

## may–june 2012

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## EDITORIAL

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This issue of HTB starts with reports from the recent UK BHIVA Conference, the Clinical Pharmacology Workshop and a few last studies from CROI. Together these reports include important aspects of care in the UK, new data on pipeline drugs and drug interactions and complications of HIV care.

Linking to earlier reports from CROI, we also review two papers from AIDS on renal health including a widely publicised US cohort study that reported significant associations between tenofovir and reduced markers of kidney function.

The regular news on generic approvals develops new relevance for services in the UK. Ten generic formulations of nevirapine recently received marketing approval for marketing in the US, as the originator patent ended last year. This also applies to coformulated AZT/3TC, with generic formulations also available.

Against an economic backdrop that is seeing established HIV care threatened by the services being opened to private tender, there will need to be a clear distinction for why many of these older drugs are no longer preferred in treatment guidelines.

This will make the new UK guidelines for adult care an essential reference for minimum standards of care.

Other guidelines published this month include updated pregnancy guidelines from BHIVA, new WHO guidelines on sero-different couples and a draft paper from NICE that includes reconising that suppressive ART, timed conception and related safety factors result in a minimal residual risk of transmission – something that will be crucial for couples unable to access sperm washing.

The treatment access news also features the “Stavudine Phase-out Festival” recently organised by HIV positive people in New Delhi, and this connects with the demands from ACT-UP, now commemorating their 25th year anniversary with a demonstration on Wall Street for both global access to treatment and better treatment.

In the links in this article we are proud to include the MSNBC news feature from the US Rachel Maddow show. As a former collaborator, activist and friend at the London organisation that gave birth to i-Base, it is good to see Rachel inspiring us with her humour, wit and political acumen, and eclipsing us with her media reach...

Happy reading and watching.

### HTB SUPPLEMENT

This issue of HTB includes a “Treatment Passport” as a supplement. This modest and understated booklet is designed to help HIV positive people track their HIV medical results and it particularly helpful for people who are newly diagnosed or just starting treatment.

As with all i-Base publications, these booklets are free in bulk to UK clinics and organisations.

## CONFERENCE REPORTS

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### 18th Annual BHIVA Conference

18–20 April 2012, UK

#### Introduction

**This year the BHIVA spring conference was held in Birmingham and as usual it included both important national research and impressive international speakers.**

In addition to more than 40 oral presentations, the meeting included case studies and over 230 posters.

The selection of reports below only highlights some of these studies. For further details please see the full programme and contact the researchers directly.

The abstracts from the conference are available free online as a PDF supplement to the April edition of HIV Medicine.

<http://onlinelibrary.wiley.com/doi/10.1111/hiv.2012.13.issue-s1/issuetoc>

As with previous years, some of these sessions will be available as webcasts and some of the slide presentations can be viewed or downloaded from the conference website.

<http://www.bhiva.org>

Reports in this issue include:

- Half of gay men in London interested in daily PrEP to reduce risk of HIV
- Recent infection is common in UK; 30% gay men aged 15-25 infected within a year of diagnosis
- One third of HIV positive people at five UK clinics have symptomatic depression: link to adherence and viral suppression - 40% cases are untreated

- Hodgkin's lymphoma: survival normalises to HIV negative rates despite more advanced disease at diagnosis
- Promising outcomes from laser ablative treatment of AIN 2/3 to prevent anal cancer
- KS in the HAART era includes patients with high CD4 and suppressed viral load: importance of KS chemotherapy for some patients in addition to ART
- 3rd vs 4th generation HIV testing: almost half of UK clinics out of step with national guidelines
- Case reports of complications from ketamine use in two MSM on ritonavir-based combinations
- Intranasal and topical corticosteroids and risk of Cushing's symptoms in HIV patients on ritonavir-based combinations
- Outcomes from PI switches to atazanavir in London
- Intimate partner violence towards HIV positive women in the UK

## Half of gay men in London would chose oral PrEP to reduce risk of HIV

**Simon Collins, HIV i-Base**

**The level of caution (and even hostility) from many healthcare workers in the UK to using PrEP to prevent HIV transmission, appears to actually increase in proportion to the evidence that supports its potential benefit.**

The practical and medical concerns relating to cost, resistance, toxicity, adherence and prescription details are all important, but when potential protection is now predicted as >99% in people who take 4-7 daily doses a week, it becomes essential that this option be available for high risk individuals, given the current statistics on continued new infections.

A study presented by the UK Health Protection Agency suggested that while PrEP may not be for everyone – a fear of those most skeptical – a significant proportion of high risk gay men see PrEP as an option they would actively choose.

The Gay Men's Sexual Health Survey is a biennial community based cross sectional survey that in 2011 (from March to June) recruited more than 1200 gay men from social venues (bars, nightclubs and saunas) in London. The questionnaires were self-completed anonymously and 1005 participants also agreed to a saliva sample for HIV testing (anonymised solely for the survey).

In addition to sexual health and behaviour, the survey asked about prior use of PEP and PrEP and "How likely is it that you would take a pill (oral dose) on a daily basis to prevent HIV infection?"

Of the 768/842 HIV negative men who answered this part of the survey, 34% reported interest in PrEP as "very likely" and 16% as "likely". Just as importantly, 15% were "unlikely" and 26% "very unlikely". The important conclusion is that while some men would not want to take PrEP at least as many (twice as many in this survey) would find a daily oral prophylactic pill acceptable.

Demographics of the 842 men who were HIV negative included mean age 34 years (SD +/- 9.2; range 18-71 years), 82% were white, 86% employed, 93% >2 years education post 16 years and 78% had an inner London postcode. While 10% had previously used PEP, only 2% had used PEP.

In multivariate analysis, the predictors for wanting to use PrEP (adjOR, 95%CI) included younger age (<35 years: aOR 1.58; 1.16-2.15), recent attendance of STI clinic (aOR 1.59; 1.03-2.46) and previous use of PEP (aOR 1.96; 1.17-3.26). Having >10 partners in the last year, unprotected anal intercourse (UAI) in the last year, or UAI with unknown status partner in the last year were statistically significant factors only in the unadjusted analysis. However, younger age (aOR 2.29; 1.68-3.13) and >10 partners (aOR 2.47; 1.76-3.48) were both strongly associated with STI attendance in the last year.

A second study on acceptability of PrEP, from a smaller survey of gay men attending Manchester Centre for Sexual Health, was presented by Thng and colleagues as a poster. [2]

Of over 3000 attendees from November 2011 to January 2012, 12% were gay men, with 95/112 men who agreed to the survey completing and returning it. The mean age was 28 years, 80% were white Caucasian, with a median of 4 sexual partners in the previous year. 84% said that they used condoms "at least 50% of the time" and staying HIV negative was important to 87%.

Willingness to use oral PrEP was reported by 64% with more than half of these replies indicating use of daily PrEP for >6 months, 90% that monitoring would be acceptable and 85% that information provided on the potential side effects also sounded acceptable.

Approximately 20% of people interested in PrEP were only interested if it could be taken around or after sex, rather than daily. 66% said that taking PrEP would not change the frequency of condom use and none said that they would stop condom use altogether. Most (86%) would be unlikely to have more partners.

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### C O M M E N T

**The emphasis on background risk is important. The most impressive data has come from the iPrEX study that enrolled generally young gay men who had multiple aspects of their lives that put them at high risk. This included young men, multiple partners, high alcohol and recreational drug use, low condom use, rare discussion about HIV prior to sex, high levels of transactional sex etc. [3]**

**PrEP is unlikely to be affordable for most people unless this is covered by public healthcare. At current therapeutic prices, daily Truvada is likely to cost several thousand pounds a year, even with intermittent dosing (the efficacy of which has yet to be established).**

The option for this intervention has the potential for a young gay man to have a higher protection than any other intervention, for what might be a short period of an otherwise long and healthy life. Last year more than 3000 gay men in the UK were diagnosed HIV positive and another HPA presentation at BHIVA highlighted that 22% of these were recent infections. When looking at the impact of age, recent infections were disproportionately higher (30%) for gay men under 25 (compared to 15% for those older than 50 years). [4]

This survey is an important first step in clearly demonstrating a high level of interest from the target group for who this intervention is likely to be appropriate and cost effective.

While this was a survey in broadly a white, educated and economically stable population, the survey was also conducted when information about the efficacy of PrEP was relatively new, and prior to the most recent efficacy data.

It also shows that it might be relatively easy to identify men at higher risk through GUM clinics and this might also broaden the demographics of people at risk, given the more recent data from CROI this year supporting higher efficacy. [5]

It now becomes a public health issue, that should be promptly recognised, both for research and service provision. It is difficult to understand why the PROUD study for PrEP in high risk gay men was turned down for NIHR funding. However, a smaller pilot study, sponsored by Gilead, still hopes to enrol 500 higher risk gay men later this year using a design that includes deferred (by 6 months) vs immediate PrEP.

#### References

1. Aghaizu A et al. Who would use PrEP? Predictors of use among MSM in London. 18th BHIVA Conference, 18-20 April 2012. Oral abstract O23.
2. Thing C et al. Acceptability of HIV pre-exposure prophylaxis (PrEP) and associated risk compensation in men who have sex with men (MSM) accessing GU services. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Poster abstract P233.
3. Grant RM et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. NEJM. 23 November 2010 (10.1056/NEJMoa1011205). Free access:  
<http://www.nejm.org/doi/full/10.1056/NEJMoa1011205>
4. Aghaizu A et al. Recently acquired HIV infections: an overview of surveillance in the UK. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Oral abstract O19.
5. Anderson P et al. Intracellular tenofovir-DP concentrations associated with PrEP efficacy in MSM from iPrEx. 19th CROI 2012, Seattle. Oral late breaker abstract 31LB.  
<http://www.retroconference.org/2012b/Abstracts/45431.htm>

## Recent infection is common in UK; 30% gay men aged 15-25 infected within a year of diagnosis

### Simon Collins, HIV i-Base

**Two years ago the UK Health Protection Agency (HPA) expanded access to avidity testing (which indicates the likelihood that HIV infection occurred within the previous 6 months) to all newly diagnosed patients.**

Additionally, the agency decided to return results to patients, with the understanding that this is more sensitive on a population than individual level.

Also called the Recent Infection Testing Algorithm (RITA) and previously referred to as STARHS (Serological Testing Algorithm for Recent HIV Seroconversion), the UK AxSYM avidity index (AI) is a guanidine-based test where a cut off AI < 0.8 is interpreted as recent infection (95%CI 5-8 months), with a 4.5% false positive rate (based on 1287 tested >1 year after diagnosis).

An analysis of the first two years results from this programme was presented at BHIVA. More than 90 clinics and 50 laboratories have joined the scheme, sending baseline samples to the HPA laboratory in Colindale, with the percentage of newly diagnosed samples in England and Northern Ireland increasing from 26% in 2009 to 46% in 2011 (reaching 60% in 2012).

Of the 6284 results available, probable risk category was 50% gay men (n=2848) and 50% heterosexual (n=1146 men and 1706 women). Only 93 diagnoses related to IV drug use, but 491 samples were unclassified.

While 14% (95%CI 13.7-15.5%) of the overall cohort (917/6284) indicated recent infection, this varied significantly by risk group with more than 22% (95%CI 20.7-23.8%) of recent infections in gay men, 8% (95%CI 7.1-9.1%) in heterosexual transmissions (similar for men and women) and 4% (95%CI 1.2-10.6%) in IDUs.

There was also a striking inverse correlation between older age and risk of recent infection among gay men. Recent infection accounted for approximately 30% of diagnoses in men aged 15-24 (n=118), 25% of those aged 25-34 (n=268), 18% aged 35-50 (n=209) and 13% aged > 50 years (n=37).

For heterosexual transmissions, younger age was less dramatic, but accounted for approximately 18% of women and 10% of men aged 15-24 and 8% women and 13% men in the 25-34 age group.

These results included a caution on the need for estimates of population incidence rates in order to interpret these findings. A survey of the acceptability of this service for healthcare staff has already been published in HIV Medicine, with an ongoing patient survey still ongoing. This is essential due to the potential for results to be used together with sexual history in identifying possible source partners.

#### C O M M E N T

**These results are an important new aspect of the important work carried out by the HPA. The UK is the only country currently using avidity testing for all new diagnoses and that returns results to patients.**

Ref: Aghaizu A et al. Recently acquired HIV infections: an overview of surveillance in the UK. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Oral abstract O19.

## **One third of HIV positive people at five UK clinics have symptomatic depression: link to adherence and viral suppression – 40% cases are untreated**

**Simon Collins, HIV i-Base**

**The ASTRA study (Antiretrovirals, Sexual Transmission Risk and Attitudes) is a UK multicentre prospective study using self-completed questionnaires relating to HIV and depression in over 3000 HIV positive people. Importantly, the study also correlates responses to adherence and clinical outcomes.**

The PHQ-9 questionnaire used in the study classifies participants according to presence/absence of depressive disorder (DD) or major depressive disorder (MDD) and a depression severity score (DSS) that divided diagnoses (from a scale of 0-27) into none, minimal, mild, moderate or severe.

Results from the first 2175 responses (from February to November 2010) were presented by Fiona Lampe from University College London in an oral abstract session. Baseline demographics for this analysis included: 16% women; 73% MSM; 10% heterosexual men. Mean age was 44 (range 18-80). Ethnic classification was: 70% white; 15% Black African; 14% other ethnicity. Approximately 86% were on ART, 9% of whom were not suppressed (VL >50 copies/mL).

For the primary endpoints, the prevalence was 26.6% (95%CI: 24.8-28.5) for DD and 19.1% (95% CI 17.4-20.7%) for MDD, with 27% participants having moderate or severe depression by DSS ( $\geq 10/27$ ).

Perhaps surprisingly, in multivariate analysis, there were no significant differences in DD by gender, ethnicity, country of birth or ART. Younger age was associated with higher depression rates (32% age <30 to 17% at age >60,  $p=0.028$ ).

Significant associations ( $p<0.001$  for each trend) were seen with socio-economic factors including employment status (15% employed, 43% unemployed, 52% sick/disabled), education level (19% university vs 32% other), income (defined as 'money to cover basic needs: 13% 'yes mostly' through to 53% 'no') and social support – a measure of supporting relationships (9% "high" through to 66% "low").

Depression also correlated positively with duration of infection (20% <2 years, 24% 2-10 years, 30% 10-20 years and 35% >30 years), which is interesting given that depression was higher with younger age. Current CD4 count or ART status had no relationship to depression scores.

Higher rates of depression were closely related to lower adherence and lower rates of viral suppression. This ranged from 24% in people who had not missed ART in the past two weeks to 29% with one missed dose, 34% with two missed doses and 42% with 3 or more missed doses.

The percentage of patients with detectable viral load by depression index 14% for those with DD vs 7% for those with no DD, 13% vs 8% for MDD versus no MDD, and ranged from 7% none to 18% severe (DSS) in the non-depressed vs severely depressed groups respectively. The association between depression and viraemia remained significant after adjusting for clinic and self-reported adherence.

The study also indicated that these symptoms may be largely undiagnosed and untreated for many patients. Of the 579 people with depressive disorder (DD) by questionnaire 241 were receiving medication or other treatment and 338 were not. Conversely, of the 1596 people without depression, 200 were on (presumably effective) treatment and 1396 were not.

The total prevalence of depression (symptoms or treatment) was 35.8% (779/2175) in this study, of whom 43% (338/779) were untreated.

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

**This is a large study that included six different UK centres (the Royal Free, Mortimer Market, Homerton, North Manchester, Brighton and Eastbourne) with a broad patient demographic.**

**It is probably the largest UK study to date to comprehensively look at HIV and depressive symptoms and highlights very high rates of depression with a strong indication that this is likely to be under diagnosed and under treated.**

**These results, especially if confirmed in the full analysis (enrollment is now completed) support the important of identification and management of depression as an important part of HIV care.**

Ref: Lampe F et al. Depression and virological status among UK HIV outpatients: results from a multicentre study. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Oral abstract O10.

Further details, including the slides from this presentation are on the ASTRA study website:

<http://www.astra-study.org/>

## **Hodgkin's lymphoma: survival normalises to HIV negative rates despite more advanced disease at diagnosis**

**Simon Collins, HIV i-Base**

**High levels of treatment response to chemotherapy for Hodgkin's Lymphoma (HL) in the HAART era were reported in a combined analysis from five clinics, showing similar rates of event-free and overall survival compared to HIV negative controls.**

Chloe Orkin and colleagues analysed all cases of HL diagnosed at five London teaching hospitals from 1997-2010 who were treated with 4-6 cycles of AVBD (adriamycin, bleomycin, viznblastine and dacarbazine). Of these, 97/237 were HIV positive and 90/97 were on HAART during HL treatment. HIV viral load was undetectable in 52/86 HIV positive patients with data and low (<6,000 c/mL) in others but 53% (47/97) had CD4 <200 cells/mm<sup>3</sup>.

HIV patients were older (median age: 41 vs 31 years, p<0.001), more likely to be male (88% vs 59%; p<0.001). They also had more advanced disease. This included higher rates of: mixed cellularity (54% vs 19%, p<0.001), stage 3/4 at diagnosis (80% vs 33%; p<0.001), B-symptoms (81% vs 36%; p<0.001), Hb <10.5 g/dL (46% vs 20%; p<0.001), albumin <4 g/dL (76% vs 35%, p<0.001) and a higher International Prognostic Score (IPS 3 in 71% vs 22%; p<0.001).

Over median follow-up of 59 months (range 8–172), similar response rates (74% vs 81%), duration of response (33 vs 44 months), 5-year event-free survival (59% vs 65%) and 5-year overall survival (79% vs 88%) were seen in the HIV positive vs HIV negative groups respectively, see Table 1. In the combined group, 40 patients relapsed at a median time of 7 months (range: 1–106).

