

# HIV treatment bulletin

## S O U T H

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## htb south

HIV Treatment Bulletin

HTB is a quarterly journal published in electronic format by HIV i-Base.

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## EDITORIAL

Welcome to the third of HTB South and thank you to all those of you who have given us nice feedback on the first two issues! As we go to press we have just returned from the 16th Conference on Retroviruses and Opportunistic Infections in Montreal.

We have included two excellent pregnancy studies from Botswana in this issue and expect a big splash in HTB South number four.

We also include reports from the 9th International Congress on Drug Therapy in HIV Infection, held in Glasgow, and articles from some of our favourite websites including Richard Jefferys' basic science blog and the University of Liverpool's HIV drug interaction site.

HTB South is supported by the Monument Trust.

### Southern African HIV Clinician's Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinician's Society has grown to a membership of over 15 000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

The Southern African HIV Clinician's Society is the largest special interest group within the South African Medical Association (SAMA). It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

For more information about the Society or on how to become a member please visit:

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## CONFERENCE REPORTS

### 16th Conference on Retroviruses and Opportunistic Infections

8-11 February 2009, Montreal

#### Introduction

The Conference on Retroviruses and Opportunistic Infections (CROI) is held annually in North America and is the most important scientific conference in HIV. This year's meeting was no exception and the proportion of research from non-industrialised settings continues to grow and we have included a couple of excellent pregnancy studies from Botswana in this issue. Our next issue will contain our full reports, including new research on maternal health and mother to child transmission, TB, paediatrics new drugs and strategies, aging and side effects.

In the meantime this conference has an excellent website that includes webcasts of the oral presentations, abstracts and posters:

<http://www.retroconference.org/2009>

### High rates of HIV acquisition in pregnancy and post partum in Francistown, Botswana

Polly Clayden, HIV i-Base

In an oral presentation Lydia Lu from the CDC showed worrying findings from a study of HIV incidence during pregnancy and the first post-partum year (in which the majority of women breastfed) among women in Francistown, Botswana [1].

Dr Lu explained that women are routinely tested for HIV in Botswana at a median of 22 weeks gestation. However, this strategy may fail to identify women with acute infection in the window period or infection acquired after testing. Maternal seroconversion during pregnancy or breastfeeding greatly increases the risk of mother to child transmission.

The study included women with a documented negative HIV test during pregnancy: 400 on maternity wards, and 400 attending immunisation clinics with infants age 9-15 months.

To calculate the number of women infected post testing and in turn paediatric infections, the study investigators assumed a total of 43,000 annual births in Botswana and a 32.4% HIV prevalence, giving 29,068 women whose first ante natal clinic (ANC) test is negative. The transmission rate for mothers receiving prevention of mother to child transmission (PMTCT) interventions in Botswana is currently 4.7%. Using data previously reported describing very high rates among women seroconverting during pregnancy and breastfeeding, receiving no intervention, they assumed rates of 73% and 36% respectively among post partum transmissions [2].

Rapid testing and counselling were conducted in accordance with local guidelines, and HIV-positive women were referred for HIV care, PMTCT, and infant testing. Women tested on maternity wards (n=400) had a median interval of 17 weeks from their

negative test and those attending immunisation clinics with available data (n=244) a median of 62 weeks (with infants of a median age of 11 months).

Dr Lu reported HIV incidence of 5/400, 1.3% (95% CI, 0.5-3.1%) among women tested on maternity wards and 7/244, 2.9% (95% CI 1.3-5.6) at immunisation clinics.

The investigators calculated an overall HIV incidence of 1.8% at one year (see table 1).

**Table 1: Calculation to estimate incidence at 1-year post partum**

Incidence	(2.9-1.3)	1.6%	1.8%
Weeks	(62-17)	45 weeks	52 weeks

They then estimated, of 43000 pregnant women in Botswana in 2007, 13932 (34.7%) were diagnosed during ANC and the remainder, 29068 (65.3%), assumed to be HIV negative. Of this group 378 (1.3%) would be infected during pregnancy and 450 (1.8%) while breastfeeding.

A transmission of 4.7% among 13932 women would result in 620 HIV-positive infants. A transmission rate of 73% among 378 women infected in pregnancy would result in 276 HIV-positive infants; and of 36% among 450 women infected 1-year post partum would result in 186. Therefore they estimated incident cases of maternal HIV to account for 462/1082 (43%) of infant infections.

The investigators concluded: "In this mature and successful PMTCT programme, new and undetected maternal infections may be causing nearly half of infant infections." They offered a number of recommendations including: better prevention strategies; routine re-testing; identification of the most appropriate intervention in pregnancy (start HAART?) and the safest infant feeding for women with new infections while breastfeeding.

#### C O M M E N T

**These data, while sobering, provide one of the most important messages from this conference and the investigators must be congratulated for such a clear analysis.**

**Previous reports from other settings have revealed transmissions that are most likely attributed to maternal seroconversion. In a survey of mothers and infants at 6-month immunisation in KwaZulu-Natal, Rollins et al reported a group of women (7.6%), having tested HIV-negative during the antenatal period but with HIV antibodies identified in the dried blood spots of their infants and 31.2% of these infants were infected [3]. The investigators suggested that these women may have been in the window period at the time of their HIV tests or they may have been infected during pregnancy. And among the 54 infants born to undiagnosed women reported in the Perinatal Transmission Survey of HIV in England, at least 20% were born following maternal seroconversion during pregnancy [4].**

**The significant question is, of course, what to do about it? To which, as yet, there is simply no straightforward answer. The investigators suggest better prevention strategies, but coy discussions about "husbands" that we heard following the presentation are unlikely to be very effective. Some have suggested that this would be a potential useful role for PrEP.**

**Re-testing is an obvious answer, but when? Too early and the risk of seroconversion remains, too late and the efficacy of PMTCT interventions decrease and earlier in utero infection will be missed.**

**It is unclear what was meant by, “better infant feeding”. Avoiding breastfeeding completely for all women? But the same group last year showed scary mortality findings from a group of formula fed infants in the PMTCT programme in Francistown, when the water became contaminated [5].**

**This issue provides a big obstacle to prevention of paediatric HIV.**

References

1. Lu L, Legwaila K, Motswele C et al. HIV Incidence in Pregnancy and the First Post-partum Year and Implications for PMTCT Programs, Francistown, Botswana, 2008. 16<sup>th</sup> Conference on Retroviruses and Opportunistic Infections 2009. Montreal. Abstract 91.
2. Humphrey JH et al. Mother to child transmission among Zimbabwean women who had their primary HIV infection during pregnancy or while breastfeeding. 16<sup>th</sup> International AIDS Conference. Toronto. 2006.
3. Rollins N, Mzolo S, Little K et al. HIV prevalence rates amongst 6 week old infants in South Africa: the case for universal screening at immunisation clinics. 16<sup>th</sup> International AIDS Conference, 2006, Toronto. Abstract THAC0104.
4. Perinatal transmission of HIV in England 2002-2005. October 2007. Download from CHIVA website (last accessed February 26<sup>th</sup> 2009)  
<http://www.chiva.org.uk/publications/PDF/2007/perinatal.pdf>
5. Creek T, W Arvelo W, Kim A et al. Role of infant feeding and HIV in a severe outbreak of diarrhoea and malnutrition among young children, Botswana, 2006. 14th Conference on Retroviruses and Opportunistic Infections, 2007, Los Angeles. Abstract 770.

**Risk factors for adverse pregnancy outcomes in Botswana**

**Polly Clayden, HIV i-Base**

It is unclear whether the use of highly active antiretroviral treatment (HAART) in pregnancy is associated with adverse outcomes and data from resource-limited settings are particularly lacking.

A poster authored by Jennifer Chen, Roger Shapiro, and co-workers from Botswana and the USA showed results from a prospective review of obstetrical records of women who delivered at 20 weeks or greater in four facilities in Botswana between October 19, 2007 and June 30, 2008.

This study particularly evaluated stillbirths, preterm delivery (<37 weeks gestation) (PTD), low birth weight (<2500g) (LBW), small for gestational age (SGA) and neonatal death.

The investigators found 5676 recorded birth outcomes, of which 5327 (94%) women had a documented HIV test. Among those with an HIV test, 1629 (30.6%) had a positive result.

The investigators observed high overall rates of: still birth, 2.7% and 3.6%; PTD, 20.6% and 27.3%; LBW, 13.5% and 20.4%;

SGA, 19.4% and 23.8% and neonatal death, 1.9% and 2.7% in HIV negative and positive women respectively.

Of the HIV positive group, 146 women received no antiretrovirals (ARV); 471 received AZT; 112 initiated HAART and 127 continued HAART from prior to the current pregnancy. Median CD4 counts were 283 cells/mm<sup>3</sup> for those receiving no ARV and 417 cells/mm<sup>3</sup>, 266 cells/mm<sup>3</sup> and 378 cells/mm<sup>3</sup> for women who initiated AZT, initiated HAART, and continued HAART from prior to the current pregnancy respectively.

The majority of women initiated on HAART or AZT did so at 28 weeks gestation, so the investigators noted that they were unable to capture early pregnancy outcomes comparing these groups.

CD4 cell count was lower among women who received HAART (p<0.0001).

The investigators found in multivariate analysis, HAART was associated with SGA and possibly with stillbirths, and this association remained after adjustment for CD4 cell count (See table 1).

