

# january–march 2015

## CONTENTS

### EDITORIAL

### CONFERENCE REPORTS

22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle, Washington

- Introduction
- Pipeline ART: tenofovir alafenamide (TAF)
- Pipeline ART: maturation inhibitors and an attachment inhibitor
- No HIV transmissions between gay couples when viral load is undetectable: preliminary results from “Opposites Attract” study in Australia, Thailand and Brazil
- PrEP reduced HIV risk by at least 86% in PROUD: no transmissions likely from people taking meds
- “On demand” PrEP dosing in IPERGAY: 86% reduced risk of HIV, no transmissions with active drug use
- Other HIV PrEP studies at CROI 2015: implementation of oral PrEP and problems with tenofovir gel
- Early HIV treatment and isoniazid prophylaxis: why TEMPRANO results do not yet support universal ART at CD4 >500 cells/mm<sup>3</sup>
- Unintended pregnancies with levonorgestrel implant due to drug interactions with efavirenz-based ART
- Three drug ART best for preventing vertical transmission to infants: results from the PROMISE study
- 3 in 5 breastfeeding women with viral load >1,000 copies/mL are undiagnosed in Kenya, Malawi and South Africa
- Point of care HIV PCR test for infant diagnosis: good performance but poorer results in youngest age group
- Weekend off ART is non-inferior to continuous ART in young people taking efavirenz-based regimens: results from BREATHER study
- Increased cardiovascular risks in HIV positive children in Uganda and Zambia partially reversed by ART
- Lopinavir/ritonavir in young children is superior to nevirapine after five years: results from long term follow up of IMPAACT P1060
- Long-term safety and efficacy of tenofovir in children
- UK case of HIV remission: ten years off-ART in patient with prior progression and treated during seroconversion

2

3

### CONFERENCE REPORTS

21

XXIV International HIV Drug Resistance Workshop , 21-22 February 2015, Seattle, Washington

- Introduction
- Prevalence of transmitted drug resistance globally: highest in Australia, US and some European countries but between-country differences in all regions
- Higher rates of K65R in non-B subtype in large UK cohort and implications of tenofovir resistance in resource-limited settings
- Drug resistance and integrase inhibitors: potential impact of HIV subtype
- Drug resistance in children after PMTCT and early treatment

### ON THE WEB

26

- START study video
- NAT report: Young MSM in the UK
- RITA special issue: HIV and diabetes
- Guidance on reporting results of clinical trials

### FUTURE MEETINGS

26

### PUBLICATIONS AND SERVICES FROM i-BASE

27

### DONATION FORM

28

## 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)

Editor: Polly Clayden

Contributing Editor: Simon Collins

#### Medical Consultants:

Dr Karen Beckerman, Albert Einstein College of Medicine. New York.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Paul Blanchard, British School of Osteopathy, London.

Dr Martin Fisher, Brighton & Sussex University Hospitals.

Prof. Diana Gibb, Medical Research Council, London.

Dr Gareth Hardy, Case Western Reserve Univ. Cleveland.

Dr Saye Khoo, University of Liverpool Hospital.

Dr Leigh Johnson, University of Cape Town.

Prof. Clive Loveday, International Laboratory Virology Centre.

Prof. James McIntyre, Chris Hani Baragwanath Hosp. South Africa.

Dr Graeme Meintjes, GF Jooste Hospital, Cape Town.

Dr Stefan Mauss, Düsseldorf.

Prof Andrew Phillips, Royal Free Hospital, London.

Dr Graham P Taylor, Imperial College, London.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

Prof Francois Venter, WRHI, Johannesburg.

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

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

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

Articles written and credited to i-Base writers, as with all i-Base originated material, remains the copyright of HIV i-Base, but these articles may be reproduced by community and not-for-profit organisations without individual written permission and reproduction is encouraged. A credit and link to the original author, the HTB issue and the i-Base website is always appreciated.

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.

**HIV i-Base, 57 Great Suffolk Street, London SE1 0BB T: +44 (0) 20 7407 8488  
F: +44 (0) 20 7407 8489**

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

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

## EDITORIAL

**This issue of HTB South includes our first reports from CROI 2015 which as usual was a conference that was rich with new data.**

The detailed results from the UK PROUD trial and the French/Canadian "on demand" IPERGAY show that oral PrEP is an extremely effective option for gay men and transgender women at high risk of HIV. Many other PrEP studies reported effective implementation results, but low adherence seems to explain much lower efficacy rates for African women using tenofovir gel.

The TEMPRANO study looking at timing of ART and isoniazid prophylaxis in the Ivory Coast was a significant achievement, but our comments caution against interpreting the results to support universal ART at CD4 counts above 500. Instead, the details of the comparator group further highlights the continued importance of the ongoing START study.

We include a worrying report of unintended pregnancies with the levonorgestrel implant in women taking efavirenz. As efavirenz-based first line is likely to remain widely recommended for a large proportion of women of child bearing age, effective contraception for women receiving this treatment is a public health priority.

Also concerning, was that in a three-country survey conducted by Médecins Sans Frontières (in Malawi, Kenya and South Africa), a large proportion of pregnant or breastfeeding women were HIV positive with viral load greater than 1000 copies/mL.

Results from the PROMISE study showed ART is best for preventing vertical transmission – supporting WHO and other guidelines.

Good news from the BREATHER study reported that weekend-off ART is non-inferior to continuous treatment in young people taking efavirenz-based regimens. A key result was an improved quality of life, without jeopardising their care.

Finally, an important UK case of HIV remission in someone who started treatment during seroconversion and that cautiously might be categorised as functional cure. With important differences to the VISCONTI cohort, the challenge is now to explain the mechanism.

This issue also includes reports from the XXIV International Drug Resistance Workshop – held just before CROI – particularly on the implications of antiretroviral resistance in resource-limited settings.

More to follow from CROI 2015 and related meetings in the next issue of HTB South, but we will continue to post ahead-of-press articles to the i-Base website, for those who want news a little earlier.

### The Southern African HIV Clinicians Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinicians 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 Clinicians 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: <http://www.sahivsoc.org>

**Tel: + 27 (011) 341 0162 Fax: +27 (011) 341 0161**

## CONFERENCE REPORTS

### 2015 Conference on Retroviruses and Opportunistic Infections (CROI)

23-26 February 2015, Seattle

#### Introduction

The 2015 Conference on Retroviruses and Opportunistic Infections (CROI) was held from 23-26 February in Seattle, Washington.

CROI is the most important annual scientific and medical HIV conference. This year the conference opened with important news on oral pre-exposure prophylaxis (PrEP), including the PROUD and IPERGAY studies, topical PrEP and other HIV prevention options - including research to reduce mother to child transmission. Other key sessions included HIV-related complications, antiretrovirals in the pipeline and HIV pathogenesis - especially in the context of cure research.

Abstracts for each study are available in a searchable online database and some posters are available to download as PDF files.

<http://www.croiconference.org/abstracts/search-abstracts>

All plenary lectures and oral presentations are online as webcasts.

<http://www.croiwebcasts.org>

Articles included in this issue of HTB are:

- Pipeline ART: tenofovir alafenamide (TAF)
- Pipeline ART: maturation inhibitors and an attachment inhibitor
- No HIV transmissions between gay couples when viral load is undetectable: preliminary results from "Opposites Attract" study in Australia, Thailand and Brazil
- PrEP reduced HIV risk by at least 86% in PROUD: no transmissions likely from people taking meds
- "On demand" PrEP dosing in IPERGAY: 86% reduced risk of HIV, no transmissions with active drug use
- Other HIV PrEP studies at CROI 2015: implementation of oral PrEP and problems with tenofovir gel
- Early HIV treatment and isoniazid prophylaxis: why TEMPRANO results do not yet support universal ART at CD4 >500 cells/mm<sup>3</sup>
- Unintended pregnancies with levonorgestrel implant due to drug interactions with efavirenz-based ART
- Three drug ART best for preventing vertical transmission to infants: results from the PROMISE study
- 3 in 5 breastfeeding women with viral load >1,000 copies/mL are undiagnosed in Kenya, Malawi and South Africa
- Point of care HIV PCR test for infant diagnosis: good performance but poorer results in youngest age group
- Weekend off ART is non-inferior to continuous ART in young people taking efavirenz-based regimens: results from BREATHER study
- Increased cardiovascular risks in HIV positive children in Uganda and Zambia partially reversed by ART
- Lopinavir/ritonavir in young children is superior to nevirapine after five years: results from long term follow up of IMPAACT P1060

- Long-term safety and efficacy of tenofovir in children
- UK case of HIV remission: ten years off-ART in patient with prior progression and treated during seroconversion

CROI 2015: ANTIRETROVIRALS

### Pipeline ART: tenofovir alafenamide (TAF)

Simon Collins, HIV i-Base

**Of several new pipeline compounds with new data at CROI 2015, the most advanced in development was tenofovir alafenomide (TAF), the new version of tenofovir.**

TAF is notable for a low milligram dose (10 mg or 25 mg) that achieves intracellular drug levels that are 4-fold higher and plasma levels that are 90% lower, than with 300 mg of tenofovir disoproxil fumarate (TDF).