**Table 1: Responses to ABVD chemotherapy in HIV positive vs HIV negative people**

	HIV positive	HIV negative	p-value
Complete response rate	74%	81%	NS
Median duration of response	33 mo	48 mo	NS
5-yr event-free survival	59% (95%CI: 46–69)	65% (95%CI: 56–72)	NS
5-yr overall survival	79% (95%CI: 67–87)	88% (95%CI: 80–92)	p=0.06 (NS)

**C O M M E N T**

**These results are important and impressive, despite including data from the early HAART era, and especially given the more advanced disease at HL diagnosis.**

Ref: Orkin C et al. HIV Status does not Impact on Outcome in Patients with Hodgkin Lymphoma Treated with ABVD Chemotherapy in the HAART Era. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Oral abstract O13.

## Promising outcomes from laser ablative treatment of AIN2/3 to prevent anal cancer

**Simon Collins, HIV i-Base**

**The incidence of anal cancer is higher in HIV positive compared to negative populations with lower rates of clearance (87% vs 38% at 5 years) and progression rates from high-grade anal intraepithelial neoplasia (AIN 2/3) in observational studies range from approximately 8-14% over 5 years.**

Thornhill and colleagues reported on retrospective results (median 69 months follow-up, range 36-180 months) from treating 91 patients (35 AIN 3; 56 AIN 2) with laser ablative treatment at Homerton Hospital in east London. [1]

Most patients were male (82/91) and MSM (80/82). Mean age was 36.9 (range 20–68). Of the 56 HIV positive patients, 66% (n=37) had a CD4 nadir of <200 cell/mm<sup>3</sup>. 45% (25/56) had been HIV positive for 15 years or more.

None of the patients in this cohort developed anal cancer suggesting that treatment may have prevented lesion progression in some patients.

The single case of anal cancer in this cohort, not included in this analysis follow-up was less than 3 years was a 49 year-old man (HIV positive for 21 years) with a CD4 nadir of 8. He had advanced 3 quadrant AIN 3 disease that presented late.

A second poster reported prospective first year results from a new ano-rectal outpatient clinic for HIV positive patients at the Royal Free Hospital. [2]

This is a monthly clinic for patients with a history of anal warts or previously diagnosed AIN. Symptomatic patients are screened by anoscopy +/- (surgical) evaluation under anaesthesia (EUA) where indicated. Patients were referred by their clinic doctor or self referred through promotion throughout the clinic.

Data was compiled from 73 patients seen over 12 months. Median (IQR) demographics included: age 45 years (IQR 41–50) years, 91% were MSM (67/73), 85% Caucasian (61/73). 95% (69/73) were on ART, 82% (60/73) with undetectable viral load. CD4 at presentation and CD4 nadir were 511 (362–741) and 152 (26–288) cells/mm<sup>3</sup> respectively. Median time since HIV diagnosis was 15 years (10–20), with 11(6–13) years on HARRT. 75% (55/73) were smokers.

Anoscopy +/- EUA for screening was undertaken for 40% (30/73). Of these 27% (8/30) were diagnosed with AIN: AIN-1 (3), AIN-2 (2), and AIN-3 (3). 3/8 had prior diagnosis of AIN, the remainder were all newly diagnosed. 3/30 (10%) were diagnosed with ASCC and were managed by the surgeons and oncologists.

The clinic plans to expand the service to include a screening clinic specifically targeting all HIV positive, MSM who are >40 years, or have low CD4 nadir, or HIV infection > 10 years to undergo routine screening for AIN with Human Papilloma Virus (HPV) cytology, HPV typing and baseline anoscopy.

C O M M E N T

**Greater awareness of AIN in HIV positive gay men, easier access to screening and the necessary support to diagnose complications is important.**

**The variable progression rates, lack of natural history data and recent availability of effective treatments all highlight the urgent need for randomised data for the benefit of screening.**

References

1. Thornhill J et al. Treatment of anal intraepithelial neoplasia and prevention of anal carcinoma. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Poster abstract 64.
2. Grover D et al. Anal intraepithelial neoplasia: single centre experience. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Poster abstract 68.

## **KS in the HAART era includes patients with high CD4 and suppressed viral load: importance of KS chemotherapy for some patients in addition to ART**

### **Simon Collins, HIV i-Base**

An overview of Kaposi's Sarcoma (KS) in the HAART era was given by Mark Bower from the Chelsea and Westminster Hospital who focussed on the continued use for KS chemotherapy and included recent cases of KS in patients with high CD4 counts (>350 cells/mm<sup>3</sup>) and who have undetectable viral load.

While the incidence of KS has dramatically reduced since 1997 and 80% of patients diagnosed with early stage KS (T0) and with good immunity (CD4>150) commonly don't need additional treatment to ART [2] more advanced staging (T1 – any tumour-associated oedema or ulceration, extensive oral KS or non-nodal visceral KS) and reduced immune function (CD4 <150) should be treated with liposomal anthracycline in addition to ART (or paclitaxel for refractory KS).

The Chelsea and Westminster Hospital cohort from 1996 to 2012 now includes 521 first cases of KS. Most are men (94%) with 17% (86/521) in black Africans. Median age and CD4 counts at presentation are 38 years (range 16-71) and 168 cells/mm<sup>3</sup> (range 0-1200) with 66% (n=342) at stage T0 and 34% (n=177). Survival rates in the T0 and T1 groups at 14 years (Kaplan-Meier) are approximately 80% and 65%, respectively. These differences were driven mainly by an early impact <3 years of visceral involvement and presence of oedema/ulceration (later impact > 6 years), rather than oral involvement.

Of note, 15% of new diagnoses (80/521) were in people on established ART (> 3 months), 6% (n=32) had an undetectable viral load and 4% (n=20) had both undetectable viral load and a CD4 count >350 cells/mm<sup>3</sup>.

The Chelsea and Westminster group has also reported KS as an IRIS-related complication (defined as rapid KS progression during the 2-4 month window after starting ART) in 7% of patients (10/150) who started ART with a KS diagnosis, but higher rates have been reported (20%) in cohorts that only use ART and not concomitant KS treatment. Recurrent KS has also been reported in virologically suppressed patients with similarly good immune responses.

As well as efficacy in addition to ART reported in a recent randomised clinical study (though not greater survival in an African setting) [4], the importance of KS chemotherapy is also supported by minimal toxicity or prolonged negative impact on CD4 responses. This is now primarily for any patient with stage T1 disease and for the management of KS related to IRIS or in suppressed patients.

References

1. Bower M. Kaposi's Sarcoma in the era of HAART. BHIVA invited lecture. 18th BHIVA Conference, 18-20 April 2012, Birmingham.
2. Bower M et al. The effect of HAART in 254 consecutive patients with AIDS-related Kaposi's sarcoma. AIDS 24 August 2009, 23:1701-6.  
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## **3rd vs 4th generation HIV testing: almost half of UK clinics out of step with national guidelines**

### **Simon Collins, HIV i-Base**

In 2011, prompted by calls to the i-Base phonenumber reporting wide diversity in the information given to people contacting GUM clinics for HIV testing, i-Base wanted to understand why this was often different to UK guidelines. Although 4th generation HIV tests are recommended at four weeks post exposure, many people were still being advised to wait for three months.

Results from the prospective community survey of 112 randomly selected GUM clinics that was then undertaken, were presented by Emma Rezel from the London School of Hygiene and Tropical Medicine, in an oral presentation at BHIVA. [1]

A mystery patient scenario was used to conduct a semi-structured questionnaire at the point of contact or a contact the caller was immediately forwarded on to. This was to mimic the reality of advice and information made available in a natural situation to a member of the public calling a clinic with queries about HIV testing.

In response to the question "Is it a third or fourth generation test?" 40% of clinics stated it was a 4th generation test, 6% gave some indication that it was a 4th generation test, for example, mentioning that it could detect the presence of an antigen, 4% stated or gave some indication that they used a 3rd generation test, 2% stated they used both, 1% said they used a PCR test. However, 31% didn't know, 8% gave an inaccurate or unclear response, and 8% didn't answer.

Responses to the question "How accurate are the results and when should I come and get tested?" were equally mixed with only 24% of clinics mentioning the accuracy of fourth generation tests at 4 weeks post exposure and 36% only referring to accuracy at 12 weeks suggesting 3rd rather than 4th generation testing procedures were being referred to.

Although nearly all clinics mentioned the need for the caller to come into the clinic, only 41% were sensitive and non-judgmental and put the service-user at ease, providing responses:

*"There's no need to be anxious. A nurse will answer all your questions if you go in for an appointment."*

*"Even if he was positive, it depends on various factors, like, if he's on treatment and if there's blood-to-blood transmission. HIV is hard to catch so don't worry".*

By contrast, 13% of clinics scored particularly poorly in terms of sensitivity to the anxieties of the caller provide confusing or unsympathetic responses:

*"We don't understand it all so I doubt you will either."*

*"If you don't know much about him, why did you have unprotected sex with him?"*

*"We only see positive tests amongst heterosexuals who have sex with someone from Africa."*

*"If you're not prepared for a positive result, don't come in for a test."*

While these examples produced some of the few lighter moments during the conference, the implications of these findings was not lost on many attendees, especially given that an earlier BHIVA audit reported 4th generation tests being used by 95% of clinics that responded.

The i-Base study found no difference between geographical location of clinics (London vs out of London) but did find a statistically significantly better responses when callers were able to speak to a doctor, nurse or health advisor rather than an administrator or receptionist, suggesting that some degree of retraining be developed for anyone taking direct calls from members of the public.

In response to this issue, i-Base have produced a new non-technical guide to HIV testing and the risk of sexual transmission, free to order for UK clinics. [2]

### **BASHH statement on the window period (March 2010)**

- HIV testing using the latest (4th generation) tests are recommended in the BHIVA/BASHH/BIS UK guidelines for HIV testing (2008).
- These assays test for HIV antibodies and p24 antigen simultaneously. They will detect the great majority of individuals who have been infected with HIV at one month (4 weeks) after specific exposure.
- Patients attending for HIV testing who identify a specific risk occurring more than 4 weeks previously, should not be made to wait 3 months (12 weeks) before HIV testing.
- They should be offered a 4th generation laboratory HIV test and advised that a negative result at 4 weeks post exposure is very reassuring/highly likely to exclude HIV infection.
- An additional HIV test should be offered to all persons at 3 months (12 weeks) to definitively exclude HIV infection. Patients at lower risk may opt to wait until 3 months to avoid the need for HIV testing twice.

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## **Case reports of complications from ketamine use in two MSM on ritonavir-based combinations**

**Simon Collins, HIV i-Base**

**Zhou and colleagues from Brighton and Sussex Hospitals presented a poster detailing two cases of bile duct and liver complications related to recreational use of ketamine.**

Both patients had regularly used ketamine for 12 months and were taking ritonavir-boosted PIs. Patients presented acutely with nausea, vomiting and epigastric pain. ALT was raised at 3.2X and 10.1X the upper limit of normal (ULN) and an ALP raised 1.7X and 2.5X ULN for cases 1 and 2 respectively.

Case one was a 38 year old Caucasian man with CD4 count of 788 cells/mm<sup>3</sup> and undetectable viral load on stable ART (abacavir/3TC/darunavir/ritonavir) who reported daily use of 1-2 g ketamine.

Case two was a 25 year old Asian man with a CD4 count of 154 cells/mm<sup>3</sup> and viral load of 6,500 copies/mL on ART (tenofovir/FTC/lopinavir/ritonavir), with poor adherence, who used 1 g ketamine 3 times a week and high alcohol use (>70 units/week).

Antinuclear, antimitochondrial, anti-smooth muscle and anti-liver kidney microsomal antibodies, serum copper, serum caeruloplasmin, ferritin, transferrin, A1-antitrypsin HBV, HCV and CMV serology were all negative in both cases on more than one occasion. Magnetic resonance pancreatocholangiogram (MRCP) showed marked dilatation of the common bile duct (CBD) to 18mm (6X normal) and 14mm (4.5X normal) for cases 1 and 2 respectively. No underlying ductal obstruction was seen by ERCP.

Symptoms resolved after the discontinuation of ketamine with normalisation of LFTs and reduction in CBD diameter by 28% at 4 weeks (case 1) and 29% reduction at 12 weeks (case 2).

Although these complications are known with recreational ketamine the authors stated that these are first reports in HIV positive patients and suggested a possible faster progression (after ketamine use for 12 months vs 4 years) that may have been compounded by inhibitory impact of ritonavir on the CYP3A4 major pathway for ketamine elimination.

Ref: Zhou J et al. Dilated common bile duct and deranged liver function tests associated with ketamine use in two HIV positive MSM. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Poster abstract 226.

## **Intranasal and topical corticosteroids and risk of Cushing's symptoms in HIV patients on ritonavir-based combinations**

**Simon Collins, HIV i-Base**

**Although iatrogenic Cushing's syndrome has previously been reported as a complication from the drug-drug interaction between ritonavir and corticosteroids (we included two cases in HTB last year), two posters at BHIVA this year highlighted low awareness of this interaction, and that this can also occur with intranasal and topical formulations.**

Neal Marshall and colleagues from the Royal Free Hospital reported on 11 patients using ritonavir-based combinations who were also prescribed glucocorticoids: intra-articular/epidural triamcinolone (n=6), inhaled/intranasal fluticasone (n=4) and topical clobetasol (n=1). [1]

All patients had biochemical evidence of marked adrenal dysfunction and were referred to an endocrinology clinic. One or more features of Cushing's syndrome manifested in 7/11. These symptoms can be similar to lipodystrophy (weight gain on the trunk and face but not limbs, fat accumulation in the neck and shoulders, facial swelling ("moon face"), skin and hair changes and multiple other adrenal complications.

Replacement steroids due to prolonged adrenal suppression were prescribed for 10/11 patients and 4/10 had complete, but delayed, recovery of the hypothalamic-pituitary-adrenal (HPA) axis. Other features included vertebral crush fracture after long term inhaled fluticasone (n=1), and significant deterioration of type 2 diabetes after intra-articular triamcinolone injection (n=1).

The poster stressed the importance of individualised care: switching to a non-PI based combinations when available or using alternatives to fluticasone and triamcinolone.

The second poster reported on two patients attending the Lawson Unit in Brighton who had marked adrenal insufficiency following injections of triamcinolone. Both cases were women on ritonavir-including combinations, summarised below (from the study abstract). [2]

Case 1 presented with a 4 week history of postural dizziness, lethargy, weight gain, facial swelling and had noticed difficulty getting up from a chair. She had a history of seronegative arthropathy, and had received a triamcinolone injection into both shoulders and trochanteric bursae 2 weeks before the onset of symptoms. She had cushingoid facies, with truncal obesity, abdominal striae, oral candida and proximal myopathy. A random glucose was 16.2mmol/L her random cortisol was low at 30 nmol/L and a short synacthen test showed adrenal insufficiency (baseline cortisol 14 nmol/L, 30mins 242 nmol/L, 60mins 302 nmol/L). She required steroid replacement therapy, and insulin to control her hyperglycaemia.

Case 2: A 58 year old lady attended for routine HIV monitoring blood tests and reported weight gain and increased appetite. She was HIV positive and stable on treatment with Truvada / atazanavir / ritonavir. Her CD4 count was noted to have fallen to 118 (22%) from 398 (28%), her HIV viral load remained <40copies/mL. On review it was noted she had gained 2.5kg in weight and appeared Cushingoid. She had received an intra-articular injection of triamcinolone acetate into her right knee 4/52 earlier. A random cortisol was low at 67nmol/L and a subsequent short synacthen test revealed adrenal insufficiency (Baseline 210nmol/L, 30mins 360nmol/L, 60mins 441nmol/L). 3 weeks later, her adrenal function had recovered without steroid replacement therapy.

This poster concluded: "Triamcinolone injections should be avoided in patients taking ritonavir. There are no case reports of a similar interaction between methylprednisolone and ritonavir, which may be a safer alternative to triamcinolone."

### References

1. Marshall N et al. Secondary adrenal suppression and Cushing's syndrome caused by ritonavir boosted effects of inhaled fluticasone, injected triamcinolone and topical clobetasol: a case series. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Poster abstract P121.
2. Conway K et al. Steroids strike again – but where is the warning? 18th BHIVA Conference, 18-20 April 2012, Birmingham. Poster abstract P141.

## Outcomes from switches to atazanavir/r in London

**Simon Collins, HIV i-Base**

From April 2011, ARV prescribing in London clinics was changed to reflect the outcomes of therapeutic tendering by the London HIV Specialist Commissioning Group (LSCG) for drugs that have similar activity. This resulted in potential bulk discounts for some drugs if predetermined sales targets were met, while maintaining clinical criteria for prescribing based on efficacy and safety data.

In practice, this involved prescribing Kivexa rather than Truvada, when clinically appropriate for patients starting treatment and use of atazanavir/ritonavir as first-line PI, and switching to atazanavir/ritonavir when clinically appropriate, for patients using other protease inhibitors.

Whilst this important change in public prescribing was undertaken with the assurance of six monthly audits for patient outcomes, the London Commissioners have still to publish their data.

The first public data on the outcomes of one aspect of this policy – use of atazanavir switching – were presented from an audit from the Royal Free Hospital of 201 patients changing PI therapy (total 232 switches) between April 2011 and January 2012. Of these, 21 were excluded as they were switches away from atazanavir/r (62% due to side effects).

The majority (85%) of the remaining cases (153/180) switched to atazanavir/r, half (55%) due to the tender process, 28% for toxicity or intolerance, 7% viral failure/resistance and 10% for other/unknown reasons.

Only 22 people switched to darunavir/r and 5 to lopinavir/r. Reasons for not using atazanavir/r in these patients included: resistance (26%), drug interactions (22%), prior intolerance of atazanavir (11%) and using mono/dual PI therapy (19%).

Rates of short-term discontinuation (within 3 months) were similar in people who switched due to the tender (12/78; 15%) compared switching to atazanavir for other reasons (8/51; 16%), or switching to other ARVs (0/15; 0%),  $p=0.26$ . Use of tenofovir had no impact on discontinuation: 16% using tenofovir (14/90) vs 11% without tenofovir (6/54),  $p=0.46$ .