**Table 1: Multivariate analyses of HIV positive women**

Risk factor	Stillbirth	PTD	SGA
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
HAART continued vs all others*	2.0 (0.9, 4.4)	1.2 (0.8, 1.9)	<b>1.8</b> <b>(1.2, 2.8)</b>
HAART initiated vs AZT initiated by 30 weeks	3.7 (0.9, 15.6)	1.2 (0.6, 2.7)	<b>2.8</b> <b>(1.4, 5.7)</b>
HAART continued vs HAART initiated**	--	--	0.7 (0.4, 1.2)

\* All others includes positive women on no ARV intervention and those who later initiated ARVs.

\*\*Multivariate analyses that compared women who continued HAART with those who initiated HAART were not performed for the outcomes stillbirth and preterm delivery, since women who continued HAART had more opportunities for events in pregnancy.

The investigators also found anaemia to be associated with PTD (p=0.0001) in HIV positive women, but anaemia was not associated with HAART use. However, they reported hypertensive complication at delivery was more common among women receiving HAART from prior to the current pregnancy (p=0.02) and was a risk factor for stillbirth, OR 7.2 (95% CI 3.8, 13.7), PTD, OR 1.7 (95%CI 1.3,2.4) and SGA, OR 2.1 (95% CI 1.4, 3.0). They suggest that this may be a potential explanation for some associations between HAART and adverse outcomes.

They wrote, “High risk obstetrical and neonatal care need to be prioritised in Botswana to address the large number of HIV-infected pregnant women with increasing access to HAART for treatment and PMTCT.”

**C O M M E N T**

**These data add to the accumulating evidence that HAART in pregnancy may be associated with adverse outcomes and re-emphasise the importance of Phase 4 studies. Importantly they**

come from the region of the world where ARVs will be most widely prescribed in pregnancy. Understanding the mechanisms and determining whether these events are substance-specific or part of the spectrum of immune reconstitution will help policy makers and healthcare workers to make decisions about therapy.

Botswana is planning a pilot of universal HAART for 50,000 HIV-positive pregnant women, which is expected to generate important large-scale outcome data.

#### Reference

Chen J, H Ribaud H, Ogwu et al. A et al. Risk Factors for Adverse Pregnancy Outcomes among HIV-infected Women in Gaborone, Botswana. 16<sup>th</sup> CROI. Abstract 949.

## CONFERENCE REPORTS

### 9th International Congress on Drug Therapy in HIV Infection

9-13 November 2008, Glasgow

#### Introduction

The Glasgow conference, held every two years, has now produced webcasts from many of the lectures and these are online, together with the conference abstracts.

Abstracts and webcasts can be accessed via the congress website at the following link:

<http://www.hiv9.com>

Abstracts are also online as a supplement to the Journal of the International AIDS Society 2008.

<http://www.jiasociety.org/supplements/11/S1>

The following reports from the conference are included in this issue of HTB South:

- Summary of antiretroviral studies at Glasgow
- The Antiretroviral Pregnancy Registry: individual drug safety reports on health of infants exposed to ARVs during pregnancy
- Initial results from PENTA 11 trial of planned treatment interruptions in children
- Inflammation and coagulation markers askew in children with higher HIV RNA
- Dosing of lopinavir/ritonavir in the CHIPS cohort
- Number needed to treat to harm (NNTH) analysis of impact of underlying cardiovascular factors on risk of abacavir-related heart attack
- Bone disease and HIV
- Renal tubule damage with tenofovir despite normal glomerular function

### Summary of antiretroviral studies at Glasgow

#### Simon Collins, HIV i-Base

The following short summaries cover some of the new research presented on current and pipeline antiretrovirals.

Please see abstract links for further details of each study.

#### Unboosted atazanavir as maintenance treatment in naïve patients

JF Delfraissy presented results from a 48-week study that randomised 252 treatment-naïve patients after a 26-30 week induction phase of boosted atazanavir/r 300/100mg plus 2 RTIs, to either continue or switch to once-daily unboosted atazanavir

(400mg) plus continued RTIs. Only patients suppressed to <50 copies/mL were randomised to switch. Tenofovir was not allowed as an RTI because of the negative drug interaction with atazanavir.

Of 252 patients at baseline (median CD4 245 cells/mm<sup>3</sup>; median HIV-RNA 4.95 logs), 30 discontinued (nine for side effects) and 50 failed to reach undetectable viral load and continued on boosted ATV/r. This left 172 patients who were randomised 1:1 to either ATV or ATV/r.

At week 48, the ATV arm demonstrated similar (non-inferior, margin 15%) efficacy with 78% and 86% of patients suppressed to <50 and <400 copies/mL respectively, compared to 75% and 81% of patients who remained on boosted ATV.

CD4 responses were similar. Although there were more discontinuations prior to week 48 with boosted atazanavir (14% vs 8%), fewer patients on ATV/r experienced virological rebound (7 vs 11). None had emergence of PI resistance.

As expected, side effects favoured unboosted ATV: grade 3–4 total bilirubin in 47% vs 14% and mean percent triglyceride change from the switch to week 48 was +9.8 vs. -27.0, both for ATV/r & ATV, respectively.

#### C O M M E N T

**The balance between maintaining suppression and improved tolerability may make maintenance treatment without ritonavir an option for some naïve patients who have tolerability difficulties, but this will also reduce the safety buffer zone for adherence times.**

Reference: Delfraissy JF et al. Efficacy and safety of 48-week maintenance with QD ATV vs ATV/r (both + 2NRTIs) in patients with VL <50 copies/mL after induction with ATV/r + 2NRTIs: study A1424136. 9th International Congress on Drug Therapy in HIV Infection. 9-13 November 2008, Glasgow. Abstract O415.  
<http://www.jiasociety.org/content/11/S1/O42>

#### **Darunavir/r vs lopinavir/r: 96-week resistance results from TITAN study**

The Phase 3 TITAN study has previously reported superiority of darunavir/r (DRV/r) compared to lopinavir/r (LPV/r), with 67.5% vs. 59.5% patients achieving <400 copies/mL (difference 8%, 95% CI 0.1–15.8, p=0.03), in almost 600 treatment-naïve patients.

Virological failure was higher in the LPV/r arm (25.6%, n = 76) was higher than in the DRV/r arm (13.8%, n = 41).

Primary PI mutations were found in 25/72 of LPV/r and 7/39 for DRV/r patients with matched resistance results (with darunavir/r V32I occurred in three patients, I47V and L76V in two patients and M46I, I54L, I54M and L90M in one patient).

NRTI mutations occurred in 20/72 the LPV/r arm compared to 4/39 in the DRV/r, with similar proportions of patients losing phenotypic sensitivity to the study protease inhibitor. The majority of patients failing darunavir/r retained susceptibility to other PIs: amprenavir (31/31), atazanavir (29/30), indinavir (31/32), LPV (33/33), nelfinavir (24/26), saquinavir (31/31) and tipranavir (34/35). Susceptibility to the background NRTIs (20/55 vs. 4/35) or any NRTI (27/66 vs. 7/38) was also reduced in significantly more lopinavir/r patients.

#### C O M M E N T

**The differences between darunavir/r and lopinavir/r suggest a greater potential role for darunavir/r, and once-daily darunavir/r has recently been approved in Europe. The retained phenotypic sensitivity to second-line protease options is encouraging, but this will need confirmation with clinical results.**

Reference: De Meyer S et al. Resistance development in virological failures with DRV/r or LPV/r: 96-week analysis of the Phase III TITAN trial in treatment-experienced patients. 9th International Congress on Drug Therapy in HIV Infection. 9-13 November 2008, Glasgow. Abstract O424.

<http://www.jiasociety.org/content/11/S1/O46>

#### **Apricitabine 48 week results**

Final 48 week results were shown from a Phase 2b study of apricitabine (ATC), a new cytidine analogue similar to 3TC, in approximately 40 treatment-experienced patients with resistance to 3TC (at baseline, 52% of patients had ≥3 thymidine mutations and 76% had ≥1 non-NRTI mutation). At week 24 all patients switched to the higher dose 800mg ATC.

By week 48, around 90% patients achieved viral suppression <50 copies/mL in all arms. CD4 increases were ~ +260 cells/mm<sup>3</sup> in the ATC arms vs +200 cells/mm<sup>3</sup> in the 3TC arm. No significant ATC-related SAEs were reported.

Reference

Cahn P et al. 48-week data from Study AVX-201 - A randomised phase IIb study of apricitabine in treatment-experienced patients with M184V and NRTI resistance. Abstract O414.

<http://www.jiasociety.org/content/11/S1/O41>

#### **The Antiretroviral Pregnancy Registry: individual drug safety reports on health of infants exposed to ARVs during pregnancy**

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

In an oral presentation Karen Beckerman described the role of the Antiretroviral Pregnancy Registry (APR) and presented the latest analysis of compiled data. [1, 3]

The APR is an international registry, started in 1989, to prospectively monitor potential birth defects in infants exposed to antiretrovirals in utero. It is one of the largest ongoing pregnancy registries in the world.

The objectives of the registry are to provide early warning of major teratogenicity; estimate risk of birth defects and collect supplementary data from animal, clinical and epidemiological studies. Data collection is through voluntary enrollment by healthcare providers of pregnant women exposed to antiretrovirals, and in turn infant follow up.

This analysis looked at the ability to detect, at 80% power with Type I error rate of 5%, potential increases in birth defect prevalence in infants following first trimester exposure (during which organogenesis occurs), vs. second and third trimester exposures.

