EMA, to the system.

Throughout the project the Agency worked together with stakeholders, including patients and healthcare professionals, to ensure that their needs were taken into account, to the extent possible at this stage, when designing the register.

The Agency will continue to work with stakeholders to improve the functioning of the EU Clinical Trials Register, in particular by enhancing the quality and completeness of data, and improving the search functionality. Plans for the future also include the publication of summaries of clinical trial results, on which draft guidance has already been published for consultation by the European Commission. Publication of trial results summaries will require a major upgrade to the existing system, the start of which will depend on finalisation of the guideline and availability of budget and resources.

The details in the clinical trial description include the:

- design of the trial;
- sponsor;
- investigational medicine (trade name or active substance identification);
- therapeutic areas;
- status (authorised, ongoing, complete).

Unfortunately the EU Clinical Trials Register website does not:

- provide information on the results of clinical trials;
- provide information on non-interventional clinical trials of medicines (observational studies on authorised medicines);
- for the period May 2004-March 2011 provide information on clinical trials where investigator sites are outside of the European Union and the European Economic Area. (However, information on clinical trials which are part of an agreed paediatric investigation plan (PIP) and were conducted outside the European Union and the European Economic Area will be published retroactively on the website by March 2012.);
- provide access to the authorisation document from the national medicine regulatory authority or the opinion document from the relevant ethics committee;
- provide information on clinical trials for surgical procedures, medical devices or psychotherapeutic procedures;

- manage the process for joining any clinical trial published on the website;
- provide navigation and web content in languages other than English.

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C O M M E N T

**This development by the European Medicines Agency (EMA) on interventional clinical trials on medicines is an important first step in this resource for European patients.**

**Treatment advocacy is severely restricted when even a basic registry of ongoing studies is not mandatory. Transparency in ongoing research is an issue of public safety.**

Source: EU press release. European clinical trials registry now online. (21 March 2011).

Links:

The EU clinical trials register is at:  
<https://www.clinicaltrialsregister.eu>

Information on EudraPharm:  
<http://eudrapharm.eu/eudrapharm>

Information on EudraCT  
<https://eudract.ema.europa.eu/>

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ON THE WEB

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*Guidelines:*

Sexually Transmitted Diseases Treatment Guidelines, 2010 Centers for Disease Control and Prevention, MMWR December 17, 2010; 59(RR12):1-110.

[http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5912a1.htm?s\\_cid=rr5912a1\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5912a1.htm?s_cid=rr5912a1_w)

*Community resources and publications:*

**TAG hepatitis C pipeline report**

Tracy Swan's 2011 Hepatitis C Treatment Pipeline Report produced by the Treatment Action Group in New York is a must-read. This clear concise and comprehensive overview of research shows that hepatitis C treatments in 2011 have a similarly dramatic potential as HAART had for HIV in 1996.

Issues covered include diagnostics, drug resistance, access to, and delivery of treatment, and population-specific focus on the new HCV drugs, as well as research recommendations.

FDA approval of two hepatitis C-specific protease inhibitors, the first of the coming wave of oral antiviral drugs, is anticipated later this year. Dozens of other drugs are in development.

Download

<http://cts.vresp.com/c/?TreatmentActionGroup/b5f575334e/9e21c20d7a/9ae5755cb4/id=4416>

*Free journal articles:*

**Evidence for the innate immune response as a correlate of protection in human immunodeficiency virus (HIV)-1 highly exposed seronegative subjects (HESN).**

Tomescu C et al. Clinical & Experimental Immunology. Published online: 17 March 2011. DOI: 10.1111/j.1365-2249.2011.04379.x  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2249.2011.04379.x/full>

The description of highly exposed individuals who remain seronegative (HESN) despite repeated exposure to HIV-1 has heightened interest in identifying potential mechanisms of HIV-1 resistance. HIV-specific humoral and T cell-mediated responses have been identified routinely in HESN subjects, although it remains unknown if these responses are a definitive cause of protection or merely a marker for exposure.