Although unrelated to the London guidelines, a separate study from the Chelsea and Westminster Hospital reported on outcomes from 192 patients who switched from lopinavir/r to either atazanavir/r ( $n=103$ ) or darunavir/r ( $n=89$ ) from May 2004 to May 2011 and who had at least two years of follow-up.

### C O M M E N T

**The London tender is expected to save more than £5 million over the first year with additional savings through to year two. This snapshot appears to support the safety of the PI-switch component of the London prescription changes. However, this does not replace the Commissioners own audit, results of which are still awaited.**

Ref: Marshall N et al. Switching to atazanavir due to therapeutic tenders: short term outcomes. 18th BHIVA Conference, 18-20 April 2012, Birmingham. Poster abstract P195.

## Intimate partner violence towards HIV positive women in the UK

**Rebecca McDowall, HIV i-Base**

**Although previous studies outside of the UK have reported higher levels of intimate partner violence (IPV) towards HIV positive women there is a lack of UK based data on this subject. A joint study between Homerton University Hospital and City University, London presented findings of above average IPV rates at an inner city, outpatient HIV clinic.**

Results from the cross-sectional study were presented by Rageshri Dhairyawan, in an oral presentation. [1] Data was collected using a standardised questionnaire, evaluated using the HARK tool which asks whether the respondent has been humiliated, afraid, raped or kicked/hit by a partner. [2]

Of 314 women invited to participate, 198 consented and 191 women answered questions on IPV. Median age was 38 years (range 21-71 years); 70% were African, 20% black UK, 6% white and 4% other. Logistic regression models were fitted to estimate adjusted odds ratios (AOR).

Over half of the women (52%, 99/191) reported lifetime experience of IPV, 14% (27/191) within the last year and 14% during pregnancy. Women reporting IPV within the last year included: humiliation (12%), being afraid (9%), rape (3%) and hit/kicked (4%).

There were statistically significant associations between lifetime experience of IPV and self-reported mental health problems (AOR 3.44; 95% CI 1.24, 9.57) and black ethnicity not born in Africa (AOR 4.63 compared to being born in Africa, 95% CI 1.06, 20.11). Older age was associated with a reduced risk (AOR 0.92 per year increase; 95% CI 0.86, 0.97). Importantly, IPV was not found to be associated with socioeconomic or immigration status, educational background or substance misuse (all  $p > 0.1$ ).

In questions following the presentation it was asked whether a comparative study had been conducted in the local HIV negative population. This had not been done as a part of this study but rates of IPV in the study population were described as being higher than the local prevalence in women in primary care. The study highlighted a need for greater awareness of IPV experienced by HIV positive women in the UK, and screening was recommended in women attending HIV clinics.

#### References

1. Dhairyawan R et al. Intimate partner violence in women living with HIV attending an inner city clinic in the UK. 18th BHIVA Conference, 18-20 April 2012. Oral abstract O5.
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## CONFERENCE REPORTS

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### **13th International workshop on Clinical Pharmacology of HIV Therapy**

**16–18 April 2012, Barcelona**

#### **Introduction**

**This important annual workshop always includes studies that are not presented at other meetings and it is appreciated that the organisers have made both the abstract book and many of the presentations available to download in PDF format.**

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

[http://regist2.virology-education.com/abstractbook/2012\\_3.pdf](http://regist2.virology-education.com/abstractbook/2012_3.pdf)

Reports on drug interactions are selected, and in some cases summarised, from a full report produced by the pharmacology group at Liverpool University ([www.druginteractions.org](http://www.druginteractions.org)).

The full Liverpool report is available online and in PDF format.

[http://www.hiv-druginteractions.org/data/NewsItem/94\\_13%20PKW%20Barcelona.pdf](http://www.hiv-druginteractions.org/data/NewsItem/94_13%20PKW%20Barcelona.pdf)

Studies in this HTB include:

- Studies on pipeline ARVs: Quad, elvitegravir/cobicistat, cobicistat, GSK1265744, BMS986001 dolutegravir, GSK-1265744, long acting formulations (monthly injections): rilpivirine-LA, raltegravir and patient views.
- Washout pharmacokinetics of transplacental raltegravir in neonates
- Interactions between malaria drugs and etravirine or darunavir/r
- Antimalarial amodiaquine and nevirapine
- Atazanavir/ritonavir plus raltegravir
- Atazanavir/ritonavir and voriconazole not to be coadministered
- Milk thistle (silymarin) and darunavir/ritonavir
- Echinacea and etravirine
- Warfarin and ARVs: impact of African American race and ritonavir

Abbreviations used in these reports include:

C<sub>max</sub> = Maximum concentration; C<sub>min</sub> = minimum concentration; AUC = Area Under the Curve; GMR = Geometric Mean Ratio; IC<sub>90/50</sub> = Inhibitory Concentration needed to reduce viral production by 90/50% in vitro.

### **Studies on pipeline ARVs**

#### **Simon Collins, HIV i-Base**

**This year the PK Workshop was notable for a number of important studies on ARVs that are already advanced in the pipeline. Please see the study abstracts and Liverpool University report for more details on each study.**

#### **Quad**

Quad is an investigational four-drug single pill formulation of the integrase inhibitor elvitegravir with the booster cobicistat plus tenofovir and FTC. Quad is currently submitted to the FDA (with a decision expected by August 2012). Several studies at the workshop provided drug interaction data on components of this and other Gilead pipeline compounds.

#### **Elvitegravir/cobicistat**

An oral presentation included three separate PK interactions studies. [1]

Coadministration of elvitegravir/cobicistat with rosuvastatin (10 mg single dose) had no significant effect on elvitegravir exposure, but increased rosuvastatin AUC by 38% and C<sub>max</sub> by 89%, although this was not considered clinically relevant.

Coadministration of elvitegravir/cobicistat and rifabutin (300 mg once daily alone or 150 mg every other day with EVG/COB) in a 13-day study reduced elvitegravir C<sub>trough</sub> by 67%. Although rifabutin exposure remained similar, the active metabolite increased by 4.8 to 6.3-fold, increasing antimycobacterial activity by 21%. Coadministration is not recommended based on the reduction in elvitegravir C<sub>trough</sub>.

A third component of this study reported that a reduced dose of elvitegravir/cobicistat (85 mg/150 mg) with atazanavir (300 mg daily) – using the cobicistat to boost both elvitegravir and atazanavir – resulted in modest reductions in atazanavir C<sub>max</sub> (GMR 76.1; 90%CI 59.1, 96.9) and C<sub>trough</sub> (GMR 80.5; 90%CI 55.6, 117) and comparable AUC and C<sub>max</sub> for elvitegravir, with higher C<sub>trough</sub>. (GMR 192; 90%CI 163, 225) compared to elvitegravir/cobicistat 150 mg/150 mg.

### **Cobicistat: the PK booster in Quad**

Although most research has until now used cobicistat dosed at 150 mg once-daily, a study reported that used twice-daily (150 mg BID) this resulted in approximately 4-fold higher exposure (compared to once-daily). While cobicistat had a similar impact to ritonavir when boosting darunavir, this was not seen with tipranavir. Tipranavir exposure was markedly lower when boosted by cobicistat and cobicistat exposure was 90% lower compared to cobicistat alone. [2]

Comparable bioavailability results were also presented for two fixed dose formulations of darunavir/cobicistat (800 mg/ 150 mg) compared with darunavir/ritonavir (800 mg/100 mg). [3]

### **GS7340 – tenofovir prodrug**

Although selection of the 25 mg dose for single compound of the tenofovir prodrug GS7340 has been reported, the boosting effect that cobicistat has on GS7340 means 10 mg doses are being studied in coformulations. [4]

These include with elvitegravir/cobicistat/FTC in a new version of Quad (Quad+) and with darunavir/cobicistat/FTC in a single-pill PI-based fixed dose combination. [5, 6]

### **Dolutegravir**

Dolutegravir, an integrase inhibitor in development by ViiV, is primarily metabolised by UGT1A1, but uses CYP3A as a minor route (10-15%), However there is no clinical impact from inducing or inhibiting major CYP, UGT or transported pathways (except OCT2).

A helpful review of currently known interactions presented at the workshop, included significantly increased dolutegravir exposure with atazanavir (boosted and unboosted) and reduced exposure with darunavir, fosamprenavir, tipranavir, efavirenz and rifabutin (by 30%-75% and not considered clinically significant for treatment naïve patients). [7]

However, etravirine reduced dolutegravir by 88% but this might be overcome if coadministered with lopinavir/r or darunavir/r (which in turn increases dolutegravir exposure). Dolutegravir needs to be given twice daily with rifampin. Antacids need to be separated by at least two hours, due to metal cation chelation rather than a pH effect.

### **GSK-1265744**

A follow-up integrase compound from GSK/ViiV called GSK-1265744 reported no interactions when the oral formulation was dosed with oral etravirine in 12 HIV negative adults. [8]

This study is relevant as GSK-1265744 is also being developed as a long-lasting injection formulation. Studies will compare pharmacologic properties to oral administration and also to the long acting formulation of the NNRTI rilpivirine, with potential for use as both treatment and PrEP. [9, 10]

### **BMS-986001**

BMS-986001 is an NRTI with a similar structure to stavudine (d4T) but a safety profile that is unlikely to be associated as it is a weak inhibitor of DNA synthesis in vitro and therefore not expected to affect mitochondrial function and in turn cause the side-effects associated with d4T.

The workshop included a Phase I/II dose finding study in treatment-experienced patients (off treatment for at least 3 months). Following 10 days monotherapy, median reductions in viral load on day 11, were 0.97, 1.15, 1.28 and 1.15 log in the 100, 200, 300, and 600 mg groups, respectively (vs -0.07 in the placebo group) from median baseline levels across groups of 4.3 – 4.6 log (range 3.5–5.3 for the whole study). [11]

This was a new analysis by BMS from a study that was first presented two years ago. [12]

### **Long acting formulations (monthly injections): rilpivirine-LA, raltegravir, patient views**

The development of a nanosuspension formulation of the NNRTI rilpivirine that could be given by intramuscular injection was reported several years ago.

A single-dose pharmacokinetic study in HIV negative people reported prolonged exposure in plasma, genital compartments and rectal following single 300, 600, or 1200 mg doses [13], together with a study reporting a lack of negative drug interactions between rilpivirine and dolutegravir (both also presented this year at CROI) [14]

While this compound was presented for its potential to reducing the reliance on daily adherence in the context of PrEP, it might also be an important option for HIV treatment. This would require other long lasting formulations of ARVs to construct a combination. The development of a similar formulation for dolutegravir is clearly of interest. [15]

A safety issue for long-acting formulations, especially in the absence of an antidote to rapidly eliminate the active compound in the event of a severe adverse reaction, might be covered by a period of oral dosing to confirm individual tolerability, especially as both integrase and NNRTI classes have been associated with hypersensitivity reactions.

A recent survey of 400 HIV positive patients attending two US clinics reported 61%, 72% and 84% interest in ART injections based on weekly, two-weekly and monthly formulation respectively, with higher interest in people with concerns about adherence, although 35% were also concerned about needle use. [16]

#### References

Unless stated otherwise, references are to the Programme and Abstracts of the 13th International Workshop on Clinical Pharmacology of HIV Therapy, 16-18 April 2012, Barcelona. These are published in *Reviews in Antiviral Therapy & Infectious Diseases – Volume 3: 2012* and available free in PDF format online.

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## Washout pharmacokinetics of transplacental raltegravir in neonates

### Polly Clayden, HIV i-Base

#### There are limited data to guide dosing of antiretrovirals in neonates (and limited approved drugs for this age group).

There is an urgent need for new options both for prophylaxis for neonates at high risk of infection and to treat vertically infected young infants.

Raltegravir (RAL) was recently approved by the FDA for use in children aged two years and above; pharmacokinetics (PK) in infants aged four weeks to two years is under evaluation.

RAL primarily uses the UGT1A1 pathway. UGT1A1 is reduced in neonates but increases in the first weeks to months of life. This pathway is the same as that used by bilirubin and competition for protein binding sites might result in kernicterus. This effect is unlikely unless RAL exceeds typical peak concentrations (approx 4500 ng/mL) by 50 to 100 fold. The toxicity profile of RAL in infants is currently unknown.

At the PK workshop, 2012, Diana Clarke from Boston Medical Centre presented data from IMPACT P1097. This is an ongoing phase 4 multicentre trial designed to determine washout PK in infants born to HIV positive women who received RAL in pregnancy and to evaluate the safety of in utero/intrapartum exposure in infants. These data will help develop neonatal dosing regimens for future study.

Women who received at least two weeks of RAL (400 mg twice daily) prior to study entry and continued in labour were enrolled.

Maternal and cord blood samples were obtained within one hour of delivery as well as neonatal blood samples at four time points: 1-5, 8-14, 18-24, and 30-36 hours after birth. RAL concentrations were determined using a validated HPLC-MS-MS method. The neonatal half-life was estimated using the terminal 3 concentration- time points. Safety of in utero/intrapartum exposure to RAL was evaluated through 20 weeks follow up. **Data are geometric mean (%CV).**

Twelve mother/infant pairs were enrolled and data were available for nine pairs. The mean gestational age of the infants was 37.5 weeks and mean birth weight was 3.33 kg. The majority 8/12 were delivered by planned caesarean section, three by spontaneous vaginal delivery and one by forceps/vacuum.

Mean maternal RAL concentration at delivery was 772 ng/mL (113%). Mean cord blood RAL concentration (at mean 3.6 hours after maternal dosing) was 880 ng/mL (78%). Mean cord blood to maternal delivery concentration ratio was 1.14 (55%). Cord blood to maternal plasma concentration increased by approximately 1.5 by 2 to 4 hours after maternal dosing.

Mean last infant RAL concentration at 30 to 36 hours was 407 ng/mL (range 42.1 to 1401 ng/mL). Mean infant RAL half-life was 23.2 hours (range 9.3-87.8 hours). RAL elimination was highly variable.

No safety issues were observed in the first 20 weeks of life.

Simulations combining these data plus PK from 4 weeks to 6 months in P1066 will be used to determine dose and dosing frequency for neonates.

## C O M M E N T

**Raltegravir has important characteristics that make its potential use in pregnancy and for uninfected (and infected) infants compelling.**

**Because of its rapid first and second phase viral decay plus good transplacental transfer, new BHIVA guidelines recommend women who are untreated in pregnancy or do not initiate treatment until after 28 weeks receive it as part of their regimen. There are limited reports from the UK, presented at the recent BHIVA meeting, which we will cover in the next issue of HTB as we have with previous presentations [2, 3, 4].**

**Investigation into use of raltegravir in neonates is ongoing.**

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## Interactions between malaria drugs and etravirine or darunavir/r

**[www.drug-interactions.org](http://www.drug-interactions.org)**

**The interactions at steady state between artemether/lumefantrine (40/480 mg for three days) and etravirine (200 mg twice daily) or darunavir/r (600/100 mg twice daily) were investigated in two HIV negative groups (n=14 each).**

Etravirine decreased the AUC of artemether, dihydroartemisinin and lumefantrine by 38%, 15% and 13%, respectively. Darunavir/r decreased the AUCs of artemether (16%) and dihydroartemisinin (18%) but increased lumefantrine AUC by 2.75-fold. Co-administration of artemether/lumefantrine had no effect on the AUCs of etravirine, darunavir or ritonavir.

The antimalarial activity of artemether may be lowered in the presence of etravirine and therefore, the combination should be used with caution.

Pharmacokinetically, darunavir/r can be co-administered with artemether/lumefantrine without dose adjustment however co-administration is not recommended with other drugs that may cause QTc prolongation (such as lumefantrine).

Ref: Kakuda T et al. Pharmacokinetic interaction between etravirine or darunavir/ritonavir and artemether/lumefantrine in healthy volunteers: a randomised trial. 13th PK Workshop, Barcelona, 2012. Oral abstract O\_05.

## No interaction between antimalarial amodiaquine and nevirapine

**[www.drug-interactions.org](http://www.drug-interactions.org)**

**The impact of nevirapine-based ART on the disposition of amodiaquine/artesunate (600/200 mg once daily) was investigated in a parallel group study in 21 HIV positive patients (n=10 nevirapine; n= 11 ART naïve controls).**

No significant differences in the pharmacokinetics of amodiaquine or desethylamodiaquine (the active metabolite) were identified between groups, however considerable interpatient variability was observed. Comparing the control to NVP group, AUCs were 242±78 vs 197±94 ng/ml.h (p=0.26) for amodiaquine and 21,311±21,012 vs 13,121±7947 ng/ml.h (p=0.26) for desethylamodiaquine, respectively. C<sub>min</sub> of the active metabolite did not differ between groups (137±65 vs 124±52, p=0.26).

Four individuals in the control group discontinued the study protocol due to weakness, vomiting, diarrhoea, and dizziness, while no subjects in the NVP group experienced treatment-limiting adverse effects. Previous studies have reported similar exposure to artesunate when used with nevirapine.

Ref: Fehintola FA et al. Pharmacokinetics of amodiaquine and desethylamodiaquine in HIV-infected patients with and without nevirapine-containing antiretroviral therapy. 13th PK Workshop, 16–18 April 2012, Barcelona. Poster abstract P\_05.

## Pharmacokinetics of atazanavir/ritonavir plus raltegravir

[www.drug-interactions.org](http://www.drug-interactions.org)

**Current dosing for raltegravir is 400 mg twice daily, but atazanavir increases raltegravir exposure by 40-72% probably through UGT1A1 inhibition.**

This pharmacological pilot phase II study investigated the pharmacokinetics of raltegravir 400 mg once daily in 6 HIV positive men receiving 2 NRTIs plus atazanavir/r. Three patients were taking tenofovir/FTC.

Half-dose raltegravir exposure, when combined with atazanavir/r, seemed to be adequate in the majority of patients, with only one trough value below the IC<sub>95</sub> (15 ng/ml). Raltegravir AUC, C<sub>max</sub> and C<sub>trough</sub> (median, IQR) were 14497 ng.h/ml (13845-28325), 3984 ng/ml (3863-6703) and 40 ng/mL (22-51), respectively. Median (IQR) atazanavir AUC, C<sub>max</sub>, and C<sub>trough</sub> were 26414 ng.h/mL (23037-33109), 2284 ng/mL (1706-2666) and 526 ng/mL (397-604), respectively. Median (IQR) ritonavir AUC, C<sub>max</sub> and C<sub>trough</sub> were 9147 ng.h/mL (8052-12860), 1107 ng/mL (983-1244), 99 ng/mL (61-183), respectively.

