

## april–june 2012

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## htb south

### HIV TREATMENT BULLETIN SOUTH

HTB South is a quarterly journal published by HIV i-Base.

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

To order copies send an email to: [subscriptions@i-Base.org.uk](mailto:subscriptions@i-Base.org.uk)

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HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies. All editorial policies are strictly independent of funding sources. HIV South is supported by The Monument Trust. Nathan Geffen is remunerated from this grant.

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**HIV i-Base is a registered charity no 1081905 and company reg no 3962064. HTB was formally known as DrFax**

## Editorial

This issue of HTB South includes conference reports from the pharmacology workshop and CROI. Both include studies of several of the more promising pipeline drugs – both for adults and children – that might offer better options in the future to current standard of care.

We have also included an update on bedaquiline – a new TB treatment for MDR patients that is urgently needed in this region.

WHO have now released guidance for testing, counselling and treatment of people in serodifferent relationships and having a negative partner is also considered as a reason to start treatment in the new BHIVA guidelines. Also, recognising the protective benefit of ART, NICE guidelines from the UK no longer recommend sperm washing for HIV positive partners of HIV negative women wishing to conceive, if the man is stable on treatment.

### **Southern African HIV Clinician's Society**

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

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

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

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

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## CONFERENCE REPORTS

### 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, cobisistat, 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
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- Atazanavir/ritonavir and voriconazole not to be coadministered
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- 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.

#### Cobisistat: 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 IMPAACT 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.**

### References

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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>troughs</sub> 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

**The Conference on Retroviruses and Opportunistic Infections (CROI) conference is probably the most important annual scientific HIV meeting and it is also one of the most accessible for people who are unable to attend the meeting.**

Most of the presentations are available to watch free online without registration. This includes web casts of the opening lectures, oral presentations and poster discussions.

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

<http://retroconference.org>

This issue includes:

- Cure research takes centre stage: proof of concept for activating the latent reservoir
- Quad fixed-dose integrase combination: phase 3 studies at week 48
- Dolutegravir studies continue to show promise
- Tenofovir prodrug: 10 day monotherapy study sets dose at 25 mg for easier coformulation
- Paediatric formulations of ARVs: including an exciting new class
- Lower malaria risk in children receiving lopinavir/ritonavir-based compared to NNRTI-based ART
- High prevalence of d4T-associated lipodystrophy including lipoatrophy in children
- Lopinavir/ritonavir monotherapy in children
- Stopping treatment after early ART in infants
- Treatment interruptions in children
- PrEP: PK modeling of daily TDF/FTC (Truvada) provides close to 100% protection against HIV infection
- Risk of HIV reinfection may be similar to risk of initial HIV infection
- Case report: homozygous CCR5 delta-32 protection overcome by infection with X4 virus
- No association between atazanavir and MI or stroke in D:A:D
- Hepatitis C: telaprevir and boceprevir in coinfection
- Herpes Zoster vaccine safe and effective in HIV positive people
- High dose flu vaccine improves antibody responses in HIV positive people
- 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

CROI 2012: CURE RESEARCH

### Cure research takes centre stage: proof of concept for activating the latent reservoir

**Simon Collins, HIV i-Base**

**For the last two years the major HIV conferences, including CROI and the International AIDS Society (IAS) have included cure research prominently in the main programme. This is new and significant.**

At CROI in 2010, Anthony Fauci, head of the US National Institute of Allergy and Infectious Diseases (NIAID) announced that the US government would be launching new funding for cure research. [1]

Many of the researchers in this field have been working on a cure years, some for decades. But the new drive for this research to receive better funding is clearly an important factor in how quickly future progress will be made.

The new funding may, in part at least, have also been driven by the responsibility that America has assumed as the largest donor for global HIV treatment programmes. Over the last ten years, ARV access in low and middle-income countries has increased from less than 0.5 million people in 2002 to over 6.5 million people in 2012. A long-term alternative to lifelong treatment is therefore likely to be an economic as well as a medical necessity. While current cure research uses specialised and expensive procedures, as with all new developments, including ARVs, high initial costs would hopefully be driven down to become more widely affordable.

The IAS has also been developing a leadership role to coordinate global funding for cure studies and to hopefully focus on a research map that will minimise duplication. [2] The IAS organised workshops prior to each of its last two conferences and another is planned prior to the Washington meeting in July 2012. [3] Several community workshops, including one before CROI this year have also contributed to broadening awareness of the potential for a cure. [4, 5]

In addition to an oral abstract session this year, CROI included several helpful presentations of the current research in the preconference workshops for young investigators, particularly the overview by John Mellors and the talk on animal models for latency by Vincente Planelles. [6, 7]



## The Berlin cure

Whether through mediated immunity (referred to as a functional cure) or eradication (a sterilising cure), the ability to overcome lifelong treatment has always been an ultimate goal, even while the focus for recent years shifted to achieving more effective, tolerable and durable treatments.

The first report of a cure following stem cell transplantation from a donor who was naturally resistant to HIV infection (he was homozygous for the delta-32 deletion in CCR5) was at CROI in 2008 [8] and increasing press coverage since had made this a highly publicised case, and brought optimism to cure research.

The mechanism responsible for curing Timothy Brown (a.k.a. the Berlin Patient) who has been off treatment now with no evidence of HIV for over four years has not been isolated to a single component from a complex and risky set of procedures.

In addition to myeloablative chemotherapy and total body irradiation to kill both HIV infected and uninfected immune cells, he received antithymocyte globulins, cyclosporin, mycophenolate acid (MMF) and gemtuzumab (anti-CD33) that would also have killed HIV-infected and uninfected cells, followed by allogeneic stem cell transplants from a donor homozygous for delta-32 mutation, which should have reseeded an immune system resistant to CCR5 HIV infection, he developed graft vs host disease (GVHD) indicating he had accepted the donor immune system. These procedures have a 25% mortality risk and he underwent each procedure twice as the course was repeated.

An oral presentation at CROI reported on ten patients on suppressed ART who underwent autologous (self-donated) hematopoietic stem cell transplantation for AIDS related lymphoma, which is a less risky procedure than that used by Tim Brown. Unfortunately, persistent HIV viraemia was still detected in 9 of 10 patients post-transplant, with a median viral load of 1.5 copies/mL (range: <0.2 to 26) and median total HIV-1 DNA of 554 copies/million PBMCs (range: <0.4 to 2179). 2-LTR circles were detectable post-transplant in only 2 of 10 patients (range: 1 to 7 copies/million PBMC). The only patient with undetectable plasma viral load had the highest levels of HIV-1 DNA and 2-LTR circles. Additionally, plasma viraemia persisted in a patient with undetectable HIV-1 DNA in PBMC. Although the authors concluded that this showed that the CCR5 delta-32 donor was essential in the Berlin case, patients in their study also did not have total body irradiation, graft vs. host disease, and were reinfused with their own stem cells, which could have included HIV-infected T-cells. [9]

A further US study is about to open of allogeneic stem cell transplant in HIV positive people with bone marrow failure with the hope that 1 or 2 of the 15 patients may also be able to be matched to a delta-32 donor to see if the Berlin case can be repeated. [10]

This will involve overcoming the difficulty of finding and matching a delta-32 donor who is also compatible on 8 HLA types. At the community cure meeting prior to CROI, John Zaia from the City of Hope Cancer Centre near Los Angeles described an initiative to develop an inventory of cord blood stem cell donors as an international resource, and to date, out of 13,000 donors tested, 90 have been identified as being homozygous for the CCR5 delta-32 deletion. [5]

## First activation of latently infected resting T-cell reservoir *in vivo*

While many aspects of this research are controversial, there is broad consensus on the need for a strategy to overcome the reservoir of long-lived, latently infected, resting CD4 cells that harbour integrated HIV and that are not reached by current ART.

Most notably, an oral presentation at CROI included results from a proof of concept study that viral latency might be overcome. David Margolis from the University of North Carolina presented results in an oral late breaker presentation that the use of a single dose of the histone deacetylase (HDAC) inhibitor vorinostat (suberoylanilide hydroxamic acid, SAHA) is able to activate latently infected resting CD4 cells. [11] In 2005, Margolis presented results from using another HDAC inhibitor, valproic acid, to stimulate the latent reservoir.

Of the 11 human histone deacetylase, HDACs 1, 2, and 3 are the primary enzymes that limit activation of HIV integrated into cells by producing a barrier that maintains latency. Vorinostat is a selective inhibitor of HDAC 1, 2, and 3 that has been shown to induce HIV expression from latently infected resting cells *ex vivo*. However, vorinostat, although approved as a cancer treatment also has mutagenic properties.

In this proof of concept study, the change in the latent reservoir was determined by measuring cell associated HIV RNA specifically in the resting cell population. This involves harvesting approximately four billion lymphocytes from each aviraemic patient by leukopheresis that are treated with magnetic antibody beads to leave 200-1000 resting CD4 cells that can be tested by RNA PCR.

Six study participants had baseline measures of activation, that were tested *ex vivo* after exposure to vorinostat and that demonstrated that a change was measurable in all patients. Each patient also undertook a single 200 mg safety dose and a separate single 400 mg dose of vorinostat for a PK study to decide the timing for the second leukopheresis used to determine efficacy.

Following a second, therapeutic 400 mg dose, all six patients responded with a highly significant mean 4.8 fold increase (range 1.5-10-fold) of RNA expression in resting CD4 cells ( $p < 0.01$ ). The treatment was well tolerated with no reported side effects associated with vorinostat and none greater than grade 1. Of note, and perhaps surprisingly, no increases in HIV plasma RNA were detected using a single copy/mL test.

The study concluded that is the first demonstration of activation of latent resting HIV-infected CD4 cells *in vivo*. However, these results are still preliminary. While the proof-of-concept is exciting, Margolis suggested that this might be seen as the equivalent of a "ddC moment in relation to HAART".

Additionally, other molecules may be more effective compounds to activate latency and *in vitro* data suggesting panobinostat as more active that vorinostat were presented in a poster. [12]

Earlier in the same conference session Liang Shan reported that latently infected resting CD4 cells treated with vorinostat survived despite viral cytopathic effects, even in the presence of autologous CD8 cells from most patients on ART concluding "that stimulating HIV-1-specific CTL responses prior to reactivating latent HIV-1 may be essential for successful eradication efforts and should be considered in future clinical trials". [13]

## Treatment during early infection

Theoretically, the easiest targets for cure research might be those patients diagnosed earliest in their infection, who promptly start treatment and who maintain suppressed viraemia for many years.

Although the latent cell reservoir is established within weeks of infection and is likely to be slowly reduced after years on effective ART, in nearly all patients, viraemia rapidly returns within weeks if treatment is interrupted. Even when HIV is reduced to being present in less than 1 in 1.7 billion cells, this is sufficient for systemic infection to quickly be reestablished (within two months) if treatment is stopped. [14]

While levels this low might question the importance of a treatment to target the viral reservoir, they can so far only be achieved with very early treatment and/or many years of viral suppression. The need to reduce the viral reservoir more quickly will be a concern for everyone else who started ART during chronic infection.

Rapid viral rebound without treatment has been widely reported in numerous treatment interruption studies. However, several small cohorts have also reported viral control in a minority of patients, usually in those who initiated treatment in acute infection and maintained undetectable viral load for several years.

Last year at CROI, the ANRS Visconti study reported small numbers of patients who started treatment in early infection (after seroconversion, median viral load >100,000 copies/mL), maintained viral suppression for >3 years on treatment and who have subsequently controlled viraemia off treatment for >6 years. [15] This year at CROI similar cases were reported in posters by two other groups.

Maria Salgado and colleagues reported a single case of a patient who initiated treatment during seroconversion (viral load >750,000 c/mL, western blot indeterminate) for three years and after stopping ART has since maintained viral load suppressed to <50 copies/mL off-treatment for more than nine years. Initial and current viral isolates are dual CCR5/CXCR4 tropic and fully replication-competent *in vitro*. Minimal viral evolution has been detected over the 11 years.

He is reported to currently have low titers of neutralising antibodies to heterologous and autologous HIV-1 isolates, and his CD8+ T cells do not have potent HIV suppressive activity suggesting a mechanism other than CTL-mediated suppression reported in elite controllers. [16]

Alain Lefeuvre from General Hospital, Toulon (who is also one of the key organisers of the International HIV Persistence Workshop that has been meeting every two years since 2003) reported that 17% (8/45) of a cohort of patients treated at seroconversion for a median of 2.2 years (range 1.8 to 4.0) have remained off treatment for more than 10 years, two of whom remain suppressed to <20 copies/mL (median 2,500 copies/mL for the other six). The 37 people who restarted treatment (due to confirmed CD4 decline to <350 cells/mm<sup>3</sup>) did this after a median of 5.0 years (range 3.0-8.0) off-treatment. The study suggested the protective mechanism could be relate to early ART reducing the HIV reservoir but also emphasised that such responses seem to be rare. [17]

A poster from Joseph Margolick and colleagues reported small differences in viraemia between people diagnosed in early infection (within a year of infection) and randomised to immediate treatment (n=57) year) and those who did not start early treatment (n=24). However, study numbers were very low at the evaluation point (24 months after stopping treatment of 24 months after diagnosis) due to ~20% loss to follow-up and exclusion of people who restarted

treatment for other reasons. [18]

Generally small differences were also reported from early treatment in the larger SPARTAC study that randomised almost 400 people (diagnosed within 6 months of infection) to deferred ART or immediate treatment for either 3 months or 12 months, and who then stopped treatment. [19]

However, in the context of eradication research, two oral presentations suggested that early treatment, while too late to prevent the establishment of the viral reservoir, might reduce the pool of latently infected cells.

Maria Buzon and colleagues estimated the size of the viral reservoir in patients treated for more than ten years who initiated ART within 3 months of infection (n=9) and compared levels integrated and total HIV DNA levels to people who started treatment during chronic infection (n=26) and to elite controllers (n=37). [20]

Integrated and total DNA levels were significantly lower in both primary treated (p=0.06 and p=0.001, respectively) and elite controllers (p=0.003 and p<0.0001, respectively) compared to those treated in chronic infection. In addition, the ratio between total and integrated HIV-DNA was significantly lower in early treated and elite controllers (both p=0.04 vs chronic) with no differences between acute and EC groups.

Although patient numbers were small, differences were also reported when comparing how soon treatment had been started with patients treated during Fiebig stage III or IV vs stage V having significantly lower levels of both total and integrated HIV DNA after two years.

An oral presentation by Alan Perelson from the Los Alamos National Laboratory used mathematical modelling to look at the impact of early treatment of 27 people treated during acute infection on the size of the latent reservoir, and the relationship of both to initial viral load and target cell ability. [21]

This study also reported that earlier ART, including earlier during primary infection, had a measurable impact related to the initial size of the reservoir, with patients who already started with very low levels of resting cell infection (who also had low levels of peak viral load) experiencing less change in the reduction of resting cell decay. The model also suggested that CD4 T cell increases in response to successful ART was not increasing the viral reservoir.

## Research into a functional cure

Other groups are focusing on immunological interventions that would support a functional rather than eradicating cure.

Pablo Tebas from the University of Pennsylvania, presented additional safety and efficacy results from the use of zinc finger nuclease (ZFN) modification of CD4 cells (using SB-738) to a CCR5-deleted phenotype (in development by Sangamo BioSciences). [22]

This process involves harvesting cells by apheresis, treating them with SB-738 to produce 13-35% of cells with CCR5-deletions *in vitro*. The cells are then expanded, cryopreserved and 5-30 billion cells are reinfused into the donor patient.