In the first TAF oral presentation, David Wohl from University of North Carolina presented results from a prespecified combined analysis of two randomised TAF studies (O104 and O111). [1]

The development programme for TAF is notable for prioritising coformulations rather than the individual drug and these studies compared two fixed-dose combinations (FDCs): elvitegravir/cobicistat/FTC/TAF (n=866) vs elvitegravir/cobicistat/FTC/TDF (Stribild), (n=867), starting with similar baseline characteristics and finding similar results. Dosing for each FDC is one pill, once-daily.

Both studies were randomised, double-blind, placebo controlled non-inferiority studies (lower margin of 95% CI = 12%), with primary endpoints of viral suppression to <50 copies/mL at week 48.

Baseline characteristics were closely matched between arms. Median age was 44 years; 85% were men, 15% women; 25% had black or African descent and 19% were Hispanic/Latino. The median CD4 and viral load were 405 cells/mm<sup>3</sup> and 4.58 log copies/mL, respectively; with 12% <200 cells/mm<sup>3</sup> and 23% >100,000 copies/mL.

At week 48, viral load was <50 copies/mL in 92% (TAF) vs 90% (TDF), difference +2.0% (95% CI: 0.7% to +4.7%). Approximately 5% (n=45) and 8% (n=71) discontinued treatment during the study, leaving 821 vs 796 participants in the primary analysis. When stratified by baseline viral load below/above 100,000 copies/mL results were 94% vs 91% (above) and 87% vs 89% (below), in the TAF vs TDF arms respectively. CD4 increases were also similar when stratified by baseline CD4 below (86% vs 89%) and above (86% vs 89%) 200 cells/mm<sup>3</sup>.

Efficacy results were not affected by age (above/below 50 years) or sex, but were slightly lower in both arms in black vs non-black participants: 88% vs 83% (below 50) and 94% vs 93% (above 50).

Increases in CD4 count were significantly higher with TAF: +211 vs +181 cells/mm<sup>3</sup>, p=0.024.

Of 4% of participants in each arm with viral failure, 1.8% (n=16) vs 2.2% (n=19) had resistance testing, with similar low rates of resistance to either NRTI (n=7 vs 5) or NNRTIs (n=5 vs 3).

The pattern of similar results continued for side effects: approximately 45% were drug-related but only 1% were grade 3/4, and 0.3% were serious - with discontinuations by only 0.9% (n=8) and 1.5% (n=15), in the TAF vs TDF arms, respectively. Five deaths were attributed

to stroke (1), alcohol intoxication (1), alcohol and drug intoxication (1) and myocardial infarction (2).

Common side effects (18% diarrhoea, 16% nausea, 13% headache, 12% upper respiratory tract infection, etc) were mild, with no cases of proximal renal tubulopathy in either study.

With marginal differences between FDCs for efficacy endpoints, the interest shifted to bone, renal and lipid results presented the following day by Paul Sax from Brigham and Women's Hospital and Harvard Medical School, Boston.

In this analysis, renal differences included less reduction from baseline in eGFR (Cockcroft-Gault) in the combined TAF compared to the TDF groups: median -6.6 vs -11.2 mL/min;  $p < 0.001$ . The four renal discontinuations were all in the TDF groups: renal failure (2), decreased GFR (1), nephropathy (1). Significant median percentage changes from baseline of four sub-clinical markers of proteinuria all favoured TAF: protein -3% vs +20%, albumin -3% vs +7%, retinol binding protein +9% vs +51% and beta2 microglobulin -32% vs +24%; all  $p < 0.001$ .

Mean percentage changes in bone measured by DEXA also favoured TAF vs TDF: at spine -1.30% vs -2.86% and hip -0.66% vs -2.95%; both  $p < 0.001$ .

Finally, median changes from baseline in lipid parameters (mg/dL) all increased more in the TAF vs TDF arms: TC +29 vs +14; LDL +14 vs +5; HDL +7 vs +4; (all  $p < 0.001$ ); and TG +19 vs +8,  $p = 0.027$ . However, there were no significant differences between arms in change from baseline of the TC:HDL ratio ( $p = 0.84$ ) or in the use of lipid lowering drugs ( $p = 0.42$ ).

A poster at CROI provided preliminary renal, bone and lipid data on use of TAF in patients with moderate-mild (stage 3-2) renal impairment, defined as eGFR 30-69 mL/min. [3]

This was 48-week data from a 96 week Phase 3 study in 242 stable patients on treatment (with or without TDF) with an undetectable viral load ( $< 50$  copies/mL) for at least six months, who were switched to the single tablet combination of elvitegravir/cobicistat/FTC/TAF (E/C/T/TAF). The primary endpoint was the change in eGFR from baseline to week 24. Hepatitis B/C were exclusion criteria. Patients were stratified by eGFR  $< 50$  mL/min ( $n = 59$ ) and  $> 50$  mL/min ( $n = 162$ ).

Baseline characteristics included median age 58 (IQR: 52, 65) years, 21% women, 18% African descent, median CD4 632 cells/mm<sup>3</sup>. Differences in the  $< 50$  vs  $> 50$  groups included re-switch TDF use in 58% vs 69%, hypertension in 50% vs 34%, median eGFR 43 vs 60 mL/min/1.73 m<sup>2</sup> (57 vs 77 when adjusted for age and sex), clinically significant proteinuria 58% vs 35% and clinically significant albuminuria in 64% vs 32%, respectively. Boosted PI was used by 44% of the overall group (breakdown by TDF use not provided).

At week 48, 222/242 (92%) remained virologically suppressed ( $< 50$  copies/mL), with data not available for 22 people (7%). There were seven discontinuations due to side effects: two for renal failure (eGFR decline), diarrhoea, choking, fatigue, joint swelling, sleep disorder and bladder cancer.

At week 24, median (IQR) changes in eGFR (Cockcroft-Gault) was -0.4 (-4.8, +4.5) and adjusted eGFR (CKD-EPI cystatin C) was +3.8 (-4.8, +11.2) mL/min/1.73 m<sup>2</sup>. Changes by baseline stratification appeared similar. Actual eGFR measured by iohexol clearance in a sub group of 32 patients remained similar at baseline and at weeks 2, 4, 8, and 24. Changes in proteinuria and albuminuria remained stable or improved for nearly all patients, with only 5%, 2% and 0% worsening in participants with baseline grade 0, 1 and

2, respectively. There were no cases of proximal renal tubulopathy or Fanconi syndrome.

Median (IQR) changes in bone mineral density (BMD) at week 48 increased by 1.9% (-0.3, +4.3) in the spine and 0.9% (-0.3, +2.7) in the hip (both  $p < 0.001$ ), although BMD was reduced in more than 25% of patients at both regions.

Changes in lipids (mg/dL) from baseline to week 48 showed differences when stratified by prior TDF use: TC +19 vs -11; LDL +7 vs -4; HDL +1 vs -4; and TG +12 vs -1; with changes in TC:HDL ratio of +0.3 vs +0.2, all in the prior-TDF vs no-TDF groups respectively.

## COMMENT

**TAF is probably a better drug than TDF, and the sub-clinical markers may have advantages. However, these were not sufficiently important for patient care for Gilead to prioritise its development.**

**Gilead had in vitro data on the potential benefits of TAF (formerly GS-7340) in 2001 and held back on development for over a decade before presenting Phase 1 data at CROI in 2011. [4, 5]**

## References

Unless stated otherwise, all references are to the Programme and Abstracts of the 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle.

1. Wohl D et al. Tenofovir alafenamide (TAF) in a single-tablet regimen in initial HIV-1 therapy. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Oral late breaker abstract 113LB.  
Abstract: <http://www.croiconference.org/sessions/tenofovir-alafenamide-taf-single-tablet-regimen-initial-hiv-1-therapy>  
Webcast: <http://www.croiwebcasts.org/console/player/25755>
2. Sax P et al. Renal and bone safety of tenofovir alafenamide vs tenofovir disoproxil fumarate. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Oral late breaker abstract 143LB.  
Abstract: <http://www.croiconference.org/sessions/renal-and-bone-safety-tenofovir-alafenamide-vs-tenofovir-disoproxil-fumarate>  
Webcast: <http://www.croiwebcasts.org/console/player/25797>
3. Pozniak A et al. Safety of tenofovir alafenamide in renal impairment. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Poster abstract 795.  
Abstract: <http://www.croiconference.org/sessions/safety-tenofovir-alafenamide-renal-impairment>
4. Eisenberg EJ, He GX, Lee WA. Metabolism of GS-7340, a novel phenyl monophosphoramidate intracellular prodrug of PMPA, in blood. Nucleosides Nucleotides Nucleic Acids. 2001 Apr-Jul;20(4-7):1091-8. doi: 10.1081/NCN-100002496. <http://www.ncbi.nlm.nih.gov/pubmed/11562963>.
5. Markowitz M, Zolopa A, Ruane P, et al. GS-7340 demonstrates greater declines in HIV-1 RNA than TDF during 14 days of monotherapy in HIV-1 infected subjects. 18th CROI; 27 February – 4 March 2011; Boston, MA. Late breaker oral abstract 152LB.

## Pipeline ART: maturation inhibitors and an attachment inhibitor

### Simon Collins, HIV i-Base

**Several studies at CROI 2015 included tentative results using compounds from two new classes of drugs - maturation inhibitors and attachment inhibitors. These results will be especially important for people who already have reduced options due to drug resistance to existing classes.**



## Maturation inhibitors

Maturation inhibitors work at a late stage of viral replication, blocking protease cleavage and leading to the release of immature HIV that is not infectious.