The AUC of raltegravir 400 mg once daily in this study was similar to the AUC of the 800 mg once daily dosage in the QDMARK study (14895 ng.h/ml), and resulted in two-fold higher than the reported AUC values with standard 400 mg twice-daily dosage (6340 to 6910 ng.h/ml). However, QDMARK reported that raltegravir 400 mg once-daily with atazanavir/r resulted in poorer rates of viral suppression.

Atazanavir concentrations were comparable to historical data and C<sub>trough</sub>s were above the target level (150 ng/mL) in all patients.

Ref: Calcagno A et al. Pharmacokinetics of raltegravir 400 mg once-daily in combination with atazanavir/ritonavir plus two NRTIs. 13th PK Workshop, 16–18 April 2012, Barcelona. Poster abstract P\_05.

## Atazanavir/ritonavir and voriconazole not to be coadministered

[www.drug-interactions.org](http://www.drug-interactions.org)

**Voriconazole is a broad spectrum antifungal mainly metabolised by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9.**

Due to genetic polymorphism of CYP2C19, voriconazole AUC is on average 2-4 fold higher in CYP2C19 poor metabolisers (PM) than in extensive metabolisers (EM). In a majority CYP2C19 EM population low dose ritonavir decreased voriconazole AUC by ~40%, likely due to induction of CYP2C19 by ritonavir.

This study assessed the two-way drug interactions when adding voriconazole to ritonavir-boosted atazanavir in both CYP2C19 EM and PM healthy subjects. Voriconazole was administered alone on days 1-3, atazanavir/r (300/100mg once daily) administered alone on days 11-20, and the drugs coadministered on days 21-30. The voriconazole doses were 200 mg twice daily (400 mg twice daily on days 1 and 21) for EM subjects and 50 mg twice daily (100 mg twice daily on days 1 and 21) for PM subjects. A total of 20 EM and 7 PM subjects completed the study.

In EMs, coadministration decreased voriconazole AUC and C<sub>min</sub> by 33% and 39%, respectively; atazanavir AUC and C<sub>min</sub> decreased 12% and 20%, respectively. In PM subjects, coadministration increased voriconazole C<sub>max</sub> and AUC by 4-6 fold; atazanavir AUC and C<sub>min</sub> decreased by 20% and 31%, respectively. ritonavir C<sub>max</sub> and AUC were generally unchanged in either population. The decrease in voriconazole AUC seen in EM subjects, (33%) is similar to the historical observation of 39% when voriconazole was given with low dose ritonavir. In PM subjects, coadministration markedly increased voriconazole exposure, likely through inhibition of CYP3A4. These results support the current recommendation that coadministration is not recommended unless an assessment of the benefit/risk justifies the use of voriconazole.

Ref: Zhu L et al. CYP2C19 genotype-dependent pharmacokinetic drug interaction between voriconazole and ritonavir boosted atazanavir in healthy subjects. 13th PK Workshop, 16–18 April 2012, Barcelona. Abstract: O\_08.

## Milk thistle (silymarin) and darunavir/ritonavir

[www.drug-interactions.org](http://www.drug-interactions.org)

**The effect of the botanical supplement milk thistle (silymarin, 150 mg every 8 hours) on the pharmacokinetics of darunavir/ritonavir (600/100 mg twice daily) was investigated in 15 HIV positive patients.**

In the presence of milk thistle, Darunavir AUC, C<sub>max</sub> and C<sub>trough</sub> decreased by 14% (GMR 0.86; 90%CI 0.67-1.10), 17% (GMR 0.83; 90%CI 0.68-1.02) and 6% (GMR 0.94; 90% CI 0.70-1.26), respectively.

As all patients had darunavir concentrations well above the median protein-binding-adjusted IC<sub>50</sub>, the study concluded that no dose adjustment for darunavir/r appears to be necessary.

Ref: Molto J et al. Effect of milk thistle on the pharmacokinetics of darunavir/ritonavir in HIV-infected patients. 13th PK Workshop, 16–18 April 2012, Barcelona. Abstract: P\_04.

## Echinacea and etravirine

[www.drug-interactions.org](http://www.drug-interactions.org)

**The botanical echinacea was originally not recommended for HIV positive people because of a negative impact on the immune system.**

This concern may have been over cautious, though there is little evidence supporting a clinical benefit. A study in 15 HIV positive people reported no effect on etravirine levels (AUC, C<sub>max</sub> and C<sub>trough</sub> increased by 4%, 3% and 3% respectively, when coadministered Echinacea purpurea 500 mg supplement was also taken (500 mg, 3 times daily) for 14 days.

Ref: Molto J et al. Interaction between echinacea purpurea and etravirine in HIV-infected patients. 13th PK Workshop, Barcelona, 2012. Abstract: P\_03.

## Warfarin and ARVs: impact of African American race and ritonavir

**Simon Collins, HIV i-Base**

**The commonly prescribed anticoagulant warfarin is highly susceptible to interactions with antiretroviral mediated through CYP 2C9, 2C19, and/or 3A4 pathways, although data are limited.**

This retrospective, case-control (1:2) study compared the warfarin maintenance dose (defined as the dose required to maintain goal INR) between patients on ART (n=18) and patients not on ART (n=36). ART was PI-based (n=9: mainly lopinavir/r), NNRTI-based (n=7, mainly efavirenz), and PI+NNRTI-based (n=2). The warfarin maintenance dose (mean±SD) differed significantly between cases and controls (8.6±3.4 mg vs 5.1±1.5 mg, p<0.01), but not across ART regimens (PI: 8.8±4.6 mg; NNRTI: 8.6±1.8 mg; PI+NNRTI: 7.3±3.3 mg; p=0.86).

African American race and ritonavir dose were independent predictors of warfarin dose; with an expected increase by 3.9 mg ([95%CI: 0.88-7.0], p=0.02) if African American or by 3.7 mg ([95%CI: 0.53-6.9], p=0.03) if the total daily ritonavir dose is 200 mg. Higher empiric warfarin doses and/or more vigilant monitoring and dosage adjustments may be required in these patients.

Ref: Darin KM et al. The clinical implications of antiretroviral drug interactions with warfarin: a case-control study. 13th PK Workshop, 16–18 April 2012, Barcelona. Abstract: P\_18.

## CONFERENCE REPORTS

### 19th Conference on Retroviruses and Opportunistic Infections (CROI)

**5–8 March 2012, Seattle**

#### Introduction

**This issue of HTB continues our coverage from the 19th CROI with reports on HIV and the brain, side effects and complications, pregnancy and women's health.**

Abstracts and PDF files for many of the full posters are also online.

<http://retroconference.org>

This issue includes:

- HIV and the brain: longitudinal results from CHARTER and other studies
- Systolic blood pressure and risk of myocardial infarction in HIV infection
- Risk of non-AIDS defining malignancies and immune suppression
- Renal impairment in the D:A:D study
- Early data for rilpivirine long acting formulation supports further investigation for PrEP
- Hormonal contraception: HIV transmission and progression rates
- Darunavir use during pregnancy

Abstracts and presentations are available at these links:

<http://retroconference.org/>

CROI 2012: HIV AND THE BRAIN

## **HIV and the brain: longitudinal results from CHARTER and other studies**

**Nathan Geffen, CSSR**

The purpose of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study is to research how central and peripheral nervous system HIV-related complications are affected by ART. [1] The study has been running since 2002 with several sites in the United States comprising about 1,600 patients. The CHARTER group presented numerous studies at CROI 2012. [2] Those studies that appear to have the most direct impact on diagnosing, predicting or preventing neurocognitive decline are discussed here.

### **Asymptomatic neurocognitive impairment (ANI) is associated with worse functional outcomes**

Blackstone and colleagues assessed 578 participants with a comprehensive neuropsychological battery, self-report questionnaires of cognitive complaints and everyday functioning, as well as performance-based tasks measuring employment capacity and medication management. Of these 375 patients were classified as normal and 175 met criteria for ANI. A further 40 met criteria for symptomatic HIV associated neurocognitive disorder (HAND) of whom 14 had HIV-associated dementia.

The symptomatic HAND group reported significantly more symptoms of depression and had lower current CD4 counts. After controlling for current CD4 and depression symptoms, the ANI participants had worse employment capacity than the normal participants, but were comparable to the HAND group ( $p < 0.001$  for both comparisons). There were no between-group differences on the test of medication management. The researchers concluded their study suggests ANI is a less benign condition than is widely perceived. They indicate that their findings are consistent with research showing that mild neuropsychological impairment is associated with worse functional outcomes. They further suggest that performance-based tests of everyday functioning should be incorporated into the diagnosis of HAND. [3]

### **Longitudinal study examining neurocognitive impairment**

Heaton and colleagues followed neurocognitive function in HIV-positive patients measured by comprehensive laboratory, neuromedical, and neurobehavioral assessments every 6 months, over 18 to 42 months. [4]

The study reported that 99 (22.7%) participants experienced neurocognitive decline, 266 (61%) remained stable, and 72 (16.5%) improved over 18 to 42 months. However, the only predictors in the multivariate Co regression analysis were having a confounding co-morbidity (RR 2.4; 95%CI 1.4, 4.0;  $p=0.0015$ ), being off ART (RR 1.6; 95%CI 1.1, 2.5;  $p=0.025$ ) and low CD4 count (RR 1.1; 95%CI 1.02, 1.21;  $p=0.017$ ).

In another study by Heaton on what appears to be the same cohort, patients with ANI ( $n=84$ ) and mild neurocognitive disorders (MND) ( $n=57$ ) were more likely to experience statistically meaningful decline than neurocognitively normal patients ( $n=246$ ) (23%, 30% vs 13%;  $p=0.004$ ). Also ANI patients were less likely to improve than the neurocognitively normal group (7% vs 21%;  $p=0.008$ ). These results were used to validate the ANI and MND as clinically important factors associated with reduced cognitive function over time and is consistent with Blackwell's findings. [5]

### **Biomarkers for predicting neurocognitive performance**

CHARTER researchers have been looking for biomarkers that predict cognitive decline. Cerebrospinal fluid (CSF) was collected from nearly 350 study participants, of whom 85% were on ART. Follow-up samples were collected within approximately a year for 70% of subjects. There were no associations at baseline between biomarkers and neurocognitive impairment. However interesting associations were found after follow-up. A lower baseline ratio of sphingomyelin to ceramide predicted a decline in neurocognitive performance ( $p=0.047$ ). Sphingomyelin is a lipid that mainly occurs in nerve tissue. Ceramide is a lipid that occurs in large concentrations in cells and is one of the components of sphingomyelin. The authors note that the predictive potential of this ratio appeared to be driven by increases of certain species of ceramide over time. Lower levels of some multiple cholesterol esters were also associated with neurocognitive decline ( $p$  ranged from 0.046 to 0.007, depending on the species).

On the other hand, high levels of two triglycerides at baseline predicted neurocognitive improvement ( $p=0.005$  and  $p=0.006$  for the two species). At follow-up these were lower, suggesting they normalised over time. [6]

Another study by CHARTER researchers tested a panel of biomarkers to predict cognitive impairment. Just under 100 people with HIV were categorised into four groups: stably normal, stably impaired, reliably worsening and reliably improving. All underwent neurocognitive testing, phlebotomy, and lumbar puncture at two time points separated by a median of just over 6 months (IQR 5.6 to 70). The researchers measured CCL2, CXCL10, CX3CL1, CXCL12, IL-6, TNF-alpha, soluble TNF receptors (sTNFR, p75) and sCD14. 74% of patients were on ART at the first time point (median current CD4 of 394 cells/mm<sup>3</sup> and median nadir of 110 cells/mm<sup>3</sup>), of whom 54% had undetectable viral loads in plasma and CSF. A combination of sCD14, CCL2, CXCL10, sTNFR, TNF-alpha predicted neurocognitive status in 92% of patients. Allowing a higher misclassification rate, 20%, meant that TNF-alpha could be removed from the panel.

For patients with normal performance at the first time point, a combination of sCD14, IL-6, CXCL12, CCL2 and sTNFR correctly classified the cognitive status of 94% at the second time point. Allowing for a 20% error rate, sCD14, CXCL12 and IL-6, correctly classified 82%, including all subjects in the stably normal group. For subjects with impaired performance at the first time point, CCL2, TNF-alpha, sCD14 and CX3CL1 classified 96% correctly. CCL2 and TNF-alpha correctly classified 81%, including all people in the stably impaired group.

The two most frequently identified biomarkers were sCD14 and CCL2. These are indicators of monocyte or macrophage activation. All cases of neurocognitive stability were correctly classified. [7]

Another biomarker study compared neurocognitive status in 34 HIV-positive patients virally suppressed on ART to 34 age-matched HIV-negative controls. Each patient had two visits. Differences between the two cohorts are not reported but one interesting finding was that of 13 subjects who were impaired at the first visit, 10 remained impaired at the second visit, and all but one of the 21 neuropsychologically normal subjects remained normal. Subjects who remained impaired showed little change in their baseline adjusted sCD163 level, while those who remained normal showed a drop in baseline adjusted sCD163 (least squares means: -1.1 versus -280;  $p=0.056$ ). [8]

**Role of central obesity and diabetes**

Another CHARTER sub-study presented by Allen McCutchan and colleagues looked at the relationship between diabetes, obesity and cognitive decline in 130 HIV positive patients. [9]

Neurocognitive impairments was diagnosed in 40% of participants. Age and longer duration of infection predicted impairment. So did waist circumference but this was only measured in 55 participants. There was no association with BMI, HOMA score (a predictor of insulin resistance) and leptin levels. Self-reported diabetes was associated with impairment in patients in this sub-study. This contrasts with an analysis of the whole CHARTER cohort which found an association in patients older than 55 only but not patients younger than 55.

**Cytomegalovirus (CMV) levels and cognitive decline**

Letendre and colleagues studied 138 HIV-positive people to determine associations between CMV levels, neurocognitive characteristics, disease and demographics. CMV antibody concentrations were measured by enzyme-linked immunosorbent assay.

Higher CMV antibody levels were associated with older age ( $r = 0.23$ ;  $p = 0.006$ ), lower nadir CD4 cell counts ( $r = -0.34$ ;  $p < 0.0001$ ), ART use ( $p = 0.004$ ), and worse global deficit score ( $r = 0.17$ ;  $p = 0.04$ ). For patients not taking ART higher CMV antibody levels were also associated with higher HIV RNA levels in CSF ( $r = 0.29$ ;  $p = 0.05$ ) but not in plasma. Multivariate analysis showed that worse global deficit score was associated with higher CMV antibody levels, more co-morbid conditions, and an interaction between CMV antibody level and plasma HIV RNA ( $p = 0.02$ ).

Analysis of the interaction identified that higher CMV antibody levels were only associated with worse global deficit scores among subjects who had undetectable HIV RNA in plasma.

The authors conclude that higher CMV antibody levels were associated with worse neurocognitive functioning. They suggest their findings have implications for earlier initiation of ART, for the aging of the HIV population, and for the effect of CMV on HIV in the central nervous system. They also say that their findings add to existing data that suggest that CMV prophylaxis may be beneficial. [10]

Another finding relevant to older age and cognitive functioning in people with HIV comes from a study of over 205 CHARTER patients. These patients provided 162 CSF and 230 plasma samples. Tenofovir CSF ( $n=44$ ) concentrations increased more steeply with age than plasma ( $n=44$ ). Efavirenz concentrations increased in CSF ( $n=66$ ) in patients older than 55 with a less steep and steadier increase with age for plasma ( $n=77$ ) concentrations. Plasma ( $n=109$ ) atazanavir concentrations slightly declined with age while CSF ( $n=58$ ) concentrations remained stable. Higher ARV concentrations were also associated with worse neurocognitive functioning, which the authors note may indicate drug neurotoxicity. They concluded that more data in older HIV-positive people was needed to validate their findings. [11]

**European AIDS Clinical Society (EACS) guidelines for diagnosing HAND not sensitive enough**

Ignacio Perez-Valero and colleagues compared the recently released EACS guidelines and the HIV Dementia Scale (HDS) for diagnosing symptomatic and non-symptomatic HAND. [12]

CHARTER's comprehensive neurobehavioral assessments that involve several hours of comprehensive testing were used as the gold standard.

**Table 1: Specificity and sensitivity of EACS and HDS for detecting symptomatic and asymptomatic HAND**

	Sensitivity %	Specificity %
EACS screen for symptomatic HAND	57	95
EACS screen for HAND	15	91
HDS screen for symptomatic HAND	52	64
HDS screen for HAND	50	73

While the authors stated that neither EACS nor HDS screens had sufficient sensitivity for detecting cases for referral, concluding that EACS sensitivity is especially poor if the full range of HAND is considered, they failed to consider that the EACS guidelines were established to provide increased awareness for a simple intervention, based not only on the limited time that most doctors have with patients, but also that for many doctors, assessing NCI is not currently a significant aspect of HIV management. These results do not mean that easy to use evaluations that within minutes can clarify, even roughly, the urgency for some referrals, or do not have a place in clinical care.