Results were combined from three studies: one in ART responders (baseline CD4 >450 cells/mm<sup>3</sup>) who subsequently interrupted treatment (group 1, n=6) and two in immune non-responders (baseline CD4 <500 cells/mm<sup>3</sup>) who have not interrupted treatment (group 2, combined n=15). Initial results from these studies were presented at CROI and ICAAC conferences last year.

Most patients were male, white, mean age 48, with a long history of HIV infection (median 12 and 18 years in group 1 and 2 respectively). Mean CD4 count and CD4:CD8 ratio were 921 ( $\pm 222$ ) cells/mm<sup>3</sup> and 1.4 ( $\pm 0.6$ ) in group 1 and 335 ( $\pm 89$ ) cells/mm<sup>3</sup> and 0.7 ( $\pm 0.3$ ) in group 2.

Duration of follow-up is now a mean 325 days (range 90–738 days).

After infusion, CD4 cells increased by about 1500 cells/mm<sup>3</sup> in group 1 (n=6), these then decreased during the treatment interruption but which remained significantly above baseline during follow-up. CD4 responses in group 2 involved an increase of about 500 cells/mm<sup>3</sup> which then dropped by about 200-300 which then remained stable out to over a year in the patients who did not interrupt treatment. The expansion of CD4 cells was associated with increases in IL-2, IL-7 and IL-15.

The CD4:CD8 ratio increased significantly in both groups, normalising and remaining at approximately 1.0 throughout follow-up in the group 1 and increasing to approximately 2.5 for the six patients in group 2 decreasing during the treatment interruptions but then remaining stable.

The modified cells continued to be detected through follow-up at 2% of circulating CD4 cells at 48 weeks for most patients. Levels were higher during the treatment interruption for group 2 and then dropping to 2%. Circulation of cells to other tissue sites was confirmed by multiple rectal biopsies where levels of the CCR5-modified cells were comparable to those in blood or higher throughout follow-up.

During the treatment interruption viral load rebounded over the first 8 weeks to around 100,000 copies/mL in a similar way to other interruption studies dropping by one log during the last 4 weeks off-treatment to levels that were generally higher than pre-ART. After three months, when treatment was restarted, viral load become undetectable again in all six patients. One person, later found to be heterozygous for the delta-32 mutation, had a lower rebound (to 10,000 c/mL) and then resuppressed viral load to undetectable by week 8 and remained undetectable off treatment until restarting as per protocol at week 12.

This group used a new method to measure changes in the viral reservoir based on levels of HIV DNA sensitive to low copy numbers (although unable to distinguish between integrated DNA and 2-LTR circles. They reported no detectable change in 4/6 patients with one person have a transient 4-fold increases at week 12 and 20 during the interruption but returning to baseline levels and one person experiencing a 9-fold increase that returned to baseline 16 weeks after restarting treatment.

Side effects were mild and transient, mainly within 24 hours of the infusion (mild chills, fever, headache, fatigue) but included one report of arthritis lasting a few days and abnormal garlic-like body odour.

Next steps include using immunomodulatory drugs such as cyclophosphamide to promote engraftment and increase the percentage of modified cells and studying other patients who are heterozygous for the delta-32 deletion.

Several studies presented studies where pegylated interferon (peg-IFN) was added to ART prior to stopping HIV treatment and continuing peg-IFN. The results suggested that viral rebound was delayed by the peg-IFN via an immune-mediated rather than antiviral mechanism, but these were small studies with short-term follow up (12 and 24 weeks). [23, 24, 25]

## C O M M E N T

**The timeline for a cure at this meeting was optimistically referred to as being at least ten years. HIV is a tricky puzzle: the virus is resilient and the range of immune responses is complex. Nevertheless, these advancements in several key and linked areas are crucial advances.**

**Several networks are encouraging collaborative research in order to be able to compare and evaluate different approaches. [26, 27]**

**Numerous compounds that are already licensed are already being looked at for their potential to overcome latency. These include prostratin, lonomycin, thapsigargin (a calcium pump inhibitor), PMA, typhostin-A (a non-selective typhosin phosphate inhibitor), CD3/CD8 antibodies for TCR signaling, PLA, toll like receptor 7 (TLR7 including GS-9620) and protein kinase-C (PKC) agonists. Several companies including Gilead and Merck are already screening for and have identified other potential HDAC inhibitors.**

**The important of informed community participation in partners in this research is particularly important given the ethical considerations for study volunteers. If a mechanism is discovered to cure HIV more widely, it may still only work in some patients.**

**With current treatment able to nearly normalise life expectancy, a cure has a high bar to overcome. Some of this research will involve asking people on stable treatment to interrupt therapy and some of the interventions will have potentially greater toxicity than their current ART. At least for the foreseeable future, the potential risks in these initial studies are likely to outweigh any personal benefits.**

**Treatment during primary infection early treatment may put someone at a preferential state to respond to parts of a strategy to cure HIV, and some people diagnosed this early may want to take this decision. Because the latent pool is smaller in such patients, those initiating ART during acute HIV may be the best candidates for pilot studies attempting HIV eradication.**

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## CROI 2012: ANTIRETROVIRALS

**Quad fixed-dose integrase combination: phase 3 studies at week 48****Simon Collins, HIV i-Base**

**The fixed dose, single-pill, four-drug formulation of elvitegravir/cobicistat/tenofovir/FTC, developed under the name Quad, is likely to be closest to regulatory approval (and has an FDA hearing in May).**

At CROI, results were presented from two randomised, double blind, placebo controlled Phase 3 studies. One study comparing Quad to efavirenz/tenofovir/FTC (Atripla) was an oral session and another comparing Quad to atazanavir/ritonavir plus tenofovir/FTC was a poster. [1, 2]

The primary endpoints in both studies were the proportion of patients with undetectable viral load (< 50 copies/mL) at week 48 by intention-to-treat analysis, with non-inferiority defined by a lower margin of -12% and that included patient stratification by baseline viral load above and below 100,000 copies/mL. Virological efficacy was around 90%, tolerability was good and discontinuations were notably low in all arms and Quad was found to be non-inferior compared to the comparator combinations in both studies.

Study 236-0102 compared Quad to Atripla enrolled 700 treatment-naive patients in the US and Puerto Rico and Paul Sax from Brigham and Women's Hospital, Boston, presented the results. [1]

Baseline characteristics included: mean age 38 years and low median viral load (31,000 copies/mL) although one third of participants started at >100,000 c/mL. Mean CD4 count was just under 400 cells/mm<sup>3</sup> with 12% of participants starting below 200, 32% starting at both 200 to 350 and 350-500 and 23% starting at >500 (percentages for Quad arm but similar to Atripla). The study was largely male (88%) with ethnicity 61% white, 31% African Americans and 8% other. Less than 5% of participants in each arm had either HBV or HCV coinfection.

Discontinuations before week 48 were similar in 11% vs 13% in the Quad vs Atripla arms for broadly similar reasons.

Viral load was suppressed to undetectable in 88% vs 84% patients (difference +3.6%, 95%CI -1.6 to +8.8) meeting criteria for non-inferiority, with 7% of patients in each arm having virological failure and 5% vs 9% having missing data (all Quad vs Atripla, respectively). Responses by subgroup (viral load, CD4, race, sex, age and



adherence level were not significantly different but trended to favour Quad. CD4 increases favoured the Quad arm with +239 vs +206 cells/mm<sup>3</sup> respectively (p=0.009).

Approximately half of the patients in each arm failed with mutations associated with resistance to either integrase inhibitors (mainly E92Q) or NNRTIs (mainly K103N) in 8/14 vs 8/17 respectively.

Most side effects were reported as mild (grade 1) with statistically significant differences including more nausea in the Quad arm (21% vs 14%) and more abnormal dreams (15% vs 27%), insomnia (9% vs 14%), dizziness (7 vs 14%) and rash (6% vs 12%) in the Atripla arm. Discontinuations related to side effects occurred due to rash (0 vs 1.4%), renal abnormalities (1.4% vs 0), depression (0.3% vs 0.9%), abnormal dream (0 vs 0.6%) in the Quad vs Atripla arms respectively with 3% in each arm stopping due to both fatigue and paranoia.

The most frequent grade 3 or 4 laboratory abnormalities occurring in greater than five patients in each arm were broadly similar and generally low including creatinine kinase (5% vs 11%), AST (2% vs 3%), ALT (1% vs 3%), GGT (2% vs 5%), neutrophils (2% vs 3%), amylase (2% each arm) and haematuria (2% vs 1%), all in Quad vs Atripla respectively.

Serum creatinine increased by approximately 0.1-0.2 mg/dL by week 2 in the Quad arm which was maintained through to week 48 compared to no change with Atripla (p<0.001).

Increases in fasting total cholesterol, LDL and HDL cholesterol were significantly greater in the Atripla compared to the Quad arms but there was no difference between groups in the more clinically significant TC:HDL ratio or in triglycerides (+7 mg/dL in each arm).

The second Quad study, called 236-0103, compared Quad to atazanavir/ritonavir plus tenofovir/FTC (Truvada). It enrolled 708 treatment-naïve patients and results were presented by Edwin DeJesus in a poster. [2] Baseline characteristics were broadly similar to the 236-0102 study: mean age 38 years, 90% male, and 74% white. CD4, viral load and hepatitis coinfection were also similar, with 40% of participants having viral load  $\geq 100,000$  copies/mL. Exclusion criteria for this study included eGFR < 70 mL/min.

Virological efficacy (<50 copies/mL) at week 48 was 92% vs 88% (difference +3.5%, 95%CI -1.0% to +8.0%) in favour of Quad, which met criteria for non-inferiority. In patients with baseline viral load  $\geq 100,000$  copies/mL, response rates were 85% vs 82% (NS). Virologic failure (FDA snapshot algorithm) was 5%, in both arms. Median CD4 increases were similar at +207 vs 211 cells/mm<sup>3</sup> and discontinuation rates for side effects were 4% vs 5% (both in Quad vs atazanavir/r arms, respectively).

Side effects occurring in  $\geq 5\%$  of patients, were similar in each arm, apart from elevated bilirubin levels which were significantly higher in the atazanavir/ritonavir arm. Discontinuations occurred due to diarrhoea (4% vs 5%), pyrexia (1% vs <1%), nausea (1% vs 0), nausea, vomiting and fatigue (each <1% vs 1%) and jaundice, dizziness, ocular icterus and drug eruption (each 0 vs <1%). The most frequent grade 3 or 4 laboratory abnormalities occurring in at least 2% in either arm were broadly similar including creatinine kinase (6% vs 7%), haematuria (4% vs 2%), AST (2% vs 3%), ALT (2% vs 2%), amylase (2% each arm) and increased bilirubin (1% vs 58%), all in Quad vs atazanavir/ritonavir arms respectively. Serum creatinine increased by approximately 0.08 mg/dL by week 2 in the Quad arm which was 0.12 mg/dL at week 48 compared to 0.05 with atazanavir/ritonavir (p<0.001). Median change in CLCr from baseline was -12.7 mL/min in Quad and -9.5 mL/min (p <0.001).

Lipid increases were similar for TC, LDL and HDL cholesterol (all p=NS) but triglycerides increased by less in the Quad arm (+5 vs +23 mg/dL, p=0.006).

Median changes in bone mineral density were similar in each group. Spine changes reduced by about 3% at week 24 and remained stable, with reductions at week 48 of -2.45% vs -3.48% (p=0.25 for between arm comparison). Reductions at the hip were continuous slopes for both combinations of about -1.5% vs -2.0% at week 24 and -2.87 vs 3.59% at week 48 (p = 0.12).

In an answer to a question about clinical management of increases in serum creatine, in reference to increases seen in both Quad studies, Paul Sax stated that a statistical analysis of the data suggested that an increase of 0.4 mg/dL or greater was a cut-off for concerns about potential tenofovir renal tubular toxicity.

When asked whether paired cystatin C in serum would distinguish between tenofovir and cobicistat associated changes Sax said that this was a possibility, but that it might be affected by other HIV-related factors. The question of cost was also raised in the context of results that had not demonstrated superiority, perhaps related to study size.

## C O M M E N T

**Quad has already been submitted for regulatory approval to Western regulatory agencies with an FDA decision expected by August 2012.**

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## Dolutegravir studies continue to show promise

### Simon Collins, HIV i-Base

**Results from the SPRING-1 dose-finding study of dolutegravir/abacavir/3TC compared to efavirenz/tenofovir/FTC (Atripla) were presented in a late-breaker oral session and were broadly similar at 96 weeks to 48 week results for the 50 mg arm. [1]**

Two hundred and five subjects were randomised to receive dolutegravir at 10 mg, 25 mg or 50 mg once daily compared to efavirenz. Participants were 86% male, 80% white, 26% >100,000 copies/mL viral load, and 67% used tenofovir/FTC as the nucleoside backbone.

At week 96 the proportion of subjects with viral load <50 copies/mL (TLOVR) was 79%, 78% and 88% in the 10 mg, 25 mg and 50 mg arms respectively vs 72% in the efavirenz arm. Virological failure



occurred more frequently in the lower dose arms: in 13% (n=7), 8% (n=4), 4% (n=2) and 8% (n=4) of the 10 mg, 25 mg, 50 mg and efavirenz arms respectively but these were low study numbers and half these patients who counted as failure by TLOVR analysis resuppressed to below 50 copies/mL by week 96. No mutations associated with resistance to integrase inhibitors or NNRTIs were seen in these patients.

CD4 increases were not statistically different at week 96: +338 cells/mm<sup>3</sup> for the combined dolutegravir arms vs +301 cells/mm<sup>3</sup> for efavirenz ( $p = 0.155$ ).

Only two people discontinued dolutegravir due to side effects (one in each of the 25 mg and 50 mg arms) compared to five in the efavirenz group. Side effects were lower in the dolutegravir arms although serious side effects were similar. The only grade 3/4 lab abnormalities were single cases of ALT elevation associated with acute hepatitis C. No differences in renal markers were observed between the two groups.

A second oral presentation reported from a phase 1 pharmacokinetic study in HIV negative people that an increased dolutegravir dose (50 mg twice-daily) overcomes an interaction with rifampin. [2]

Five other posters expanded the profile of this important new integrase inhibitor.