Despite greater than 1.2 log reductions to the maturation inhibitor bevirimat in Phase 2 studies in responders, approximately 50% of participants had no response due to common naturally occurring polymorphisms at and around the codon 370 region in gag. It is therefore exciting that other companies are developing molecules that overcome this problem.

At CROI 2015, this included results from the first part of a Phase 2b, 10-day monotherapy study using BMS-955176 - a new maturation inhibitor from Bristol-Myers Squibb. [1]

BMS-955176 has greater potency (IC<sub>50</sub> 2-13 nM) compared to bevirimat, with potential for once-daily dosing. This dose-finding study randomised 60 participants who were predominantly (92%) treatment-naïve, to 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 120 mg (n=8 for each) or placebo (n=2, matched to each group).

Baseline characteristics across arms included median CD4 count of 437-539 cells/mm<sup>3</sup> and low viral load - from 3.6 - 4.1 log copies/mL. Participants were men (apart from one woman) and white (apart from three non-white).

At each of the three higher doses, comparable reductions of -1.4 logs were reported at day 10, which were sustained for a further week after drug was discontinued. Maximum median reduction in viral load was -1.7 log copies/mL in the 40 mg arm. Results were broadly similar for each group, irrespective of baseline gag polymorphisms associated with reduced activity to bevirimat.

Side effects reported by >5% of participants included headache, abnormal dreams, night sweats and diarrhoea, but were broadly similar between active and placebo groups and there were no discontinuations. No serious side effects or laboratory abnormalities were reported, other than two single cases of transient grade 3 neutropenia (one in each of the 80 mg and 120 mg groups). Phase 2b clinical studies are already planned to start Q2 2015 but these were not yet listed at [clinicaltrials.org](http://clinicaltrials.org) when we went to press.

GSK also has maturation inhibitors in development. Although promising details on GSK 2578999 were presented at the Drug Resistance Workshop [2] this compound is not going forward [2] and preclinical information on a second compound, GSK 2828232 were presented in a poster at CROI 2015. [3]

GSK 2828232 had an IC<sub>50</sub> of 0.8-4.3 nM against a broad spectrum of 26 isolates covering a range of genotypes, and is not affected by previous PI-experience. Multiple-dose Phase 1 studies in HIV negative volunteers looking at food and drug interactions and safety have either already been conducted or are ongoing.

## Attachment inhibitor: fostemsavir

There are already two approved ARVs that support the efficacy of blocking viral entry: maraviroc which is a CCR5 coreceptor inhibitor and enfuvirtide (T-20) which blocks gp-41, but which is now rarely used.

At CROI 2015, 48-week results were presented from an ongoing Phase 2b dose-ranging study of fostemsavir (formerly BMS-663068), a gp-120 blocker from Bristol-Myers Squibb. [4]

Earlier reports from this study included approximate viral load reductions of 0.7 to 1.5 log copies/mL after 7 days of monotherapy (ten patients per arm), and broadly similar viral efficacy across arms for the week 24 primary endpoint (approximately 50 participants per arm).

The study randomised 251 treatment experienced participants to one of four doses of fostemsavir (groups 1-4: 400 mg or 800 mg twice-daily, or 600 mg or 1200 mg once-daily), with a control group taking atazanavir/ritonavir (300 mg /100 mg). All participants also received tenofovir DF (300 mg once-daily) and raltegravir (400 mg twice-daily).

Baseline characteristics were similar between groups. Median age was 39 years, 60% were male and 38% were white. Median CD4 and viral load was 230 cells/mm<sup>3</sup> (with 38% <200) and 4.85 log copies/mL (with 43% >100,000), respectively. Approximately 50% of participants had virus with at least one major mutation associated with NRTI, NNRTI or PI resistance.

In the modified intent-to-treat (mITT) analysis (FDA Snapshot), the percentage of patients with viral load <50 copies/mL was 82%, 61%, 69% and 68% in groups 1-4 respectively, compared to 71% in the control. Using a cut-off of <400 copies/mL, the results were 86%, 76%, 84% and 80% vs 75%, respectively.

Response rates from people with baseline viral load above vs below 100,000 copies/mL were lower in all arms but similar to the atazanavir/r control group. There were no significant differences between active and control groups for CD4 responses or safety results other than those already associated with atazanavir/r.

Responses in the fostemsavir groups were not affected by baseline IC<sub>50</sub> and this will not be an exclusion criterion in future studies. Two other posters at CROI 2015 included new results on this compound.

The first was a modeling study, supported by clinical and virological results from which BMS has selected the 600 mg twice-daily dose to go forward for further studies. [5]

The second poster reported that no dose adjustment was needed when fostemsavir was taken with both darunavir/ritonavir and etravirine together, because the approximately 50% increase in level of fostemsavir from the boosted-PI was roughly compensated by the 50% reduction caused by the NNRTI. [6]

## References

Unless stated otherwise, all references are to the Programme and Abstracts of the 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle, Washington, USA.

- Hwang C et al. Antiviral activity/safety of a second-generation HIV-1 maturation inhibitor. CROI, 23-26 February 2015, Seattle. Oral late breaker abstract 114LB.  
Abstract: <http://www.croiconference.org/sessions/antiviral-activity-safety-second-generation-hiv-1-maturation-inhibitor>  
Webcast: <http://www.croiwebcasts.org/console/player/25756>
- Tang J et al. GSK2578999, an HIV-1 maturation inhibitor with improved virology profile against Gag polymorphisms. XXIV International Drug Resistance Workshop, 21-22 February 2015, Seattle. Oral abstract 63.
- Jeffrey J et al. GSK2838232, a second generation HIV-1 maturation inhibitor with an optimized virology profile. CROI, 23-26 February 2015, Seattle. Poster abstract 538.  
<http://www.croiconference.org/sessions/antiviral-activity-safety-second-generation-hiv-1-maturation-inhibitor>
- Thompson M et al. Attachment inhibitor prodrug BMS-663068 in ARV-experienced subjects: week 48 analysis. CROI, 23-26 February 2015, Seattle. Poster abstract 545.  
Abstract: <http://www.croiconference.org/sessions/attachment-inhibitor-prodrug-bms-663068-arv-experienced-subjects-week-48-analysis>  
Poster: <http://www.croiconference.org/sites/default/files/posters-2015/545.pdf> (PDF)
- Savant Landry I et al. HIV-1 Attachment inhibitor prodrug BMS-663068: model-based dose selection. CROI, 23-26 February 2015, Seattle. Poster abstract 509.
- Savant Landry I et al. HIV-1 attachment inhibitor prodrug BMS-663068: interactions with DRV/r and/or ETR. CROI, 23-26 February 2015, Seattle. Poster abstract 523.

## CROI 2015: PREVENTION

## No HIV transmissions between gay couples when viral load is undetectable: preliminary results from “Opposites Attract” study in Australia, Thailand and Brazil

Simon Collins, HIV i-Base

**Preliminary results from a prospective observational study in serodifferent gay couples reported no linked HIV transmissions when the HIV positive partner had an undetectable viral load, even when not using condoms. [1]**

This was from an interim prespecified analysis, but the findings are important for adding to those from the European PARTNER study that were presented at CROI last year. [2]

By December 2014, the Opposites Attract study had enrolled 234 couples in Australia (n=135), Bangkok (n=52) and Rio de Janeiro (n=47) who were already not using condoms. As with the PARTNER study, phylogenetic analysis is used to determine whether any new infections are linked to the HIV positive partner.

Only limited results were included in the poster on baseline characteristics of participants, but mean age was 36 (no SD given), and couples had been together for <12 months (39%), 1-5 years (33%) and >5 years (28%).

This analysis contained results from 150 couple years of follow up (CYFU) with only 91/150 from when condoms were not used. 152 couples contributed to follow-up 43% of which (n=65) were open relationships and 88/150 who had condomless sex. Unlike the PARTNER study, not all HIV positive people were on treatment: only 84.2% were on treatment at baseline and overall viral load was undetectable (<200 copies/mL) in 82.9%. Also at baseline, STI prevalence (details not given) was 11% and 6% in the positive and negative partners respectively.

No linked HIV transmissions were reported from 5905 times in 88 couples when condoms were not used (based on reports from the negative partner), with upper limit of 95% confidence intervals of the annual HIV incidence rates ranging from 2.46 to 6.46 per 100 couple years of follow up (CYFU). By comparison this upper limit was 184.31 when viral load was detectable at >200 copies/mL. See Table 1.

**Table 1: HIV incidence in interim analysis of Opposites Attract**

Type of condomless (CL) anal sex	New linked transmissions	Couple years of follow up (CYFU)	No. of acts	Incidence rate (95% CI)
Overall	0	150	5905	0 (0 to 2.46)
Any CL	0	91	5905	0 (0 to 4.06)
Insertive	0	78	3569	0 (0 to 4.74)
Receptive	0	57	2337	0 (0 to 6.46)
Any when VL <200 c/mL	0	89	5656	0 (0 to 4.16)
Any when VL >200 c/mL	0	2	237	0 (0 to 184.31)

### C O M M E N T

This is good news, even though it is from a very short follow-up time.

Based on the limited data so far, the Opposites Attract study is reporting that although there were no linked transmissions, there is 95% confidence that the real risk is that 0 to 6.5/100 men could become HIV positive over a year. This is from being the receptive partner and based on having sex without condoms an average of 67 times a year. However, using a one-side confidence interval, there is also a 5% (1 in 20) chance that the real risk is above 6.5/100 men per year.