**C O M M E N T**

**The effect of HIV on the brain remains an important aspect of care and these data help. While advanced HIV disease causes HAND and dementia, the biological mechanisms are poorly understood. Whether HIV or ARVs contribute to cognitive decline in asymptomatic patients, especially at higher CD4 counts and/or controlled viraemia, with or without ART is unclear.**

**The results from CHARTER may help predict diagnosis but evidence of sub-clinical changes, while worrying, do not suggest different management, other than perhaps more careful observation.**

**Higher rates of cognitive problems in HIV positive compared to negative people, even on stable ART, are subject to confounding and the difficulty of an appropriately matched control.**

**The biomarker studies from CHARTER are interesting, but given the large number of biomarkers that were considered, some of these may be chance associations and their findings still need to be validated.**

**The study reporting an association between central obesity, diabetes and NCI did not report on the possibility of reverse causality – that NCI may have contributed to poor diet, but this is a US study so the diet may have been regionally normal – or whether a common cause be responsible for NCI and diabetes.**

**While the authors suggested “avoiding ARV drugs that induce central obesity might protect patients from or reverse neurocognitive impairment” this is easy to say but more complicated to interpret with any degree of precision, given that central lipohypertrophy has been associated with all classes of ARVs and no single ARV has been shown to be clearly protective.**

**Three key questions remain unanswered: Does pre-AIDS HIV infection significantly affect cognitive functioning? What are the long-term effects of HIV on cognitive functioning? Can earlier ART improve cognitive outcomes in people with HIV?**

**Hopefully research from the START trial, which has a neurology substudy, will provide data at higher CD4 counts (>500 cells/mm<sup>3</sup>), together with any impact of earlier ART. The substudy will have 300 recruits in each arm. [13]**

**The higher prevalence of impairment in HIV positive people suggests that neurocognitive assessment should be addressed in guidelines and integrated into routine care.**

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CROI 2012: COMPLICATIONS

## Systolic blood pressure and risk of myocardial infarction in HIV infection

Simon Collins, HIV i-Base

**A report from a large US observational cohort suggested that in HIV positive patients, increased systolic blood pressure (s-BP) may be a more significant risk for the risk of heart attack irrespective of use of hypertensive treatment, after controlling for other factors. [1]**

This might support interventions to aim for lower target levels (<120), and certainly for ensuring that BP is routinely monitored (at least annually, as recommended in BHIVA guidelines).

Data was included from more than 84,000 patients in the Veterans Aging Cohort Study Virtual Cohort (VC) who were asymptomatic for cardiovascular disease at baseline. HIV positive patients were matched on age, gender, race and clinical site in a ratio of 1:2 to HIV negative patients. Clinical data were collected prospectively from 2003 to 2008.

During a median 4.6 years follow-up, there were 443 cases of acute myocardial infarction (AMI). Nearly half (47%) of these cases were in HIV positive patients.

After adjusting for age, race/ethnicity, diabetes, dyslipidaemia, smoking, hepatitis C, BMI, renal disease, cocaine and alcohol use hazard ratios (HR) for MI were significantly higher for HIV positive vs HIV negative groups for patients with pre-hypertension (S-BP 120-139) and controlled hypertension (s-BP <140 on BP treatment) as well as for people with hypertension (s-BP >140), see Table 1.

**Table 1: Hazard ratios for AMI by S-BP and HIV status**

S-PB (mmHg) category and BP treatment (Tx)	Hazard Ratio (95%CI) +ve vs -ve *
S-BP <120, no BP Tx	1.14 (0.64-2.03)
S-BP 120-139 no BP Tx	1.88 (1.19-2.99)
<140: + BP Tx	3.11 (1.79-5.41)
>140 +/- BP Tx	3.18 (1.99-5.07)

\* reference group is HIV-negative Veterans with S-BP <120.

### C O M M E N T

**The major concern about this study is that no account was taken for ART which is strange given this was presented at CROI. This is important because some ARVs have been associated with BP in some studies and some ART drugs are also associated with a higher MI risk. It therefore remains unclear whether these results simply reflect the impact of ART.**

**Although the study can't control for ART directly, as the HIV negative population won't have received this, they could stratify the HIV positive group into those on ART and those not on ART.**

#### References

1. Armah K et al. The impact of elevated and pre-hypertensive systolic blood pressure and the risk of acute myocardial infarction in HIV+ and HIV- veterans. Oral abstract 120.  
<http://retroconference.org/2012b/Abstracts/43509.htm>
2. BHIVA monitoring guidelines.  
<http://www.bhiva.org>

## Risk of non-AIDS defining malignancies and immune suppression

Simon Collins, HIV i-Base

**Non-AIDS defining malignancies have been reported by several groups as increasing in the HAART era, with an association to immune deficiency for some non-virally mediated cancers.**

An analysis from the international D:A:D (Data Collection on Adverse events of Anti-HIV Drugs) collaborative cohort, looked at the association between the risk of non-AIDS defining malignancies (NADM), viral suppression and immune recovery.

In an oral presentation, Signe Worm reported an incidence rate (IR) of 4.98/1000 PYFU (95%CI 4.65 to 5.31) from 880 NADM diagnosed in the cohort (>40,000 patients with >176,000 PYFU) between January 2004 and March 2010. Separate incidence rates (IR/1000 PYFU: 95%CI) were collected for the most common malignancies: anal cancer (n=79; IR 0.45: 0.35 – 0.55), Hodgkin's lymphoma (n=112; IR 0.63: 0.52-0.75) and lung cancer (n=140; IR 0.79: 0.66-0.92). These rates were stable over the study period.

Patient characteristics at the time of NADM diagnosis included: 80% male, median age 50 years (IQR 44-59), median CD4 392 cells/mm<sup>3</sup> (IQR 245-580), median nadir CD4 127 (IQR 49-245), median viral load 1.7 log copies/mL (IQR 1.7-2.4). Approximately 5% of patients had a prior NADM and 10% a prior ADM. Approximately 35% were current smokers and this was adjusted for in multivariate analysis.

The incidence rates of NADM were inversely associated with all four CD4 markers (latest, nadir, time lagged (6 months prior) and time-averaged CD4 count: incidence rates of 1.0 for CD4 < 100 cells/mm<sup>3</sup> dropped to approximately 0.4/100 PYFU with CD4 counts >500 cells/mm<sup>3</sup>.

Cumulative time spent with a with low CD4 was also significant, with relative rates per additional year of 1.05 (1.04-1.06) and 1.05 (1.03-1.07) for both <100 and <200 cells/mm<sup>3</sup> analyses (both p=0.0001). However, no association was seen with recent level of HIV viraemia.

In the multivariate analysis, CD4 count per 50 cells higher (RR 0.97; 95%CI 0.95-0.98, p=0.0001), nadir CD4 < 100 (RR 1.22; 95%CI 1.03-1.44, p=0.02) and duration of suppression <200 cells/mm<sup>3</sup>, per year (RR 1.04; 95%CI 1.02-1.05, p=0.0001) were associated with risk of NADM.

The association with latest CD4 count was also seen with individual cancers (RR; 95%CI): lung (0.93; 0.89-0.97), Hodgkin's lymphoma (0.85; 0.81-0.89) and anal cancer (0.93; 0.89-0.98), all per 50 cells/mm<sup>3</sup> higher.

Additional factors were nadir CD4 count (<100 cells/mm<sup>3</sup>) for lung cancer (RR 1.43; 1.00-2.04), viral load AUC (1.35; 1.12-1.63) for Hodgkin's lymphoma and degree of immunosuppression (<200 cells/mm<sup>3</sup>) for anal cancer (RR 1.07; 1.05-1.08).

More optimistically, a successful response to ART (increasing CD4 to >200 cells/mm<sup>3</sup>) was able to overcome the association with CD4 nadir <200 cells/mm<sup>3</sup>, after two years of treatment.

While not categorised as AIDS defining complications, the association with reduced immune function highlights the importance of earlier HIV diagnosis, prompt use of ART, and perhaps closer monitoring and screening for high risk patients with CD4 counts <200 cells/mm<sup>3</sup>.

Ref: Worm S et al. NADM and immunosuppression: the D:A:D study. 19th CROI 2012, Seattle. Oral abstract 130.

<http://www.retroconference.org/2012b/Abstracts/44289.htm>

## Renal impairment in the D:A:D study

### Simon Collins, HIV i-Base

An analysis from the large prospective D:A:D cohort looked at patients with normal renal function at baseline and associations between renal changes and individual HIV drugs and changes in treatment, adjusting for renal and HIV related risk factors.

This included >22,600 patients who started ART from 2004 with eGFR >90 mL/min. Progression of renal dysfunction was defined as eGFR decline to <70 (the threshold for proactive switches away from individual ARVs with a concern for renal toxicity), confirmed eGFR <60 mL/min.

During a median follow-up of 4.5 years (IQR 2.7-6.1), approximately 2.1% patients (n=468) progressed to confirmed eGFR <70 and 0.6% (n=131) to chronic kidney disease (CKD) with incidence rates (IR; 95%CI per 1000 PY) of 4.78 (4.35 to 5.22) and 1.33 (1.10 to 1.56), respectively.

In people with reduced eGFR, tenofovir was the only ARV that was actively switched (at eGFR 60-70 vs >90) with an adjusted IR ratio 1.72 (95%CI 1.38 to 2.14). This was interpreted as being due to the general awareness of tenofovir and renal complications.

Cumulative use of tenofovir and atazanavir/ritonavir were independently associated with increased rates of confirmed eGFR ≤70, but not CKD. Lopinavir/ritonavir (Kaletra) was also associated with both increased risk for renal endpoints and abacavir was associated only with higher rates of CKD. See Table 1.

**Table 1: Cumulative exposure (IRR per year) to ART and renal endpoints in D:A:D**

ARV	confirmed eGFR <70 IRR (95%CI)	p-value	CKD IRR (95%CI)	p-value
tenofovir	1.18 (1/12-1.25)	<0.0001	1.08 (0.971-1.21)	0.16
abacavir	1.04 (0.99-1.09)	0.061	1.08 (1.00-1.17)	0.046
atazanavir/r	1.20 (1.09-1.32)	0.0002	1.16 (0.95-1.42)	0.15
atazanavir	1.10 (0.92-1.33)	0.29	0.80 (0.45-1.43)	0.45
lopinavir/r	1.11 (1.05-1.17)	0.0002	1.24 (1.13-1.36)	<0.0001
other PI/r	1.03 (0.95-1.11)	0.52	1.11 (0.97-1.26)	0.13

The relationships to use of tenofovir, atazanavir/r and lopinavir/r were with current use, whereas >1 year after drug discontinuation the rates approached 1.0. Other predictors (adjusted IRR; 95%CI) of confirmed eGFR ≤70 were age (2.63 per 10 years: 2.33 to 2.96), diabetes (1.54; 1.06 to 2.23), hepatitis B virus (1.56; 1.10 to 2.22), hepatitis C virus (1.47; 1.09 to 2.00), current CD4 count (0.75 per doubling; 0.69 to 0.82) and prior AIDS (1.38; 1.13 to 1.69).

C O M M E N T

**Although the study concluded that these rates were generally low, it also highlighted that compared to lifetime use of ART, follow-up may be too short to pick up such dramatic declines in renal function, especially if rates continue or increase with age. Nevertheless, over five years, incidence of progression of eGFR from >90 to <70 were twice as high in patients who used tenofovir (vs never used).**

**The study suggested that proactive switching from tenofovir was protective after one year and that closer monitoring of renal function may be appropriate for people using atazanavir/r or lopinavir/r.**

**See also the recent publication in AIDS of the VA cohort analysis of tenofovir and renal function, reported later in this issue of HTB.**

Ref: Ryom L et al for the D:A:D Study Group. Exposure to ARV and the risk of renal impairment among HIV+ persons with normal baseline renal function: the D:A:D study. 19th CROI, 5–8 March 2012, Seattle. Poster abstract 865.  
<http://www.retroconference.org/2012b/Abstracts/45437.htm>  
<http://www.retroconference.org/2012b/PDFs/865.pdf>

CROI 2012: PREVENTION

## Early data for rilpivirine long acting formulation supports further investigation for PrEP

### Polly Clayden, HIV i-Base

There has been considerable interest in the possibility of long acting formulations of antiretroviral drugs.

Researchers from St Stephen's AIDS Trust, London and the University of Liverpool have begun investigating the pharmacokinetics (PK) of a novel long acting formulation of rilpivirine (RPV-LA) in development at Jansen Pharmaceuticals. [1]

RPV-LA is a parenteral formulation - a nanosuspension with 300 mg of the freebase to 1 mL of liquid. This formulation makes prolonged plasma exposure possible and has the potential for monthly or less frequent dosing. Akil Jackson presented preliminary results at the 19th CROI from a phase 1 study exploring the PK in plasma, the female genital tract and male rectum over 84 days after a single intramuscular dose of RPV-LA.

The study recruited 27 eligible female healthy volunteers at the St Stephen's Centre, of which over half were of African or African Caribbean ethnicity. In addition 6 male participants were recruited to the rectum sub-study.

The women received a single intramuscular dose of RPV-LA at doses of either 300, 600, or 1200 mg. Plasma samples were collected on days 0 (pre-dose and 4 and 8 hours), 1, 3, 7, 11, 14, 21, 28, 42, 56, and 84 and genital tract fluid samples were collected at similar times from 8 hours onwards. Biopsies of vaginal epithelium from the peri-cervical fornices were taken at days 14 and (7 or 28) for tissue PK.

The intramuscular dose in the male substudy was 600 mg, with plasma PK samples collected at a similar schedule to the women and rectal biopsies taken at days 7 and 14.

RPV concentrations were quantified using HPLC-MS/MS with a lower limit of 0.25 ng/mL and PK parameters calculated using WinNonLin.

The investigators observed with a dose of 300 mg in women (n=10), there was an early peak in RPV concentrations and gradual elimination over 84 days. RPV concentrations were nearly twice that in cervical vaginal fluid than in plasma: (geometric mean; 90% CI, C<sub>max</sub> ng/mL) 52.4 (44.6 – 6.0) in plasma compared to 102.2 (72.2-132.2) in cervical vaginal fluid. The ratio of cervical vaginal fluid to plasma was (CVF:BP) 1.95 (1.45 – 2.45). Day 24 concentrations were 17.9 (14.0-31.8) in plasma, 29.1 (14.0-31.8) in cervical vaginal fluid and 18.5 (2.2 -34.8) in vaginal tissue; ratio of vaginal tissue to plasma (VT:BP) 1.04 (0.69-1.4).

With a dose of 600 mg (n=10) the genital tract concentrations were more equivalent to those in plasma: 98.4 (81.6-115.2) in plasma and 121 (68.2-174) in cervical vaginal fluid, CVF:BP 1.23 (0.86-1.60). Day 28 concentrations were 54.4 (31.5-107.3) in plasma, 61.6 (11.9-240.8) in cervical vaginal fluid and 59.6 (15.6- 171.4) in vaginal tissue, VT:BP 1.09 (0.29-1.68).

Data for 1200 mg in women (n=7) were incomplete. Results at day 28 were: 85.8 (70.8-101.2) in plasma, 120.8 (103.4-138.2) in cervical vaginal fluid and 61.0 (0.29 – 1.26) in vaginal tissue; VT:BP 0.74 (0.56-0.91).

Dr Jackson noted similar elimination proportionality across the doses. As reference he explained that an oral dose of 25 mg provides peak concentrations of about 200 ng/mL and 150 ng/mL trough.

In men (n=6) maximum plasma concentrations over 84 days with a 600 mg dose of RPV were approximately 30% higher than with the equivalent dose in women and concentrations in rectal fluid were low (possibly due to contamination by fecal fluid). These values were: 131.7 (102.5-160.8) in plasma and 36.4 (18.0 – 54.8) in rectal fluid; ratio of rectal fluid to plasma concentrations (RF: BP) 0.28 (0.19 – 0.3). Although, reassuringly tissue concentrations mirrored that of plasma and on day 14 were 97.7 (67.8-127.6) in plasma, 22.7 (1.3-43.7) in rectal tissue and 87.1 (43.9 – 130.3); ratio of rectal tissue to plasma concentrations (RT:BP) 0.89 (0.65-1.14).

Overall the investigators found all three RPV-LA doses gave prolonged plasma and genital tract exposure. Tissue compartment partitioning showed higher concentrations (at least equivalent or higher) in genital tract fluid than in plasma. Vaginal tissue concentrations were slightly

lower than genital tract fluid. Although the reason for this was unclear Dr Jackson suggested it might be due to the non-secretory nature of this mucosa. More data are needed to understand this phenomenon. Male rectum concentrations were equivalent to those observed in plasma.

He concluded that these data support the continued evaluation of RPV-LA for development as a PrEP agent. Next steps include a planned next phase study with multiple intramuscular doses to determine PK and safety and to relate the PK to ex vivo tissue pharmacodynamics to further characterise the dose response of the formulation and inform the use of the agent for this indication.

#### C O M M E N T

**While this was presented for its potential to reduce the reliance on daily adherence in the context of PrEP, this formulation might have important options for HIV treatment. This would require other ARVs with similar formulations to construct a combination. The lack of negative drug interactions between rilpivirine and dolutegravir (also presented at CROI) [2] and the development of a similar formulation of GSK-744 (follow on INI to dolutegravir) are clearly of interest. [3]**

**A safety issue for long-acting formulations, especially in the absence of an antidote to rapidly eliminate the active compound in the event of a severe adverse reaction, might be covered by a period of oral dosing to confirm individual tolerability, especially as both integrase and NNRTI classes have been associated with hypersensitivity reactions.**

**A recent survey of 400 HIV positive patients attending two US clinics reported 61%, 72% and 84% interest in ART injections based on weekly, two-weekly and monthly formulation respectively, with higher interest in people with concerns about adherence, although 35% were also concerned about needle use. [4]**

#### Reference

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CROI 2012: WOMEN'S HEALTH

## Hormonal contraception: HIV transmission and progression rates

### Polly Clayden, HIV i-Base

**Hormonal contraception (HC) is used widely – an estimated 14 million women in sub-Saharan Africa use either injectable or oral hormonal contraception – yet the impact on HIV remains unresolved despite twenty years of research.**

Two oral presentations at the 19th CROI presented new data on two aspects of possible interaction, the first from a study looking at HIV acquisition in negative women and the second disease progression in positive women using HC in Africa. [1, 2]

Sandra McCoy presented results from an evaluation of women using oral and injectable hormonal contraception in South Africa and Zimbabwe.