These included:

- Exciting results on a paediatric granule formulation that produced higher levels compared to the oral tablet in HIV negative volunteers used oral or dissolved irrespective of liquid. [3]
- Results from a single dose pharmacokinetic study in HIV positive adults with mild-moderate liver impairment suggested that dolutegravir could be used without dose modification in these patients. [4]
- Reporting a higher genetic barrier to resistance *in vitro* that may differ by HIV subtype and identification of mutations R236K and H51Y in subtype B. [5]
- Similar potency against raltegravir-associated mutations in HIV-2 as HIV-1 [6]

## C O M M E N T

**The oral presentation of the SPRING-1 study was uncharacteristically understated: “dolutegravir has some attributes that might make it interesting for use in combination therapy” before listing once-daily dosing, no boosting, low PK variability, few expected drug interactions, potentially distinct resistance profile to raltegravir and high potency at a low milligram dose.**

**Further studies with this compound will be followed closely together with the back-up GSK-1265744 compound that may be used at even lower milligram doses (5-10 mg). Low milligram compounds have the potential as less expensive options to PI-based combinations in low-income countries, if patent issues are overcome.**

**Currently, a fixed dose formulation of dolutegravir with abacavir and 3TC has completed initial PK studies.**

**On 2 April, as this issue of HTB went to press, top-line results were released from the SPRING-2 phase 3 study in treatment-naïve adults reporting dolutegravir to be non-inferior to raltegravir. [7]**

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## Tenofovir prodrug: 10 day monotherapy study sets dose at 25 mg for easier coformulation

**Simon Collins, HIV i-Base**

**Further data on the development of a tenofovir prodrug from Gilead (compound name GS-7340) were presented by Peter Ruane MD from Los Angeles. [1]**

This compound is expected to have higher potency at much lower concentrations in all cell types with EC50s compared to the current formulation of tenofovir disoproxil fumarate (TDF) of 0.003 vs 0.015 uM in PBMCs and 0.014 vs 0.06 uM in macrophages. Last year at CROI a similar dose finding 10-day monotherapy study reported viral load reductions of about -1.0 log at 50 mg and 150 mg doses, compared to 0.5 log with TDF, with plasma concentrations of GS-7340 that were 88% lower and intracellular concentrations 4-fold higher compared to TDF.

This current study randomised 38 treatment-naïve or experienced (but tenofovir sensitive) patients to 10 days GS-7340 monotherapy using 8 mg, 25 mg and 40 mg with placebo and TDF arms as controls. The primary endpoint was the time-weighted average change in viral load (DAVG) at day 11.

Baseline characteristics included: age 38 years, 97% male and 50% white/38% African American. The mean viral load and CD4 counts were 31,000 copies/mL and 478 cells/mm<sup>3</sup> respectively.

DAVG results were -0.76, -0.94, -1.13, -0.48 and -0.01 log copies/mL in the 8 mg, 25 mg, 40 mg, TDF and placebo arms respectively with median viral load reductions -1.08 (8 mg); -1.46 (25 mg); -1.73 (40 mg), -0.97 (TDF) and -0.07 (placebo). There were significant differences between both the 25 mg and 40 mg arms when compared to TDF, but not for the 8 mg dose.

Plasma tenofovir exposures across the GS-7340 groups were approximately 80 to 97% lower compared to TDF with intracellular concentrations in PBMCs 7-fold higher in the 25 mg dose and 20 fold higher with the 40 mg dose.

There were no clinically significant laboratory abnormalities or drug-related serious adverse events, no discontinuations and no evidence of resistance over the 10 days.

Phase 2 studies that are already ongoing or soon to enroll are using the 25 mg dose for development in two fixed dose formulations. One substitutes GS-7340 for TDF in Quad with elvitegravir, cobicistat and FTC (in study 292-0102) and a second in coformulation with darunavir, cobicistat and FTC to be the first once-daily single-pill PI combination (in study 299-0102).

#### C O M M E N T

**The discussion after this presentation included surprise that the dose selected for development was to be based on such a small short study and that the greater virological efficacy in the 40 mg group was not going to be explored further. Also that this decision was largely driven by the ease of coformulation with the lower milligram dose.**

**Another question was whether increased intracellular concentrations of GS-7340 accumulated in renal tubule cells. Although no renal concerns were seen after 10 day exposure this will be an important aspect of further studies. *In vitro* data in MT-2 cells, PBMCs and macrophages did not find concerns from increased levels of intracellular diphosphates. CNS penetration of GS-7340 is expected to be similar to tenofovir DF and it may also have activity against HBV.**

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CROI 2012: PAEDIATRICS

## Paediatric formulations of ARVs: including an exciting new class

**Polly Clayden, HIV i-Base**

**International guidelines recommend universal and immediate treatment of HIV-infected neonates, which poses a significant challenge given the lack of suitable formulations in this age group.**

**Three posters at CROI showed novel “sprinkle” formulations of two integrase inhibitors and a protease inhibitor.**

### Dolutegravir

Dolutegravir (DTG) is a promising integrase inhibitor currently in phase 3 of development. The compound is interesting for several reasons: once daily dosing for treatment naive patients, low milligram dose (50 mg, so potential for co-formulation and low cost), adequate plasma exposure without boosting, few expected drug interactions, an expected different resistance profile to raltegravir and a very comprehensive development plan. 96-week phase 3 data was also presented at CROI 2012 (see above).

The developers - a partnership between Shionogi & Co and ViiV Healthcare - plan to study the compound in all paediatric age groups down to young infants, a population woefully short of appropriate antiretroviral formulations. DTG is currently being studied in children 6 - 18 years in IMPAACT P1093.

Parul Patel and colleagues presented findings from an evaluation of the single dose pharmacokinetics (PK) in healthy adults of a new oral granule formulation of DTG, in development for infants and young children. [1] The granules were given with and without 30 mL of various liquids and compared to the current tablet formulation given with 240 mL of tap water.

This was a single-centre, randomised, open-label, 5-way crossover study in 20 healthy adult subjects. Subjects received a single dose of DTG 50 mg as the phase 3 tablet and in 10 g of granule given: direct to mouth with no liquid; with purified water; with mineral water containing high calcium concentrations (Contrex); or with infant formula milk. All formulations were administered in fasting state.

The study treatments were separated by seven days. Safety evaluations and serial PK samples were collected over 48 hours in each dosing period. The PK parameters of DTG were estimated using noncompartmental methods; geometric least squares (GLS) mean ratios and 90% CI were generated to compare treatments. Taste was assessed using a questionnaire that examined bitterness, sweetness and colour.

The investigators reported DTG exposures of the granule formulation were all moderately higher than the tablet formulation with or without liquids (55% - 83% and 62% - 102% for AUC 0-INF and C<sub>max</sub> respectively, see table 1). Exposure was highest when the granule formulation was given with formula milk.

Inter-subject variability from the granule formulation was modest with a coefficient variation for AUC of 31-43%. DTG was well tolerated and there were no withdrawals due to AEs. The subjects rated the taste as acceptable for all treatments.

**Table 1: Comparison of PK parameters of dolutegravir**

Granule comparison to tablet	GLS mean ratio (90% CI)	
	AUC 0-INF	Cmax
Direct to mouth	1.58 (1.46 - 1.71)	1.62 (1.49 - 1.77)
With purified water	1.57 (1.45 - 1.69)	1.66 (1.52 - 1.81)
With mineral water	1.55 (1.43 - 1.67)	1.65 (1.51 - 1.79)
With formula milk	1.83 (1.69 - 1.98)	2.02 (1.86 - 2.20)

These data indicate that the DTG granule formulation can be given without restriction on the type of liquid or can be given alone. The taste was not considered to be a barrier to further development although the investigators noted that children's preference could be different to that of adults. The granule formulation is being studied further in children in IMPAACT P1093.

### Raltegravir

The integrase inhibitor raltegravir (RAL) is approved as a 400 mg film-coated tablet for use in adults and for children aged 6 to 18 weighing > 10 kg, and 100 mg and 25 mg chewable tablets are approved for children > 2 to <12 years old at a maximum dose of 300 mg. [2]

The paediatric programme is ongoing in IMPAACT P1066 and an oral granule formulation is being studied in the youngest children and babies. Stephen Spector and colleagues from the study team presented intensive PK, and preliminary 24 weeks safety and efficacy data from cohort IV - 6-month- to <2-year-olds - receiving the RAL oral granule formulation. [3]

Nine HIV-infected children were enrolled in a dose-finding study. Entry criteria included HIV RNA >1000 copies/mL and either prior ART experience PMTCT failure. The children received weight-based RAL oral granule suspension at ~6 mg/kg, every 12 hours.

Intensive PK was performed between day 5 and 12 after which the site investigators optimised the children's background regimen. A dose was selected for continued study using an AUC<sub>12 hr</sub> targeted design (geometric mean [GM] target range of 14 to 25 uM\*h) with C<sub>12h</sub> target to exceed the RAL IC<sub>95</sub> (31 nM). Virologic suppression was defined as HIV RNA <400 copies/mL or ≥1 log drop from baseline at 24 weeks.

One child's PK data were excluded due to absorption issues. Of the remaining 8 children: 67% were male; 78% black; mean (SD) age, 13 months (6.3); log<sub>10</sub> RNA, 5.68 copies/mL (0.95); CD4 percent, 21% (9%); CD4 count, 1338 cells (822); weight, 8.3 kg (2.6), dose, 5.94 mg/kg (0.42).

The investigators reported geometric mean values of: AUC<sub>12hr</sub>, 20 uM\*h; C<sub>max</sub>, 10.7 uM; and C<sub>12h</sub>, 115 nM. These PK values are achieved study targets and are similar to those observed in 2 to < 12 year old children receiving chewable tablets. Of the 9 children enrolled, 3 had 16 grade ≥3 adverse events of which 2 were considered related to RAL.

- Patient 1: 3 low ANC and 7 reports of elevated lipase with concurrent acute Epstein-Barr virus (EBV) infection.
- Patient 2: dyspnea non drug-related; concurrent drug related elevated bilirubin and hypoglycaemia.
- Patient 3: low ANC, non drug-related.

One child had grade 1 spitting up after taking the study drug.

At week 12, 78% (95% CI 40 to 97%) of the 9 children achieved virologic suppression. The children had a median gain in CD4 percent of 5% (95% CI -3 to 7%) and CD4 cells of 687 (95% CI -297 to 1237) cells/mm<sup>3</sup> at week 12. By 24 weeks (n=7), 85% achieved virologic suppression and CD4 gain (n=8) was 5.3% (95% CI -4.0 to 18.8%) and 446 (95% CI 13 to 696) cells/mm<sup>3</sup>.

The 6 mg/kg every 12 hours dose was chosen for continued study in this age group.

### Lopinavir/ritonavir

A sprinkle formulation of lopinavir/r (LPV/r) – Lopimune - has been in development by the generic manufacturer Cipla for some time. The sprinkle formulation (40/10 mg LPV/r) consists of a finite number of mini tablets in a capsule, which is opened and sprinkled on soft food.

Jaideep A Gogtay and colleagues showed results from a randomised crossover PK study in healthy adults comparing a single dose of sprinkles from 10 capsules of LPV/r and a single dose of 5 mL Kaletra oral solution (each mL containing 80 mg lopinavir and 20 mg ritonavir).

Both formulations were administered with about 150 g porridge and 240 mL water. Blood samples were taken pre-dose and serially up to 36 hours and were analysed using a validated LCMS/MS method. PK parameters were calculated using a non-compartmental method using drug concentrations versus time profile.

Twelve subjects completed the study (ie the minimum sample size acceptable to regulatory authorities). Their PK parameters are shown in table 2.

For LPV the Ln-transformed 90% confidence interval of the least square mean of the LPV/r sprinkles and solution for the PK parameters AUC<sub>0-t</sub> and AUC<sub>0-INF</sub> fall within the conventional bioequivalence range of 80 -125% while for C<sub>max</sub> it falls just outside. For RTV AUC<sub>0-t</sub> and C<sub>max</sub> fall just outside the range but AUC<sub>0-∞</sub> falls within it. However, the investigators noted that the differences were not large. Based on this pilot PK study, the sprinkle formulation is now being studied in HIV-infected children.

### C O M M E N T S

**These data represent great strides in paediatric drug development and, if approved, these formulations will offer important treatment options for the youngest age group. Integrase inhibitors would mean a new therapeutic class for young children that might overcome some of the shortcomings of the currently available drugs. The sprinkle formulation of LPV/r, is now being studied in CHAPAS 2 and also as part of a programme by Drugs for Neglected Diseases initiative (DNDi) to come up with an affordable regimen appropriate for children under two.**

**Table 2. PK parameters of lopinavir/ritonavir administered as sprinkles and oral solution**

Drug	Formulation	AUC <sub>0-t</sub> (hr.ug/mL)	AUC 0-INF (hr.ug/mL)	C <sub>max</sub> (ug/mL)
Lopinavir	Sprinkles	86.98	92.99	6.82
	Solution	84.57	89.26	6.28
	Ln-transformed 90% CI (T/R)	87.19 – 120.52	87.76 -122.54	91.31 – 131.02
Ratio of least square mean T/R	Ln-transformed	102.51	103.71	109.38
Ritonavir	Sprinkles	6.69	6.86	0.79
	Solution	6.23	6.38	0.77
	Ln-transformed 90% CI (T/R)	88.23 – 125.15	88.63 -124.6	80.4 – 135.96
Ratio of least square mean T/R	Ln-transformed	105.08	105.09	104.55

Data to guide the dosing of children less 3 years for efavirenz (EFV), the preferred first line anchor drug for older children and adults, remains elusive. A poster at this meeting showed that CYP2B6 genotype strongly influences EFV PK and safety in this age group. [5] Aggressive dosing (~40 mg/kg) produced therapeutic EFV concentrations in most (68%) children less than 3 years with GG/GT genotype, however, this leads to excessive exposure in those with TT genotype. These data suggest that optimal use of EFV in children less than 3 years requires pretreatment genotyping, and the study protocol has been amended to include this at screening. A related poster showed data from model predicting the PK of EFV in children with different CYP2B6 genotypes, with simulations that indicate that genotype-guided dose optimisation could be used in paediatric patients. [6] Although EFV could be important for use in HIV/TB coinfecting infants, complex genotype screening, the risk of resistance from NNRTI exposure in PMTCT and the probability that boosted PIs will be universally recommended in RLS make it an unlikely option in this age group.

For older children, Abbott has developed a low dose tablet of LPV/r (100/25 mg). Another paediatric PK poster showed data from a small study of 8 children aged 4.5 to 9 years designed to evaluate the comparability, efficacy, and tolerability in stable patients switching to this tablet from the oral solution. [7] PK analysis showed mean LPV AUC and C<sub>max</sub> ratios between liquid and tablet formulations to be 1.01 and 1.02, indicating that overall, the concentrations achieved with the different formulations were essentially the same.

And recently there have been some important FDA approvals including tenofovir and raltegravir for children two years of age and above and darunavir for those three years and above, which we reported in the February edition of HTB. [8, 2, 9] Also for etravirine for children of six and above, including a new scored 25 mg tablet for paediatric use (see later in this HTB). Paediatric approval from the EMA is awaited for these drugs and unlike the US tenofovir is not approved for the 12 to 18 years age group. For details see Table 3.

For RLS it is hoped that first line treatment for children above three can be aligned with adults and dosed according to weight bands with tenofovir/3TC/EFV using suitable FDCs. A further children's PK poster showed that tenofovir given in combination with 3TC/EFV achieved comparable plasma exposure to that achieved in adults. [10] The investigators also noted that concerns remain about bone and renal toxicities with this drug.

A final poster on paediatric PK reported from a study revealing lower than expected darunavir and etravirine concentrations when the two were given together to older children and adolescents 11 years of age and above. [11] The study highlights both the importance of studying drugs in combination - to determine the contribution of drug-drug interactions - and in different populations, in this case to determine whether the results are age-related. Whether these findings will affect clinical response requires further study.

Overall the data presented at CROI (and recent FDA approvals) shows promise for paediatric HIV treatment in the near future.