The registry has sufficient numbers of reports to detect a 2-fold increase in overall anomalies following exposure to abacavir, atazanavir, efavirenz, FTC, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, d4T and tenofovir. For AZT and 3TC there are sufficient numbers of reports to detect a 1.5-fold increase in such anomalies.

Dr Beckerman presented data from 1989 to 31 July 2008. The majority of reports (88.2%) are from the US, with small numbers from elsewhere (eg UK 3.1%, SA 1%). One of the current goals of the registry is to increase non-US reporting.

During this period 11,950 pregnancies were enrolled. Of these 494 (4.1%) were awaiting outcome and 985 (8.2%) were lost to follow up. There were 10471 evaluable pregnancies; 47% were exposed to antiretrovirals during the first trimester.

9,948 (93%) live birth outcomes were available for analysis. Among this group Dr Beckerman reported an overall prevalence of defects of 2.7% (271/9,948) 2.9% (126/4329) from pregnancies with earliest antiretroviral exposure in the first trimester vs. 2.6% (145/5618) with second and third trimester exposures.

APR continues to monitor two drugs that in the past met criteria for evaluation and further monitoring: AZT was associated with an increased risk of hypospadias among infants in the Women and Infants Transmission Study (WITS), and the registry found a higher than expected, 4.4% (94/3068), defect prevalence following first trimester of ddI exposure that has no apparent pattern and is not statistically significant. Notably, defect prevalence for efavirenz exposures were, 3.2% (13/407) ie not elevated above background population risk, and were no different from first and second/third trimester exposure to any other antiretroviral.

#### C O M M E N T

**A major recent change in the APR has been the inclusion of data from the Women and Infants Transmission Study (WITS). A higher than expected incidence of hypospadias in babies exposed in utero to AZT is reported in these data, and, when added to the individual prospective reports to the register, AZT is associated with an increased risk of hypospadias. However, this association is not found when the WITS data are excluded. It is difficult to explain this discrepancy.**

**Data from the European Collaborative Study, which are summarised in the APR reports, but not included in the analysis, do not suggest any association between AZT and hypospadias.**

**The higher rate of congenital anomalies with ddI has been documented in the APR for a number of years without attracting much attention, in part due to the lack of association with a specific defect (as compared with efavirenz). However, the overall rate has steadily reduced over several years; there have been fewer reports of congenital malformations associated with ddI in recent years. It should be noted that the APR has not examined rates of congenital malformations with specific combinations (which are legion) but one explanation of the trend is that ddI is no longer prescribed with other ARVs that increase the risk of congenital malformations.**

**As in all previous reports from the APR the overall risk of congenital malformation in babies exposed during the first trimester to efavirenz is not increased. One case of spina bifida has been reported in the**

**prospective arm of the study but it is not possible to know whether this reflects an increased risk or is a chance observation.**

**Finally, it is important to note the paucity of data on all newly licensed antiretroviral therapies. These should be prescribed with caution in all women of childbearing potential, regardless of stated family planning intent.**

**A brief overview of use of antiretrovirals in pregnancy is included in the current issue of the Southern African Journal of HIV Medicine (in which HTB South is included as an insert).**

#### References

1. KP Beckerman, D Covington, K Dominguez et al. Antiretroviral Pregnancy Registry (APR) at 10,000 prospective reports. 9th International Congress on Drug Therapy in HIV Infection. 9-13 November 2008, Glasgow. Abstract 0223. <http://www.jiasociety.org/content/11/S1/O22>
2. Watts DH, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. *Journal of Acquired Immune Deficiency Syndromes: JAIDS* 2007, 44(3):299-305.
3. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2008 Wilmington, NC: Registry Coordinating Center; 2008. <http://www.APRRegistry.com>

## Initial results from PENTA 11 trial of planned treatment interruptions

**Polly Clayden, HIV i-Base**

Di Gibb presented findings from the PENTA 11 trial on behalf of the Paediatric European network for treatment of AIDS (PENTA).

PENTA 11 was a phase II randomised trial of antiretroviral treatment (ART) strategies, comparing CD4-guided planned treatment interruption (PTI) to continuous therapy (CT) in children with viral load <50 copies/mL, and CD4% >30% (2-6 years) or CD4% >25% and CD4 ≥500 cells/mm<sup>3</sup> (7-15 years). In the PTI arm, ART was stopped and restarted if a child had a confirmed CD4% <20% (<7 years) or CD4% <20% or CD4 <350 cells/mm<sup>3</sup> (>7 years).

After a DSMB review following the SMART results, the protocol was amended so that no interruption lasted longer than 48 weeks and further PTIs were only undertaken in children who spent >10 weeks off ART during their first PTI and had been back on ART for at least 24 weeks.

The trial was powered on equivalence; 2-sided with a 15% margin. The primary end-point was CD4% <15% (and/or CD4 <200 cells/mm<sup>3</sup> >7 years), new CDC C diagnosis or death. Minimum follow up was 72 weeks.

Professor Gibb reported that from 2004 to 2006, 109 children were randomised to CT (n=53) or PTI (n=56): 45% children were boys; their median age was 9.3 (range 2-16) years; 35% white, 31% black; 26% CDC stage C, median time on ART 5.7 (IQR: 3-9) years. Their median baseline CD4% was 37% (IQR: 33-41), CD4 966 (IQR: 793-1258) cells/mm<sup>3</sup>; prior to ART nadir (at age 3 years) CD4% 18% (IQR: 10-27) and CD4 627 (IQR: 320-1050) cells/mm<sup>3</sup>.

After a median of 130 (IQR: 80-144) weeks (one child lost to follow up), the investigators found that 4% of the study period

was spent off ART by children in the CT arm vs 48% in the PTI arm.

During the first PTI, 9 children restarted treatment in <10 weeks; 21 (38%) children restarted ART <48 weeks (14 failing CD4, 7 non-protocol reasons); 32 (57%) restarted at or after 48 weeks and three remained off ART. 16 children had a 2nd PTI.

Professor Gibb reported no child died or had a CDC C event. CD4 primary end points occurred in 1 (2%) CT vs 4 (7%) PTI (difference 5% [95% CI -2%, 13%],  $p=0.2$ ). 98.4% of total time in CT vs. 95.9% in PTI was spent with CD4 >350 cells/mm<sup>3</sup>.

The mean change in CD4 count from baseline to 72 weeks was -106 vs. -240 cells/mm<sup>3</sup> in CT vs. PTI (difference -134 cells/mm<sup>3</sup>, 95% CI -237, -31,  $p=0.01$ ). Differences between the two groups are difficult to interpret as some children in the PTI arm were off ART at 72 weeks. In an exploratory analysis, the mean CD4 change 0-72 weeks was -124 cells/mm<sup>3</sup> in 27 PTI children who had all been back on ART for  $\geq 24$  weeks; this is closer to the -106 value observed in CT children.

The CD4 fall of 106 cells in the CT arm is unlikely to be due to the natural fall in CD4 experienced by children throughout childhood, as children's CD4 counts normalise to those of adults by the age of 6 and the median age of the cohort was 9.3 years.

When the investigators looked at CD4 z-score change in the PTI arm from 0-24 weeks (1st PTI) after restarting, they reported that age adjusted CD4 recovery was significantly better in young children (mean, SE): -0.1 (0.3), -0.9, -1.3 for ages 2-6 ( $n=4$ ), 7-10 ( $n=20$ ) and 11+ ( $n=13$ ) years, respectively,  $p=0.02$ . Thus children <6 years almost fully recovered their CD4 values within 24 weeks, but older children did not.

At 72 weeks, 94%/85% vs. 81%/58% children had VL <400/<50 copies/mL in CT vs PTI ( $p=0.05/0.003$ ). Of the 28 PTI children back on ART for  $\geq 24$  weeks, 89%/68% had VL <400/<50 copies/mL, there was no evidence of more resistance in the PTI arm using standard genotype tests: 10 (5 CT and 5 PTI) of 13 children with 2 consecutive measurements >100 copies/mL on treatment had resistance; of these, 4 CT and 2 PTI had 4 or more mutations.

Although adverse events were more frequent in the PTI arm, these were mostly predictable (more lymphadenopathy, consistent with new onset viraemia).

With respect to both CD4 recovery and viral load suppression after PTI, Professor Gibb noted that because some children were off ART at 72 weeks, results so far are difficult to interpret and longer follow-up is essential, and is ongoing. The investigators concluded, "Longer-term assessment of all children after restarting ART will be required to fully assess risks and benefits of PTI in this population".

In the meantime, paediatricians have advised all children on PTI to be restarted on ART. These results do provide reassurance that ongoing interruption trials should continue in both chronically infected children (BANA trial in Botswana) and following primary infection (CHER trial in South Africa). Results of adherence/acceptability and immunology/virology studies alongside PENTA 11 are now being analysed.

## C O M M E N T

**The PENTA group does not currently support treatment interruptions in children outside of a study and has recommended that children in this study now restart ART. The same questions raised by the SMART study that now need to be answered in children include:**

- i) Whether children re-suppress viral load.
- ii) Whether higher sensitivity resistance tests show development of resistance.
- ii) Whether CD4 recovery similarly lags behind that of baseline levels, even 18 months after reintroduction of treatment, and
- iv) What are the long-term implications of ongoing viral replication and importance of ongoing immune activation? (See the study from Pontrelli et al below).

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Gibb DM, Compagnucci A, Green H et al. Treatment interruption in children with chronic HIV-infection: the results of the paediatric European network for treatment of AIDS (PENTA) 11 trial. 9th International Congress on Drug Therapy in HIV Infection, 9-13 November 2008, Glasgow. Abstract O222.