Approximately half of HESN lack any detectible HIV-specific adaptive immune responses, suggesting that other mechanisms of protection from HIV-1 infection also probably exist. In support of the innate immune response as a mechanism of resistance, increased natural killer (NK) cell activity has been correlated with protection from infection in several high-risk cohorts of HESN subjects, including intravenous drug users, HIV-1 discordant couples and perinatally exposed infants.

This review highlights the most current evidence in HESN subjects supporting the role of epithelial microenvironment and the innate immune system in sustaining resistance against HIV-1 infection.

The authors argue that as a front-line defence the innate immune response determines the threshold of infectivity that HIV must overcome to establish a productive infection.

### **Effectiveness and cost effectiveness of expanding harm reduction and antiretroviral therapy in a mixed HIV epidemic: a modeling analysis for Ukraine**

Alistar SS et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000423>

A cost-effectiveness study by Sabina Alistar and colleagues evaluates the effectiveness and cost effectiveness of different levels of investment in methadone, ART, or both, in the mixed HIV epidemic in Ukraine.

### **A randomised controlled trial comparing the effects of counseling and alarm device on HAART adherence and virologic outcomes**

Chung MH et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000422>

Michael Chung and colleagues show that intensive early adherence counseling at HAART initiation resulted in sustained, significant impact on adherence and virologic treatment failure, whereas use of an alarm device had no effect.

### **HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis**

Zeh C et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000430>

Analysis of a substudy of the Kisumu breastfeeding trial by Clement Zeh and colleagues reveals the emergence of HIV drug resistance in HIV-positive infants born to HIV-infected mothers treated with antiretroviral drugs.

### **Triple-antiretroviral prophylaxis to prevent mother-to-child HIV transmission through breastfeeding—the Kisumu breastfeeding study, Kenya: a clinical trial**

Thomas TK et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001015>

Timothy Thomas and colleagues report the results of the Kisumu breastfeeding study, Kenya, a single-arm trial that assessed the feasibility and safety of a triple-antiretroviral regimen to suppress maternal HIV load in late pregnancy.

#### *Medical online resources:*

## **HIV InSite Knowledge Base**

**HIV neuroretinal disorder and ageing** - Professor Mark Jacobson

<http://hivinsite.ucsf.edu/InSite?page=md-expert-jacobson>

**Hepatitis B and HIV Coinfection**

<http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-03-04>

**Hepatitis C and HIV Coinfection**

<http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-03-05>

**Immunisations and HIV Coinfection**

<http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-03-01-08>

## FUTURE MEETINGS

### 2010–11 conference listing

*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.*

15th International Workshop on HIV Observational Databases

24–26 March 2011, Prague

<http://www.hivcohorts.com>

17th Annual BHIVA

6–8 April 2011, Bournemouth

<http://www.bhiva.org>

12th International Workshop on Clinical Pharmacology of HIV Therapy

13–15 April 2011, Miami, Florida

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

6th International Workshop on HIV Transmission - Principles of Intervention

14–15 July, Rome, Italy

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

13th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV

14–16 July 2011, Rome, Italy

<http://www.intmedpress.com>

3rd International Workshop on HIV Paediatrics

15–16 July, Rome, Italy

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

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011)

17–20 July 2011, Rome

<http://www.ias2011.org/>

2nd International Workshop on HIV & Ageing

October 2011, Baltimore, USA

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

4th Annual BHIVA Conference for the Management of HIV / Hepatitis Co-infection

16 November 2011, London (venue tbc)

<http://www.bhiva.org>

BHIVA Autumn Conference including CHIVA Parallel Sessions

17-18 November 2011, London

<http://www.bhiva.org>

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## PUBLICATIONS & SERVICES FROM i-BASE

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### **i-Base website**

The i-Base website has been completely redesigned with new portals for healthcare professionals, HIV-positive people and community advocates.

It is even faster and easier to access, use and navigate.

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

All i-Base publications are available online, including editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Board (UK-CAB), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

The site also includes a web-based Q&A section for people to ask questions about their own treatment:

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

RSS news feed has been introduced for HIV Treatment Bulletin for web and PDA access - we welcome your feedback on this new way to provide treatment updates.