Dr McCoy explained that there are different possible mechanisms for increased HIV risk with HC use. Physiological and immunological changes in the genital tract of rhesus macaques in animal studies suggest the plausibility of a biological mechanism (although the extent to which data from these studies can be applied to humans remains uncertain). There also might be differences in the behavior of women who choose to use HC, for example they might be less likely to use condoms. She noted that disentangling the direct from the indirect effect is a methodological challenge

The study was an analysis using data from women aged 18 to 49 years participating in the Methods for Improving Reproductive Health in Africa (MIRA) study, a phase 3 trial of the diaphragm and lubricant gel for HIV prevention (which showed no protective effect when added to a comprehensive protection package including condoms).

MIRA participants were followed for a median of 21 months (range 12-24). They made quarterly clinic visits where they were interviewed about contraception and sexual behavior and were tested for pregnancy, HIV, and other STIs.

The investigators used Cox proportional hazards regression and marginal structural modelling to estimate the risk of HIV acquisition among non-pregnant women who reported use of combined oral contraceptive pills (COC), progestin-only pills (POP), or injectable HC (depot medroxyprogesterone acetate [DMPA] and norethisterone enantate [Net-En]) compared to women not using these methods (it was possible to differentiate between use of the two injectable methods for 86% of visits. Baseline contraceptive implant users were excluded and new users were censored at first use.

At baseline, women (n=4866) were a mean age of 29, 61% were using HC (21% COC, 14%, POP and 26% injectables). More pill users (COC 87% and POP 96%) were married than injectable contraception users (37%). Condom use was similar among HC users, 68% overall reported condom use at last sex compared to 75% of non-HC users; 26% reported always using condoms compared to 41% non HC users.

A total of 274 women seroconverted during the study, over 6913 woman years, giving a rate of 4 infections per 100 woman years.

Unadjusted and adjusted Cox models showed no association between either form of oral contraception and HIV acquisition compared to non-HC (reference): COC AHR 0.88 (95% CI 0.39-1.32), p=0.54 and POP AHR 1.02 (95% CI 0.58 – 1.81), p=0.94. However use of any injectable contraception was associated with a 37% increased risk of HIV infection, AHR 1.37 (95% CI, 1.01 - 1.86), p=0.04. When disaggregated, neither DMPA nor Net-En significantly increased risk in the subset of women for whom these data were available, respectively, AHR 1.32 (95% CI 0.92 – 1.90), p=0.13 and 1.21 (95% CI 0.67 – 2.21). While the effect was apparent in the DMPA subgroup, it wasn't statistically significant due to lack of power.

The investigators performed several sensitivity analyses including the potential effect of a 90 day exposure period after discontinuation of any type of HC and analyses restricted to women who reported only one type of HC or non-HC, and to women with no missed study visits. In all cases, the effects were consistent with those presented.

Using marginal structural models, direct effects analyses adjusted for dependent covariates including condom use, the risk associated with injectables remained but was attenuated (overall effect), OR 1.16 (95% CI 0.97 – 1.53). A further estimate, which mimics the effects of a highly unethical hypothetical trial with randomly assigned methods and with women constricted to use condoms infrequently or not at all (direct effect) showed an OR of 1.38 (95% CI 1.13 – 2.12).

Dr McCoy concluded that their results suggest a moderate increased risk of HIV acquisition among women using injectable contraception. The size of which was dependent of the method of analysis used.

The following presentation from Renee Heffron, showed results from an analysis of disease progression in HIV positive women receiving hormonal contraception participating in the Partners in Prevention Study Partners in Prevention - a randomised trial of acyclovir herpes suppression to reduce HIV transmission between discordant couples (there was no reduction in HIV transmission but disease progression was modestly slowed down, AHR 0.84, p=0.03)

Prospective data from 2269 women, with baseline CD4 counts  $\geq 250$  cells/mm<sup>3</sup> and enrolled at 14 sites in 7 countries in East and southern Africa, were analysed to compare rates of disease progression between those using and not using HC (reference).

In this study CD4 counts were measured 6 monthly, viral load at enrollment and 6 months later and contraceptive use reported monthly using standardised questionnaires. The primary outcome was a composite endpoint of initiation of ART, CD4 decline to  $< 200$  cells/mm<sup>3</sup> or death (not due to trauma).

Multivariate analysis was performed using adjusted Cox proportional hazards model. Time periods with IUDs and implants were excluded due to very small numbers.

At baseline, women were a median of about 30 years of age, most were married with at least one child and CD4 just below 500 cells/mm<sup>3</sup>. About 30% reported sex without a condom in the last month and the rate of pregnancy during follow up was about 20%. Of the total, 324 women used injectable, 95 oral and 1817 non-HC.

During follow up, 31.7% women reported using injectable and 12.1% oral HC at least once. Overall, 372 women experienced a disease progression event, giving a disease progression incidence of 11.5 per 100 woman years. For women using non-HC, the incidence rate was 12.3, and for those using any HC the rate was 8.54, AHR 0.74 (95% CI 0.56-0.99), p=0.04. Rates were 8.58, AHR 0.7 (95% CI 0.51-0.96), p=0.03 and 8.39 AHR 0.96 (95% CI 0.58 – 1.59), p=0.8, for the subgroups of women using injectable and oral HC respectively. Dr Heffron noted that injectable HC use was associated with a lower rate of disease progression in this analysis, but for oral HC the numbers were too small for this to be significant.

When the investigators performed sensitivity analyses assessing 6 months prior, enrollment or cumulative contraceptive use during the study they also found no increased risk for disease progression.

Among women who were negative at enrolment but acquired HIV during follow up with CD4  $> 500$  cells/mm<sup>3</sup> at first post seroconversion visit, the incidence rate of decline to  $< 500$  cells/mm<sup>3</sup> was 74.4 per 100 woman years overall and 92.82 and 31.17 per 100 woman years for those using non-HC and HC respectively, AHR 0.3 (95% CI 0.07 to 1.22), p=0.09.

Dr Heffron noted that these results were reassuring with regards to HC use and disease progression.

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#### C O M M E N T

**These data add a little to the unresolved questions about hormonal contraception and HIV. WHO is currently preparing systematic reviews looking at the associations with HIV acquisition in women, HIV acquisition in men and disease progression in HIV positive women.**

**We recently reported that WHO upholds guidance on hormonal contraception use:**

**[http://www.who.int/mediacentre/news/notes/2012/contraceptives\\_20120216/en/index.html](http://www.who.int/mediacentre/news/notes/2012/contraceptives_20120216/en/index.html)**

**WHO recently held an expert meeting to consider the best ways to provide information to communities and health workers. We will cover this in HTB when the statements are released.**

#### Reference

1. McCoy S et al. Oral and injectable contraception use and risk of HIV acquisition among women: MIRA study. 19th Conference on Retroviruses and Opportunistic Infections, 5-8 March 2012, Seattle. Oral abstract 20LB.
2. Heffron R et al. Hormonal contraceptive use and risk of HIV-1 disease progression. 19th Conference on Retroviruses and Opportunistic Infections, 5-8 March 2012, Seattle. Oral abstract 21.

## Darunavir use during pregnancy

### Polly Clayden, HIV i-Base

#### **Evidence based guidance for PI use in pregnancy is scarce, particularly with the newer drugs. Three posters at CROI 2012 showed findings from studies looking at safety, efficacy and pharmacokinetics (PK) of darunavir/ritonavir (DRV/r) in pregnant women. [1, 2, 3]**

A prospective, multicentre study conducted in Paris by Eve Courbon and colleagues enrolled 33 HIV positive pregnant women receiving DRV/r-containing regimens. Women were a median of 35 years old with a median CD4 of 440 cells/mm<sup>3</sup>. Nearly a third (n=12) were hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infected, and the majority (n=27) treatment experienced.

Their background regimens were: 2 NRTI (n = 25), 2NRTI+raltegravir (RAL) (n=3), 2NRTI+enfuvirtide (T-20) (n=2), 3 NRTI (n=2). Some received 800/100 mg DRV/r once daily (n=11) and others 600/100 mg twice daily (n=17). To achieve greater DRV/r exposure, a small number switched once daily to twice daily in their second (n = 1) and third trimesters (n=3).

Of the 33 pregnancies, there were 26 live births (of which 4 were pre-term), 1 elective abortion and 1 death in utero. The remaining women were still pregnant at the time of analysis.

The investigators reported DRV trough plasma concentrations of: 1973 ng/mL (1533 – 3118 ng/mL, n= 6) at first trimester, 1485 ng/mL (961 - 2240, n=12) at second trimester, 1575 ng/mL (625 - 2181, n=25) at third trimester, 1702 ng/mL (486 - 2426, n=18) at delivery.

All women except one (who was believed to be non-adherent), had median trough plasma concentrations were above the DRV 10 fold EC<sub>50</sub> for resistant HIV (approx 550 ng/mL) whether they received once or twice daily regimens.

The median ratio of cord blood to maternal DRV concentration was 0.18 (IQR 0.10 to 0.24, n=8). DRV plasma concentrations reductions were –25% between first and second trimesters and –20% between first and third trimesters for women who remained on the same dose of DRV/r.

At delivery, 4/8 and 13/18 of women receiving DRV/r once and twice daily respectively had viral load <50 copies/mL (6/8 and 18/18 were <400 copies/mL). All babies for whom data were available (19/19) were HIV negative.

A second study, conducted by Carmen Zorrilla and investigators in Puerto Rico and the US on behalf of the manufacturer, evaluated the PK of total and unbound (DRV) in pregnant women receiving 600/100 mg DRV/r containing twice daily regimens. This multicentre phase 3b study enrolled women in the second trimester and plasma concentrations were obtained pre-dose and 1, 2, 3, 4, 6, 9, and 12 hours post-dose both second and third trimesters and then 6-12 weeks postpartum.

Total DRV and ritonavir (RTV) plasma concentrations were measured using HPLC-MS/MS with a lower limit of quantification 5.00 ng/mL for both DRV and RTV. The investigators measured unbound DRV by fortifying plasma samples with 14C DRV and separating total and unbound DRV using ultrafiltration. Total and unbound 14C DRV were measured using liquid scintillation counting.

The study enrolled 16 women of a median age of 24 years and CD4 count of 421 cells/mm<sup>3</sup>. Of these, 11 had evaluable PK data.

The investigators found total DRV C<sub>max</sub> was 28% and 19% lower during second and third trimesters, respectively, compared to postpartum; but total DRV C<sub>min</sub> increased respectively by 43% and 86% in comparison to postpartum. AUC<sub>12h</sub> was 24% and 17% lower in the second and third trimesters compared to post partum.

The free fraction of DRV was slightly higher compared to post partum in both trimesters. This meant the difference in unbound C<sub>max</sub> and AUC<sub>12h</sub> was less than for total DRV.

The investigators suggested that the decreased drug exposure of DRV in pregnancy might be partially compensated for by this increased proportion of free drug as albumin and a1-acid glycoprotein (AAG) concentrations were decreased by 22% to 29% during pregnancy. Unbound DRV was >EC<sub>50</sub> (27.5 ng/mL) for protease inhibitor-resistant HIV in all women.

Total C<sub>max</sub> for RTV was 34% and 37% lower; total C<sub>min</sub> was 8% and 22% higher and AUC<sub>12h</sub> was 28% and 33% lower, respectively for second and third trimesters compared to postpartum.

As the unbound concentrations of DRV were relatively unchanged during pregnancy and postpartum, the investigators suggested no dose adjustment is needed with 600/100 mg twice daily.

Overall the women's viral load decreased over time, with 90% <50 cells/mm<sup>3</sup> in the third trimester (100% <400 cells/mm<sup>3</sup>). The investigators reported one serious adverse event (increased transaminase). Of 12 infants, 4 were born preterm and all were HIV negative by standard PCR testing.

This ongoing trial will also evaluate the effects of pregnancy on DRV/r 800/100 mg once daily, etravirine, and rilpivirine PK.

The third poster showed data from PANNA - a European network established to study the PK of new ARV drugs during pregnancy. Angela Colbers and colleagues looked at third trimester exposure to DRV, atazanavir (ATV), and RTV used as booster.

In this phase 4 study women receiving DRV/r 600 mg/100 mg twice daily or 800 mg/100 mg once daily, or ATV/r 300 mg/100 mg once daily during pregnancy were enrolled. Plasma concentrations were obtained pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours in the third trimester and at least 2 weeks postpartum. Where possible a cord blood sample and matching maternal blood sample were taken at delivery. Plasma concentrations were determined using a validated UPLC method.

Women were a median of 33.5 years of age. Their background regimens were: TDF+3TC (n=12), AZT+3TC (n=4), ABC+3TC (n=3), AZT+3TC+TDF (n=3) and one woman received DRV/r monotherapy.

Data were available for 6 women receiving DRV/r 800/100 mg once daily (3 did not have postpartum concentrations) and 3 receiving 600/100 mg twice daily. For ATV/r 300/100 mg once daily, data were available for 13 women. Cord blood and maternal samples were available for 5 women receiving DRV/r and 7 ATV/r.

This study found exposure (AUC<sub>tau</sub>) during pregnancy to DRV, ATV and RTV was decreased by respectively 36%, 33% and 53% compared to post-partum. The investigators suggested that increased volume of distribution or decreased absorption could explain this. They added that as the half-life seems to be similar during and after pregnancy, increased elimination is less likely to be the reason.

They noted that concomitant use of tenofovir (used by 14 patients) did not appear to influence DRV or ATV exposure.

In this study 2/9 women receiving DRV had concentrations below the target concentration in the 3rd trimester.

The ratio of cord blood/maternal concentrations ranged from 0.11-0.67 (n=7) and was <0.76 for DRV (n=5).

All children were HIV-negative and no birth defects were reported.

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#### C O M M E N T

**Data from these studies suggest that twice daily dosing with darunavir 600mg/ritonavir 100 mg provides adequate drug exposure during pregnancy.**

**However, the data from the PANNA study on a small sample of women taking once daily darunavir 800mg/ritonavir 100mg and data from Capparelli et al presented at the Rome paediatric workshop last year show much lower trough concentrations, which in some cases are below that recommended to achieve viral suppression. [4, 5]**

**Until more data are available twice-daily darunavir at the standard dose should be prescribed and TDM used to monitor the use of once daily darunavir during pregnancy.**

#### References

1. Courbon E et al. Safety, efficacy, and pharmacokinetic of darunavir/ritonavir-containing regimen in pregnant HIV+ women. 19th Conference on Retroviruses and Opportunistic Infections, 5 - 8 March, Seattle. Poster abstract 1011.
2. Zorrilla C et al. Total and unbound darunavir pharmacokinetics in HIV-1+ pregnant women. 19th Conference on Retroviruses and Opportunistic Infections, 5 - 8 March, Seattle. Poster abstract 1012.
3. Colbers A et al. A comparison of the pharmacokinetics of darunavir, atazanavir, and ritonavir during pregnancy and post-partum. 19th Conference on Retroviruses and Opportunistic Infections, 5 - 8 March, Seattle. Poster abstract 1013.
4. Capparelli E et al. Pharmacokinetics of Darunavir Once or Twice Daily During and After Pregnancy. 3rd International Workshop on HIV Pediatrics. 15-16 July, 2011. Rome, Italy. Poster abstract P\_72.
5. HTB. Pharmacokinetics of darunavir and fosamprenavir in pregnancy  
<http://i-base.info/htb/15489>

## ANTIRETROVIRALS

### Fosamprenavir paediatric dosing approved in US for ages 4 weeks to <6 years

**On 27 April 2012, the Food and Drug Administration approved dosing recommendations for use of fosamprenavir (Lexiva) oral suspension in pediatric patients.**

Data submitted to FDA included three studies to support a new dosing regimen for fosamprenavir (FOS), with ritonavir (RTV), in combination with other antiretroviral drugs, for the treatment of HIV-1 infection in pediatric patients from at least 4 weeks to less than 6 years of age.

The fosamprenavir label now includes dosing for pediatric patients aged at least 4 weeks to 18 years. The dosage of fosamprenavir should be calculated based on body weight (kg) and not exceed the recommended adult dose.

Twice daily dosage regimens by weight with ritonavir are as follows:

- For protease inhibitor-naïve pediatric patients (greater than or equal to 4 weeks of age) and
- For protease inhibitor-experienced pediatric patients greater than or equal to 6 months of age. (fosamprenavir plus ritonavir is not recommended for protease inhibitor experienced pediatric patients less than 6 month of age.)

Less than 11 kg	FOS 45 mg/kg plus RTV 7 mg/kg
11 kg to less than 15 kg	FOS 30 mg/kg plus RTV 3 mg/kg
15 kg to less than 20 kg	FOS 23 mg/kg plus RTV 3 mg/kg
Greater than and equal to 20 kg	FOS 18 mg/kg plus RTV 3 mg/kg

Alternatively, protease inhibitor naïve children 2 years of age and older can be administered fosamprenavir (without ritonavir) 30 mg/kg twice daily. Fosamprenavir should only be administered to infants born at 38 weeks gestation or greater and who have attained a post-natal age of 28 days. For pediatric patients, pharmacokinetic and clinical data:

- Do not support once-daily dosing of fosamprenavir alone or in combination with ritonavir.
- Do not support administration of fosamprenavir alone or in combination with ritonavir for protease inhibitor-experienced children younger than 6 months of age.
- Do not support twice-daily dosing of fosamprenavir without ritonavir in pediatric patients younger than 2 years of age.

Other sections were updated to include safety and activity data from the three open label trials in pediatric subjects aged at least 4 weeks to 18 years.

The complete updated labeling will be posted soon to on the FDA web site. Fosamprenavir is an HIV protease inhibitor manufactured by GlaxoSmithKline.

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

### FDA advisory hearing supports approval of tenofovir/FTC for PrEP

**On 10 May 2012, US FDA Antiviral Drugs Advisory Committee held an open meeting to decide on recommendations for approval for tenofovir/FTC (Truvada) to have an indication for use as Pre-Exposure Prophylaxis (PrEP) to reduce the risk of HIV transmission.**

The meeting lasted more than 12 hours, and involved the panel voting on key questions.

This included a 19:3 vote in favour of recommending approval for men who have sex with men (MSM) at risk for HIV; and a vote of 19:2 (with one abstention) for recommending approval for HIV negative partners in relationships with HIV positive partners. The vote was closer for a general use to reduce sexual transmission with 12:8 in favour (with 2 abstentions).