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## Inflammation and coagulation markers askew in children with higher HIV RNA

### Mark Mascolini, for NATAP.org

Levels of the thrombosis marker D-dimer were significantly higher in children and adolescents with an HIV viral load above 1000 copies/mL than in those with lower loads. [1] Protein C and S anticoagulant activity and antithrombin activity were lower in youngsters with high viral loads.

HIV researchers started pondering D-dimer when SMART trial investigators charted significantly rising levels of that marker in people randomised to intermittent antiretrovirals compared with steady therapy. [2] The SMART analysis also disclosed climbing concentrations of IL-6, an inflammation marker, in treatment interrupters. Higher SMART baseline levels of both D-dimer and IL-6 raised the risk of all-cause mortality.

A cross-sectional ("slice-of-time") study at Rome's Bambino Gesù Children's Hospital involved 88 children, adolescents, and young adults seen between December 2007 and June 2008. Their ages averaged 13.6 years and ranged from 3 to 25. Fifty-two cohort members (59%) were female, and 76 (86%) were taking antiretrovirals. The investigators measured the thrombosis marker D-dimer and several inflammation markers-antithrombin, protein C anticoagulant, protein S anticoagulant, and C-reactive protein.

Sixty-three youngsters (72%) had a viral load below 1000 copies, and 25 had a higher load. Sixty-eight people (77%) had a CD4% above 25% and 20 were under 25%. Sixty-one (70%) had CDC class B or C (symptomatic) HIV infection and 27 did not. Defining protein C and S activity deficiency as below 70% activity, the investigators found deficient C activity in 7 people (8%) and deficient S activity in 45 (51%). Antithrombin activity deficiency,

defined as below 75% activity, affected only 1 person.

D-dimer levels were significantly higher in cohort members with a viral load above 1000 than in those with lower loads. In contrast, activity of protein C anticoagulant, protein S anticoagulant, and antithrombin was significantly lower in the group with a high viral load. C-reactive protein did not vary significantly by viral load, CD4%, or disease stage. None of the markers correlated with age or duration of HIV infection.

The SMART analysis of D-dimer and IL-6 factored in age, race, use of antiretrovirals, viral load, CD4 count, smoking status, body mass index (BMI), prior cardiovascular disease, diabetes, use of antihypertensives or lipid-lowering drugs, total-to-HDL cholesterol ratio, and coinfection with hepatitis B or C [2]. The Italian study excluded people with hepatitis but did not specify which variables they weighed in their analysis, other than those noted above.

The investigators speculated that the better protein C and anticoagulant activity in children and adolescents with symptomatic HIV infection could reflect antiretroviral treatment of these children compared with those who had less advanced infection. But none of the markers studied varied significantly by antiretroviral treatment status. The 1000-copy cutoff for good viral control may strike some as arbitrary.

**Table 1: Inflammation and coagulation markers by viral load, CD4% and CDC class**

Parameter	VL <1000 copies/mL	VL >1000 copies/mL	p-value
D-dimer, mean ng/mL (+/-SD)	206 (+/- 100)	341 (+/- 253)	0.024
Protein C activity, mean % (+/-SD)	101.9% (+/- 26.0%)	92.0% (+/- 14.7%)	0.007
CDC class N/A: 89.9% (+/- 20.4% SD)			0.02
CDC class B/C: 103.1% (+/- 24.1% SD)			
Protein S activity, mean % (+/-SD)	75.3% (+/- 18.2%)	57.6% (+/- 21.7%)	0.0003
CD4% >25: 74.1% (+/- 19.5% SD)			0.001
CD4% <25: 57.2% (+/- 20.0% SD)			
Antithrombin activity, mean % (+/-SD)	115.5% (+/- 13.6%)	107.5% (+/- 9.2% SD)	0.005
CDC class N/A 107.2% (+/- 9.2%)			0.002
CDC class B/C: 116.15% (+/- 13.6%)			
CD4% >25: 114.6% (+/- 13.2% SD)			0.024
CD4% <25: 108.9% (+/- 11.5% SD)			

The researchers acknowledged that, "further studies are necessary to correlate such alterations with clinical events and to investigate the protective role of therapy in this particular population." This line of research bears watching since treatment interruptions remain high on the research agenda for children, who otherwise face several decades of continuous antiretroviral therapy. But if coagulation and inflammation markers signal a higher risk of non-AIDS diseases in children with higher loads while interrupting therapy (as they do in adults [2]), treatment breaks may not be worth the risk, even in children.

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## Dosing of lopinavir/ritonavir in the CHIPS cohort

### Polly Clayden, HIV i-Base

Sarah Walker from the Medical Research Council presented data from the UK/Irish Collaborative HIV Paediatric Study (CHIPS) cohort looking at paediatric dosing of lopinavir/ritonavir (LPV/r). [1]

Dr Walker explained that the licensed LPV/r paediatric daily dose is 460 mg/m<sup>2</sup> without, and 600 mg/m<sup>2</sup> with concomitant NNRTI therapy. The 460 mg/m<sup>2</sup> dose without NNRTIs was chosen in preference to 600 mg/m<sup>2</sup> in a post-hoc drug-interaction analysis [2]. Following the completion of the phase II trial, this post-hoc analysis revealed a significant interaction between NNRTI and LPV/r, leading to the lower dose being licensed for use without NNRTI. The phase II trial showed very good viral load data overall, with 79% of children <400 copies/mL at 48 weeks, but this was based on the higher 600 mg/m<sup>2</sup> dose. Because of this uncertainty some paediatricians prefer to prescribe the higher dose of LPV/r irrespective of concomitant NNRTI therapy.

In the CHIPS study the investigators evaluated the LPV/r doses prescribed without NNRTIs in the cohort from 2000–2007.

They looked at predictors of current dose, including sex, VL and CD4, age, CDC stage, height/weight-for-age, calendar year, formulation, frequency and previous PI use, using mixed models allowing child and hospital effects.

They also evaluated the impact of the LPV/r dose on viral load suppression 6 months after starting it using logistic models and over longer follow up using binomial mixed models.

Dr Walker reported, 311/1336 (25%) children in the cohort had received LPV/r without an NNRTI; for a total of 654 child-years. Of these children, 238 (77%) were still on LPV/r when they were seen last.

The median age of the children at initiation of LPV/r was 9 (IQR 5–12) years. The investigators recorded 684 doses in 299/311 children of which 52% were syrup, 38% capsules and 10% tablets. 662 (97%) doses were taken twice daily.

Overall the dose/m<sup>2</sup> could be estimated 2,748 times in 278 children (the remaining children did not have height/weight recorded). They found few (7%) doses were >10% below the 460 mg/m<sup>2</sup> target, and few (9%) >10% above the 600 mg/m<sup>2</sup> target, with the majority >410–<530 mg/m<sup>2</sup> (46%) or >530–<660 mg/m<sup>2</sup> (39%).

In a multivariate analysis, the investigators found doses were: 17 mg/m<sup>2</sup> [95%CI 0–34], higher in children who had prior CDC C event, p=0.05; 2 mg/m<sup>2</sup> [0–3] higher for every log<sub>10</sub> higher VL, p=0.02; 48 mg/m<sup>2</sup> [38–58] higher with capsules/tablets vs syrups, p<0.001; 22 mg/m<sup>2</sup> [4–40] higher with twice- vs once-daily dosing, p=0.02; 19 mg/m<sup>2</sup> [15–24], p=0.001, and 10 mg/m<sup>2</sup> [6–14], p<0.001 higher for every one unit lower current weight- and height-for-age, respectively; and 9 mg/m<sup>2</sup> [5–14] higher for every year younger over 10, p<0.05.

Dr Walker noted that the mean dose for a 10 year old, without prior CDC event, average weight and age for height receiving capsules or tablets was 546mg/m<sup>2</sup>. She also noted that dosing varied greatly by centre with some using higher and some lower doses.

The investigators found no evidence that the initial LPV/r dose was associated with significantly improved viral load suppression at 6 months and reported: <400 copies/mL, AOR=1.06 per 50 mg/m<sup>2</sup> (95%CI 0.87-1.28), p=0.58; <50 copies/mL, AOR=0.81 per 50mg/m<sup>2</sup> (95%CI 0.65-1.01), p=0.06.

The investigators concluded: “Doses were higher with capsules/tablets, likely reflecting over- rather than under-dosing when solid formulations cannot achieve exact doses. However, we found no clear evidence that higher doses improved VL suppression.”

Dr Walker added: “Opinion seems to be split as to the most appropriate LPV/r dose in children.”

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## Number needed to treat to harm (NNTH) analysis of impact of underlying cardiovascular factors on risk of abacavir-related heart attack

Simon Collins, HIV i-Base

JD Kowalska from the D:A:D study presented a model looking at the “number needed to treat to harm” (NNTH) in order to help interpret the clinical importance of the 90% increased relative risk (RR=1.90), previously reported between abacavir use and the risk of heart attack. [1, 2]

This estimate changed depending on an individuals underlying cardiovascular risk. The underlying risk was calculated based on 5-year Framingham score [3] and the relative rate was assumed to remain constant across the range of underlying risk of MI.

NNTH was calculated as:

$$\frac{1}{(\text{underlying risk of MI} \times 1.90) - \text{underlying risk of MI}}$$

The lowest NNTH values were observed in the high risk group, while the most dynamic changes in NNTH is in the low risk

group, showing an exponential relationship between NNTH and underlying risk of MI. The NNTH dropped steeply from 185 with an underlying risk of MI of 0.6% to only 5 when underlying MI risk is 20%.