By comparison, the results from the PARTNER study, reported a much smaller upper risk of 2.7/100 men based on receptive sex (with ejaculation, slightly lower without) over the same time period. The lower estimate is because the PARTNER study contains a much larger number of years of observation of men having condomless sex. Because PARTNER uses a two-sided confidence interval there is a 2.5% (1 in 40) chance that the real rate could be higher than the upper confidence limit of 1.7/100 men per year.

This detail is important for explaining why the headline result of finding zero linked transmissions means very different things in each study.

Continued follow up is important in both studies for defining a similar level of confidence in the level of risk for gay men as the PARTNER study already reported for heterosexual couples. Of interest, the Opposites Attract study includes a sub study looking at viral load in semen. [3]

In Europe, this follow-up continues in the PARTNER 2 study, which is currently looking to enrol an additional 530 gay couples from 2014-2017. Support from doctors and researchers to help this enrolment is important and new patient materials, including leaflets and posters, are now available. [4]

#### References

1. Grulich AE et al. HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Late breaker poster 1019 LB.  
<http://www.croiconference.org/sessions/hiv-transmission-male-serodiscordant-couples-australia-thailand-and-brazil>
2. Rodger A et al. HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. 21st CROI, 3-6 March 2014, Boston. Oral late breaker abstract 153LB.  
<http://www.croiwebcasts.org/console/player/22072>  
See report in HTB March 2014 for details of exposure risks and confidence intervals.  
<http://i-base.info/htb/24904>
3. Opposites Attract study website.  
<http://www.oppositesattract.net.au>
4. PARTNER 2 study website.  
<http://www.cphiv.dk/PARTNER-2>

## PrEP reduced HIV risk by at least 86% in PROUD: no transmissions likely from people taking meds

**Simon Collins, HIV i-Base**

**PrEP works in the UK. Taking a daily antiretroviral pill dramatically reduced the risk of HIV transmission for gay men and transgender women at high risk. There was little evidence of risk compensation.**

Results from the PROUD study were included in one of the opening oral sessions at CROI 2015 looking at HIV prevention, and presented by Professor Sheena McCormack from the UK Medical Research Council Clinical Trials Unit (MRC CTU) at University College London. [1] Other important PrEP studies followed immediately after.

Four months ago, the PROUD study made news when early and unexpected efficacy results prompted the researchers to change the trial design. [2] The study was planned to continue for two years after randomising 545 gay men to either immediate PrEP (daily oral tenofovir/FTC) or to PrEP that was deferred for a year. All participants received sexual health advice to reduce their risks for HIV.

In October 2014, the independent data and monitoring committee (IDMC) recommended that all participants should be offered immediate PrEP. This was because significantly more people were becoming HIV positive in the deferred group. Much earlier than expected, PROUD showed that PrEP was highly effective.

### Efficacy results at CROI

Detailed results were presented on the numbers of people who became positive in each study group and the relative protection from PrEP, together with information about adherence and risk behaviour on PrEP.

As the PROUD study is still ongoing, results for this analysis were presented up until the January 2015 extract of the data.

Study retention was good, with 523/545 (96%) of participants contributing towards 453 person years of follow up (PYFU). Rates of follow-up time that came from each group were also similar: 92% (239/261 person-years) for the immediate PrEP group and 88% (214/242) for the deferred group.

Overall, 22 participants became HIV positive during the study: 3 in the immediate PrEP group and 19 in the deferred arm. This gave HIV incidence rates of 1.3 vs 8.9 per 100 PYFU in the immediate vs deferred arms, respectively, and a difference in HIV incidence between the two groups of 7.6 per 100 PYFU (90% CI 4.1-11.2). The rate difference is important for calculating the number needed to treat (NNT) for one year to prevent one infection. This is used when calculating cost effectiveness and in PROUD the NNT was only 13 (90%CI: 9-25).

These results were highly significant, with PrEP reducing the risk of HIV by 86% (90% CI 58% to 98%) compared with no-PrEP, ( $p=0.0002$ ).

Summary details were presented for the three participants who became HIV positive in the immediate PrEP arm that suggested that they were unlikely to be taking PrEP at the time they were infected.

One participant was diagnosed at week 4, raising the possibility that he could either have been seroconverting as he entered the study, or was infected prior to achieving steady state drug levels. Although the participant was HIV negative at enrolment, PCR sampling at study entry was not possible due to a lack of sampling at that time point. As the study was designed to mimic real world use, enrolment was based on negative Ag/Ab testing and PCR samples were not collected.

The two other participants were both HIV negative at enrolment but were not in contact with their clinic for extended periods of time. So they were unable to renew their prescriptions, which were given for the first month, and then three-monthly thereafter. One participant did not return for 14 months, at which point he tested HIV positive. The other was still HIV negative at month 3, but then did not return until month 12 when they presented with seroconversion symptoms indicating a recent infection.

In the deferred arm, six participants were diagnosed at their first test during follow-up, so HIV transmission could have occurred prior to enrolment. The remaining 13 were diagnosed after having had at least one further HIV negative test.

### PEP use - before and during the study

At baseline, one third of participants (184/545) had used Post Exposure Prophylaxis (PEP) in the previous year and 17 people had used PEP more than once. PEP involves taking a combination of HIV meds for a month that includes the same drugs (tenofovir/FTC) that are used as PrEP.

During the study, 13/276 (5%) participants in the immediate PrEP group were also prescribed PEP. This was reported as generally being related to a risk of exposure during low/no PrEP adherence.

In the deferred PrEP group, 83/269 (31%) participants used PEP at least once, with a total of 174 prescriptions. Assuming that PEP was taken, this accounts for 14 PYFU when the deferred group was effectively on PrEP via PEP.

It appeared to be rare for people in the deferred arm to access PrEP, but this did occur, including one case that was supported by a drug level test.

Despite the use of PEP and occasional access to PrEP, infection rates were still significantly higher in the deferred arm.

### Adherence and risk compensation

Adherence was estimated in several ways, but these are all indirect calculations. Although monthly self-reported questionnaires included both adherence and behaviour risk these were not reported consistently enough to enable overall adherence assessments.

Adherence data is also difficult to interpret because some people adjusted PrEP use to reflect a more real-world setting. If someone's circumstances and perceived need for PrEP changed, they still remained in the study. For example, if someone stopped being sexually active or their relationship changed, this might involve extended periods when PrEP was not taken.

Based on prescription records, the average adherence in the PrEP arm could not have been higher than 86%. But this is an estimate and the prescription records also show that 14 people (5%) in the immediate group never started PrEP.

Another calculation from prescription records reported that sufficient PrEP was prescribed to only enable 56% of people to be 100% adherence. This is also problematic as 100% adherence is not even needed to provide good protection. Many people on ART are close to 100% adherent and so this is likely to be possible for some people on PrEP. It may nevertheless be helpful for people to understand that missing occasional doses may have little impact on their level of protection.

More importantly, adherence seems to have been high enough in the study not to have caused new HIV infections in the PrEP group.

The difficulty of collecting information from questionnaires meant that information on whether PrEP led to people being at higher risk of

HIV through behaviour changes is inferred indirectly from the rates of STIs reported during the study.

Consistent with baseline history, STIs were commonly reported during the study with slightly higher rates in the immediate vs deferred groups (57% vs 50%). But when looking at STIs related to HIV risk from not using a condom (notably rectal gonorrhoea and chlamydia), the difference was not statistically significant (35% vs 32%). However, the number of sexual health screens was also higher in the immediate PrEP group (974 vs 749) because of more frequent clinic visits. Nevertheless, because STI rates were similar in both groups, this can be used as an indirect measure that behaviour might not have been very different in each group.

### Safety and drug resistance

There were few reports of side effects. Of the 28 people who stopped treatment because of a medical event, only 13/28 were due to an event considered related to PrEP. Of these, 11/13 restarted PrEP. Two individuals interrupted due reduced markers of kidney function.

Of six participants whose HIV test was positive at the time of starting PrEP, 3/6 developed an M184I or M184V mutation associated with FTC resistance. All three participants were likely to have been seroconverting when they started PrEP.

There were no cases of the K65R mutation associated with tenofovir resistance.

### Baseline characteristics

The study recruited gay men in their thirties who were predominantly white, educated and employed. Baseline demographics include median age 36 (IQR: 30-43), ethnicity: white (79%), mixed (4%), Asian (4%), black (3%), Chinese (2%), Irish (2%) and other (5%); education level: 60% at university degree level or above, 17% to A-level.

Most men were in full-time (72%) or part-time (9%) employment and 8% were unemployed (11% other or no answer). Almost half (46%) were in an ongoing relationship and 30% were living with a partner. The median number of partners (for anal sex) in the previous three months was 10 (IQR: 4-20) with median of 2 (IQR: 1-5) and 3 (IQR: 1-7) times for receptive and insertive anal sex respectively.