A section on Education, Advocacy and Training includes our training manual for advocates with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 100,000 pages individual ISP accounts contact i-Base.info each month, with over 6000 hits a day.

### **Training manual – revised, updated and now fully online**

This established training resource has been revised and updated and is now online in new format.

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

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

Additional support material is included on how to understand aspects of science that might be new to a lay reader.

<http://www.i-base.info/manual/en/index.html>

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to antiretrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. Clinical trial design and the role of advocates

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

### **Generic clinic forms**

We have also posted online a set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.

These PDF files include record sheets to track CD4 and viral load results, cardiovascular risk, hepatitis, first patient visit, patient

update, day case and summary notes.

<http://i-base.info/category/publications/clinic-forms>

Please contact the i-Base office if you would like help adding your own hospital or Trust logo to these forms.

## **Report assessing the treatment information needs African people in the UK living with HIV**

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

<http://i-base.info/home/africans-and-treatment-information>

## **i-Base Book: “Why we must provide HIV treatment information”**

### **Photography by Wolfgang Tillmans**

i-Base has worked as a treatment literacy project for over six years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A meeting, held in Cape Town earlier focused on how to raise the profile of treatment literacy. One result from the meeting is a publication “Why we must provide HIV treatment information”.

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

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

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting since 2002. It now includes over 300 members from over 100 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. Membership is free,

<http://www.ukcab.net>

## **World CAB - reports on international drug pricing**

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online.

Both are available to download as a PDF file from the i-Base website.

## **i-Base treatment guides**

i-Base produce five 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 (July 2010)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment: what to do when your treatment fails (February 2011)
- Guide to HIV, pregnancy & women’s health (January 2009)
- HIV and your quality of life: guide to side effects and long-term complications (December 2010)

## **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.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on all information.

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

**Languages currently include:**

Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian and Spanish.

## Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

## 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 10 times a year in a printed version, in a PDF file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

## 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.

## ARV4IDUs

An electronic publication, produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

## Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

## Online Q&A service

***An online 'question and answer' service that now has over 1400 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).***

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

**Recent questions include:**

- Is it a blip or are my medicines not working?
- If my partner has an undetectable viral load can I get HIV?
- We are both positive, can we have a negative baby?
- My husband is undetectable, can he still infect me?
- Will London guidelines mean I have to change treatment?
- When should I start treatment?
- Is it normal to come out in spots when starting HIV treatment?
- Can I take thrush treatment with my ARVs?
- When should I start treatment?
- Would taking darunavir monotherapy mean I have 9 hours a day without active medication?

- My viral load is quite low, could it be that I am not infected?
- I have a high viral load and my headache is getting worse
- Will my CD4 count increase now I am on treatment?
- If my CD4 count is 1295, does it mean I no longer have HIV?
- I am changing from Truvada and efavirenz to Atripla, will I get lipodystrophy?
- Can I take 5HTP with my meds?
- My ex is negative, could I have got HIV from him?
- My CD4 count has gone down quickly should I be worried?
- Will cosmetics interact with my HIV meds?
- Is there research on waking sleeping cells?
- I don't want to take treatment, how can I increase my CD4 count?
- I am losing weight, is it because of my smoking?

### Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

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

Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), HTB South, Treatment 'Passports' and all our guides to managing HIV and additional reports.

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## ***h-tb***

### **HIV Treatment Bulletin**

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:

<http://www.i-Base.info>; by fax or post using the form on the back page by sending an email to: [subscriptions@i-Base.org.uk](mailto:subscriptions@i-Base.org.uk)

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HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

Some articles are reproduced from other respected sources and copyright for these articles remains with the original authors and sources, as indicated at the end of each article.

We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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## HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

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If your employer operates a Give-As-You-Earn scheme please consider giving to I-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit [www.giveasyouearn.org](http://www.giveasyouearn.org)

### REFUNDS FROM THE TAX MAN

From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

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