The importance of additional risk factors was illustrated by starting with a low risk patient (0.1% risk of MI); in this case, 1111 patients would need to be treated before seeing an abacavir-related MI. When two unfavourable risk components are present the NNTH drops to around 100 for most pairs, except smoking and low HDL, for which NNTH drops to 69. When all risk factors are unfavourable, in patients with 15% underlying CVD risk, only 7 people would need to be treated with abacavir to see a treatment associated MI. (See Table 1).

**Table 1: Change in factors contributing to underlying risk**

Underlying risk of MI in 5 years	5-year risk of MI (%)	NNTH
Low risk profile (40 year old man with none of risk factors listed below)	0.1	1111
<b>Impact of additional single risks:</b>		
If total cholesterol 240 mg/dL (6.2 mmol/L)	0.2	555
If diabetes	0.2	555
If ECG-LVH	0.2	555
If sBP 160 mmHg	0.3	370
If HDL 35 mg/dL (0.9 mmol/L)	0.3	370
If smoking	0.4	277
<b>Impact of multiple risks:</b>		
If HDL and total cholesterol unfavourable	0.8	138
If smoking and diabetes	1.1	101
If smoking and total cholesterol unfavourable	1.0	111
If smoking and sBP 160 mmHg	1.3	85
If smoking and HDL unfavourable	1.6	69
If smoking and lipids unfavourable	3.1	35
If all unfavourable combined (excluding ECG-LVH)	10.1	11
If all unfavourable combined (including ECG-LVH)	15.0	7

#### C O M M E N T

**This model supports the conclusions from both D:A:D and SMART studies to caution against using abacavir in patients with high underlying cardiovascular risk.**

**It also demonstrates the potential clinical impact from reducing other risk factors where alternative treatment options are not available.**

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## Bone disease and HIV

### Simon Collins, HIV i-Base

Many studies have highlighted the significantly increased rates of osteopenia and osteoporosis in HIV-positive individuals compared to the general population, but, although this is one of the foremost concerns in an aging patient group, very few clinics actively incorporate either screening or monitoring of bone disease into routine HIV care.

The following summary covers an overview of osteoporosis and HIV presented at the conference by Dr Paddy Mallon from University College Dublin. [1]

The WHO defines osteopenia and osteoporosis as individual bone mineral density (BMD) scores that are between -1.0 and -2.5 (for osteopenia) and > -2.5 (for osteoporosis) standard deviations from the norm. T-scores relate to levels for a 30 year-old Caucasian woman and Z-scores relate to norms adjusted for age and gender.

In the setting of HIV, where the main outcome is to reduce the risk of fracture, T-score is the best validated surrogate marker, because the main management goal is to reduce fractures and each reduction of 1.0 in the T-score indicates an approximately doubled risk of fracture.

Cross-sectional studies have shown remarkably high incidence rates of reduced bone mineral density of between 40-80% in HIV-positive people, and a prevalence of 10-15% for osteoporosis. HIV-positive people are 6.4 times more likely to have osteopenia and 3.7 times more likely to have osteoporosis. [2]

As with the general population, risk factors include patient factors (female gender, Caucasian race, family history and falls risk) and lifestyle factors (smoking, exercise and alcohol use). However, HIV-related factors (which have included duration of infection, use of PI and NRTIs, hypogonadism, steroid use, and vitamin deficiency and low BMI) are less consistently clear, perhaps because HIV-specific studies have involved lower numbers of patients to have the statistical power to find significant associations.

In the HIV-negative people, BMD increases until around age 30 where it remains stable for perhaps 5-10 years before starting to decline (at a rate of 0.5-1% per year), especially, in women during menopause (during which it declines at -2% bone volume a year). [3] Women generally have lower BMD than men.

The importance of the bone health in the context of HIV is that many people will be diagnosed and treated for HIV before they are 30, prior to reaching their natural peak bone health.

This is a particular concern for children, and recent data from the paediatric ACTG studies have shown statistically lower BMD in HIV-positive compared to HIV-negative children, and also that this increases with Tanner development stage, particularly in males. [4]

Several prospective studies suggest that BMD in HIV-positive patients on stable therapy declines at similar rates to HIV-negative individuals, perhaps with an additional decrease associated with starting treatment. In the Gilead 903 study patients using tenofovir/FTC had a greater loss in hip BMD compared to the d4T/3TC arm but this difference became non significant at year three with both groups losing 2.4-2.8% from baseline levels. [5]

Importantly, similar reductions have been reported for combinations using AZT/3TC (with efavirenz or lopinavir/r), and these reductions continued in patients after discontinuing nucleoside analogues. [6] Some studies have continued to report a potentially greater effect with protease inhibitors. [7]

Results from a sub-study of the SMART trial reported a similar rate of reduction in hip and spine BMD in patients who used continuous treatment to the studies above, but less of a reduction in patients who used CD4 guided treatment interruptions. [8]

Finally, a large US database, that included over 8,000 HIV-positive patients and over 2 million HIV-negative patients, provided convincing results that lower HIV-related BMD does result in a clinically significant increase in the risk of fractures (even though the study didn't measure BMD directly). In this study, HIV was significantly associated with increased rates of vertebral, wrist and hip fractures (overall 2.87 vs 1.77 per 100 patient years,  $p=0.0001$ ) with a slightly higher impact for men compared to women. [9]

Pathogenic mechanisms in HIV are relatively complicated. The principal hormonal control of bone disease revolves around parathyroid hormone (PTH). In the kidney this affects tubular calcium re-absorption by upregulating 1-alpha hydroxylase, which is involved with the production of active vitamin D (1.25vitD), which in turn acts upon calcium absorption in the gut to maintain serum calcium levels. In bone, PTH acts at the osteoblast level to induce production of RANKL factor. This increases osteoclast activity to shift the balance of bone turnover in favour of bone resorption, increasing calcium levels which itself feeds back to reduce levels of PTH.

Several studies have also highlighted vitamin-D deficiency in HIV-positive patients, related both to low dietary intake (40-60% patients estimated at less than 10ug daily) and access to sunlight. A US study in disadvantaged youths, in both southern and northern states, found that almost 90% had low vitamin D levels (less than 37.5nmol/L) and that these were predicted by latitude, dietary intake and alcohol use. [10]

A possible complication from HAART, presented at ICAAC this year, included preliminary findings from a small New York study of 34 men on tenofovir-containing HAART and 17 men on non-tenofovir HAART and highlighted the potential complexity of the PTH mechanism. While over 80% of the whole study group were vitamin D deficient (unrelated to use of tenofovir), significantly higher PTH levels were found in the tenofovir group (median 80 vs 55 pg/mL,  $p=0.03$ ; and 39% vs 7% with levels >65pg/mL,  $p=0.02$ ) and within the subgroup of patients with lowest vitamin D levels. [11]

Most interestingly, recent research has also suggested an interaction between bone metabolism and metabolic changes, through the production in adipose tissue of an adipokine called leptin that acts on the hypothalamus to induce the sympathetic nervous system to increase osteoclast activity. A less well-described feedback mechanism may be mediated back to adipose tissue by the bone-derived factor osteocalcin. The increase in adipose tissue generally seen in the first 6 months of HAART may therefore be directly related to the higher rates of bone loss reported in the same period.

Other pathogenic mechanisms have looked at the effect of individual ARVs on osteoblasts and osteoclasts function and vitamin D metabolism in vitro, although interpreting the clinical implications of these findings is less clear.

In terms of management, there are currently no consistent evidence-based guidelines relating to osteoporosis in HIV-positive patients and a few studies from treating men in general. Both treatment and management however should focus on reducing the risk of fractures.

Modifiable risk factors include stopping smoking, reducing alcohol intake, increasing exercise, and monitoring use of steroids. Treatment with bisphosphonates, calcitonin, parathyroid hormone and oestrogen are supported by studies in the general population. [12] Alendronate increased lumbar BMD in HIV-positive patients by an additional 4% from baseline at week 48, compared to the approximate +1.5% from vitamin D and calcium supplementation alone. [13] Vitamin D and calcium replacement, while widely used to correct low serum levels, and known to increase BMD, are less supported by data relating to their impact on reducing fractures. [14]

#### C O M M E N T

**The link between bone and metabolic changes may be particularly important. This presentation rightly concluded with a call for more research and for the productions guidelines for management and treatment in HIV.**

**A useful overview article on this issue was posted online on Medscape in December. [15]**

**A poster at this conference from the Chelsea and Westminster clinic in London reported that 20% of 74 patients (17 women, 57 men) admitted to their hospital in a two month period were vitamin D deficient (<15nmol/L) and 45% had insufficient levels (15-50nmol/L). [16]**

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## Renal tubule damage with tenofovir despite normal glomerular function

**Mark Mascolini, for NATAP.org**

Asymptomatic renal tubule damage may affect people taking tenofovir even if they have a normal glomerular filtration rate, according to findings in a prospective Spanish study. [1] Older age and treatment with tenofovir both independently predicted renal tubule dysfunction in these patients.

Madrid clinicians measured 24-hour urine in three unmatched groups: 81 antiretroviral-naïve people with HIV, 49 antiretroviral-treated people who never took tenofovir, and 154 tenofovir-treated individuals. The naïve people were significantly younger than both antiretroviral-experienced groups, but median age was similar in the non-tenofovir-experienced group and the tenofovir group (46 and 44 years). CD4 counts were statistically equivalent in the two experienced groups (572 and 487, p=0.2). Similar proportions in all three groups had hypertension or took nephrotoxic drugs (other than tenofovir), and about 25% of people in the two experienced groups had diabetes.