HIV awareness was high with participants having had a median of three HIV tests in the previous year and a third had used post exposure prophylaxis (PEP). Baseline STI history in the previous year highlighted their risk of HIV (rectal gonorrhoea 27%, rectal chlamydia 22% and syphilis 11%). At baseline, approximately 5% of participants tested had each of rectal gonorrhoea, chlamydia and syphilis. These and other baseline data have been previously presented. [3]

Further details of these results, including a Q&A document from the researchers is on the PROUD website. [4]

i-Base has also produced a nontechnical Q&A resource on these results. [5]

*Simon Collins is involved in the PROUD study as a community representative.*

## COMMENT

**The high HIV incidence in the PROUD study - far higher than the 3.0 per 100 PYFU expected - is important for precisely demonstrating that it is possible to identify people who can benefit from PrEP.**

**The results - together with those from the French IPERGAY study**

**that were presented immediately afterwards [6] - do not support widespread access to PrEP, but they do support early access for those at high risk.**

**The strength of the PROUD results support the growing need for the NHS to rapidly offer PrEP as an option to people at highest risk of HIV infection. Approximately 6000 people are diagnosed with HIV every year. This is equivalent to 500 every month or 16 every day. None of these people currently have access to PrEP.**

**The preoccupation of some policy professionals with behaviour changes - termed "risk compensation" - was one of the motivations for this pilot study rather than general early access. As with other PrEP studies, PROUD has provided evidence to allay this concern. In contrast to other PrEP studies, this is from randomised data.**

**Once efficacy is established, "risk compensation" is not used as any additional barrier use to limit access to other medicines. No one deliberately sets out to become HIV positive.**

**If anything, the very high level of protection against HIV suggests that PrEP can enable people to reduce the need for condoms, when STIs and pregnancy are not a concern.**

**The PROUD study will continue follow up until 2016, with all participants now having the chance to access PrEP.**

### References

1. McCormack S et al on behalf of the PROUD Study. Pragmatic open-label randomised trial of preexposure prophylaxis: the PROUD study. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle, Washington, USA. Oral late breaker abstract 22LB.  
Slides: [http://www.proud.mrc.ac.uk/pdf/PROUD\\_CROI%202015\\_Final.pdf](http://www.proud.mrc.ac.uk/pdf/PROUD_CROI%202015_Final.pdf) (PDF)  
Abstract: <http://www.croiconference.org/sessions/pragmatic-open-label-randomised-trial-preexposure-prophylaxis-proud-study>  
Webcast: <http://www.croiwebcasts.org/console/player/25539>
2. Collins S. UK PROUD study to provide PrEP to all participants earlier than expected: planned follow-up to continue to two years. HTB November/December 2014. <http://i-base.info/htb/27593>
3. Antonucci S et al. The UK PROUD PrEP Pilot Study: a baseline analysis. 20th International AIDS Conference (AIDS 2014), 20-25 July 2014, Melbourne. Poster abstract THPE197.  
<http://pag.aids2014.org/abstracts.aspx?aid=7659>
4. PROUD Results Key Messages and Q&A, to be used as a supplement to: PROUD key messages, Q&A and further HIV PrEP trial information.  
<http://www.proud.mrc.ac.uk>
5. HIV i-Base. Q&A on results from the PROUD study (February 2015). <http://pag.aids2014.org/abstracts.aspx?aid=7659>
6. Molina JM et al. On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial. CROI 2015. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle, Washington, USA. Oral late breaker abstract 23LB.  
Abstract: <http://www.croiconference.org/sessions/demand-prep-oral-tdf-ftc-msm-results-anrs-ipergay-trial>  
Webcast: <http://www.croiwebcasts.org/console/player/25540>

**"On demand" PrEP dosing in IPERGAY: 86% reduced risk of HIV, no transmissions with active drug use**

**Simon Collins, HIV i-Base**

**Just as eagerly awaited as the PROUD study, the second oral**



**presentation on PrEP at 2015, with results that are equally important, were presented by Jean Michel Molina from the University of Paris Diderot. [1]**

The French/Canadian approach to PrEP was to study a new “on demand” dosing strategy which was individualised to the times people had sex. So while daily PrEP has theoretical benefits for optimal drug levels, maintaining continuous prophylaxis protection, this may involve greater drug exposure than many people need.

**“On demand” dosing**

A more flexible dosing option, if proved to have similar efficacy, would relax the need for daily adherence, and in the short-term (until generic PrEP is available) has the potential to reduce the cost. This would have a similar impact on cost effectiveness calculations, especially for people who have lower HIV risk.

The dosing regimen in IPERGAY involved taking a double dose of tenofovir/FTC (i.e. two pills) before having sex. The window period for this pre-exposure dose was from 24 hour to two hours before sex. Single doses of PrEP were then taken every day for each day that the participant continued having sex without a condom. A single dose was taken on the day after the last risk exposure. For someone who was only at risk from one exposure a month, this would be considerably different compared to daily PrEP. For a person who was sexually active once a week, their dosing would approach daily PrEP.

The strength of the IPERGAY study was the potential to discover a cheaper and more flexible way to use PrEP. The double-dose strategy was developed from earlier macaque research. [2] However, the choice of using a randomised study design that included a placebo, coming after the effectiveness of PrEP had already been established, might have been a factor that limited enrolment (less than half the predicted study numbers were enrolled when the DSMB-recommended changes to IPERGAY took place in October 2014, following early efficacy findings in the PROUD study). [3, 4]

**Enrolment and baseline characteristics**

IPERGAY screened 445 participants and randomised 414 to either active tenofovir/FTC (n=206) or placebo (n=208). The modified Intent-To-Treat (mITT) analysis included 199 and 201 participants respectively, based on seven people in each group not receiving study drug (due to withdrawn consent, lost to follow up or they were found to be HIV positive). The final analysis included 176 (88%) and 177 (88%) participants, respectively.

Baseline characteristics were well matched between groups and included: median age 35 years (IQR: 29-43), >90% white, ~90% completed secondary education, 85% employed, ~80% single, 20% circumcised, 46% psychoactive drug use (in previous year). Participants in each group had median 8 (IQR: 5-15) partners in the previous 6 months. The only slight differences were that PEP had been used by 28% of the active vs 37% of the placebo group and recent STI were in 22% vs 29% of participants, respectively.

**Study results**

Over a mean follow-up of 13 months, there were 16 cases of new HIV transmission: 2 in the active arm (incidence 0.94 per 100 PY) and 14 in the placebo group (incidence 6.6 per 100 PY). This resulted in an 86% reduction in the incidence of HIV (95% CI: 40 to 99), p=0.002. The number needed to treat (NNT) for one year to prevent an infection was 18.

Importantly, both transmissions in the active arm had not been using PrEP for many months and were both still sexually active.

**Adherence and safety**

Adherence reported by pill count was similar with median 16 pills/month in each group (IQR: 12-24 in active and 10-23 in placebo), p=0.84. PEP was used by 48 participants (12%) and was similarly balance (13% vs 11%), p=0.73.

Adherence patterns by month looked heterogeneous for individuals in both arms - with some months reporting low use and some months almost daily use, reflecting the potential for real life on demand use. When participant recall was reported, PrEP was used correctly for 43% (range 35-51) of times of last sexual experience (1212 times assessed in 319 participants). Suboptimal PrEP was reported 25% of the time and no PrEP was reported 25% of the time.

Tolerability was good with similar reports in active and placebo groups. For example, any side effect was reported by 92% vs 89%, with serious side effects in 9% vs 8%.

Side effects that were drug related were mainly nausea/vomiting or abdominal pain (13% vs 6%, p=0.013) but were generally mild. There was one safety report of deep vein thrombosis from a drug-drug interaction between tenofovir/FTC and dabigatran that resolved on discontinuation.

The only significant differences in laboratory abnormalities was Grade 1 creatinine increases in 14% vs 7% of active vs placebo group, p=0.042.

i-Base has also produced a nontechnical Q&A resource on the PrEP results from CROI. [5]

**C O M M E N T**

**Both IPERGAY and PROUD were notable not just for reporting very similar efficacy results - 86% reductions in HIV transmission in arms receiving active PrEP compared to control groups (with slightly different estimated confidence intervals) - but for reporting a high probability that none of the few infections in people randomised to the active PrEP arms were likely to be on PrEP at the time of their infections.**

**Both studies provided convincing results that dampened concerns about risk compensation (the idea the perceived protection from PrEP would lead people to change their level of behaviour risk).**

**As with other PrEP studies, it appears likely that the increased focus on HIV and sexual health that comes from engaging with a PrEP programme may in fact reduce their overall risk behaviour, and that this connection might have an additional prevention role in itself.**

**Both studies resulted in the lowest NNT of any PrEP studies so far: 13 in PROUD and 18 in IPERGAY.**

**Although efficacy was similar in both studies, most participants in IPERGAY were routinely using four or more doses a week. This correlates to the modelling data from iPrEX that suggests that four doses a week provided >96% protection for men.**

**Additional follow-up is needed to comment on whether the double-dose is sufficient when used much less frequently.**

**Additional follow up is also needed for the safety concern from routinely using a double-dose over a longer time in people who are using this strategy on a weekly basis.**