While the FDA are not mandated to follow the panel recommendations, it is unusual for this not to happen. The final approval decision is expected by 15 June.

As part of this process, the FDA publish a briefing document prior to each advisory panel meeting, available in PDF format online, which compiles a review of the data.

Links and further information:

FDA briefing document (PDF)

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM303213.pdf>

## FDA advisory panel vote 13:1 for approval of Quad

**On 11 May 2012, the US FDA Antiviral Drugs Advisory Committee held an open meeting to decide on recommendations for approval for the 4-in-1, fixed dose combination (FDC) Quad (elvitegravir/cobicistat/tneofovir/FTC), manufactured by Gilead.**

The panel voted 13:1 in favour of recommending approval. The vote against came from a nephrologist and was based on the current availability of existing options for which there is more established renal safety data.

The FDA nearly always follows panel recommendations though this is not mandatory.

As part of this process, the FDA publish a briefing document prior to each advisory panel meeting, available in PDF format online, which compiles a review of the data.

Links and further information

FDA briefing document: 200-page new drug application (PDF)

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM303397.pdf>

Gilead PR. FDA committee supports approval of Gilead's once-daily Quad single tablet regimen for HIV (11 May 2012)

<http://xa.yimg.com/kq/groups/9246722/1343919779>

## TREATMENT ACCESS

### FDA approval of generic ARVs: nevirapine and Combivir now off-patent in the US

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

Drug and formulation	Manufacturer, Country	Approval date
Lopinavir/ritonavir 200 mg / 50 mg combined tablets	Hetero, India	23 May 2012
Nevirapine 200 mg tablets **	10 manufacturers: Apotex, Canada Aurobindo, India Cipla, India Hetero, India Matrix, India Micro, India Mylan, US/India Prinston Pharma, US ScieGen Pharma, US Strides, India	22 May 2012
Nevirapine oral suspension **	Aurobindo, India	22 May 2012
AZT/3TC combination tablets, 300 mg / 150 mg **	Lupin, India	15 May 2012
AZT/3TC combination tablets, 300 mg / 150 mg **	Aurobindo, India	15 May 2012
Nevirapine scored tablets for oral suspension: 50 mg and 100 mg (for children >5 kg)	Cipla, India	30 April 2012

Key: \*\* Full approval; 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 US. Tentative approval does, however make the product eligible for consideration for purchase under the PEPFAR program for use outside the US.

Full approval (\*\*) indicates that these formulations can be marketed in the US because the patent for the original drug has now expired.

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 (now at 140) is available on the FDA website:

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

## C O M M E N T

**The most notable developments this year have been the full license approvals that allows marketing in the US for generic versions of nevirapine and the combined formulation of AZT/3TC.**

**Generic versions of AZT, 3TC and nevirapine are already used in some European countries. For nevirapine this includes Ireland, Spain and Portugal, although for reasons that are not clear, UK access is not expected until 2013.**

Source: FDA list serve:

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

## Stavudine (d4T) phase-out festival in Delhi

**Simon Collins, HIV i-Base**

**On 18 May 2012, more than 80 People Living with HIV with prominent side effects from stavudine (d4T), protested at a “Stavudine Phase-Out Festival” demanding immediate phase out of the ARV from India’s National Antiretroviral Treatment (ART) program. [1]**

Delhi Network of Positive People (DNP+) along with Nai Umang, Jagriti, Love Life, Om Prakash Network of People living with HIV/AIDS, Delhi Positive Women Network and Delhi Mahila Samiti co-hosted the workshop with support from International Treatment Preparedness Coalition (ITPC) and Asia Pacific Network of People living with HIV (APN+).

Severe side effects include peripheral neuropathy, lactic acidosis and lipoatrophy (especially the loss of facial fat). No developed country uses d4T (dropped from UK guidelines in 2005) and in 2010, the World Health Organization (WHO) ART Guidelines advised member countries to develop a phase out plan for d4T. [2]

Yet, many developing countries including India, continues to use this early nucleoside analogue, and it is estimated that 50% of HIV positive people who are on treatment globally, still include d4T in their combination.

The meeting included HIV positive people, doctors and advocates.

The press release for this event included many personal experiences:

*“Since I started d4T four years ago, my looks have completely changed. How many times I will answer, to how many people, what is wrong with my looks, my face? I can’t go to drop my son anymore to school because of the severe pain in my legs. I am having extreme difficulties in attending office because of the pain that now the livelihood of my family is threatened” - Mr Munna, DNP+.*

*“Since I started Stavudine in 2008, the muscles in my legs have become so weak that I can’t walk anymore. In spite of my repeated complaint, the doctor refused to change my medication” - Ramesh, 72, a widower used to drive a cycle rickshaw to make a living. Now sitting in a wheelchair. Ramesh once lived in a rented room but is now forced to live with distant relative’s house, as he can’t afford to pay the room rent, due his neuropathy.*

*“Staring at my sunken face, people keep on asking, you are looking very weak, what is wrong with you? Why is toxic drug-Stavudine is continuously being given to us, when no one from the developed world is prescribing this drug” - Hari Singh, ex-national wrestler. “*

*As a woman, I am embarrassed with this horrible changes in my looks and my weakness, I am now scared to go out of home and meet friends or neighbors” - Ms. Krishna, expressing her fear of being stigmatised.*

You are living that’s good enough and why do you bother about your looks” was the answer Ms.Durga from Nai Umang was given by the doctors when consulted about the symptoms, that include severe pain, tingling and burning sensation on her feet besides wasted facial muscles. On another occasion Mr.Devananda, who has the same symptoms was told *“Are you the doctor or I am the doctor? I will change it as and when I think it is to be done so”* is the blunt unhelpful reply of the doctor.

References:

1. DNP+ press release (18 May 2012).
2. WHO. Stavudine (d4T) phase-out management: Guiding principles  
<http://www.who.int/hiv/topics/treatment/d4t-phase-out-management-guiding-principles.pdf> (PDF)

## SIDE EFFECTS

### Associations between tenofovir use and renal complications in VA cohort

Simon Collins, HIV i-Base

**Tenofovir is one of the most widely used antiretrovirals and the association with a generally low risk of renal complications has been widely reported. However, there has been conflicting data on potential for renal complications with cumulative use or in patients with normal renal function.**

An analysis from the US Veterans Association (VA) cohort published in the 24 April 2012 edition of AIDS reported that cumulative use of tenofovir was associated with renal complications and that this might not be reversible. [1]

From 1997-2007, more than 19,700 treatment naïve patients were reported as starting ART in the VA cohort. Discounting those without at least one of the key parameters: CD4, viral load, out-patient visit, renal markers or with renal failure however, reduced this study to 10,841 patients, 4,303 of whom used tenofovir. An era-of-use analysis adjusted for tenofovir not being approved until 2001: 85% of patients used tenofovir in the period 2005-07; 54% in 2003-05 and 17% prior to 2003).

Changes in renal function were determined by one of three criteria.

- 1) Proteinuria (urine dipstick  $\geq$ 30 mg/dL on two consecutive tests).
- 2) Rapid decline in kidney function ( $>$ 3 mL/min/1.73m<sup>2</sup> annual decline for at least two years), and
- 3) Chronic kidney disease (CKD) (eGFR  $<$  60 mL/min/1.73m<sup>2</sup> on two occasions at least 3 months apart).

Additional sensitivity analyses were also performed for time to events and for more extreme renal dysfunction. Patients with proteinuria or CKD at baseline were excluded from those analyses. Hazard ratios (HR) were calculated adjusting for demographic, time dependent and marginal structural models.

Median age was 46 years (IQR 40-52), and approximately 98% of participants were men. Ethnicity included approximately 50% black, 40% white and 10% other. Median CD4 count and viral load before treatment were approximately 200 (IQR 50-400) cells/mm<sup>3</sup> and 60,000 (IQR 15,000-220,000) copies/mL.

Prevalence of comorbid conditions at baseline (in the TDF vs no-TDF groups) included hypertension (38% vs 39%), diabetes (6.8 vs 7.9%), HCV (14 vs 17%), smoking (18% vs 19%) and dyslipidaemia (15% both groups). Renal disease at baseline included approximate median eGFR 96 (IQR 82-114) mL/min per 1.73 m<sup>2</sup>, with 4.7% vs 7.3% with eGRF  $<$ 60 mL/min/1.73m<sup>2</sup> and 19% vs 21% with proteinuria ( $>$ 30 mg/dL).

Median follow-up per individual ranged from 3.9 years (for proteinuria) to 5.5 years (for CKD), during which there were 3,400 cases of proteinuria ( $>$ 38,000 patient years), 3078 of rapid kidney decline ( $>$ 51,500 PY) and 533 CKD events ( $>$ 56,400 PY). However, participants using tenofovir only had a median of 1.0 year exposure (IQR 0.5-1.9). Therefore 25% of people providing data used tenofovir for less than 6 months, 50% for less than 12 months and 75% less than 2 years. Maximum tenofovir use was 6.3 years. The summary of events shown in Table 1, published as supplementary information, is important to estimate rates in the tenofovir vs no-tenofovir groups, given that the results are in the main paper are based on hazard ratios.

**Table 1: Summary of events and person years (PY) by exposure to tenofovir**

Outcome	Events	PY	Rate/1,000 PY
Proteinuria			
Tenofovir never used	2,646	32,421	81.6
Tenofovir ever used	754	5,711	132.0
Rapid Decline			
Tenofovir never used	2,349	43,693	53.8
Tenofovir ever used	729	7,896	92.3
Chronic Kidney Disease			
Tenofovir never used	352	46,724	7.5
Tenofovir ever used	181	9,692	18.7

All ARVs were included in the analysis, but only tenofovir had an increased association with all three renal markers, in all three adjusted analyses, see Table 2. In the time dependent analysis (adjusting for ARV use in addition to baseline demographics), each year of exposure to tenofovir was associated with 34% increased risk of proteinuria (95%CI 25-45%,  $p <$  0.0001), 11% increased risk of rapid decline (3-18%,  $p =$  0.0033), and 33% increased risk of CKD (18-51%;  $p <$  0.0001). Controlling for slightly more frequent monitoring in tenofovir users did not affect the results. Pre-existing renal risk factors did not appear to worsen the effects of tenofovir.

Table 2: Association of tenofovir exposure with risk of kidney disease outcomes.

	Demographic adjusted model. Hazard ratio (95% CI)	Time dependent Cox model. Hazard ratio (95% CI)	Marginal structural model. Hazard ratio (95% CI)
Cumulative exposure to tenofovir (per year)			
Proteinuria	1.30 * (1.22 – 1.37)	1.34 * (1.25 – 1.45)	1.24 * (1.17 – 1.32)
Rapid decline	1.1 * (1.11 – 1.24)	1.11 ** (1.03 – 1.18)	1.16 * (1.09 – 1.23)
CKD	1.44 * (1.30 – 1.60)	1.33 * (1.18 – 1.51)	1.36 * (1.22 – 1.51)
Ever exposure to tenofovir			
Proteinuria	1.70 * (1.57 – 1.85)	1.68 * (1.52 – 1.85)	1.51 * (1.36 – 1.66)
Rapid decline	1.51 * (1.39 – 1.64)	1.36 * (1.23 – 1.50)	1.50 * (1.36 – 1.67)
CKD	2.11 * (1.76 – 2.54)	1.71 * (1.38 – 2.12)	1.88 * (1.50 – 2.36)

\* all P <0.0001 except \*\* p=0.0033

Other ARVs showed weaker or inconsistent associations with kidney disease events, notably with ritonavir and lopinavir/r associated with proteinuria, atazanavir with rapid decline and indinavir with CKD. see Table 3.

Table 3: Association of renal outcomes with ARV use

Results shown only for ARVs with >= 1 statistically significant outcome

ARV	% pts with exposure	proteinuria	p	rapid decline	p	CKD	p
Tenofovir	39.7	1.34 (1.25 – 1.45)	<0.0001	1.11 (1.03 – 1.18)	0.0033	1.33 (1.18 – 1.51)	<0.0001
AZT	68.3	0.98 (0.93-1.03)	0.42	0.98 (0.93-1.02)	0.29	0.89 (0.81-0.98)	0.020
Efavirenz	49.0	0.94 (0.90-0.99)	0.026	1.01 (0.97-1.05)	0.64	0.88 (0.79-0.98)	0.018
Ritonavir	35.7	1.18 (1.09-1.27)	<0.0001	0.96 (0.89-1.04)	0.34	0.97 (0.84-1.14)	0.74
Indinavir	24.6	1.04 (0.99 – 1.09)	0.15	0.99 (0.95-1.04)	0.67	1.16 (1.06-1.27)	0.0019
Atazanavir	17.1	0.93 (0.79-1.08)	0.34	1.22 (1.07-1.40)	0.0035	0.96 (0.77-1.18)	0.69
Lopinavir/r	15.3	0.77 (0.68-0.86)	<0.0001	1.05 (0.94-1.17)	0.39	1.21 (0.91-1.60)	0.18
Saquinavir	10.7	0.91 (0.83-0.99)	0.035	1.00 (0.92-1.08)	0.97	0.89 (0.72-1.09)	0.24

The association with tenofovir exposure was consistent across sub groups by age, race, all baseline comorbidities except diabetes and CKD, viral load, CD4 and BMI.

Among those who discontinued tenofovir use, risk of kidney disease events did not appear to increase or decrease during median follow-up of 1.2 years. Previous use of tenofovir was associated with a higher risk of all complications compared to never-use.

#### C O M M E N T

**This study was widely reported based on statistically significantly increases of 34% (proteinuria), 11% (rapid decline) and 33% (CKD) per year of exposure to tenofovir, after adjusting for traditional risks for renal complications, with increases from ever-use of 68%, 36% and 71% respectively.**

**As will all medical reports, relative rates (in this case, hazard ratios) have to also be interpreted together with data that supports the absolute risks associated with both tenofovir and non-tenofovir use.**

**Even given the generally low duration of use with tenofovir and limited follow-up after discontinuation, and that was a male study, these results are clearly important, especially when supported by other studies, such as the D:A:D analysis presented at CROI (see earlier in this issue of HTB).**

**Although the optimal way to define a rapid decline in kidney function is unclear, these seem like reasonable markers to have selected even though other groups (including D:A:D) use different criteria.**

**While it is unclear whether any minimum number of eGFR measures were needed when calculating the rate of decline within a year, as**

three or more would more accurately reflect a true decline rather than annual fluctuation but it is good that they excluded assessments of renal function during in-patient episodes as many other studies have not been able to do this.

With limited follow-up, it is difficult to separate the effect of 'ever exposure' from 'cumulative exposure' (and even with longer follow-up, this isn't always straightforward), but this will only become clear in future analyses.

As renal function was not always assessed during early the HAART period, patients with these early data may have had other renal complications requiring monitoring. However, the results did not change significantly when patients prior to 2001 were excluded.

Although the method of fitting the marginal structural models may be unclear, it is somewhat reassuring that similar results were found for all three models, suggesting that the results are robust to the choice of methodological approach.

The perceived risk of tenofovir and renal complications clearly affected the choice of early switching and explains the lack of associations with more advanced stages of CKD.

#### Reference

Scherzer R et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS*. 26(7):867-875, April 24, 2012. doi: 10.1097/QAD.0b013e328351f68f  
[http://journals.lww.com/aidsonline/Fulltext/2012/04240/Association\\_of\\_tenofovir\\_exposure\\_with\\_kidney.12.aspx](http://journals.lww.com/aidsonline/Fulltext/2012/04240/Association_of_tenofovir_exposure_with_kidney.12.aspx)

## **Risk factors associated with End Stage Renal Disease (ESRD) in HIV positive patients in the US Veterans Association (VA) cohort**

### **Simon Collins, HIV i-Base**

**An analysis of the risks associated with end stage renal disease (ESRD), defined as need for dialysis or transplant, in HIV positive patients who receive care from the Veterans Association (VA) in the US was published in the May 2012 edition of the American Journal of Kidney Diseases. [1]**

This provides additional useful information to the VA analysis of the impact of ART on markers of renal dysfunction published in *AIDS* (and reviewed above). [2]

The current study was a retrospective review of >22,100 patients without ESRD who received care between 1996 and 2004. Data was retrieved for the following parameters: hypertension, diabetes, cardiovascular disease, hypoalbuminemia (serum albumin <3.5 mg/dL), CD4 lymphocyte count, HIV viral load, hepatitis C virus coinfection, proteinuria, and eGFR. The researchers were particularly interested in association between ESRD and proteinuria and eGFR.

Over a median individual follow-up of 69 months, the review identified 366 cases of ESRD with an incidence of 3/1000 patient years (PY).

In multivariate analysis, traditional comorbidities that were associated with ESRD (Hazard Ratio: 95%CI) were hypertension (HR 1.9; 1.5-2.4), diabetes (HR 1.7; 1.3-2.2), cardiovascular disease (HR 2.2; 1.7-2.7), hepatitis C virus coinfection (HR 1.9; 1.5-2.4), and hypoalbuminemia (HR 2.1; 1.8-2.5).

Although the study reported that CD4 count <200 cells/mm<sup>3</sup> (HR 1.5; 1.2-2.0; compared to CD4 >350) and HIV viral load ≥30,000 copies/mL (HR 2.0; 1.5-2.8) were associated with ESRD, when adjusted for competing risk of death before ESRD, both these HIV related factors became non-significant.

Patients who developed ESRD were more likely to have had proteinuria or eGFR <60 at baseline compared as well as other comorbidities with an exponential association relating to both factors: ranging from 6.6 /1,000 PY (urine protein excretion of 30-100 mg/dL and eGFR >60) to 193/1,000 PY (urine protein excretion ≥300 mg/dL and eGFR <30).

Similar to HIV negative studies, black patients were at 3-fold higher risk of ESRD than white patients (85% of cases were black vs 14% white).