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**Table 3: Paediatric antiretroviral pipeline**

Compound	Company	Class	Formulation and dose	Status and comments
Atazanavir (ATV)	Bristol-Myers Squibb	PI	Oral powder 50mg sachet Capsule 100, 150, 200, 300mg	Ongoing phase 2 in naïve and experienced children with or without RTV from 3 months to 6 years of age.
Darunavir (DRV)	Janssen	PI	Oral suspension 100 mg/mL 75 and 150 mg tablets.	FDA approved > 3 years of age (waiver for children < 3). Dosage of DRV and RTV is based on body weight and should not exceed the treatment experienced adult doses. DRV/RTV ratios vary according to weight and treatment experience.
Dolutegravir (DTG)	Shionogi / ViiV	INI	Older children tablets 10, 25, 50mg.  Granule formulation being evaluated.	Phase 1&2 from 6 weeks to 18 years of age. Ph 1 PK completed. Exposure of granules with different liquids exceeded that of tablets in healthy adults so can be given without liquid restriction or directly to mouth.
Elvitegravir/cobicistat (EVG/COB) Quad (EVG/COB/TDF/FTC)	Gilead	INI / booster / FDC	To be decided. Solid and liquid forms in development, separately and co-formulated as Quad (solid tablet only).	EVG treatment experienced 12 to 18 years of age. Integrated plans for paediatric studies under discussion.
Etravirine (ETR)	Janssen	NNRTI	Dispersible tablets. 25 mg (scored), 100mg.	FDA approved for experienced children >6 years weighing >16 kg. Phase 1&2 naïve /experienced 2 months to 6 years of age planned.
Lopinavir/ritonavir (LPV/r)	Cipla	PI	Sprinkles. 40/10 mg (equivalent to 0.5 mL liquid).	Similar PK to liquid in healthy adults. PK in children being evaluated. Sprinkle regimen for use in infants <2 years in RLS in development.
Maraviroc (MVC)	Pfizer / ViiV	CCR5 inhibitor	Oral suspension 20 mg/mL	Phase 4. Experienced CCR5 tropic 2 to 12 years.
Raltegravir (RAL)	Merck	INI	Oral granules for suspension 6mg/kg (100 mg sachet) 100 mg and 25 mg chewable tablets	FDA approved 400 mg tablet for children aged 6 to 18 weighing > 10 kg, and chewable tablets for aged > 2 to <12 at a maximum dose of 300 mg. Awaiting EMA approval Granules Phase 2, 2 weeks to 2 years of age. Achieved good target exposure in 6 months to <2 years of age, similar to that with older children. Neonate passive PK study.
Rilpivirine (RIL)	Tibotec / Janssen	NNRTI	Oral granules 2.5mg base/g	Phase 2 planned in children 0-12 children years of age.
Tenofovir (TDF)	Gilead	N(t)RTI	Oral powder 40 mg /1 g 150 mg, 200 mg and 250 mg tablets	Recently FDA approved for 2 to <12 years of age. Awaiting EMA approval for 2 to 18 years of age.

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## Lower malaria risk in children receiving lopinavir/ritonavir-based compared to NNRTI-based ART

**Polly Clayden, HIV i-Base**

**Children with HIV in sub-Saharan Africa have significant morbidity and mortality risk from malaria. Interventions including bed nets and cotrimoxazole are not sufficient to decrease the risk in this population.**

HIV and malaria parasites both encode aspartic class proteases, offering the possibility that HIV protease inhibitors (PIs) might have antimalarial properties. Furthermore, in vitro studies have demonstrated some activity against *Plasmodium falciparum* with PIs.

In an oral presentation, Jane Achan from Uganda presented findings from a study conducted by investigators from Makerere University College of Health Sciences and Infectious Diseases Research Collaborations in Kampala and the University of California, San Francisco, to compare the efficacy of lopinavir/ritonavir (LPV/r)-based and NNRTI-based ART regimens on malaria risk reduction in HIV positive children.

The study was a randomised open label trial of 170 children with a median age of 3 years of age (range 2 months to 6 years) conducted in Tororo, Uganda between September 2009 and July 2011. The children were either, ART-naïve (approximately 70%) and eligible for treatment, or receiving NNRTI-based ART and virologically suppressed (<400 copies/mL). They were randomised to receive either NNRTI- or LPV/r-based ART and followed for 2 years. All children received bed nets and cotrimoxazole and treatment for uncomplicated malaria with artemether-lumefantrine, the standard of care in Uganda and many African countries.

Following malaria diagnosis, the children attended the clinic on days 1, 2, 3, 7, 14, 21 and 28. Lumefantrine levels were measured on day 7 as this has been shown to be an independent predictor of malaria.

The analysis was ITT and the investigators compared the incidence of malaria between the study arms using Poisson regression.

Dr Achan reported a 41% reduction in malaria associated with LPV/r-based ART, see Table 1.

When the investigators looked at possible explanations for this reduction, they found a 29% non-significant direct effect of LPV/r on the children's first episode of malaria HR 0.71 (95% CI 0.45-1.12), p=0.14. An evaluation of the risk of recurrent malaria following treatment with artemether-lumefantrine, however, found LPV/r associated with a 54% reduction in risk HR 0.4 (95% CI 0.22-0.76), p=0.004.

Median lumefantrine levels on day 7 were 926 (IQR 473 – 1910) ng/mL vs 200 (IQR 108 – 510) ng/mL in the LPV/r vs NNRTI arms respectively, p<0.001, which Dr Achan explained might be associated with the boosting effect of ritonavir.

Dr Achan summarised the possible reasons for the lower risk observed in the LPV/r arm as follows:

- PK effect of LPV/r on lumefantrine leading to a prolonged post treatment prophylaxis effect following treatment with artemether-lumefantrine.
- Direct antimalarial effect of LPV/r.
- Antiparasitic synergy between LPV/r and lumefantrine.

She concluded: "This study highlights the possibility of pharmacoenhancement as a tool for reducing the burden of malaria in highly endemic settings."

### C O M M E N T

**These data are interesting. Conversations after the session suggested that this study adds to the argument for recommending LPV/r-based ART for all infants and young children, but the issue of resistance was also raised with one drug in a combination having a prolonged half-life.**

Ref: Achan J et al. Significant reduction in risk of malaria among HIV+ children receiving lopinavir/ritonavir-based ART compared to NNRTI-based ART, a randomised open-label trial. 19th CROI, 5–8 March 2012, Seattle. Oral Abstract 26.

<http://www.retroconference.org/2012b/Abstracts/43194.htm>

## High prevalence of d4T-associated lipodystrophy including lipoatrophy in children

**Polly Clayden, HIV i-Base**

**Data describing lipodystrophy in children from sub-Saharan Africa are extremely limited. However use of d4T is widespread among children receiving ART in the region: in 2008 to 2009 approximately 90% of children on ART were taking d4T.**

Two posters at CROI 2012 described substantial rates of lipodystrophy in South African children aged 3-12 and less than 2 years respectively.

Steve Innes and colleagues from the Children's Infectious Diseases Clinical Research Unit (KID-CRU), Tygerberg Children's Hospital and

**Table 1: Comparison of malaria risk NNRTI vs LPV/r**

Malaria	NNRTI			LPV/r			IRR (95% CI)	p-value
	Events	PYAR	Incidence	Events	PYAR	Incidence		
All	176	78.2	2.25	109	82.3	1.32	0.59 (0.36-0.97)	0.04
Complicated episodes	2	78.2	0.026	2	82.3	0.024	0.80 (0.06-11.16)	0.87

PYAR= person years at risk

Stellenbosch University Cape Town performed a cross sectional study of 100 of 300 children on ART at the Tygerberg Family HIV Clinic and 34 HIV-negative controls. [1]

In this study, two clinicians graded fat changes visually using a standardised scale and a dietician took anthropometric measurements of trunk and limb fat. DXA was performed in a sub study of 42 patients and 34 controls. The duration of ART use was recorded.

Using linear regression models the investigators compared fat distribution captured by DXA and anthropometrics among children who were HIV negative, HIV positive with lipoatrophy and HIV positive without lipoatrophy, adjusted for age and sex. The risk factors for clinical lipoatrophy were evaluated by logistic regression.

This reported prevalence of lipoatrophy was 36% (95% CI 26 - 45%). DXA and anthropometrics confirmed significant, substantial extremity fat loss in children with clinical lipoatrophy.

Mean adjusted DXA total limb fat was 2.7 kg (95% CI 2.4 - 2.9), 1.7 kg (95% CI 1.4 - 2.1) and 2.3 kg (95% CI 2.1 - 2.6) in HIV negative, HIV positive with lipoatrophy and HIV positive children without lipoatrophy respectively,  $p = 0.001$ . Limb fat vs limb lean ratios were respectively, 0.63 (0.56 - 0.7), 0.36 (0.25 - 0.46) and 0.62 (0.54 - 0.7),  $p = 0.0001$ .

Mean adjusted anthropometrics found biceps skin-fold thicknesses of 5.5 mm (5.0 - 5.9), 4.2 mm (3.6 - 4.7) and 5.3 mm (4.9 - 5.7), in HIV negative, HIV positive with lipoatrophy and HIV positive children without lipoatrophy respectively,  $p < 0.0001$ . Triceps skin-fold thicknesses were respectively 8.7 mm (8.1 - 9.4), 7.1 mm (6.2 - 7.9) and 8.9 mm (8.3 - 9.6),  $p < 0.0001$ .

The investigators noted that diagnosis by visual grading correlated well with anthropometry and DXA, which are not commonly available in developing countries.

In multivariate analysis, controlling for age, sex and CD4 percentage, the greatest risk factor for clinical lipoatrophy was duration of d4T use,  $p = 0.0008$ . Cumulative d4T use was also associated with reductions in biceps and triceps skin-fold thickness,  $p = 0.008$ . Each additional year of accumulated d4T exposure gave an odds ratio of 1.9 (95% CI 1.3 - 2.9),  $p = 0.002$ .

The investigators wrote: "The prevalence of lipoatrophy is higher in our cohort than non-African cohorts. Our data identify cumulative d4T exposure as the greatest risk factor for lipoatrophy, highlighting the urgent need for all children to transition to alternative medication."

Stephanie Shiao and colleagues from the NEVEREST study team described the prevalence of lipodystrophy and associated patterns of regional fat distribution and metabolic alterations in young children who had started ART at less than 2 years of age. [1]

They performed an evaluation of 156 vertically infected children who started ART at Rahima Moosa Mother and Child Hospital, Johannesburg with lopinavir/ritonavir (LPV/r) + 3TC + d4T, and were randomised to either continue LPV/r ( $n = 85$ ) or switch to nevirapine (NVP) ( $n = 71$ ), while continuing 3TC + d4T. This was done on exit from the NEVEREST 2 trial after approximately 4 years on ART.

Clinicians assessed the children visually for signs of lipodystrophy, including lipoatrophy and lipohypertrophy. Anthropometrics, bio-impedance analysis, viral load, CD4, fasting total cholesterol, HDL,

LDL, and triglycerides were measured. Measurements of regional fat - including trunk-extremity skin-fold ratios were estimated. Outcomes were compared across lipodystrophy groups defined as, lipodystrophy, possible lipodystrophy and no lipodystrophy.

The investigators used multiple linear regression to assess differences in arm, trunk and leg fat across lipodystrophy groups, adjusted for total fat, sex and age.

They found, of 156 children with a mean age 5.1 who initiated ART at a mean age of 10.7 months, 13 (8.4%) children were defined as having lipodystrophy, 18 (11.5%) as having possible lipodystrophy and 125 (80.1%) as no lipodystrophy. All 13 children defined as having lipodystrophy had lipoatrophy and 6 also had signs of lipohypertrophy.

There were no differences in age, sex, age at ART initiation, duration of ART, weight-for-age z-scores, height-for-age z-scores, body mass index, or proportion of children with a viral load  $< 50$  copies/mL among the three lipodystrophy groups.

There was no difference in the proportion of children with lipodystrophy between those who remained on LPV/r and those who switched to NVP, respectively 7.1% vs 9.9%,  $p = 0.51$ .

The children with lipodystrophy had significantly less body fat than children with no lipodystrophy, measured by mean ( $\pm$ SD) skin-fold sum, 34.1 mm ( $\pm 5.7$ ) vs 42.0 mm ( $\pm 11.1$ ),  $p = 0.0016$ . Children with lipodystrophy had greater trunk-arm 0.53 mm ( $\pm 0.07$ ) vs 0.50 mm ( $\pm 0.05$ ),  $p = 0.028$  and trunk-leg skin-fold ratios 0.61 mm ( $\pm 0.07$ ) vs 0.55 mm ( $\pm 0.06$ ),  $p = 0.004$ , than children without lipodystrophy.

Lipid concentrations were similar across groups, except for mean triglycerides level which was greater for children with lipodystrophy compared to those without, 101 ( $\pm 45$ ) vs 80 ( $\pm 34$ ) mg/dL,  $p = 0.045$ . The proportion of children with triglycerides  $> 150$  mg/dL was greater for children with lipodystrophy and those with possible lipodystrophy compared to those without, respectively 23.1% vs 4.8% and  $p = 0.0422.2\%$  vs 4.8%,  $p = 0.023$ .

"A substantial portion of young children who initiated d4T-containing ART before two years of age have lipodystrophy as classified by clinical criteria..." the investigators concluded, adding: "Lipodystrophy can be cosmetically stigmatising and adversely affect adherence to ART. Finding a substantial proportion of young children with lipodystrophy has implications for future adherence, especially during adolescence when awareness of physical appearance is greatly heightened."

#### C O M M E N T

**These reports are concerning and the rate reported by Innes et al particularly is high compared to other (generally anecdotal) reports from other parts of Africa. This may be because children were properly evaluated, although it is not clear whether there was blinding to laboratory results when the clinical diagnosis was made but visual grading correlated well with anthropometry and DXA.**

**In South Africa, where FDCs are not generally used, the 1 mg/kg doses of d4T will usually be rounded up using stand alone products resulting in a dose at least equivalent 40 mg in adults (Steve Innes, personal communication), so the effects might be less or occur over a longer duration of exposure with a lower dose.**

**This possibility in children has been used to argue for a controversial study in adults, of lower dose (20 mg) d4T, which, the investigators hope, will mitigate the drug's toxicity. As is usual in adult studies, Innes et al identified "cumulative d4T exposure as the greatest risk factor for lipodystrophy" and since d4T toxicity is both dose and time dependent - as we have stated before - it seems most unlikely that this could be reduced to acceptable levels in this way and there are better solutions on the horizon. [3, 4, 5]**

**A Thai study suggests that some lipodystrophy in children may be reversible after substitution with another NRTI and results from CHAPAS 3 will clarify whether this occurs. [6] But for the proportion for whom it is not reversible, as Shiao et al wrote, this can be stigmatising and adversely affect adherence to ART, particularly during adolescence when awareness of physical appearance is particularly sensitive (though when is it not?). Adult guidelines have for many years stressed that lipodystrophy is better to avoid than to treat. Children should also therefore be protected from this side effect.**

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## Lopinavir/ritonavir monotherapy in children

### Polly Clayden, HIV i-Base

Induction/maintenance strategies in children are frequently discussed but underexplored and documented.

A poster authored by Pope Kosalaraksa and colleagues from the HIV-NAT 077 study team showed week 144 results for virologically suppressed Thai children switching to lopinavir/ritonavir (LPV/r) monotherapy.