## References

1. Molina JM et al. On demand PrEP with oral TDF-FTC in MSM: results of the ANRS Ipergay trial. CROI 2015. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle, Washington, USA. Oral late breaker abstract 23LB.  
Abstract: <http://www.croiconference.org/sessions/demand-prep-oral-tdf-ftc-msm-results-anrs-ipergay-trial>  
Webcast: <http://www.croiwebcasts.org/console/player/25540>
2. Garcia-Lerma et al. Intermittent prophylaxis with oral Truvada protects macaques from rectal SHIV infection. *Science Trans Med*, 2010, Jan 13;2(14):14ra4. doi: 10.1126/scitranslmed.3000391.  
<http://www.ncbi.nlm.nih.gov/pubmed/20371467>
3. Collins S. IPERGAY PrEP study shows early efficacy in protecting gay men from HIV: all participants to switch to active drug. (29 October 2014).  
<http://i-base.info/ipergay-prep-study-shows-early-efficacy-in-protecting-gay-men-from-hiv>
4. ANRS press release. A significant breakthrough in the fight against HIV/AIDS: A drug taken at the time of sexual intercourse effectively reduces the risk of infection. (29 October 2014).
5. HIV i-Base. Q&A on results from the PROUD study (February 2015).  
<http://pag.aids2014.org/abstracts.aspx?aid=7659>

## Other HIV PrEP studies at CROI 2015: implementation of oral PrEP and problems with tenofovir gel

### Simon Collins, HIV i-Base

**Although the headline PrEP news at CROI 2015 went to the PROUD and IPERGAY studies (see reports above), important additional PrEP trials covered implementation and alternative dosing with oral PrEP and disappointing news that tenofovir gel was not effective in African women.**

Raphael Landovitz set the context for the meeting in a plenary lecture about oral PrEP including implementation scale-up, especially the initially low but now increasing uptake in the US. [1]

This included reference to the difference pharmacokinetics of tenofovir and FTC with 10-100 fold higher tenofovir exposures in rectal compared to cervico-vaginal tissue. This suggests that the adherence requirement may be higher for women (6/7 doses/week) compared to men (when >4 doses/week still confers high level protection).

Referring to the heat map modelling by Abbas et al showed that the population effect on reducing infections seen in high effectiveness studies is not reduced even if risk behaviour increases, [2] noting the risk compensation has not been reported from randomised PrEP trials, including in open-label studies.

Also drug resistance has generally been rare (~2% of infected, 0.06% of exposed) in studies with frequent clinic attendance, this is due to either sufficiently high adherence to protect against infection or sufficiently low adherence to not provide selective pressure. As expanded access to PrEP involves less frequent HIV testing in real life settings, monitoring is warranted for the higher risk of resistance from continuing (or returning) to use PrEP after occult HIV infection and prior to diagnoses (~25%).

The time for daily dosing to reach protective levels has been estimated as needing five days for men to reach 99% protection for rectal exposure (95% CI: 69% to 100%) and that after reaching steady state, protection might be maintained (in men) at >90% for seven days, but dramatically drops thereafter. [3]

In contrast, it is likely to take three weeks of daily dosing for women to reaching estimated protective levels.

Although side effect reports have been low in clinical studies, this is also in the context of low adherence and therefore much lower actual drug exposure.

This talk noted the tremendous potential for PrEP to become new options that HIV negative people can use to take control of their protection against HIV.

### PrEP as a bridge to ART in serodifferent couples

Jared Baeten from the University of Washington, presented important results from using short-term PrEP as a "bridge" by HIV negative partners in serodifferent couples until the HIV positive partner started ART, and for six months (or longer) after. [4]

The Partners Demonstration Project enrolled more than 1000 serodifferent high risk heterosexual couples in Kenya and Uganda between November 2012 and August 2014. Based on a population incidence of 5.3/100 person-years (95% CI: 3.2 to 7.6), approximately 20 new infections were expected.

However, up until July 2014, only one incident HIV infection was reported from 440 person-years of follow-up. This was an observed HIV incidence of 0.2/100 person-years (95% CI: 0.0 to 1.3),  $p < 0.0001$  vs predicted. During the 440 person-years of follow-up, PrEP was used 47% of the time, ART 17%, both 25%, and neither 11%.

The single transmission occurred with evidence of low PrEP adherence and in the absence of ART.

The potential benefit from PrEP as a bridge during the first six months of ART was also reported in a poster from the Partners PrEP study, based on transmission risks during three periods: (1) after diagnosis while eligible for ART but not on ART; (2) during the first six months that the positive partner was on ART; and (3) when the positive partner had been on ART for >6 months. [5]

During 510 person-years of follow-up for negative partners in periods 1, (175 PY), 2 (168 PY) and 3 (167 PY), there were 3 phylogenetically linked HIV infections in each of groups 1 and 2 and no HIV infections in group 3. The numbers of sex acts was roughly comparable between groups, as was the generally high reported use of condoms (~90-92% of times).

HIV incidence (95% CI) was 1.71 (0.35 to 5.01), 1.79 (0.37 to 5.22) and 0.00 (0.00 to 2.20) per 100 person-years, in groups 1, 2 and 3, respectively.

Details were not provided on whether unlinked infections occurred, although PrEP in the pre-ART and early ART periods would also provide protection from other partners.

### PrEP as public health strategy to reduce new infections in San Francisco

Robert Grant, from University of California San Francisco, provided an update on the recent use of PrEP in San Francisco and the potential impact on population rates of HIV transmission that included modeling data for reducing rates by 70%. [6]

Based on 2014 data, 94% of HIV positive people in San Francisco are diagnosed, 88%-91% are on (or have used) ART, 88% of those in care and 62% overall are virally suppressed. These rates have been stable for three years and PrEP use started to increase in 2013. From 2007 to 2013, annual diagnoses fell from 515 to 359 and HIV-related mortality fell from 515 to 359 and from 323 to 182.

Using public health data, population survey and results from clinical studies, the group modelled targets for future programmes. Of the estimated 50,000 HIV negative gay men in the city, approximately

one third (16,000) were thought eligible for PrEP based on not using condoms with two or more recent partners), and a third of these (5000 men) had used PrEP in the previous 12 months. PrEP use positively correlated with risk, with 63% of men in one survey reporting recent condomless sex having used PrEP.

The impact of PrEP was based on data from iPrEX-OLE, that reported 81% continued use of PrEP after 12 months, of whom 92% were adherent with >4 doses a week.

Modelling looked at PrEP uptake by 95% of those at risk achieved 70% reduction in expected new infections (to 125 a year), with 14,000 follow up years of PrEP use. Modelling greater roll out of treatment (from current 62% to target 90%) had additive benefits to bring annual diagnoses numbers to 100/year.

### Greater real-life coverage from daily vs alternative dosing in African women

The HPTN 067 ADAPT is an international study that was testing alternative dosing strategies for oral PrEP in the US, Thailand and South Africa. The full study includes MSM, transgender women and women who have sex with men who are at high risk of HIV. Results from the South African cohort of 191 African women in Cape Town were presented at CROI 2015 as a late breaker poster. [7, 8]

The study design include a five-week lead-in phase when all participants were prescribed daily oral PrEP, with one weekly dose being directly observed therapy (DOT) at the clinic. PrEP was not taken during week five, to assess drug levels and PK in plasma, BPMCs and hair samples (also collected at weeks 10 and 30). At week six, participants were randomised to one of three unblinded self-administered dosing groups, and followed for 24 weeks.

- 1) Continuing daily PrEP (D).
- 2) Twice-weekly PrEP plus a post-intercourse dose (T).
- 3) By exposure - taking PrEP before and after sex (E).

Behaviour/risk exposures were based on weekly telephone interviews. All participants also receive counselling for adherence support, risk reduction and condom advice plus free condoms and lube at baseline and throughout the study.

The study hypothesis was that non-daily PrEP would lead to greater overall protection with fewer side effects. To assess this, drug coverage was defined as >1 pill in the 4 days before and >1 pill taken in the 24 hours after sexual intercourse and adherence was defined as the percentage of pills taken (monitored by an electronic pill box).

Of 294 women screened in Cape Town, 7 (6.8%) were HIV positive (using a rapid test), 191 were enrolled, and 179 were randomized at week six (there were two further HIV positive results). Participants were generally young (median age 26 years, range 18-52), single (80% were unmarried) and not employed (83% unemployed).

Results were presented for each strategy at week 30. Over follow-up, there were significant differences in levels of sexual activity with approximately 2000, 1000 and 1500 events in the D, T and E groups, respectively ( $p=0.002$ ). Daily PrEP as a strategy resulted in significantly greater drug coverage of events (75%, 56% and 52%) and adherence (76%, 65% and 53%) D, T and E groups, respectively ( $p<0.001$ ). Drug levels at weeks 10 and 30 were also significantly higher with daily PrEP ( $p=0.03$  in plasma and 0.006 in PBMCs) although levels also dropped in all three groups by the end of the study, see Table 1.

Although it was not a study endpoint, there was no significant difference in new infections between the strategies, (1, 2 and 2 in the D, T and E groups respectively), although it is unclear if this was adjusted for numbers of exposures and/or PrEP coverage.

### Tenofovir gel fails to show efficacy in FACTS 001 study in South African women

Results from the randomised, double-blind, placebo-controlled Phase 3 study FACTS 001 study reported low efficacy of 1% tenofovir gel used pericoitally in 2059 young women (median age 23, IQR: 20 to 25) at nine rural and urban clinics in South Africa. [9]

As low adherence in the VOICE study had failed to show a protective benefit from daily use of the same gel, FACTS 001 included a specific focus on adherence.

The gel was provided in single-applicators and the dosing strategy involved a pre-dose (up to 12 hours before sex) and post dose (up to 12 hours after sex), with no more than one dose in any 24 hour period.