When stratified by race, the adjusted hazard ratios for ESRD for each risk factor were similar between the white and black race groups, with the exception of diabetes (HR 4.5; 2.3-9.0 vs 1.6; 1.2-2.1) white vs in black individuals respectively, (p for interaction=0.002).

The study was not designed to look at the long-term effects of ART or individual drugs and kidney function. A similar proportion of patient with and without ESRD used ART

The researchers concluded that staging patients with CKD jointly by eGFR and proteinuria resulted in strong risk stratification for ESRD in HIV positive patients and that this could be used broadly in clinical practice.

#### C O M M E N T

**Event rates of ESRD were reported as comparable to those of myocardial infarction reported in the D:A:D study [2], although it is notable that ESRD in D:A:D is considerably lower (with <100 ESRD compared to >900 MI's). This appears to be accounted for by race as similar proportions of patients without ESRD were black and white (42% vs 36% respectively), but 85% of patients with ESRD were black compared to 13% who were white.**

**The study also discussed a limitation from not having biopsy results to distinguish HIVAN from other pathologies.**

**The potential to use combined proteinuria and eGFR to stage risk of ESRD in HIV positive patients warrants further study. Given the VA is an almost exclusively male cohort, this finding needs to be looked at in mixed populations.**

Reference

1. Jotwani V et al. Risk factors for ESRD in HIV-Infected Individuals: Traditional and HIV-Related Factors: VA Study/risk factors. American Journal of Kidney Diseases American Journal of Kidney Diseases. Volume 59, Issue 5, Pages 628-635, May 2012; DOI: 10.1053/j.ajkd.2011.10.050. [http://www.ajkd.org/article/S0272-6386\(11\)01662-3/abstract](http://www.ajkd.org/article/S0272-6386(11)01662-3/abstract)
2. Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.

## **20% people switch Atripla due to efavirenz side effects: late switches are common**

**Simon Collins, HIV i-Base**

**The experience from use of fixed-dose combination, efavirenz-based treatment (Atripla) as first-line therapy in the UK was published ahead of print in the journal AIDS.**

This analysis included 472 patients from the Chelsea and Westminster Hospital in London. Case notes were retrospectively reviewed to collect safety and efficacy data on the patients who changed treatment.

Patients were predominantly male (94%), median age 37 years (IQR 31–43), and white (75%). Approximately 6% were black African, 3% Asian, 5% other. Median CD4 count and viral load when starting treatment were 285 cells/mm<sup>3</sup> (IQR 208–362) and 16,000 copies/mL (IQR 708– 54,000) respectively. Median total cholesterol at baseline was 4.3 mmol/l (IQR 3.8 – 5 mmol/L).

Over follow-up, 19% of patients (89/472) switched treatment, most commonly (71%) due to CNS-related side effects (63/89). The median time to treatment switch (in 63 patients with data) was 294 days (IQR 108–495 days) with the median duration of first CNS event (available for 53 patients) was 27 days (IQR 7–104 days). Efavirenz was switched mainly to etravirine (n=39), atazanavir/r (n=15) and darunavir/r (n=6). The commonest symptoms (in these 53 patients) were nightmares or vivid dreams in 28 (44%), insomnia in 27 (43%), depression in 22 (35%), dizziness in 12 (19%), fatigue in 9 (19%) and anxiety in 8 (13%).

The notes highlighted six patients with CNS toxicity that had a prior documented history of depression, two of whom were on antidepressants. Of three patients who stopped ART without their doctors knowledge, one later presented with PCP and another with drug resistance. Another three individuals attempted suicide by drug overdose that they directly attributed to their CNS toxicity (one on concomitant HCV treatment).

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

**Although limited information was available for many of these parameters, the time taken for many patients to switch is important to highlight. This is likely to be for many factors, but routinely accessing patients on efavirenz-based combinations for common symptoms (sleep disturbance, depression, dizziness, fatigue and anxiety) will be important to ensure optimal patient care.**

**Some of these examples, with commonly prescribed drugs at an extensively experienced centre, were clearly traumatic and avoidable, given the wide range of alternative options.**

**The importance of individualising care in the content of broadly prescriptive treatment guidelines is also clear.**

Ref: Scourfield A et al. Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals. Concise communication. AIDS, published ahead of print.

[http://journals.lww.com/aidsonline/Abstract/publishahead/Discontinuation\\_of\\_Atripla\\_R\\_\\_as\\_first\\_line.98950.aspx?AuthenticationFailureReason=LoginFailed](http://journals.lww.com/aidsonline/Abstract/publishahead/Discontinuation_of_Atripla_R__as_first_line.98950.aspx?AuthenticationFailureReason=LoginFailed)

## **GUIDELINES**

### **New UK guidelines: Treatment of HIV-1 positive adults with antiretroviral therapy (2012)**

**Simon Collins, HIV i-Base**

**In April 2012, the British HIV Association (BHIVA) published online the new adult treatment guidelines. This includes revisions to the initial draft published a month earlier for comment.**

This is the first update since 2008, with the delay related to a new methodology that hopefully will enable NICE accreditation. This is a key objective if HIV care is to defer as a model for national care to the expertise in this document. Although the guidelines have always been evidence-based, the new methodology involved identifying key clinical questions and related criteria, and then evaluating responses from the results of a more thorough a systematic literature search.

The guidelines focus on when to start initial treatment, which drugs to use, supporting patients on therapy and management of treatment failure. They include key recommendations and auditable outcomes and emphasise patient involvement in clinical decisions (section 3).

Section 8 is sub-divided to cover coinfection with TB, viral hepatitis, HIV-related cancer, neurocognitive impairment, renal disease, cardiovascular disease and women's health.

Significant points in the new document include:

- ART can be used at any CD4 count (with no upper limit above 350) as an individual patient choice to reduce risk of infection to sexual partners.
- Current evidence prioritises tenofovir/FTC over abacavir/3TC for choice of dual NRTIs.
- Equal evidence supports one of four choices for the third component: atazanavir/ritonavir, darunavir/ritonavir, efavirenz or raltegravir.
- That outside of a clinical trial, there is insufficient evidence to recommend boosted PI monotherapy over current 3-drug stand-of-care.
- Age >50 years is no longer an independent factor for deciding when to start treatment – notably, the UK guidelines have dropped this just as the US DHHS guidelines included a new section on HIV and ageing.

These guidelines are also welcomed as a reference for minimum standard of care for HIV positive people and community advocates.

Although a small point in clinical terms, it also is encouraging to see the title of the guidelines reflect the more modern community preference to refer to HIV positive people rather than HIV-infected patients.

Links and PDF downloads:

Treatment of HIV-1 positive adults with antiretroviral therapy (2012)

[http://www.bhiva.org/TreatmentofHIV1\\_2012.aspx](http://www.bhiva.org/TreatmentofHIV1_2012.aspx)

<http://www.bhiva.org/documents/Guidelines/Treatment/2012/120430TreatmentGuidelines.pdf>

## **New UK guidelines: Management of HIV infection in pregnant women (2012)**

**The new guidelines for the management of HIV during pregnancy, the first revision since 2008, will help enable more HIV positive women to have a similar experience in childbirth as women who are HIV negative.**

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of human immunodeficiency virus (HIV)-positive pregnant women in the UK.

The guidelines are aimed at clinical professionals directly involved with, and responsible for, the care of pregnant women with HIV infection.

Links and PDF downloads:

Management of HIV infection in pregnant women (2012)

<http://www.bhiva.org/PregnantWomen2012.aspx>

<http://www.bhiva.org/documents/Guidelines/Treatment/2012/120430PregnancyGuidelines.pdf>

## **WHO guidelines for testing, counseling and treatment in serodifferent couples: ART at CD4 >350 to reduce transmission**

**Nathan Geffen, TAC**

**In April 2012 the WHO released new guidelines for HIV testing and treatment in couples. This document is important because it includes the broad recommendation that ART be used to prevent transmission at any CD4 count. [1]**

These guidelines were originally planned to be distributed at the International AIDS Society meeting in Rome in July 2011. [2] However, for reasons that have never been publicly clarified, publication was withheld and activist organisations, including i-Base, responded with a letter to the WHO. [3]

While much of the text has been reedited, the summary recommendations are essentially unchanged (including the option to use ART at CD4 counts >350 to reduce the risk of transmission), see Table 1. The final document now benefits from a more considered discussion on PEP, PrEP and treatment as prevention.

Although all the recommendations are graded strong, only recommendations 4 and 5 are based on high-quality evidence, primarily HPTN 052. [4]

**Table 1: Summary recommendations and level of evidence**

	Recommendation	Level of evidence
1.	Couples and partners should be offered voluntary HIV testing and counselling with support for mutual disclosure.	Strong recommendation, low-quality evidence.
2.	Couples and partners in antenatal care settings should be offered voluntary HIV testing and counselling with support for mutual disclosure.	Strong recommendation, low-quality evidence.
3.	Couples and partners voluntary HIV testing and counselling with support for mutual disclosure should be offered to individuals with known HIV status and their partners.	Strong recommendation, low - quality evidence for all people with HIV in all epidemic settings / Conditional recommendation, low-quality evidence for HIV-negative people depending on country specific HIV prevalence.
4.	People with HIV in serodiscordant couples and who are started on antiretroviral therapy (ART) for their own health should be advised that ART is also recommended to reduce HIV transmission to the uninfected partner.	Strong recommendation, high-quality evidence.
5.	HIV-positive partners with >350 CD4 cells/mm <sup>3</sup> in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners.	Strong recommendation, high-quality evidence.

Reference:

- Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: Recommendations for a public health approach. WHO, April 2012  
[http://whqlibdoc.who.int/publications/2012/9789241501972\\_eng.pdf](http://whqlibdoc.who.int/publications/2012/9789241501972_eng.pdf)
- World Health Organisation. (Unpublished). Couples HIV testing and counselling and antiretroviral therapy for treatment and prevention in serodiscordant couples. Recommendations for a public health approach.  
<http://dl.dropbox.com/u/193052/PrimaryDocuments/WHO/WHOguidelinesForSeroDiscordantCouples-2011.pdf> (PDF)
- ARASA et al. 2011. Open letter to WHO on delayed testing and treatment guidelines for discordant couples.  
<http://www.tac.org.za/community/node/3110>
- Cohen MS. 2011. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493-505.  
<http://www.ncbi.nlm.nih.gov/pubmed/21767103>

## **NICE guideline on fertility treatment proposes alternatives to sperm washing**

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

#### **National Institute for Health and Clinical Excellence (NICE) are updating their fertility recommendations (last guidance was 2004).**

The 2012 draft includes a section on viral transmission with the review question: "What is the effectiveness and safety of sperm washing to reduce the risk of viral transmission?" It specifically addresses transmission risk of HIV when HIV positive male partners are on treatment and when HIV negative women use pre-exposure prophylaxis.

On review of the evidence the guideline concluded that recommendations should be in concordance with 'Swiss Criteria' ie if a person meets the following criteria then they are not sexually infectious:

- The person adheres to antiretroviral therapy, the effects of which must be evaluated regularly by the treating physician, and
- The viral load has been suppressed (<50 copies/mL) for at least six months, and
- There are no other sexually transmitted infections.

Where these criteria were not met couples would still be advised to have sperm washing. The guidance acknowledges that there might be some couples who would still be anxious about transmission with unprotected intercourse and request sperm washing, despite the HIV positive man being adherent on ART with a viral load of less than 50 copies/mL. In these circumstances the recommendation is that the request should be considered. Couples should be made aware that fertility rates would be lower with sperm washing and IUI compared with unprotected intercourse at the time of ovulation.

In situations where ART was being used and viral loads were undetectable the guidance highlights that sperm washing only reduced viral loads rather than eliminating it, so there would be little or no added benefit from this option.

Source:

National Collaborating Centre for Women's and Children's Health, Commissioned by the National Institute for Health and Clinical Excellence Draft for stakeholder consultation. Fertility: assessment for people with fertility problems (update, May 2012).

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

<http://www.nice.org.uk/nicemedia/live/12157/59278/59278.pdf> (PDF)

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## OTHER NEWS

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### **ACT-UP at 25: tax Wall Street, end AIDS**

**Liz Highleyman, HIVandHepatitis.com**

**On 25 April this year, the grass roots community HIV organisation ACT-UP organised a demonstration in Wall Street, New York, to mark 25 years of activism.**

The AIDS Coalition to Unleash Power, better known as ACT UP, held its first major action – a demonstration on Wall Street demanding access to experimental HIV drugs and an end to discrimination against people with AIDS – on March 24, 1987. The group's eye-catching graphics and savvy use of the media received widespread attention, and soon ACT UP chapters were springing up across the U.S. and around the world.

ACT UP is now credited with lasting changes in the way new drugs are developed and approved, clinical trials are conducted, and healthcare providers relate to patients. Persistent activism, combined with the efforts of dedicated researchers and a bit of good luck, led to effective antiretroviral therapy that enables HIV positive people who receive timely treatment to have a near-normal life expectancy.

To commemorate the 25th anniversary, several recent articles have looked at ACT UP's history and legacy, as well as what still remains to be done. Two documentaries - David France's "How to Survive a Plague" and Jim Hubbard and Sarah Schulman's "United In Anger" - have recently premiered.

Links:

ACT UP 25th Anniversary action in New York, April 25.

<http://www.actupny.com>

Rachel Maddow on MSNBC TV: (Rachel was formerly an activist at HIV i-Base's nascent AIDS Treatment Project)

<http://video.msnbc.msn.com/the-rachel-maddow-show/47213127#47213127>

25 years later, activists recall ACT UP's legacy, Liz Highleyman, Bay Area Reporter.

<http://www.ebar.com/news/article.php?sec=news&article=67538>

The Living After the Dying, Frank Bruni, New York Times.

[http://www.nytimes.com/2012/03/18/opinion/sunday/bruni-the-aids-warriors-legacy.html?\\_r=1](http://www.nytimes.com/2012/03/18/opinion/sunday/bruni-the-aids-warriors-legacy.html?_r=1)

ACT UP 25 years later, Tommi Avicelli Mecca, Salon.com

[http://open.salon.com/blog/avimecca/2012/03/18/act\\_up\\_25\\_years\\_later](http://open.salon.com/blog/avimecca/2012/03/18/act_up_25_years_later)

Pictures from a Battlefield, David France, New York Magazine.

<http://nymag.com/news/features/act-up-2012-4>

How to Survive a Plague: New Film Chronicles History of AIDS Activism in U.S.

[www.howtosurviveaplague.com/](http://www.howtosurviveaplague.com/)

United in Anger: History of ACT-UP film

<http://www.youtube.com/watch?v=OTNC3ab8oq8>

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## FUTURE MEETINGS

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### **Conference listing 2012**

**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.

20th Intl HIV Drug Resistance Workshop

9–13 June 2012, venue tbc

<http://www.informedhorizons.com/resistance2012>

14th International Workshop on Co-morbidities and Adverse Drug Reactions (Lipodystrophy Workshop)

19–21 July 2012, Washington

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

7th Intl Workshop on HIV Transmission

19–20 July 2012, Washington

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

4th Intl Workshop on HIV Paediatrics

20–21 July 2012, Washington

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

Towards a Cure: IAS pre-conference symposium

20–21 July 2012, Washington

<http://www.iasociety.org/Default.aspx?pageld=606>

19th IAS World AIDS Conference

22–25 July 2012, Washington

<http://www.aids2012.org>

3rd Intl Workshop on HIV and Ageing

5–6 November 2012, Baltimore, USA.

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

**11th Intl Congress on Drug Therapy in HIV**

**11–15 November 2012, Glasgow**

<http://www.hiv11.com>

## PUBLICATIONS & SERVICES FROM i-BASE

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### **i-Base website**

**The i-Base website is designed with portals for healthcare professionals, HIV-positive people and community advocates.**

It is fast and easy 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 services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

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

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

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

The advocacy resources include an online training manual 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 the website each month, with over 6000 hits a day.

### *Non-technical treatment guides*

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

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

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

- Introduction to combination therapy (April 2012)
- HIV testing and risks of sexual transmission (February 2012)
- HIV and quality of life: side effects & complications (December 2010)
- Guide to changing treatment and drug resistance (February 2011)

- Guide to HIV, pregnancy & women's health (September 2011)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)

### *Publications and reports*

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

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

#### **HTB South**

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

#### **HTB Turkey**

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB and produced three times a year by an independent group of Turkish doctors, activists and health care workers.

#### **ARV4IDUs**

An electronic publication, Antiretroviral Treatment for Injecting Drug Users (ARV4IDUs) is produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

#### **Why we must provide HIV treatment information**

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

### *Translations of i-Base publications*

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

In addition, PDF files of some of the translated publications are available online.

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

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

Languages include:

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

### *Advocacy resources*

#### **Online treatment training for advocates**

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

Entry-level curriculum relating to HIV and treatment. Eight modules include: immune system and CD4 count; virology, HIV and viral load; an introduction to antiretrovirals (ARVs); side effects of ARVs; opportunistic infections and coinfections: HIV and pregnancy; drug users and HIV; and clinical trial design and the role of advocates

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

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

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 480 members from over 120 organisations. The CAB has a separate website, where reading material, reports and presentations from all meetings are posted. Membership is free.

<http://www.ukcab.net>

### *Phoneline and information services*

#### **Treatment information request service: 0808 800 6013**

i-Base runs a specialised treatment information service.

We can provide information by phone, email and online based on the latest research.

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 1500 questions online. Questions can be answered privately, or with permission, can be answered online.

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

## Other resources

### Treatment 'Passports'

Booklets for HIV-positive people - whether newly diagnosed or positive for a long time - to record health and treatment history. Like other publications, they are available free as single copies, or in bulk.

### Generic clinic forms

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>

i-Base can add your hospital or Trust logo to these forms.

### Order publications and subscribe by post, fax or online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK.

<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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## *htb(e)*

### HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:

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

by sending an email to: [subscriptions@i-Base.org.uk](mailto:subscriptions@i-Base.org.uk)

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- Guide To HIV and hepatitis C coinfection (March 2009)  
1  5  10  25  50  Other \_\_\_\_\_
- Clinical Trials: a community guide to HIV research (March 2009)  
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