In this study children with two consecutive viral load results <50 copies/mL at least 3 months apart while receiving double PI-containing second line regimens for at least 12 months were switched to LPV/r monotherapy. Virological failure was defined as two viral load results  $\geq 500$  copies/mL or three of  $\geq 50$  copies/mL. Children failing LPV/r monotherapy resumed treatment with their previous double PI regimen. The primary endpoint was the proportion of children with virological suppression <50 copies/mL at 144 weeks.

There were 40 children enrolled in the study, of which 90% received saquinavir as their second PI and the remainder indinavir. 3TC was used by 28%, AZT by 10% and EFV by 5%. At the time of enrollment the children were a median age of 11.7 (IQR 10.2-13.5) years, weight of 29.4 (IQR 24.1 – 40.20) kg and CD4 percentage 27% (IQR 23.5-29.5%) cells/mm<sup>3</sup>.

None of the children had disease progression over 144 weeks of follow up, one child died in a car accident and two were lost to follow up.

At 144 weeks 31/37 (83.8%) were virologically suppressed. The proportion of children remaining on monotherapy with virological suppression was 22/24 (92%). Eleven children experienced virological failure with lopinavir monotherapy with a median viral load measurement of 1740 (IQR 598-21,450) copies/mL. No major LPV/r mutations (L10F, M46I, L76V, V82A) were reported among 10/11 children who failed and genotype testing. When they resumed their previous double PI regimen, 7/11 (63%) children had virological suppression at week 144.

In multivariate analysis viral load at switch to LPV/r monotherapy of  $\geq 50$  copies/mL was the only predictor of failure, OR 4.4 (95% CI, 1.3-14.8). Although all children had <50 copies/mL at screening, 10% had  $\geq 50$  copies/mL at baseline. Sex, CDC class, CD4 percent nadir, CD4 percent at switch and adherence by pill count were not associated.

There were no significant changes in CD4 percent, fasting cholesterol, triglyceride, and glucose from baseline.

The investigators noted that frequent viral load monitoring is needed for early detection of virologic failure with this strategy.

#### C O M M E N T

**This study shows a high rate of failure in about a third of children who switched to LPV/r monotherapy. Whether there are children that could benefit from this induction/maintenance strategy (probably not treatment experienced) remains an interesting question in RLS, where starting with a LPV/r-containing regimen in infancy is gaining momentum in settings with concerns about cost and NRTI toxicity.**

**Looking at darunavir/r monotherapy vs darunavir/r in a triple regimen and also once vs twice daily is currently under discussion for PENTA 17.**

Ref: Kosalaraksa P et al. Lopinavir/ritonavir monotherapy in HIV+ children; week 144 results. 19th CROI. Seattle WA. March 5-8 2012. Poster abstract 962.  
<http://www.retroconference.org/2012b/Abstracts/43511.htm>

## Stopping treatment after early ART in infants

**Polly Clayden, HIV i-Base**

**In an oral late breaker, Mark Cotton presented the final results from the Children with HIV Early Antiretrovirals (CHER) trial.**

Interim results from CHER, announced in 2007, demonstrated the need for early ART in HIV-infected infants and influenced guidelines worldwide. The standard of care is now universal treatment for infants less than one year (and in WHO guidelines in children up to two years), initiated as early as possible.

In the study, infants <12 weeks of age with CD4 percent  $\geq 25\%$  were randomised to receive deferred ART (ART-Def), immediate ART stopping after 40 weeks (ART-40W) or immediate ART stopping after 96 weeks (ART-96W). The recommendation that enrolment to ART-Def cease and all children be assessed to start ART was made by the DSMB in June 2007, as starting ART immediately reduced deaths by 75%. All children received treatment with lopinavir/ritonavir (LPV/r) + 3TC + AZT.

Treatment initiation in the deferred arm and re-initiation in the other two were in accordance with previous WHO guidance at a threshold of CD4 percent <25% in infants and <20% after infancy or with clinical disease progression. The primary endpoint was death or progression to CDC severe B or CDC C disease. All analyses were intent-to-treat using time-to-event methods.

A total of 377 infants were enrolled in CHER between 2005 and 2007. They were a median age of 7.4 weeks with a CD4 percent of 35% at baseline and 341 (91%) completed the study. Median follow up was 249 weeks (4.8 years) and the maximum was 309 weeks (5.9 years). The overall proportion of follow up time on ART in the three study arms were 81%, 70% and 69% in ART-Def, ART-40W and ART-96W respectively.

Approximately 75% in the ART-40W and 65% in the ART-96W arms re-initiated treatment by 240 weeks. The median time to starting ART in ART-Def was 20 (IQR 16-25) weeks and to restarting ART after interruption in ART-40W and ART-96W was 33 (IQR 26-45) and 70 (IQR 35-109) weeks, respectively. Difference between the two deferred arms was 37 (95% CI -11 to 85) weeks,  $p=0.13$ . By the end of the trial only 7 children had switched to second line antiretroviral therapy.

When the investigators looked at the total primary endpoints in the study they found 39 (25%) in ART-Def, 31 (25%) in ART-40W and 25 (20%) in ART 96-W. This was mainly due to at least double the number of deaths in ART-Def compared to the other two arms: 22 (18%), 11 (9%) and 9 (7%) in ART-Def, ART-40W and ART-96W respectively. Dr Cotton noted that there were no cases of regimen limiting toxicity.

Time to primary outcome compared to ART-Def, showed 23% fewer events in ART-40W, 42% fewer in ART-96W and 35% fewer in the two arms combined. Hazard ratios (HR) relative to ART-Def were ART-40W, 0.73 (95% CI 0.46-1.17),  $p=0.19$ ; ART-96W, 0.58 (95% CI 0.35-0.96),  $p=0.05$  and ART-40W/ ART-96W 0.65 (0.43 - 0.98),  $p=0.04$ .

Progression to CDC B or C or death was also reduced by 50% and 60% respectively. HR relative to ART-Def were ART-40W, 0.5 (95% CI 0.3-0.8),  $p=0.005$  and ART-96W and 0.4 (95% CI 0.3-0.7),  $p=0.0003$ . There were 43, 27 and 18 events in the ART-Def,

ART-40W and ART-96 arms respectively. For encephalopathy there were 9, 5 and 2 events.

When the investigators compared the ART-40W and ART-96 arms – including 34 additional children included after ART-Def stopped enrollment ( $n=143$  in each remaining arm) – there was no difference between the two in time to primary outcome, HR 0.84 (95% CI 0.51 – 1.4),  $p=0.49$ . The majority of deaths in both arms occurred early, during the initial period of ART.

At the end of the trial 30 (25%) children in ART-40W and 46 (33%) in ART-96W never started continuous ART and CD4 percent was a median of approximately 30% in both arms.

Dr Cotton concluded that treatment during early infancy protects against HIV-related high mortality and morbidity and ART interruption after infancy appeared to be safe. But further analyses of virologic suppression and resistance and immunological response to restarting and interrupting treatment are needed.

### C O M M E N T

**Stopping treatment in infants who receive ART during acute infection appeared to be safe in CHER. Although Andy Prendegast questioned the value of the short duration off treatment before restarting (33 and 70 weeks after 48 and 96 weeks of early ART respectively), in his excellent overview exploring “controversies and consequences of early initiation” of ART in infants. [2]**

**Conflicting results to those from CHER were reported from The Optimising Paediatric HIV-1 Therapy 03 (OPH03) Study - a randomised trial of continued vs interrupted treatment in infants with CD4 >25%, following at least 24 months of ART and restarting if CD4 dropped to 25% - which was stopped by the DSMB due to the high proportion of children restarting by three months. [3] In this study, 42 children were randomised (21 in each arm) and 18/21 in the interruption arm (86%) restarted, the majority (14/21) before 3 months. The children in OPH03 differed from those in CHER in that they were initially treated with ART at a median of about 5 months of age with a lower pre-ART CD4 percentage. However although lower CD4 percentage at randomisation was predictive of starting treatment after <3 months ( $p=0.04$  vs > 6 months) but neither age at ART or pre-ART CD4 were (both  $p=0.7$ ).**

**Dr Prendegast questioned whether one or two years early treatment was enough and noted that there was no comparison to early continuous ART.**

**Emphasising the controversies, a speaker from the floor declared he was “shocked” that treatment interruptions were even being considered in children and suggested such an approach belonged in the “middle ages”.**

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CROI 2012: INFECTION & PREVENTION

## PrEP: PK modeling of daily TDF/FTC (Truvada) provides close to 100% protection against HIV infection

Simon Collins, HIV i-Base

### Introduction

**New research at CROI suggested that protection against HIV could be close to 100% from daily TDF/FTC (Truvada) and this should change previous reservations about PrEP as an intervention. [1]**

In some studies, daily Truvada dramatically reduced the incidence of HIV infection, especially in high-risk individuals, (by 42% in MSM in the iPrEX study) but produced conflicting results in other studies (notably the FEM-PrEP study in heterosexual African women).

All studies have proved complicated to interpret due to the high rates of self-reported adherence but the likely very low rates of actual adherence demonstrated in PK sub-studies finding low levels of tenofovir and FTC in both active and placebo arms. The projected efficacy of PrEP increased dramatically when PK results were taken into account (to 92% in iPrEX). [2]

This proven protection could potentially increase real-life adherence compared to that seen in historical studies. If someone knows they will be protected rather than being a participant in a placebo controlled trial, and that this protection is so effective it could eliminate the risk of HIV, this could change the pattern of low use, even in less adherent patients.

PrEP studies are further complicated by the differences in pharmacokinetic properties of individual drugs, by differences in absorption of each drug in the male and female genital tract as well as in rectal tissue, and by the intracellular concentration of the active metabolites at each sites. Differences between human and animal drug absorption may limit how closely efficacy against vaginal and rectal exposure can be interpreted from macaque studies.

At CROI new modeling data showed that the protection from PrEP may be even greater than previously thought. The report that protection approaches 100% argues for new considerations for how PrEP might be incorporated as a health intervention.

Other studies at the meeting addressed some of the concerns for why PrEP has not been universally protective in other some studies.

### iPrEX: modeled prediction of 99% protection with daily adherence

Peter Anderson and colleagues presented a late breaker oral PK analysis of intracellular drug concentrations in the iPrEX study and correlated this with levels of adherence in the Strand Study. [1]

This group used regression model to estimate efficacy of PrEP based on intracellular levels of tenofovir diphosphate (TDF-DP) in viable PBMCs from 48 cases matched to 144 uninfected controls. The researchers then established TDF-DP levels achieved on observed therapy of 2, 4 and 7 day dosing in a separate PK study of 24 HIV negative volunteers (the Strand study). Finally, they used the iPrEX regression models from i-PrEX on the Strand study data to estimate PrEP efficacy based on 2, 4 and 7 day dosing.

In iPrEX, detectable tenofovir levels in either plasma or cells was seen to have steadily fallen from baseline to time of infection, to only 8% of cases (at infection) compared to approximately 40% of uninfected controls. In the month prior to infections these rates were 11% vs 50% respectively suggesting that infections occurred during periods of low drug exposure.

In the Strand study, dosing 2, 4 and 7 days a week produced median (IQR) levels (fmol/million cells) of TDF-DP of 11 (6-13), 32 (25-39) and 42 (31-47) respectively. This compared to levels of 11 fmol/M (4-11) in 8% of iPrEX cases with detectable TDF and 16 fmol/M (9-47) in the 44% of controls with detectable levels. Daily dosing could be imputed from drug levels for 18% of iPrEX controls (and that 82% controls were likely to be taking less than daily dosing).

Regression modelling produced and estimated EC90 of 16 fmol/M viable cells (95%CI 3-28) with sensitivity estimates of less than 23 fmol/M producing estimates for risk reduction of 76% (56-96%), 96% (90->99%) and 99% (96->99%) for 2, 4 and 7 day dosing (see Table 1).

**Table 1: Estimates for risk reduction in iPrEX**

Doses/week	TDF-DP fmol/M viable cells (95%CI)	Risk reduction (95%CI)
2 / week	9 (7 -13)	76% (56-96%)
4 / week	30 (23 - 37)	96% (90->99%)
7 / week	45 (32 - 59)	99% (96->99%)

### C O M M E N T

**This study involved 615 v-PBMC and 1146 plasma samples were tested from 1212 time points (302 cases, 910 controls) but limitations include that drug levels were only proximal to time of exposure and that the impact of FTC levels were not studied.**

**The confidence intervals for the target IC90 of  $\geq 15.6$  fmol/M viable cells (95%CI 3.0 to 28.2) appears wide and this should be confirmed in future studies.**

### Partners PrEP: protection in serodifferent heterosexual couples

Jared Beaten and colleagues presented updated results from the randomised Partners PrEP Study, a randomised placebo controlled study of both TDF/FTC and TDF only in 4758 negative partners of HIV positive people who were not yet eligible for ARV therapy. [3]

The study was conducted in nine urban and rural sites in Kenya and Uganda. HIV negative partners were seen monthly for HIV testing, adherence and prevention counselling and HIV positive partners were seen every three months and approximately 20% in each arm started ARV treatment when recommended by national guidelines.



The placebo arm was discontinued in July 2010 following a recommendation by the study DSMB and those preliminary results had already been presented. Placebo arm participants were then randomised to either of the active arms and follow up continues until December 2012.

Approximate baseline characteristics for the negative partner included: just over 60% male; median (IQR) age 33 years (28, 40; with 11% less than 25 years). Although the median (IQR) duration of partnership was 7 years (3, 14) the time they had know about their partners HIV status was only 4-5 months (0.1, 2.0 years). Median CD4 count of the positive partner was almost 500 cells/mm<sup>3</sup> (IQR 375, 660).

Study retention was greater than 95% with median follow up of 23 months (IQR 16 - 28, range 1-36). This involved more than 7800 person years of follow up (PYFU) and >99,000 study visits, with >95% dispensing of study meds.

Of the 96 new HIV diagnoses in negative partners, 14 were found to be in acute infection at baseline by retrospective PCR testing after HIV seroconversion, leaving 82 acquisition events in the primary study. Of these, 17 occurred in the TDF arm vs 13 in the TDF/FTC arm vs 52 in the placebo arm giving incidence rates/100 PYFU of 0.65, 0.50 and 1.99 respectively. This produced highly significant protection rates of 67% (95%CI 44-81%) and 75% (95%CI 55-87%) compared to placebo, in the TDF and TDF/FTC arms respectively (both p<0.0001). There were no significant differences between the two active arms (p=0.23) and both ruled out the predefined lower efficacy of -30%.

Although 60% of the negative partners were men, 45/82 infections occurred in women (n= 8 vs 9 vs 28; incidence 2.81 in women vs n=9, 4 and 24; incidence 1.49 in men; in single vs dual vs placebo arms respectively. Protection was seen for both men and women with non statistically significant differences for the differences in the results observed in men vs women (p=0.65 for single and p=0.24 for dual PrEP (see Table 2.)

**Table 2: Efficacy by gender**

	Efficacy (95% CI)	p-value	Interaction
<b>TDF</b>			
women	71% (37-87)	p=0.002	p=0.65
Men	63% (20-83)	p=0.01	
<b>TDF/FTC</b>			
women	66% (24-84)	p=0.005	p=0.24
men	84% (54-94)	p,0.001	

There were no differences between serious adverse events between arms including placebo (7% each arm) or confirmed laboratory abnormalities (each arm had <1% grade 2 or higher creatinine increase, 9% phosphorus decrease). During the first month there was significantly more mild nausea or fatigue in the active arms but these became similar to placebo rates at later time points.