**Table 1: Drug coverage and adherence in HPTN 067 ADAPT study**

	Daily (D)	Twice-weekly-plus (T)	Pre-/post-sex (E)	p-value (across 3 groups)
n	60	59	60	
HIV infections	1	2	2	0.87 NS
No. of times people had sex (events)	1954	1078	1533	0.002
New HIV infections	1	2	2	NS
% events fully covered	75	56	52	<0.001
% of events partially covered (pre-only, post-only)	22 (21, 1)	39 (30, 9)	41 (33, 8)	<0.001
% events not covered	3	6	7	NA
Total pills needed	9758	3629	2295	<0.001
Total pills used	7441	2850	2002	<0.001
Total % adherence	76	65	53	<0.001
% detectable in plasma (if sex in prior 7 days): at weeks 10, 30	92, 79	86, 62	80, 53	0.03
% >9.1 fmol/106 target in PBMC: at weeks 10, 30	80, 65	50, 46	57, 32	0.006

This was an endpoint-driven study requiring 118 new HIV infections, powered to show 45% efficacy with an HIV incidence rate of 3.5/100 PY and allowing for 13% loss to follow up.

After approximately 3035 person years of follow up, there were 61 vs 62 infections in the gel vs placebo groups respectively, with the same incidence rate in each arm (4.0 per 100 PYFU; 95% CI: 3.1 to 5.2) and an Incidence Rate Ratio of 1.0 (95% CI: 0.7 to 1.4).

Several analyses were presented for whether this outcome was related to adherence or product effectiveness (given that positive results were reported in the CAPRISA 004 study).

Based on returned applicators, average adherence was reported as 75% overall, with participants using the gel for 50-60% of the time in both group. Only 13% of women were categorised as being highly adherent based on using the gel >80% of the times they had sex.

A nested case control study of participants in the tenofovir arm (56 cases, 158 controls) tested for tenofovir drug levels in quarterly cervical-vaginal lavage samples (1075 samples, median 5 (range 1-11) per person). Overall, 22% women had detectable levels at all visits, 65% at some, and 13% at no visits.

Importantly, detectable tenofovir levels were significantly associated with 52% reduction in HIV risk (aHR 0.48; 95% CI: 0.23 to 0.97,  $p=0.04$ ).

As comment, the conclusion emphasised that the study results showed that participants had actively engaged with this intervention but that better products were needed in order for women to be able to achieve sufficient protective drug levels.

#### References

Unless stated otherwise, all references are to the Programme and Abstracts of the 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle, Washington, USA.

<http://www.croiconference.org>

- Landovitz RJ. PrEP for HIV prevention: what we know and what we still need to know for implementation. Plenary lecture PL1. CROI 2015, 23-26 February, Seattle. Oral abstract 20.  
Abstract: <http://www.croiconference.org/sessions/prep-hiv-prevention-what-we-know-and-what-we-still-need-know-implementation>  
Webcast: <http://www.croiwebcasts.org/console/player/25535>
- Abbas UL et al. Potential impact of antiretroviral chemoprophylaxis on HIV-1 transmission in resource-limited settings. (19 September 2007). PLoS ONE 2(9): e875. doi:10.1371/journal.pone.0000875.  
<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0000875>
- Seifert SM et al. Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. Clin Infect Dis. (2015) 60 (5): 804-810. Published online: 18 November 2014. doi: 10.1093/cid/ciu916.  
<http://cid.oxfordjournals.org/content/60/5/804.abstract?sid=a7a28f55-8701-4084-af42-5ef9116af369>
- Baeten J et al. Near elimination of HIV transmission in a demonstration project of PrEP and ART. CROI 2015, 23-26 February, Seattle. Oral abs 24. Abstract: <http://www.croiconference.org/sessions/near-elimination-hiv-transmission-demonstration-project-prep-and-art>  
Webcast: <http://www.croiwebcasts.org/console/player/25541>
- Abstract: Mujugira A et al. HIV-1 transmission risk persists during the first 6 months of antiretroviral therapy. CROI 2015, 23-26 February, Seattle. Poster abstract 989.  
Abstract: <http://www.croiconference.org/sessions/hiv-1-transmission-risk-persists-during-first-6-months-antiretroviral-therapy>  
Poster: <http://www.croiconference.org/sites/default/files/posters-2015/989.pdf> (PDF)
- Grant RM et al. Scale-up of preexposure prophylaxis in San Francisco to impact HIV incidence. CROI 2015, 23-26 February, Seattle. Oral abstract 25.  
Abstract: <http://www.croiconference.org/sessions/scale-preexposure-prophylaxis-san-francisco-impact-hiv-incidence>  
Webcast: <http://www.croiwebcasts.org/console/player/25542>
- Bekker L-G et al. HPTN 067/ADAPT Cape Town: A comparison of daily

and nondaily PrEP dosing in African women. CROI 2015, 23-26 February, Seattle. Late breaker poster abstract 978LB.

Abstract: <http://www.croiconference.org/sessions/hptn-067adapt-cape-town-comparison-daily-and-nondaily-prep-dosing-african-women>

Poster: <http://www.croiconference.org/sites/default/files/posters-2015/978LB.pdf> (PDF)

- HPTN 067 ADAPT study website.

[http://www.hptn.org/research\\_studies/hptn067.asp](http://www.hptn.org/research_studies/hptn067.asp)

- Rees H et al. FACTS 001 Phase III trial of pericoital tenofovir 1% gel for HIV prevention in women. CROI 2015, 23-26 February, Seattle. Oral late breaker abstract 26LB.

Abstract: <http://www.croiconference.org/sessions/facts-001-phase-iii-trial-pericoital-tenofovir-1-gel-hiv-prevention-women>

Webcast: <http://www.croiwebcasts.org/console/player/25543>

#### CROI 2015: TREATMENT STRATEGIES

### Early HIV treatment and isoniazid prophylaxis: why TEMPRANO results do not yet support universal ART at CD4 >500 cells/mm<sup>3</sup>

Simon Collins, HIV i-Base

**The TEMPRANO study presented as an oral late breaker looked at timing of TB prophylaxis and the timing of ART in TB-endemic countries. Even though the study concluded that ART should be started at CD4 counts above 500, the results were to some extent historical and highlight the continued importance of the ongoing START study.**

TEMPRANO was sponsored by the French ANRS and conducted in nine clinics in Abijan, Ivory Coast. It used a 2x2 factorial design to look at both timing of ART and use of isoniazid preventive therapy (IPT) for TB. [1]

Although WHO guidelines recommend (IPT) to all HIV positive people, in resource-limited settings this is often limited by the difficulty of ruling out active TB and a concern for developing drug resistance. In TEMPRANO, early ART involved starting treatment at any CD4 count below 800 cells/mm<sup>3</sup> and WHO-ART was based on the current WHO guidelines.

Importantly for interpreting the results, the WHO guidelines changed the CD4 criteria for starting treatment during the course of the study from 200 (March 2008 to December 2009) to 350 (December 2009 to July 2012) and then to 500 (July 2012 to December 2014).

The study enrolled 2076 HIV positive adults with a CD4 count <800 cells/mm<sup>3</sup> who were not yet eligible for ART, and 2056 participants were included in the final analysis.

The four study arms were: (1) early-ART with IPT, (2) early-ART without IPT, (3) WHO-ART with IPT and (4) WHO-ART without IPT. The IPT was once-daily isoniazid (300 mg) for 6 months, starting one month after study entry. ART was tenofovir/FTC plus efavirenz or lopinavir/r; or plus AZT if coinfecting with HIV-2.

The primary endpoint was severe HIV-related morbidity. This was defined as all cause-mortality, any AIDS-defining event, severe bacterial diseases, and non-AIDS cancers. Other grade 3-4 morbidities were secondary endpoints.

Baseline criteria were balanced between arms and included: 78% women, median age 35 (IQR: 30-42), 90% were WHO stage 1 or



2, and 35% were positive for latent TB using Quanti-FERON IGRA test. Median CD4 count (cells/mm<sup>3</sup>) was 465 (IQR: 369-573) and was <350 in 21%, 350-500 in 38% and >500 in 41% of participants. Median viral load was 4.7 log copies/mL (IQR: 4.0-5.3) with 25% <10,000 copies/mL and 25% >120,000 copies/mL.

During a median follow-up time of 29.9 months (IQR: 29.9, 30.0), 597 (58%) of the WHO-ART arms started ART and 927 (90%) of the IPT arms used IPT and 94% of these (868/927) completed 6 months. Only 54 participants (2.6%) were lost to follow up.

There were significantly fewer events that independently favoured the use of early-ART (6.6% vs 11.4%,  $p=0.0002$ ) and IPT (7.2% vs 10.7%,  $p=0.005$ ), with a 44% reduction with early ART and a 35% reduction with IPT, see Table 1.

**Table 1: Severe morbidity in TEMPRANO study at 30 months**

	% events	n	Rate / 100 PY	adj HR	p
WHO ART	11.4%	111	4.9		
Early ART	6.6%	64	2.8	0.56	0.0002
No IPT	10.7%	104	4.7		
IPT	7.2%	71	3.0	0.65	0.005

Over 30 months there were 204 events and 47 deaths, see Table 2. The most common event was TB (85/204) with 41/85 in the WHO ART arm with no IPT. Half the TB events were pulmonary. Bacterial events (56/204) were largely pneumonia (23/56) or isolated bacteremia (13/56). There were very few AIDS-related cancers ( $n=5$ ), non-AIDS cancers ( $n=4$ ) or other serious non-AIDS events ( $n=7$ ).