Creatinine clearance was lower in tenofovir takers (109 mL/min) than in the other groups (119 mL/min in the nontenofovir treated group and 123 mL/min in the untreated group), but not significantly so. Fractional tubular resorption of phosphorus was significantly lower in the tenofovir group than in either of the other groups: 82% versus 87% in naïve patients (p<0.001) and 85% in non-tenofovir-treated people (p=0.002).

The investigators defined altered tubular function as having two of the three following conditions: nondiabetic glucosuria, reduced tubular resorption of phosphorus, or pathologic aminoaciduria. By

that definition, 22% taking tenofovir had tubular damage versus 6% taking a nontenofovir regimen ( $P = 0.01$ ) and 12% taking no antiretrovirals ( $P = 0.06$ ). Among people taking tenofovir, 51.4% had fractional tubular resorption of phosphorus (versus 27.1% taking a nontenofovir regimen,  $P = 0.003$ ); 11.4% had fractional excretion of uric acid (versus 0 taking a nontenofovir regimen,  $P = 0.01$ ); and 19.5% had beta2 microglobulinuria (versus 4.3% taking a nontenofovir regimen,  $P = 0.01$ ).

Multivariate analysis determined that a tenofovir-containing regimen independently raised the risk of renal tubule damage more than 20 times (odds ratio 21.6, 95% confidence interval 4.1 to 13,  $P < 0.001$ ). Every extra year of age raised the risk 6% (odds ratio 1.06, 95% confidence interval 1.0 to 1.1,  $P = 0.01$ ). Variables that did not affect the risk of tubule damage in this analysis were gender, body weight, history of hypertension or diabetes, viral load, CD4 count, length of antiretroviral therapy, protease inhibitor therapy, concomitant nephrotoxic drugs, or hepatitis B or C virus coinfection. Kaplan-Meier survival analysis confirmed a significantly higher risk of tubule dysfunction with tenofovir than with a nontenofovir combination ( $p < 0.001$ ).

The investigators concluded that tenofovir, though "relatively safe," may be linked to functional damage of the proximal renal tubule. And that damage may be asymptomatic when studied prospectively. They proposed that "the long-term consequences of abnormal tubular dysfunction in patients on tenofovir warrant close examination."

#### Reference

Labarga P et al. Kidney tubular abnormalities in HIV patients treated with tenofovir with normal glomerular function: results of a prospective study of 284 patients. 9th International Congress on Drug Therapy in HIV Infection, 9-13 November 2008, Glasgow. Abstract P128. <http://www.jiasociety.org/content/11/S1/P128>

## TREATMENT ACCESS

### FDA approval of generic ARVs

The US Food and Drug Administration (FDA) has recently granted tentative approval for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
Paediatric abacavir/3TC 60mg/30mg tablets	Aurobindo, India	19 December 2008
FTC (emtricitabine) 200mg tablets	Matrix, India	23 December 2008
d4T (stavudine) 15 mg, 20 mg, 30 mg and 40 mg	Aurobindo, India	29 December 2008
d4T (stavudine) oral solution 1mg/mL	Aurobindo, India	29 December 2008
d4T (stavudine) 15 mg, 20 mg, 30 mg and 40 mg	Hetero, India	29 December 2008

"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 programme for use outside the United States.

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/docs/obdetail.cfm?App\\_No=3D021360&TABLE1=3DOB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?App_No=3D021360&TABLE1=3DOB_Rx)

#### C O M M E N T

**The approval FDC of low dose (60/30mg) abacavir/3TC tablets is particularly important as this allows children with body weight down to 5kg. The Glaxo Smith Kline formulation, although approved for children, are the same dose as adult tablets (ie are ten-fold higher at 600/300mg).**

**They are scored, which is important for splitting half-doses, and are also dispersible in water. Both are intended for paediatric patients 3 months - 16 years of age.**

**The new formulations of d4T have more limited interest given the widespread shift away from d4T, even in WHO guidelines for ARV use in resource-limited countries. As d4T is now off-patent in the US, these generic formulations can also be used there.**

**This brings the total of FDA approved generic drugs and formulations to 80 since the programme started. 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/oashi/aids/lists/serve/archive.html>

## Lost benefit of ARVs in South Africa

### Nathan Geffen, Treatment Action Campaign

Two studies have calculated the number of excess AIDS deaths due to the South African government's delayed rollout of highly active ARV treatment (HAART) and prevention of mother-to-child transmission (PMTCT).

Nicoli Natrass analysed what would have happened if PMTCT had been rolled out from 1998 instead of 2001 and HAART was rolled out at the same rate as the Western Cape Province (from 10% in 2000 to 65% in 2007), the province credited with the most expeditious implementation. [1]

She compared these scenarios using the Actuarial Society of South Africa's ASSA2003 model [2] and estimated that 343,000 deaths could have been averted.

Pride Chigwedere and colleagues at Harvard School of Public Health used a slightly different method. [3]

They argued that reduced drug prices and the availability of resources from programmes like the Global Fund and PEPFAR enabled the South African government to implement PMTCT and HAART earlier. South Africa's public sector HAART programme only moved beyond pilot sites in 2004. According to the WHO and UNAIDS 3x5 records, South Africa scaled up HAART from less than 3% in 2000 to 23% in 2005. The authors considered the number of life-years that could have been saved had the state initiated its ARV programme at 5% coverage in 2000, scaling up to 50% by end of 2005, which is lower than the 85% achieved by Botswana or 71% by Namibia. They used UNAIDS estimate of AIDS deaths to determine the number of people who were eligible for HAART but did not receive it.

For PMTCT, they used data from the Department of Health's PMTCT Task Team showing that coverage rose from less than 3% in 2000 to 30% in 2005 and compared this to a programme that started with 5% coverage in 2000 and scaled up to 55% in 2005.

Their model calculated that the delayed HAART rollout resulted in 2.2 million lost person-years and over 330,000 deaths. Delayed PMTCT resulted in over 35,000 excess infections and 1.6 million lost person-years. This is a total of 3.8 million lost person-years.

Both studies were intentionally conservative. For example, Chigwedere et al. assumed low estimates for additional life-expectancy on HAART (6.7 years) and paediatric infections. Both studies assumed low peak coverage rates in the alternative scenarios and that only the sub-optimal single-dose nevirapine PMTCT regimen was feasible. Neither took into account less tangible parameters such as deaths due to the promotion of quackery and infections due to poor state condom messaging and equivocation on the cause of AIDS.

Chigwedere et al. also performed several sensitivity tests. They found, for example, that by varying HAART peak coverage from 40% to the Namibian rate of 71%, excess deaths varied from about 226,000 to 503,000. They concluded: "Access to appropriate public health practice is often determined by a small number of political leaders. In the case of South Africa, many lives were lost because of a failure to accept the use of available ARVs to prevent and treat HIV/AIDS in a timely manner."

## C O M M E N T

**These studies both calculated very similar estimates for the number of lives lost due to the delayed rollout of HAART and PMTCT, even though they use different methodologies. Communication between Natrass and Chigwedere after the latter's paper was published shows that they were unaware of each other's work. This increases confidence in their findings.**

**Their calculations confirm that the policies of President Thabo Mbeki and Minister of Health Manto Tshabalala-Msimang resulted in hundreds of thousands of avoidable deaths. Mbeki and Tshabalala-Msimang also created long-term problems, such as the proliferation of quackery and loss of public confidence in scientific medicine.**

**The Rome Statute of the International Criminal Court, to which South Africa is a signatory, defines the "intentional infliction of conditions of life, inter alia the deprivation of access to food and medicine, calculated to bring about the destruction of part of a population" as a crime against humanity.**

### References

1. Natrass N. AIDS and the Scientific Governance of Medicine in Post-Apartheid South Africa [Internet]. African Affairs. 2008 Feb 7;107(427):157-176.[cited 2008 Sep 11 ].  
<http://afraf.oxfordjournals.org/cgi/content/abstract/107/427/157>
2. Actuarial Society of South Africa. ASSA2003 [Internet]. [cited 2008 Jan 8 ].  
<http://actuarialsociety.co.za/Models-274.aspx>
3. Chigwedere P, Seage G, Gruskin S, Lee T, Essex M. Estimating the Lost Benefits of Antiretroviral Drug Use in South Africa [Internet]. J Acquir Immune Defic Syndr. 2008 Oct 16; [cited 2009 Jan 5 ].  
<http://www.ncbi.nlm.nih.gov/pubmed/18931626>

## DRUG INTERACTIONS

### Recent reports on new drug interactions

A selection of the latest news and reviews from the Liverpool University pharmacology team at [hiv-druginteractions.org](http://www.hiv-druginteractions.org) are included below.

<http://www.hiv-druginteractions.org>

#### Drug interactions with integrase inhibitors

This is an outstanding review on the pharmacology of integrase inhibitors with a substantial section on raltegravir drug-drug interactions and elvitegravir drug-drug interactions. There are four tables summarising all known interactions to date. The authors conclude that overall raltegravir has a low propensity for clinically meaningful drug interactions, whereas elvitegravir (with the presence of ritonavir) has modest potential for interactions.

The review is highly recommended and will appear in 2009. An advance version is available online, but minor changes may still occur before final publication.