Although there was one person with K65R tenofovir mutation and one person with M184V FTC mutation in the people with confirmed acute infection at baseline, no mutations were detected in infections from the main study. Four cases of NNRTI resistance was seen indication transmission of resistant virus.

About one third of participants reported additional sexual partners (41% men, 9% women)

PK results for drug levels of tenofovir in each of the active arms in the Partners in PrEP study were presented in a second oral presentation by Deborah Donnell. [4]

This study used the 29 cases (n=17 single arm, n=12 dual arm) compared to drug levels in 100 uninfected controls from each arm, using multiple samples throughout the study (at months 1, 3, 6, 12, 18, 24, 30, and 36. Drug levels were tested using LCMS with lower limit of quantification of 0.3 ng/mL. Based on other studies tenofovir would be detected for nine days after a single dose and tenofovir levels at steady state from daily dosing would be >40 ng/mL.

**Tenofovir was detected in >80% of samples in uninfected controls compared to 56% of samples of cases and in only 31% (6/17) of single arm and 25% (3/12) of dual arm samples at the seroconversion visit. This produced relative risk reduction associated with detectable drug of 86% (95%CI 57%, 95%; p<0.001) and 90% (95%CI 56%, 98%; p=0.002) in the single and dual arms respectively. Only 4/9 cases of infections with detectable drug had levels > 40 ng/mL consistent with high adherence.**

Patterns of adherence in controls suggested than non- or poorly adherent patients did not change their adherence of the study. By contrast, about 50% of highly adherent patients maintained this through the study but 25% either dropped to lower adherence and 25% to non-adherence.

Several other analyses were presented from the Partners in PrEP study at CROI. These included:

- A report on nearly 300 pregnancies during the study, with similar rates in each of the three arms and no safety concerns, and suggesting a specific use for PrEP in serodifferent couples wanting to have a baby. [5]
- Details of ARV update in the 817 positive partners whose CD4 count declined during the study making them eligible to start treatment, with only 420 (55%) initiating treatment. Factors included reluctance to start, loss to follow up and unavailability of treatment. [6]
- High (>90%) positive acceptance to use PrEP amongst negative partners with lower, but still high (60%) interest from positive partners in earlier treatment as prevention. [7]
- Implications from PrEP protection on the rate of false positive results from rapid tests. From over 99,000 tests, 266 were positive on dual rapid tests. Of these, 37% (99/266) were confirmed true positive by ELISA, 58% (155/266) were false positive by ELISA and 4.5% (12/266) were indeterminate. False positives were more common in the active arms 69% (110/159) vs 45% (45/107) in the placebo arm due to the lower incidence of HIV. [8]
- Modelling factors for a risk score to determine the population characteristics for most effective use of PrEP as an intervention. [9]

### Why PrEP did not work in FEM-PrEP

Another late breaker oral presentation provided results from the FEM-PrEP study in which daily TDF/FTC (Truvada) used as PrEP was not effective. The FEM-PrEP study, which had enrolled just over 2000 of the planned 3900 participants was closed in April 2011 due to lack of efficacy between daily TDF/FTC compared to placebo in over 2000 African heterosexual women.

The DSMB recommended stopping the study when the study was only half way through enrollment when 28 infections had been seen in each arm. More pregnancies occurred and side effects were also higher in the active arm.

The final results from the study were presented at CROI by Lut Van Damme and colleagues. [10]

Baseline characteristics included approximately 60% younger than 25 years, 50% condom use, 13% had transactional sex with other than primary partners. However, 70% of participants thought they were at low risk for HIV, but 15% had Chlamydia and 6% had gonorrhoea at screening. Women had sex on average four times a week (mean 3.7, range 0-28).

Of 68 infections occurring during the main study, 33 infections occurred in the active arm (incidence rate, 4.7/100 person-years) and 35 in the placebo group (IR, 5.0/100 person-years), with an estimated hazard ratio (HR) for infection of 0.94 (95%CI 0.59 to 1.52,  $p = 0.81$ ). Although seven infections were discounted due to lack of product at the study clinic, a sensitivity analysis censoring women at last date of product use did not change the main results (HR 0.82; 95%CI 0.49-1.36,  $p=0.44$ ).

Tolerability generally good with no grade 3 events but included more nausea in the active group.

There were five cases of FTC-associated resistance (one in the placebo arm) but no cases of resistance to TDF.

As with other PrEP studies, adherence rates were very high by self-report (>95%) and pill count (~90%) but a pharmacokinetic analysis in a case-control sub study indicated that this was at best likely to be 20-30% in either arm, with detection lower in cases vs controls. Adherence levels below 50% in each arm also removed the power of this study to be able to detect a real impact of the active arm.

Of interest, an opinion piece by Anneke Grobler and colleagues in the 13 March edition of AIDS on the design challenges for future prevention studies includes a table that calculates projected effectiveness found with different levels of true efficacy of the comparator and new intervention in combination with different adherence levels. [11]

### C O M M E N T

**Although the lack of protection in this study was assigned to low adherence, this may be more complex as adherence was also low in iPrEX. This may also involve the baseline risk of participants and perception of risk, perhaps explaining the differences seen in other heterosexual studies such as TDF-2.**

**There may also be implications by gender related to pharmacokinetic and intermittent adherence highlighted in macaque studies, including the poster reported below.**

### Intermittent TDF/FTC (Truvada) in macaques: vaginal, cervical and rectal tissue and cell PK

Jessica Radzio and colleagues from the CDA in Atlanta presented results from a pharmacokinetic study in macaques. [12]

This study was important for studying both tenofovir and FTC in tissue site and intracellular levels. Both drugs peaked - at two hours in plasma and five hours in vaginal secretions - and then declined to low levels at 24 hours. In rectal secretions, levels increased more slowly and steadily, only peaking at 24 hours but then remaining high for at least 24 hours.

This aspect of the PK profile in macaques is comparable to that seen in women. The group then looked at active intracellular levels of the active metabolites of each drug, FTC-TP and TFV-DP.

FTC drug levels were very similar in vaginal, cervical, rectal and lymphoid tissue compared to cell biopsies with vaginal:rectal ratio of 1.04 in cells and 2.10 in tissue at 24 hours. This was similar for cervical:rectal ratios. However levels of tenofovir in vaginal, cervical and lymphoid tissue, both in tissue and cells was dramatically lower, while remaining high in rectal tissue and cells, with vaginal:rectal tissue concentrations ratios dropping to 0.04 for intracellular levels and 0.02 in tissue, with similar results for cervical:rectal ratios (0.04 and 0.03 respectively).

The group then looked at whether these levels would be sufficient for vaginal exposure in six macaques following oral dosing and repeat low dose exposure weekly for up to 18 weeks (through four menstrual cycles) to SIV to approximate to human sexual exposure, with six macaque controls. TDF/FTC or placebo was given 24 hours before or two hours after exposure. All control animals became infected quickly, mainly in the first menstrual cycle but none of the active macaques receiving intermittent TDF/FTC became infected over 18 weeks suggesting that the lower PK may be protective even with intermittent PrEP to prevent vaginal transmission.

This study reported a pattern of ratio (rather than absolute concentrations) suggesting this validates the macaque model for future studies. Although this study only looked at -24 plus +2 hour dosing for vaginal exposure, the rectal macaque studies emphasised the +2 hour dose to be essential and the protection from the pre-exposure dose extended from 1 to seven days. However dosing only 2 hours before exposure correlated with significantly reduced protection, though this was still higher than if no pre-exposure dose was given.

### C O M M E N T

**The potential for close to 100% protection against HIV infections with alternate or daily dosing should prompt pilot programmes that include access to this option in individuals who are at the highest risk for HIV.**

**For many people, higher risk behaviour and vulnerability to infection may be associated with a relatively short period of someone's life. Whether this is a period of weeks, months or several years, the option to use an oral prophylaxis when other prevention methods are unlikely to be used, can prevent the complications of life-long infection and treatment.**

## **TDF/FTC (Truvada) has already been submitted to the FDA for an indication for use as PrEP with a decision expected later this year.**

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## **Risk of HIV reinfection may be similar to risk of initial HIV infection**

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

**The risk of HIV reinfection, sometimes called superinfection, has not been clearly established. Given the risk of initial sexual HIV infection from a single exposure in population studies is commonly calculated as generally low (although these estimates are dependent on the background prevalence) this is difficult to assess in small studies.**

Genetic analysis is specialised and expensive and the biological evidence is strongly supported by the many viral sub-clades and recombinant forms that can only have occurred in vivo. The extensive global viral diversification provides the most practical evidence for reinfection.

Case studies have highlighted cases where reinfection with drug resistant HIV has clinical implications leading to either more rapid disease progression or treatment failure and reduced future treatment options. Although initial reports were in early or acute initial infection, cases have also included people in chronic infection, indicating that this may not be restricted by immune responses to the initial infection and in people on suppressed ART, indicating that the pressure from PrEP/PEP can also be overcome.

Three studies at CROI focused on issues of reinfection.

Andrew Redd and colleagues from the US NIH and Johns Hopkins University used high-throughput deep sequencing to retrospectively test for HIV superinfection in two regions of the viral genome (p24 and gp41) in 203 people from the Rakai Community Cohort Study (RCCS) in Uganda, who seroconverted from 1997-2002 with later samples for a total 15,000 person years of follow up (PYFU). This was compared to the primary HIV incidence rate for the HIV negative general heterosexual population in Rakai (n = 20,220; > 100,000 PY).

They identified reinfection in 7/149 people with identifiable sequences in the seroconverter cohort (1.44/100 PY (95%CI 0.37 to 2.51), all from significant changes in the gp41 region. These seven cases were initially infected with sub-type D. Four of the reinfections were with new sub-type D and three with sub-type A.

There were 1152 new infections in the general population over the same period giving an incidence rate of 1.15/100 PY (95%CI 1.08 to 1.21). This was not significantly different to from the primary HIV incidence rate (incidence rate ratio = 1.26, 95%CI 0.50 to 2.60; p = 0.26).

Differences between the risk factors for the people with reinfection (inherently at greater risk than the general population because they were clearly more susceptible to infection) were adjusted for using propensity score matching increased the background incidence rate to 3.28 /100 PYFU (95%CI 2.0-5.3) based on the baseline data but this reduced to 2.51 /100 PYFU (95%CI 1.5-4.3) using the follow up time point (when the difference between groups were more narrow).

The authors concluded: “Although other studies have examined superinfection in small groups of high-risk individuals, this is the first study to directly compare HIV superinfection rates to HIV incidence in a general heterosexual population. The finding that HIV superinfection occurs at approximately the same rate as primary HIV incidence has multiple public health ramifications, and could have significant implications for HIV vaccine research.”

In a second oral presentation, Keshet Ronen from Fred Hutchinson Cancer Research Centre and colleagues looked at the incidence of reinfection in a high-risk cohort of female sex workers in Mombasa, Kenya who were enrolled within six months of initial infection and followed for two years. This is a cohort of almost 3000 HIV negative women who have been followed prospectively with monthly visits, 311 of whom have seroconverted since 1993, with median follow-up of five years.

This group amplified and analysed ~500 bp amplicons in gag, pol, and env from plasma RNA to identify cases of multiple infection. Between

100 and 2000 sequences were obtained per genomic region per time point for a total of ~380,000 sequences.

In earlier studies this group identified 12 cases of reinfection in 56 women. In this new analysis a further 94 women have been identified, with 7 cases of reinfection in the 63 women who have so far had data analysed. They presented combined result of 19 cases of superinfection among 117 women over 621 person-years of follow up (incidence of 3.06% PYFU for reinfection vs to 3.25 for initial infection) and ongoing screening and analysis continues to reach the 150 cases needed to be powered to compare these rates, adjusting for other risks. In this study, timing of reinfection was addressed and included cases plausibly occurring five or more years after initial infection.

However, some researchers suggest the possibility that cases attributed to reinfection could come from initial dual infections, with one infection outgrowing the other after several years. In the absence of being able to confirm a reinfection event by phylogenetic comparisons to the second donor an indirect way to rule out initial dual infection would be to look for closest ancestor for each dual strain to estimate whether one infection has been present for longer than the other.

A poster from the UCSF group that have previously presented this position included two cases where reinfection (superinfection) was initially described based on limited sample sequencing but that more sensitive analyses suggested were serially expressed dual infections (SEDI). [3]

#### C O M M E N T

**The consensus after both studies seemed to be that initial HIV infection is not protective of subsequent infections. Researchers were divided over whether initial infection potentially increases the risk of second infection or whether longer duration of follow-up (>2 years) might uncover CTL responses.**

**Others suggested that cases of reinfection in these studies could easily have been underestimated by not looking early enough after initial infection and only reporting phylogenetically different infections. Further research is needed to determine risks for reinfection, currently assumed to generally be similar to those for initial infection (behaviour risk, viral load of the transmitting partner, STIs, genetics etc).**

**Ascribing reinfection to initial dual infection (SEDI), requires either one source partner (prompting the question of how this person became dually infected?) or exposures from multiple sources at a close time point, which becomes practically very close to dual infections as one infection must have predated the other, even if this involved a short window period.**

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## Case report: homozygous CCR5 delta-32 protection overcome by infection with X4 virus

**Simon Collins, HIV i-Base**

**A sobering and important report documented the case study of a man who was homozygous for the CCR5 delta-32 mutation that generally provides effective protection against infection from HIV.**

With most circulating (and infectious) virus using the CCR5 co-receptor, individuals with this deletion in both chromosomes who are exposed to HIV provide a dead-end for the infection, with the virus unable to infect CD4 cells without the use of the coreceptor.

This case of a 39 year-old man - who was diagnosed in 1996 - was identified by Ester Ballana and colleagues after retrospectively testing DNA from stored peripheral blood mononuclear cells (PBMCs). The man had started treatment within 6 months of diagnosis, at a CD4 count of 520 and viral load of 3,500 copies/mL. Sequence analysis of the env gene indicated homogeneous X4 virus.

Fifteen years after seroconversion, total HIV-1 proviral DNA was 60 copies/million PBMCs. CD4 count had only increased to 600-700 over this time but HLA haplotype analysis showed multiple alleles associated with slower HIV progression including HLA-B\*5701 and HLA-A\*2402.

Ref: Ballana E et al. HIV-1 infection in a CCR5-D32/D32, HLA-B\*5701, and HLA-A\*2402 subject: a case report. Poster abstract 292.  
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CROI: SIDE EFFECTS

## No association between atazanavir and MI or stroke in D:A:D study

**Simon Collins, HIV i-Base**

An update from the D:A:D cohort on the risk of cardiovascular events was presented as a poster. The D:A:D is a large cohort that includes more than 49,000 HIV positive people from Europe, Australia and the US that in recent years has become sufficiently powered to be able to look at associations between safety outcomes and individual HIV drugs.

The cohort now includes 844 cases of myocardial infarction and 523 strokes, both from over 300,000 patient years of follow up (PYFU) and this year accrued sufficient data on atazanavir (>37,000 PYFU) to present this analysis. Previous associations had been reported for cumulative exposure to indinavir and lopinavir/r but not for saquinavir or fosamprenavir.



The rate of MI was 0.28 /100 PYFY (95%CI 0.26 to 2.30) in those with no exposure to atazanavir and 0.20 (0.12 to 0.32) in those with >3 years exposure. The rate of stroke was 0.17 (0.16 to 0.19) and 0.17 (0.10 to 0.27) in the same groups respectively.

The relative rates (RR) for MI and stroke were 0.95 (95%CI: 0.87, 1.05; p=0.30) and 0.90 (95%CI: 0.81, 1.01; p=0.07) after adjustment for clinical and demographic factors including ARV use. No association was seen with cumulative exposure (<1, 1-2, 2-3, >3 years) or after further adjustment for bilirubin. Rates were similar for atazanavir used with and without ritonavir.

**Table 1: Rate (95%CI) of MI or stroke and exposure to atazanavir**

	No ATV	>3 years
MI	0.28 (0.26 to 2.30)	0.20 (0.12 to 0.32)
Stroke	0.17 (0.16 to 0.19)	0.17 (0.10 to 0.27)

Reference

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<http://www.retroconference.org/2012b/Abstracts/45367.htm>

CROI: HCV COINFECTION

## Hepatitis C coinfection studies

### Simon Collins, HIV i-Base

**The conference included very encouraging results from the first studies of telaprevir (tradename Incivek, Vertex) and boceprevir (tradename Victrelis, Merck) in people with HIV/HCV coinfection.**

Both studies generally showed similar response rates in HIV/HCV coinfection to those seen in HCV mono-infection. Sustained virological response (SVR) results at 12 weeks are highly predictive of SVR at week 24.

### Telaprevir: SVR-12 results in HIV/HCV coinfection

SVR results at 12 weeks after treatment, from a double-blind, placebo controlled Phase 2 study telaprevir in combination with pegylated

interferon (peg-IFN) + ribavirin (RBV) in 60 patients with HIV and HCV genotype-1 coinfection were presented by Douglas Dieterich. [1]

Patients were randomised to either telaprevir (750 mg every 8 hours) or placebo, plus PEG-IFN alpha-2a (Pegsys) + RBV, (800 mg/day) for 12 weeks followed by 36 weeks of peg-IFN+RBV. This was a two-part study depending on whether patients were using ART (Part B, n=47) or not (Part A, n=13). In the ART arm atazanavir/ritonavir (n=23) or efavirenz (n=24) based regimens were allowed (with an increased telaprevir dose for efavirenz patients).

Baseline characteristics included: mean age of 46 years; 88% male; 27% African American; 68% with subtype 1a and 3% had cirrhosis. HCV RNA was >800,000 IU/mL in 92% and 81% of no-ART and ART groups respectively; median CD4 counts were approximately 500-600 cells/mm<sup>3</sup> (range 300 - >1,100).

Undetectable HCV RNA in the combined active vs placebo groups were achieved by 68 vs 4.5%, 82% vs 32%, 63 vs 4.5% and 74% vs 55% at week 4, 12, weeks 4 and 12, and week 24 respectively, see Table1). ART use did not affect response rates. Outcomes by baseline HCV RNA were not presented.

Both safety and tolerability of telaprevir in combination with peg-IFN+RBV was comparable to that previously observed in HCV-mono-infected patients. No severe rashes were reported.

### Interactions between telaprevir and antiretrovirals

Interaction data between telaprevir and HIV drugs was also included in the same presentation. Telaprevir concentrations were similar with efavirenz and atazanavir to reference concentrations with mean (90%CI) C<sub>min</sub>, C<sub>avg</sub> and C<sub>max</sub> of 93 ng/mL (56, 156), 97 ng/mL (64, 146) and 101 ng/mL (72, 143) with efavirenz and 131 ng/mL (77, 222), 107 ng/mL (70, 165) and 98 ng/mL (69, 140) with atazanavir, respectively.

The mean concentration ratios to reference levels were also close to 100% for levels of efavirenz and atazanavir, indicating the higher efavirenz dose is sufficient to overcome this interaction.

Telaprevir can only be used with boosted atazanavir, efavirenz (with a higher dose of telaprevir--1125 mg tid (vs. 750 mg tid) or raltegravir. Background nucleosides are tenofovir plus FTC or 3TC

### Boceprevir: SVR-12 results in HIV/HCV coinfection

SVR results at 12 weeks after treatment from a randomised double-blind, placebo controlled study of Merck's boceprevir (BOC) with pegylated interferon (peg-IFN) + ribavirin (RBV) in 98 patients with

**Table 1: Interim HCV RNA BLQ (%) response rates with telaprevir in HIV/HCV coinfection**

N (%)	No ART		EFV/TDF/FTC		ATZ/r/TDF/FTC	
	T/PR	PR	T/PR	PR	T/PR	PR
N	7	6	16	8	15	8
Week 4 (RVR)	5 (71)	0	12 (75)	1 (12)	9 (60)	0
Week 12 (oRVR)	6 (66)	2 (33)	14 (80)	2 (25)	11 (73)	3 (38)
Week 4 and 12 (eRVR)	4 (57)	0	12 (75)	1 (12)	8 (53)	0
Week 24	6 (86)	2 (33)	12 (75)	4 (50)	10 (67)	6 (75)

T: telaprevir; P: peg-IFN; R: ribavirin. BLQ: undetectable: lower limit of quantification: 25 IU/mL; limit of detection 10-15 IU/mL.

HIV and HCV genotype-1 coinfection were presented by Mark Sulkowski. [2]

In this study, all patients were on stable antiretroviral treatment (not including NNRTIs, AZT or ddI) with suppressed viral load (<50 copies/mL). ART regimen included atazanavir/r (n=31), lopinavir/r (n=25), darunavir/r (n=17), other PI (n=7), raltegravir (n=10) and other (n=2).

Patients were randomised (2:1) ratio to receive boceprevir 800 mg every eight hours (n=64) or placebo (n=34) plus pegylated interferon- $\alpha$ -2b (Peg-Intron) and weight-based RBV (600 to 1400 mg/day). All patients also had a four-week lead-in phase with peg-IFN + RBV.

Baseline characteristics included: mean age of 45 years; 69% male; 82% white. 88% had HCV RNA >800,000 IU/mL and 65% were genotype 1a. Median CD4 counts were approximately 580 cells/mm<sup>3</sup> (range 200 - >1,500). Only 4 patients had cirrhosis.

HCV RNA levels were undetectable in 59% vs 23% of patients at week 12 and 64% vs 29% at week 48 in the boceprevir vs control groups with SVR rates 12 weeks after the end of treatment of 61% vs 26% (see Table 2).

Treatment responses were broadly similar for all PIs in the boceprevir group (57-67%) with a lower response in the raltegravir group (43%) but these were small patient numbers. Neither of the patients using maraviroc or efavirenz (contrary to protocol) achieved 12 week SVR. By week 48, 2 and 3 patients in the boceprevir and control groups, respectively, had HIV RNA virologic failure.

Discontinuations occurred in 24 (38%) vs 18 (53%) patients, due to adverse event (20% vs 9%), treatment failure (9% vs 41%), loss to follow up (2% vs 0) and patient choice (5% vs 3%).

Compared to the control group, BOC patients were more likely to have decreased appetite, pyrexia, dysgeusia, vomiting, asthenia, anemia, and neutropenia.

**Table 2: Interim HCV RNA BLQ (%) response rates with boceprevir in HIV/HCV coinfection**

	B/PR	PR
N	64	34
Discontinuation	24 (38%)	18 (53%)
week 4 (pegIFN/RBV lead-in)	3 (4.7%)	3 (8.8%)
week 8	27 (42%)	5 (15%)
week 12	38 (59%)	8 (23%)
week 24	47 (73%)	11 (32%)
week 48 (EOT)	42 (66%)	10 (29%)
SVR 12	37/61 (61%)	9/34 (26%)

B: boceprevir; P: peg-IFN; R: ribavirin.

### Important drug interactions between HIV PIs and boceprevir

A late breaker poster was presented by researchers at Merck reporting significant drug interactions between boceprevir and HIV protease inhibitors (atazanavir, lopinavir and darunavir) in HIV negative volunteers. [3] This highlighted not just the complexity for future HCV treatment in people already on ART, but also the importance of conducting major drug-drug interaction studies prior to coadministration in new studies.

Boceprevir significantly decreased the exposure of the PIs by up to 41-75% for AUC<sub>0-last</sub>, C<sub>max</sub>, and C<sub>min</sub> [GMR (90% CI)]. Coadministration with boceprevir also decreased the exposure of ritonavir AUC<sub>t</sub> by 34%, 22%, and 27% in the atazanavir, lopinavir and darunavir groups, respectively. Co-administration with atazanavir/r did not alter boceprevir AUC<sub>t</sub>, but co-administration with lopinavir/r and darunavir/r decreased boceprevir AUC<sub>t</sub> 45% and 32%, respectively.

**Table 3: Geometric mean ratio (90% CI) for interaction between boceprevir and HIV PIs**

	AUC <sub>0-last</sub>	C <sub>max</sub>	C <sub>min</sub>
ATZ	0.65 (0.55, 0.78)	0.75 (0.64, 0.88)	0.51 (0.44, 0.61)
LPV/r	0.66 (0.60, 0.72)	0.70 (0.65, 0.77)	0.57 (0.49, 0.65)
DRV	0.56 (0.51, 0.61)	0.64 (0.58, 0.71)	0.41 (0.38, 0.45)

### C O M M E N T

**These results are important for people with HCV genotype 1 who are in need of urgent treatment.**

**The interaction data between these HCV drugs and antiretrovirals in these studies was luckily not associated with high rates of treatment failure.**

**For further information on HCV drug interactions please see the excellent online resource produced by the pharmacology team at Liverpool University.**

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

**UK consensus guidelines for use of these new HCV drugs were recently published online with free access, and although are not HIV-specific, they include a reference to coinfection being a population where their use should be considered. [4]**

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CROI: IMMUNISATION

## Herpes Zoster vaccine safe and effective in HIV positive people

**Simon Collins, HIV i-Base**

Encouraging results were presented from the ACTG A5247 study on the use of two doses of a live varicella zoster virus (VZV) vaccine (Zostavax, Merck) in almost 400 HIV positive people who were VZV positive or who had herpes zoster (HZ)/shingles outbreak at least one year before study entry, and who were virally suppressed on stable ART. [1]

The incidence and severity of HZ and post herpetic neuralgia (PHN) is higher in HIV positive people and early use of early acyclovir treatment is not always effective. As susceptibility to HZ increases with reduced age-related immune function, a protective vaccine response already demonstrated in HIV negative people > 60 years [2] would be particularly important for HIV positive people.

Participants from over 40 US sites were randomised 3:1 to active or placebo arms and stratified by CD4 count at screening: >350 (high) vs 200-349 (low) cells/mm<sup>3</sup>. Vaccinations were given on day 0 and at week 6, with immune responses evaluated at weeks 2, 6, 8, 12, and 24.

Primary endpoints were safety (if  $\leq 18$  patients in the active arm had primary safety endpoints) and efficacy (change in VZV gpELISA titer at 6 weeks post each vaccination).

Baseline characteristics included: 84% male; 66% white, 31% black, 22% Hispanic; median age 49 years. Median CD4 count and CD4 nadir in the high (n=203) and low (n=192) groups was 602 (nadir 276) and 283 (nadir 106) cells/mm<sup>3</sup> respectively. Almost all participant had a previous AIDS event (>97%) with 75 having prior VZV and 33% HZ > 1 year prior to entry.

In the safety analysis, there were no significant differences between the active and placebo groups and none of the 15 primary endpoints in the active arm were vaccine related. Injection site reactions were seen more frequently in the active group (42% vs 12%,  $p < 0.001$ ). VZV-like rashes were seen in 3 active and 2 placebo patients with PCR showing negative or non-vaccine-strain results.

Geometric mean fold-rise in VZV antibody titre increased by 1.75 ZV vs 1.09 placebo from baseline to week 6 ( $p < 0.001$ ) and this remained similar at week 12 (indicating no change from the second dose). Patients with higher CD4 count at baseline had slightly higher antibody titer over time ( $p = 0.024$ ).

These responses were similar to those seen in HIV negative patients > 60 years. However this study was not powered to detect difference in HZ outcome and post-study follow up is not planned.

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## High dose flu vaccine improves antibody responses in HIV positive people

**Simon Collins, HIV i-Base**

Noah McKittrick and colleagues presented results from a randomised, double-blinded study comparing standard (15-ug/strain) to high dose (60 ug/strain) flu vaccine in 195 HIV positive adults. This study used the trivalent, inactivated, unadjuvanted, split-virus vaccine Fluzone (Sanofi Pasteur). Antibody titers to three strains (H1N1, H3N2 and B) were measured using the hemagglutination-inhibition (HAI) assay.

Baseline characteristics included: 71% male, 68% African American and median age 45 (range 20-78) years. The median CD4 and nadir CD4 count of 452 (IQR 293 - 629) and 180 (IQR 53 - 318) cells/mm<sup>3</sup> respectively. In this group, 89% were on HAART and 89% of these 89% had viral load <200 copies/mL.

Approximately half the patients had protective titers at baseline. By week 3, geometric mean antibody titers and the proportion of individuals with protective HAI titers were higher in participants vaccinated with the HD. Greater responses were seen in the high vs low dose groups but this was only significant for H1N1 +9% (0.9 to 17.8%,  $p = 0.04$ ), and B +12% (1.5 to 22.6%,  $p = 0.03$ ) with a non-significant difference H3N2 + 4% (-3.6 to 12.1%,  $p = 0.39$ ).

Both vaccines were well tolerated with no differences between groups and no serious adverse events.

The high dose group achieved protection rates of 80-90% (similar to standard dose in HIV negative studies) increased from 50-70% previously reported for standard dose use in HIV positive people.

Ref: McKittrick N et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV+ individuals: a double-blinded, randomized trial. 19th CROI, 5-8 March 2012, Seattle. Oral abstract 97.

<http://www.retroconference.org/2012b/Abstracts/44150.htm>

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/mm3), 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.**

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## 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/mm3 (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/mm3 dropped to approximately 0.4/100 PYFU with CD4 counts >500 cells/mm3.

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/mm3 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/mm3, 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/mm3 higher.

Additional factors were nadir CD4 count (<100 cells/mm3) 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/mm3) for anal cancer (RR 1.07; 1.05-1.08).

More optimistically, a successful response to ART (increasing CD4 to >200 cells/mm3) was able to overcome the association with CD4 nadir <200 cells/mm3, 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/mm3.

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.

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).**

**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 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.  
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<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 1mL 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 pericervical 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, Cmax 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.

## 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.
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## 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 EC50 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 Zorrila 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  $\alpha$ 1-acid glycoprotein (AAG) concentrations were decreased by 22% to 29% during pregnancy. Unbound DRV was >EC50 (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.

#### 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

### 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/tenofovir/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)

## Global action over the challenge to India's patent laws

### Rebecca McDowall, HIV i-Base

**From 6-10 February 2012, activists from Delhi to New York, Johannesburg to London took to the streets to appeal to the Indian government and European Commission (EC) to act to ensure that the developing world continues to have access to affordable medicines.**

Currently, the EU is pushing for India to adopt measures that would choke generic production in the country, and by restricting generic exports, threaten access to medicines for millions of people worldwide. Negotiations on the proposed India-EU Free Trade Agreement (FTA) were expected to culminate at the EU-India Summit, which took place in New Delhi on 10 February 2012.