Ref: Hazuda DJ et al. Emerging pharmacology: Inhibitors of Human Immunodeficiency Virus integration. *Rev Pharmacol Toxicol*, [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/18928385>

#### Serum bilirubin increases when PEG-interferon and ribavirin are used with atazanavir

This was a retrospective study of 72 HCV/HIV co-infected patients who initiated HCV therapy (peg-IFN weekly and ribavirin 1000-1200 mg/day) and were on either an atazanavir-containing regimen (n=36) or other antiretrovirals (not including indinavir, n=36). Fourteen subjects in the atazanavir group and six in the control group were then excluded from analysis due to poor drug adherence.

The major finding was that on average serum bilirubin increases following initiation of peg-IFN and ribavirin were 1.9-fold higher in patients on atazanavir than in controls. In the atazanavir group, the proportion of patients with grade 3-4 hyperbilirubinaemia increased from 2/22 to 10/22 after beginning hepatitis therapy. No controls developed hyperbilirubinaemia.

The elevation in serum bilirubin levels is directly related to the haemoglobin decline as a result of ribavirin use and haemolysis. The clearance of the increased bilirubin is compromised by atazanavir.

Ref: Rodriguez-Novoa S et al. Increase in serum bilirubin in HIV/hepatitis-C virus co-infected patients on atazanavir therapy following initiation of pegylated-interferon and ribavirin. *AIDS*, 2008, 22(18): 2535-2548.

<http://www.ncbi.nlm.nih.gov/pubmed/19005277>

#### Drug interactions between efavirenz and itraconazole

This is a case report of the interaction between itraconazole and efavirenz in a woman with disseminated histoplasmosis and HIV-1 infection. Previous data in healthy volunteers have shown a decrease of about 40% in exposure of itraconazole and its active metabolite (hydroxyitraconazole) and a recommendation to consider alternative antifungal treatment. Here the authors

recommend that by the use of therapeutic drug monitoring of both efavirenz and itraconazole individual optimization of dosage can be made so that a change in therapy is not necessary. In this case the patient had a good clinical response and obtained therapeutic concentrations with a regimen including efavirenz 400 mg once daily and itraconazole 800 mg once daily.

Ref: Huet E et al. Therapeutic monitoring is necessary for the association itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. *AIDS*, 2008, 22(14): 1885-1886.

<http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=403>

#### Effect on tacrolimus when switching from nelfinavir to fosamprenavir

This case report outlines the change in tacrolimus trough blood concentrations when 4 HIV-infected orthotopic liver transplant patients were switched from nelfinavir (1250 mg twice daily) to fosamprenavir (1400 mg twice daily without ritonavir) due to the EMEA ruling on nelfinavir in June 2007. After the switch, tacrolimus trough concentrations dropped significantly (>50%) and a marked dosage increase was required to attain the desired target concentration. The cases highlight the need for caution in immunosuppressed patients when switching or starting a protease inhibitor.

Ref: Pea Fet al. Drop in trough blood concentrations of tacrolimus after switching from nelfinavir to fosamprenavir in four HIV-infected liver transplant patients. *Antivir Ther*, 2008, 739-742.

<http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=404>

#### Elvitegravir with tipranavir/ritonavir or darunavir/ritonavir

Two studies are described evaluating potential pharmacokinetic interactions among elvitegravir and ritonavir-boosted tipranavir or darunavir.

In the tipranavir study healthy volunteers received elvitegravir/ritonavir (200/100 mg once daily) alone, or tipranavir/ritonavir (500/200 mg twice daily) alone, or elvitegravir (200 mg once daily) in combination with tipranavir/ritonavir (500/200 mg twice daily). For the darunavir study subjects received elvitegravir/ritonavir (125/100 mg once daily) alone, or darunavir /ritonavir (600/100 mg twice daily) alone, or elvitegravir (125 mg once daily) in combination with darunavir /ritonavir (600/100 mg twice daily). Steady state pharmacokinetics for elvitegravir, tipranavir, darunavir and ritonavir were determined.

No subjects discontinued for adverse events during treatment with elvitegravir/ritonavir alone. On coadministration, AUC and C<sub>max</sub> of elvitegravir/tipranavir and elvitegravir/darunavir were within prespecified no-effect boundaries versus treatment alone; trough concentrations were also not substantially altered. The authors concluded that elvitegravir can be added to tipranavir/ritonavir or darunavir/ritonavir regimens without dose adjustment.

Ref: Mathias AA et al. Effect of ritonavir-boosted tipranavir or darunavir on the steady-state pharmacokinetics of elvitegravir. *J Acquir Immune Defic Syndr*, 2008, 49(2): 156-162.

<http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=405>

## BASIC SCIENCE

Recent basic science updates from Richard Jeffery's excellent web log.

### Cause for caution on HIV cure report

#### Richard Jefferys, TAG

An avalanche of media coverage has been loosed by the recently announced case of an individual who may have been "functionally cured" of HIV infection.

The term functional cure has entered the lexicon due to the impossibility of formally proving that HIV has been entirely eradicated from the body; due to that limitation, long-term absence of detectable virus without therapy has been adopted as a reasonable definition of a cure, prefixed with the "functional" caveat.

The individual in this case is a 40 year old, HIV-infected American living in Berlin who had been on successful antiretroviral therapy prior to developing acute leukemia. The treatment for this condition involves bone marrow transplantation, which carries a 30% risk of mortality and is frequently associated with post-procedure complications. Due to the individual's HIV infection, his doctors found a donor who was homozygous for the delta32 mutation, which completely abrogates expression of CCR5 (the major HIV co-receptor) on cells. Preparation for transplantation involves chemotherapy and radiation to essentially wipe out the immune system in order to prevent transplant rejection (with the salutary side effect of also depleting HIV-infected immune cells). The donor cells successfully engrafted but leukemia initially returned, requiring a second transplantation. Since that time – now close to two years ago – the individual has been free of leukemia, and HIV has remained undetectable without further antiretroviral treatment.

As can be gleaned from the press articles, opinions are divided on the significance of what has occurred. Some researchers have suggested it is a "proof of principle" that gene therapies with the capacity to block CCR5 expression could be curative.

However, a 1999 review of bone marrow transplants in people with HIV [1] identified two similar instances in which virus did not reappear after the procedure, so the contribution of the delta32 status of the donor in this current case is uncertain (although it is also possible that the prior examples also involved delta32 donors, unbeknownst to the doctors).

The 1999 review also offers a grim perspective on the mortality associated with the procedure: the longest documented survival was around 300 days. While cynics might question whether AIDS professionals (including this writer) have their own self-serving reasons to express skepticism about cure claims, the complexity and danger of bone marrow transplantation clearly severely limits its use. It also must be stressed that while the individual is said to be "recovering," there are no details available regarding his current health.

Despite the many caveats, the case may be able to inform the pursuit of safer curative strategies. The Foundation for AIDS Research (amfAR) has already sponsored a small meeting of experts to discuss the subject, attended by Mark Schoofs

who wrote the first mainstream media article in the Wall Street Journal in November. [2]

One lesson may be that depleting HIV reservoirs to very low levels – if it can be done safely – will be beneficial, perhaps tipping the balance in favor of the host such that any residual virus can be controlled. If the individual remains well enough and is willing to undergo further evaluation, additional analyses to look for HIV in tissues will be important, along with evaluations of HIV-specific immunity. The presence of HIV-specific T cells carrying the donor delta32 mutation would suggest that sufficient viral activity has occurred after the transplantation procedure to induce new immune responses while, conversely, the absence of such responses might add to the evidence that HIV has been rendered completely inactive. Given that the case is now under the spotlight, the doctors involved will hopefully be forthcoming with updates as more information becomes available.

Source: TAG basic science blog (14 November 2008)  
<http://www.treatmentactiongroup.org/basicsciblog.aspx>

#### References

1. Huzicka I. Could bone marrow transplantation cure AIDS?: review. *Med Hypotheses*. 1999 Mar;52(3):247-57. PMID: 10362285. <http://www.ncbi.nlm.nih.gov/pubmed/10362285>
2. Schoofs M. A Doctor, a Mutation and a Potential Cure for AIDS. *Wall Street Journal*. (7 November 2008). <http://online.wsj.com/article/SB122602394113507555.html>

### Low-level HIV replication versus latency: identifying the source of viral rebounds during treatment interruption

#### Richard Jefferys, TAG

In HIV research, there is a persistent and vigorous debate around the question of whether or not viral replication persists in the face of successful antiretroviral therapy. During a plenary session at the International AIDS Conference in Mexico City back in August, Bob Siliciano made a compelling argument that, in most cases, antiretroviral therapy completely shuts down virus production. [1]

Now, a new paper in PNAS provides additional support for this view. [2]

Beda Joos and colleagues evaluated a staggering 1,753 genetic sequences from the envelope region of HIV, sampled over the course of a treatment interruption trial known as SSITT (Swiss-Spanish Intermittent Treatment Trial). The study design involved a series of two-week treatment breaks followed by a prolonged interruption (therapy was subsequently reinitiated according to the CD4 and viral load thresholds used in current treatment guidelines).

The researchers used the sequence data to plot the relationships between the different viruses, using a technique called phylogenetic analyses. For each study participant analyzed, the sequences were used to define "the most recent common ancestor" (MRCA), which is the virus sequence from which all the others derived. Viruses that appeared during treatment interruptions (TIs) were then compared to the MRCA, to see if the sequences suggested that there had been ongoing replication and evolution while the study participants were on ART. The

results showed that the rebounding viruses during TI were actually more distant from the MRCA than the viruses detected when the participants first entered the study. The researchers conclude: "the striking lack of a temporal relationship between rebounding virus and pretreatment viruses strongly suggests that rebounding virus originates from reactivated, latently infected cells rather than from a cellular pool or compartment engaged in low-level replication."