The Summit was expected to be the climax of a five-year-long

negotiation process over an EU-India Free Trade Agreement (FTA). The agreement seeks to strengthen trade relations between the two economies and holds promise of huge development for many Indian industries. It also, however, is a source of concern for the global health because India is the world's largest producer of generic medicines making it the "pharmacy of the developing world".

India currently produces 80% of ARVs used in the developing world and 90% of paediatric HIV medicines. Despite curtailment of generic production following India's inclusion into the World Trade Organisation in 2005, the country has successfully utilised TRIPS flexibilities to ensure that it still produces affordable medicines for for the world's poorest countries.

The FTA, however, threatens to over rule India's national patent laws and increase restrictions on generic pharmaceutical production from within the country.

One of the most harmful provisions within the agreement – that of data exclusivity – was the focus of activist pressure throughout 2011. The provision (known as data monopolies in the US) requires manufacturers of all generic formulations to conduct new clinical trials rather than simply demonstrating equivalence to the innovator drug, even though the FDA recognises the scientific safety and rigour of bioequivalence studies. If these trials are not conducted the generic company would be required to wait 10 years to gain access to the original trial data.

Following widespread pressure from global health advocates and activists and resistance from the Indian government the EC announced that this provision has been removed from the agreement. Despite this assurance the newer drafts of the agreement indicate that similar provisions, albeit in subtler wordings, are being pushed to be included in the final agreement.

Further harmful inclusions into the agreement include:

- Border measures - restricting the exportation of generic drugs out of the country.
- Intellectual Property enforcement measures - putting third parties such as treatment providers at risk of court cases and police action.
- The 'Investment Chapter' that would remove the Indian government's right to place public health before private profits by allowing companies to directly sue the government in disputes over IP rights.

In the end, no agreement was reached on 10th February and the negotiations between the EC and India are ongoing. As pressure grows to come to an agreement in the near future there is increasing concern that provisions harmful to access to medicines may be slipped into the FTA. The consultation process is being conducted with little sign of accountability or transparency, leaving activists largely in the dark about these worrying provisions. Ongoing pressure is essential to protect India's generic industry and ensure that the developing world retains access to the affordable medicines it needs.

For more information, and to become involved in the campaign please see:

<https://action.msf.org>

<http://www.healthpovertyaction.org/campaigns/trading-with-lives/>

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

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

<http://donttradeourlivesaway.wordpress.com/>

<http://students.stopaidscampaign.org/>

Pictures of the Global Week of Action are online:

<http://www.msfacecess.org/our-work/hiv-aids/article/1755>

The Stop AIDS Campaign is an initiative of the UK Consortium on AIDS and International Development.

### What can you do

Sign on to MSF initiated letter to Commissioner De Gucht, DG Trade:

[https://action.msf.org/en\\_CH](https://action.msf.org/en_CH)

### Video demonstrations

London

<http://www.flickr.com/photos/stopaidscampaignactivism/sets/72157629201133095/>

India

<http://www.facebook.com/media/set/?set=a.329076807136539.88526.144687138908841&type=1>

Nepal

<http://www.facebook.com/media/set/?set=a.329076807136539.88526.144687138908841&type=1>

France

<http://www.actupparis.org/spip.php?article4754>

South Africa

<http://www.msf.org.za/event/picket-against-fta-threats-indian-generics-johannesburg>

Malaysia

<http://www.facebook.com/notes/stop-the-eu-india-free-trade-agreement/malaysian-groups-will-protest-tomorrow-at-eu-office-in-kuala-lumpur/381058168586572>

Report shown on Sky News

<http://news.sky.com/home/world-news/article/16169181>

## Why global health activists are fired up about Novartis

### Brook K. Baker, Health GAP

**On 22 February 2012, the eve of the Swiss pharmaceutical company's annual shareholders meeting in Berne, Switzerland, 50 AIDS activists, students, and community group members protested at Novartis's Institute for BioMedical Research in Cambridge, Massachusetts.**

The protest was part of a global day of action drawing attention to the pharma giant's pending lawsuit against cancer patients and the government of India, aiming to reinterpret India's strict patent standards.

Novartis is seeking to establish a binding court precedent that will make it much easier to obtain overlapping and successive patents on minor variations to existing medicines – a precedent that will increase the number of patents on medicines and extend the length of patent monopolies, thereby limiting and delaying generic competition. In the absence of generic competition, Novartis and other “Big Pharma” companies will be able to set prices affordable to elites, but unaffordable to the broad mass of poor people in India. Because India is the “pharmacy of the developing world,”

Novartis's case threatens affordable global access to all categories of life-saving and health-enhancing medicines.

Indian generic companies manufacture 80 percent of the antiretrovirals used to treat people living with HIV/AIDS around the world. Although the manufacturing of existing AIDS and other medicines is not threatened specifically by this court case, the threat with respect to newer and future medicines is very real. With more frequent and longer patent monopolies, poor people and poor governments will be priced out of access for many, many years.

### Background of the case

This court case is part of a long series of legal actions by Novartis designed to eviscerate India's lawful efforts to restrict the widespread practice of “ever-greening” by pharmaceutical companies. In these instances, pharmaceutical companies seek new or additional 20-year patent monopolies for minor changes to existing medicines and chemical entities based on those minor changes.

In the present case, scientists had invented a basic compound imatinib, which is used to treat certain cancers. It was first patented globally in 1993, but not in India. Thereafter, researchers at Novartis tweaked the basic compound, resulting in a 30 percent improvement in the drug's absorption into the body. This revised active pharmaceutical ingredient became the basis of a powerful anti-cancer medicine called Gleevec in the U.S. and Glivec in India. In 1998, Novartis filed a patent application on the revised drug in the India Patents Office and in many other countries.

Although the Gleevec/Glivec patent was granted in 40-plus countries that had relatively weak patent standards, the patent was denied in India for three simple reasons:

1. Prior to 2005, India (like many countries before it) did not grant patents on medicines at all. Although the 1994 World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) forced India to start granting patents on medicines in 2005, TRIPS did not require India to retroactively grant patents on medicines invented before 1995.
2. India enacted Section 3(d) of its patent law, a so-called exclusion that does not ordinarily allow patenting of variations, new uses, new combinations, and new formulations of preexisting chemical entities.
3. India incorporated a narrow exception to the no-patent-for-variations rule if, but only if, a patent applicant could demonstrate that changes to an existing substance actually showed significantly increased efficacy – which the Indian courts decided does not include changes in absorption, among other things.

Novartis continues to take action to reverse the patent' office's denial of its patent application, and allow section 3(d) to be reinterpreted to allow routine “ever-greening” of minor modifications to existing medicines based on a minimal showing of any positive effect.

### Global protests

Demonstrators in Cambridge tried to deliver a Silver Urn (for the ashes of people who would die if Novartis's court challenge is successful) to Novartis officials, but they were barred from the building and ordered off the premises by Cambridge police. Demonstrators in Washington, DC, delivered an “indictment” against Novartis's CEO, and protesters in New York City “occupied” Novartis offices. Organised by Health

GAP, Student Global AIDS Campaign, Occupy Boston Health Justice Group, these protesters and others were joined by a larger group of protestors at the Novartis annual general meeting in Basel. There, activists from Act Up Paris, Act Up Basel, Médicines Sans Frontières, Oxfam, the Berne Declaration and others showed videos and interacted with shareholders, many of whom were sympathetic to the campaigners' protests against Novartis's lawsuit.

### Novartis's reaction

In response to the protests, Novartis issued a statement to Pharamlot: "We believe that working through the judicial system is the legitimate and appropriate approach to gaining clarity on the unique aspects of India's patent law .... We disagree with assertions ... that access to medicines is threatened by our case. The basis of this argument is false and very misleading. Currently available generic drugs launched in India before 2005 – including HIV/AIDS medicines and generic versions of Glivec – will continue to be available under a grandfather clause in the Indian patent law regardless of the legal outcome of our case. All pharmaceutical products, including HIV/AIDS medications, have been patentable in India under the existing patent law since 2005, and some have been patented."

This defense is patently evasive – the part truth that tells a lie. Yes, there is some degree of grandfathering, even for Glivec; yes, since 2005, India has patented some medicines. However, India has tried to limit patent monopolies, to address public health needs, and to ensure access to medicines within the bounds of the TRIPS Agreement. Novartis's statement ignores that is trying to erase those legislative efforts, hiding behind the fig leaf of seeking "clarity."

Source: Baker BK. Why global health activists are fired up about Novartis. Web blog 27 February 2012.

<http://sciencespeaksblog.org/2012/02/27/why-global-health-activists-are-fired-up-about-novartis/>

## Obama's global, domestic & HIV research budget backslides on existing commitments

### TAG press release

**On 14 February, the US activist organisation TAG issued a press release, summarised below, that criticised President Obama's recent budget and policy announcements.**

Treatment Action Group (TAG) is deeply disappointed by President Obama's proposed cuts to PEPFAR (President's Emergency Plan for AIDS Relief) and bilateral TB funds, freezing of NIH (National Institutes of Health) research as well as the insufficient attention to the worsening domestic AIDS crisis in the administration's fiscal year 2013 budget plan. "Why does President Obama want to turn his back on the most effective, life-saving global health and development program in history?" said Mark Harrington, Executive Director of TAG,

Since 2003, PEPFAR has been the most efficient and effective U.S. global health initiative ever. [...] Now, in a stunning reversal, President Barack Obama has proposed an incomprehensible cut of over a half billion dollars — nearly 13% decrease of \$543 million — in what can

only be interpreted as a clear signal that the President may allow PEPFAR to expire when its current authorisation ends next year.

While Administration officials may argue that these cuts will be partly offset by program efficiencies, lower drug prices, and the proposed increase in U.S. support to the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) — which TAG supports — the reality is that U.S. support alone cannot reverse the deep effects of the broken promises of the G-20 and the other Global Fund donors. By cutting the PEPFAR budget, over half a million people will be denied life saving HIV treatment, and countless new HIV and TB/HIV infections will occur that could have been averted.

"For the first time since he entered office, President Obama also proposed a flat budget for the National Institutes of Health (NIH) — undermining our ability to translate scientific advances into cures, and jeopardising [the US] long term status as the global leader in health research. President Obama would have turned back the clock on the search for an AIDS cure, and better treatments for Hepatitis C and TB." said TAG's Director of Communication and Advocacy, Lei Chou.

Furthermore, the Administration's 2013 proposal continued an unbroken string of insufficient support for U.S. Centers for Disease Control and Prevention's (CDC) work to fight the two leading killers of people with HIV — tuberculosis and viral hepatitis. [...] The \$67 million increase for ADAP (AIDS Drug Assistance Programme) will not come close to meeting the increasing demand [...] for the most marginalised amongst us.

Source: TAG press release, (16 February 2012).

<http://www.treatmentactiongroup.org/press>

See also: Cohen J. Global health advocates aren't impressed with budget plan. Science (14 February 2012).

<http://news.sciencemag.org/scienceinsider/2012/02/global-health-advocates-arent.html>

President's budget request reflects strong commitment on global AIDS

<http://blog.aids.gov/2012/02/presidents-budget-request-reflects-strong-commitment-on-global-aids.html>



## 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 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.

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.

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.**

**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

**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

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 eGRF 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 context 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?](http://journals.lww.com/aidsonline/Abstract/publishahead/Discontinuation_of_Atripla_R__as_first_line.98950.aspx?)

TUBERCULOSIS

**Update on bedaquiline phase II trial**

**Nathan Geffen, CSSR**

**Two year follow-up data on the first stage of the two-stage Phase II randomised placebo controlled trial of bedaquiline (formerly TMC207) has been published. We have previously reported the eight weeks results of this study, which was published in the NEJM in 2009. [1-3]**

In this study, bedaquiline or placebo was added to the first eight weeks of standard background treatment for MDR TB. As previously reported, bedaquiline significantly reduced the time to culture conversion by 24 weeks (HR 2.253; 95% CI: 1.08 to 4.71; p=0.031) (

The follow-up study sheds important light on the development of resistance to standard MDR TB regimens and the potential for the addition of a new drug to protect against this.

At two years, 24 of the original 47 participants remained in the trial. Of the 23 patients who discontinued, 13 were in the placebo group and 10 in the bedaquiline group. Twelve subjects discontinued during the first 24 weeks and a further 11 discontinued before completion of follow-up at 104 weeks, seven patients citing the frequency and intensity of follow-up visits as the reason for withdrawal. Interestingly, two subjects in the placebo arm were withdrawn at week 63 because of increasing levels of drug resistance. One of the 24 patients was culture-negative at baseline and removed from analysis. All 23 patients who remained on the trial to 104 weeks were culture-negative, except one on bedaquiline.

As previously reported, the only adverse event associated with bedaquiline was nausea (26% vs 0%). Otherwise adverse events were similar between the two arms: hearing impairment (13% and 21%), extremity pain (17% and 13%), acne (9% and 17%), and noncardiac chest pain (4% and 17%) in the bedaquiline and placebo groups respectively.

At baseline, resistance to first-line agents, obtained from 39 patients, was high: ethambutol (66%), pyrazinamide (67%) and streptomycin (80%). Resistance was much lower in second-line agents: ofloxacin (13%), kanamycin (13%) and capreomycin (8%).

Excluding resistance to ethambutol and ethionamide, only one patient receiving bedaquiline acquired resistance to companion drugs, but five patients receiving placebo (4.8% vs 21.7%; p=0.18) (acquired resistance to companion drugs, and resistance to ofloxacin was acquired in four patients receiving placebo and none receiving bedaquiline (0% versus 22%).

The authors noted that the acquisition of additional resistance during the trial, mainly in the placebo group, especially in the form of ofloxacin or kanamycin resistance that led to pre-XDR TB, despite directly observed therapy, is reason for grave concern. They explained that the study's baseline resistance, which is supported by other studies in the United States and South Africa, shows the potential weakness of commonly used standardised regimens for the treatment of MDR TB.

C O M M E N T

**At the time of writing, discussions have been taking place between the South African government, the Medicines Control Council,**



**Tibotec, the Southern African HIV Clinicians Society, the Global TB Community Advisory Board, the Treatment Action Campaign and Medecins Sans Frontieres to get pre-approval access to bedaquiline. The resistance data published in this study adds yet another reason to justify pre-approval access. There is a legitimate concern that pre-approval access to bedaquiline could lead to resistance developing before the drug is even on the market. But as this study shows, the addition of bedaquiline to MDR TB regimens might reduce the risk of patients developing pre-XDR TB. The numbers are small and will need confirmation in larger trials, which are ongoing, but the argument for pre-approval access is strengthened by these data.**

#### References

1. Diacon AH et al. 2012. Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance. *Antimicrob. Agents Chemother.* 2012, 56(6):3271. DOI: 10.1128/AAC.06126-11.  
<http://www.ncbi.nlm.nih.gov/pubmed/22391540>
2. Geffen N. TMC207 reduces time to sputum conversion in phase II trial in patients with drug-resistant TB. *HTB South* April 2009.  
<http://i-base.info/htb-south/559/>
3. Diacon AH et al. 2009. The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis. *N Engl J Med* 2009; 360:2397-2405.  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0808427>

## 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)

## HIV i-BASE

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- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV
- HIV testing and risks of sexual transmission

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

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