Source: TAG basic science blog (20 November 2008)  
<http://www.treatmentactiongroup.org/basicsciblog.aspx>

#### References

1. Siliciano R. HIV persistence on patients on HAART: re-evaluating prospects for eradication. XVII Intl AIDS Conference, 3-8 August 2008, Mexico City.

[http://www.kaisernetwork.org/health\\_cast/hcast\\_index.cfm?display=etail&hc=2909](http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=etail&hc=2909)

2. Joosa B et al. HIV rebounds from latently infected cells, rather than from continuing low-level replication. PNAS October 28, 2008 vol. 105 no. 43 16725-16730

<http://www.pnas.org/content/105/43/16725>

## OTHER NEWS

### **EMEA supports extension of D:A:D study until at least 2012 and the new remit to include non-AIDS cancers and kidney disease**

The EMEA released the following press release on the D:A:D Study on 3 February 2009.

#### **European Medicines Agency welcomes the continuation of D:A:D study**

The European Medicines Agency (EMA) has welcomed the commitment of the sponsors to continue the D:A:D study at least until 2012. This ensures that the study, which was started on the initiative of the EMA in 1999, will remain one of the most powerful pharmacovigilance tools to monitor the long-term safety of antiretroviral medicines.

D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) is a prospective study based on multinational cohort collaboration, which includes data from 33,308 patients in 11 ongoing HIV cohorts in Europe, Australia and the United States of America.

The D:A:D study was started in response to a request from the EMA to all marketing authorisation holders of antiretroviral medicines. It set out to conduct a collaborative review of the cardiovascular safety and metabolic and body composition changes possibly associated with HIV treatment. The scope of the study was extended in 2005 to also investigate liver-related safety.

Although marketing authorisation holders of antiretroviral medicines contribute to the funding of the study, it is run in scientific independence. This is ensured by an independent scientific steering committee, which takes all scientific and procedural decisions, and by the so-called HAART Oversight Committee, which administers funds for studies, follows their progress and ensures their completion and reports regularly to the EMA. The Oversight Committee includes representatives of academia, patient organisations, the EMA and the US Food and Drug Administration (FDA).

Due to its large size and long follow-up, the D:A:D study has had a pioneering role in drug safety, helping to address existing and new emerging safety concerns, as well as to learn more about HIV infection itself. This is likely to serve as a model for future collaborative observational studies that will analyse the safety of whole therapeutic classes of medicines.

During the January 2009 meeting of the EMA's Committee for Medicinal Products for Human Use (CHMP) representatives of the HAART Oversight Committee and the steering committee presented the achievements made over the last ten years and the plans for the study's continuation.

The study now monitors all authorised antiretroviral medicines. In addition, the marketing authorisation holders for any new antiretroviral medicines authorised in the future will be required to take part in the study.

D:A:D will continue to explore cardiovascular and liver-related safety. An association between antiretroviral combination therapy and myocardial infarction was identified in 2003. Further follow-up established that this is mainly explained by cumulative exposure to protease inhibitors. More recently an association with the recent use of abacavir and didanosine is being investigated.

The study will also be expanded to consider whether antiretroviral medicines affect the risk of contracting non-AIDS defining cancers and endstage kidney disease, as well as to examine patterns of causes of death over time and laboratory markers of liver and kidney function.

The results from the first ten years of the study have shown that the benefit-risk balance of antiretroviral medicines remains strongly positive and that the overall mortality of HIV-infected patients has dramatically declined since the introduction of highly active antiretroviral therapy (HAART).

Source:

EMEA Press Release: European Medicines Agency welcomes continuation of D:A:D study (3 February 2009). Doc. Ref. EMEA/44937/2009.  
<http://www.emea.europa.eu>

## Applications to approve non-refrigerated ritonavir submitted to EMEA and FDA

On 21 January 2009, Abbott announced that it has submitted applications seeking registration for a new tablet formulation of the protease inhibitor ritonavir (Norvir) with the European and US regulatory authorities. This new formulation will not require refrigeration.

Data from a pivotal bioavailability study, which compared the new formulation to the current ritonavir soft gel capsule was presented at the XVII International AIDS conference in Mexico City (AIDS 2008) in August 2008.

The expected timelines for decisions on the applications were not included in the announcement, nor whether they have been accepted for accelerated approval.

Source: Abbott press release (21 January 2009)

## Report refutes HIV denialist claims on childrens HIV trials

### Simon Collins, HIV i-Base

Several years ago, allegations from a fringe group of HIV denialists who claiming that foster children in New York were used as guinea pigs for adult HIV drug trials, gained media publicity when used as a basis for a BBC documentary. It is important that these have been quashed following a lengthy investigation, detailed in a recent article in the New York Times. [1]

Complaints to the BBC after the documentary was aired in 2004, also resulted in a lengthy apology and retraction recognising the inappropriate balance used in their programme. [2]

An independently commissioned investigation determined that city officials had acted in good faith and in the interests of the children, many of whom were seriously ill.

The report, from the Vera Institute of Justice, an independent nonprofit group, is now available online [3]. It also found that foster children were not removed from their families because a parent had refused to consent to a child's treatment, and that researchers did not specifically select foster children for enrollment in the trials. While the foster children were overwhelmingly black and Hispanic, as some critics, this mirrored the demographics of children with HIV infection in the city at the time.

### C O M M E N T

**This was probably one of the most inappropriate and inflammatory HIV-related stories to be picked up by mainstream media who themselves failed to appropriately research the real issues: that children are generally denied access to potentially life-saving pipeline compounds until after they have been approved for adult care.**

#### References

1. Foderaro L. Study refutes claims on AIDS drug trials, New York Times (27 January 2009).  
[http://www.nytimes.com/2009/01/28/nyregion/28foster.html?\\_r=1](http://www.nytimes.com/2009/01/28/nyregion/28foster.html?_r=1)
2. BBC Admits that "Guinea Pig Kids" is Misleading, Erroneous: Apologises for HIV Denialist Bias and False Allegations about NYC AIDS Drug Trials  
<http://www.aidstruth.org/BBC-Apologizes-for-HIV-Denialist-Bias.php>  
Link to BBC letter  
<http://www.aidstruth.org/Complete-BBC-complaint.pdf>
3. Ross T et al. The Experiences of New York City Foster Children in HIV/AIDS Clinical Trials. Available online:  
<http://www.vera.org/cyj/hivtrials-pubs.html>

## FUTURE MEETINGS

### 2009 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.

25-27 March 2009: 7th European HIV Drug Resistance workshop, Stockholm

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

1-3 April 2009: 15th Annual Conference of the British HIV Association (BHIVA), Liverpool

<http://www.bhiva.org>

15-17 April 2009: 10th Intl Workshop on Clinical Pharmacology of HIV therapy, Amsterdam

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

4-6 June 2009: 5th Intl HIV and Hepatitis Co-infection workshop, Lisbon

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

9-13 June 2009: XVIII International HIV Drug Resistance Workshop, Fort Myers, Florida

<http://www.informedhorizons.com/resistance2009>

25 - 26 June 2009: 4th Intl Workshop on Hepatitis C Resistance & New Compounds, Boston

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

26-27 June 2009: 4th Intl Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston

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

16-18 July 2009: 1st Intl Workshop on HIV Paediatrics, Cape Town

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

16-18 July 2009: 4th Intl Workshop on HIV Transmission, Cape Town

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

19-22 July 2009: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009), Cape Town

<http://www.ias2009.org>

12-15 September 2009: 49th ICAAC, San Francisco

<http://www.asm.org>

29 October-1 November 2009: 47th IDSA, Philadelphia.

<http://www.idsociety.org>

## ABOUT HIV i-BASE

HIV i-Base is an HIV-positive led treatment information service. We produce information both for clinicians and other health workers and for people with HIV.

Our publications are used and have been adapted in many countries and settings.

Our fully searchable website is designed to be fast to access, easy to use, and simple to navigate.

All i-Base publications are available online.

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

i-Base produce five non-technical treatment guides, which are available online as web pages and PDF files.

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

- Introduction to combination therapy
- A guide to changing treatment
- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV

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

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

Recent questions include:

- What makes someone a fast progressor?
- What does the word 'analogue' mean in HIV treatment?
- What does genotype stand for and other questions
- What can I do for my CD4 to rise?
- What is your life expectancy if treatment is not an option?
- Can I take omega-3 and multivitamins with ARVs?
- What does the rise of CD8 mean?
- Does finasteride (Propecia) interact with HIV drugs?
- What does a CD4% of 8 mean for starting treatment?
- Are there interactions between scabies lotions and ARVs?
- What tests are used when somebody is HIV-positive?
- Can I get HIV-related illnesses with a CD4 over 200?
- Can I still have AIDS even if my test is negative?
- What do these lab results mean?
- How many combinations are there before salvage?
- Could I have lipoatrophy if I am not on meds?
- Are aches in my fingers and knees a side effect?
- Should my partner take Sustiva and Truvada separately?
- Can we have have an HIV-negative baby?

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.

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



**HIV i-Base**  
**[www.i-Base.info](http://www.i-Base.info)**



**Southern African HIV Clinician's Society**  
**[www.sahivsoc.org](http://www.sahivsoc.org)**

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