In an analysis of participants who enrolled with a baseline CD4 count >500 cells/mm<sup>3</sup> (849/2056 participants), early ART was associated with a significant 44% reduced risk (10.1% vs 5.8%; aHR 0.56,  $p=0.03$ ). However, the 39% reduction with IPT (9.7% vs 6.1%; aHR 0.61,  $p=0.56$ ) was not statistically significant.

However, early ART was associated with a higher risk of the secondary endpoints of serious grade 3/4 events during the first six months of ART (aHR 1.92,  $p=0.007$ ). After six months, this was reduced compared to the WHO ART arm (aHR 0.74,  $p=0.03$ ). In the IBT analysis, there were no significant differences in grade 3/4 events either during the first six months (aHR 0.80,  $p=0.36$ ) or later (aHR 1.01,  $p=0.97$ ).

Of the 40 TB strains isolated during follow-up, 5/40 were resistant to isoniazid alone and 4/40 were multidrug resistant to at least isoniazid and rifampicin, with no significant difference by IPT arm.

Although the study concluded that starting ART with a CD4 >500

cells/mm<sup>3</sup> reduced HIV morbidity, the presenter did not clarify that much of the follow-up time was compared to waiting until CD4 counts <200 cells/mm<sup>3</sup>, which is already known to be suboptimal.

## COMMENT

**The TEMPRANO study is one of the key studies looking at treatment strategies and this seven year study is a significant achievement. However, understanding the comparator group in these results is essential before any conclusion can be made about starting ART at CD4 counts above 500 cells/mm<sup>3</sup>.**

This CD4 >500 analysis includes approximately 1200 people who were enrolled before January 2010 when the WHO guidelines still recommended deferring treatment until the CD4 counts dropped to 200 cells/mm<sup>3</sup>. [2] Although the study concluded that starting with a CD4 count >500 cells/mm<sup>3</sup> reduced HIV morbidity, this was against a comparator of <200 cells/mm<sup>3</sup> for much of the follow-up time. Further analysis is needed before any comment can be made on whether any benefit was seen compared to starting at 350 cells/mm<sup>3</sup>.

This further analysis is essential given that the ongoing international START study, with site in both developed and resource-limited settings, compares the risks and benefits of starting >500 to 350 cells/mm<sup>3</sup>, with results due in 2017. [3]

Importantly, TEMPRANO used three different deferral strategies, and only a limited number of people were randomised after the CD4 count for starting ART in the deferred arm was raised to 350 cells/mm<sup>3</sup>. Additionally, the presentation at CROI did not detail how closely participants in the deferral arm kept to the protocol. In earlier randomised controlled trials, including the Haiti trial [4], many people in the deferred arm started treatment at much lower CD4 counts than the protocol recommended, and led to increased HIV-related events at CD4 counts <200 cells/mm<sup>3</sup>.

It is important that the TEMPRANO and START research teams are working collaboratively to compare designs of the two studies, including applied deferral strategies, assessment of adherence to the strategy and endpoints. As part of this, START will be able to present additional analysis to the START Data and Safety Monitoring Board on sub groups in TEMPRANO that resemble the START design (i.e. >500 vs 350 cells/mm<sup>3</sup> analysis).

**Table 2: Breakdown of serious events in TEMPRANO study (n=2056)**

	Overall (n=2056)	WHO ART (n=511)	WHO ART + IBT (n=512)	Early ART (n=515)	Early ART + IPT (n=518)
Total events	204	75	60	41	28
All cause death	47	16	10	13	8
TB (pulmonary, disseminated)	85 (43, 42)	41 (20, 21)	16 (4, 12)	17 (11, 6)	11 (8, 3)
Bacterial	56	14	28	7	7
AIDS cancers	5	1	2	1	1
non-AIDS cancers	4	0	3	0	1
Other non-AIDS events	7	3	1	3	0

## References

1. Danel C et al. Early ART and IPT in HIV-infected African adults with high CD4 count (Temprano Trial). 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Oral late breaker abstract 115LB.  
Abstract: <http://www.croiconference.org/sessions/early-art-and-ipt-hiv-infected-african-adults-high-cd4-count-temprano-trial>  
Webcast: <http://www.croiwebcasts.org/console/player/25757?mediaType=slideVideo&>
2. TEMPRANO study cumulative enrolment.  
<http://mereva.isped.u-bordeaux2.fr/temprano/>  
[http://mereva.isped.u-bordeaux2.fr/temprano/html/temprano\\_documents/fichiers/Temprano%20study%20enrollment%20curve\\_20130109.pdf](http://mereva.isped.u-bordeaux2.fr/temprano/html/temprano_documents/fichiers/Temprano%20study%20enrollment%20curve_20130109.pdf) (PDF)
3. Strategic Timing of AntiRetroviral Treatment (START) study.  
<http://insight.cabr.umn.edu/start>
4. Severe P et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med* 2010; 363:257-265 (15 July 2010). DOI: 10.1056/NEJMoa0910370  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0910370>

## CROI 2015: WOMEN'S HEALTH

## Unintended pregnancies with levonorgestrel implant due to drug interactions with efavirenz-based ART

**Polly Clayden, HIV i-Base**

**Three unintended pregnancies in women with levonorgestrel sub-dermal implants, receiving efavirenz (EFV)-based ART in a pharmacokinetic (PK) study, were reported in a late breaker presentation at CROI 2015. [1]**

Preliminary data from this study, conducted in Uganda, were shown at the HIV Drug Therapy Glasgow Congress, 2014. [2,3] At 24 weeks EFV significantly decreased exposure to levonorgestrel – the active progesterone component of one commonly used contraceptive implant. Levonorgestrel concentrations in women receiving EFV-

based ART were approximately half of those in women not receiving ART, despite the EFV group having significantly lower body weight.

The final 48-week results were shown at CROI. Kimberly Scarsi presented the findings on behalf of investigators from University of Nebraska Medical Center, Makerere University, Uganda, and Liverpool University.

The study was a non-randomised, parallel group, PK evaluation comparing levonorgestrel concentrations in Ugandan women not yet eligible for ART (control group, n=17) and on stable EFV-based ART (n=20).

The women had a two-rod (75 mg/rod) levonorgestrel sub-dermal implant inserted at enrolment. Sampling for PK was performed before the implant and at 1, 4, 12, 24, 36 and 48 weeks after insertion. The investigators used a validated LC-MS/MS method, with an assay calibration range of 50-1500 pg/mL for the evaluation. PK data were reported as geometric means (GM) and GM ratio.

All participants were black Africans, with a mean age of 30 years at baseline. Women in the control group had a higher baseline body weight (73 kg) compared to those in the EFV group (59 kg),  $p < 0.01$ . Women in the EFV group had undetectable viral load for a median of 10 months (range 5-66) before study entry.

Levonorgestrel PK data are presented in Table 1. These data show a 45-57% reduction in levonorgestrel concentrations, starting with a rapid reduction in the first week and persisting throughout the study period. Levonorgestrel AUC was reduced by 48%.

There was considerable interpatient and inpatient variation in levonorgestrel concentration: coefficient of variation, respectively 43% and 26%.

Dr Scarsi noted that although PK was the primary objective of this evaluation, three (15%) unintended pregnancies occurred in the EFV arm during the study period (none in the controls). Two were identified at week 48 visit – after which the EFV arm was closed – and one at an early discontinuation visit.

**Table 1: Levonorgestrel pharmacokinetic results (pg/mL and GM with 90% confidence interval)**

Week	Control group (n=17)	EFV group (n=20)	EFV:control GM ratio
1	1070 (783 – 1356)	462 (370 – 553)	0.43 (0.41 – 0.47)
4	667 (541 – 792)	359 (280 – 473)	0.54 (0.52 – 0.55)
12	590 (475 – 704)	327 (268 – 385)	0.55 (0.55 – 0.56)
24	528 (423 – 633)	280 (212 – 348)	0.53 (0.50 – 0.55)
36	618 (520 – 716)	279 (149 – 409)	0.45 (0.29 – 0.57)
48	580 (477 – 684)	247 (209 – 285)*	0.43 (0.42 – 0.44)
AUC**	22.24 (18.55 – 25.92)	11.60 (9.38 – 13.83)	0.52 (0.51 – 0.53)

\* n=11, excludes 2 pregnant women and 6 who did not reach week 48 because arm closed; \*\*AUC 0-36 wk (ng\*wk/mL). AUC = area under the curve.

**Table 2: Levonorgestrel concentrations in unintended pregnancies (pg/mL)**

Week	Pregnancy 1	Pregnancy 2	Pregnancy 3
1	693	501	185
4	631	411	201
12	348	363	125
24	297	268	150
36	299	303	122
Pregnancy identified	Wk 48 (2 weeks post conception)	Wk 48 (10 weeks post conception)	Wk 43 (2 weeks post conception)

The proposed levonorgestrel threshold for efficacy – based on historical data – is 180 pg/mL. Levonorgestrel concentrations for the three women who became pregnant during the study are shown in Table 2. The highest levonorgestrel concentration at which a woman became pregnant in the study was 303 pg/mL. Fifteen out of 20 participants (75%) in the EFV arm (none of the controls) had levonorgestrel concentrations below this threshold.

#### C O M M E N T

**EFV induces cytochrome P450 3A4, giving the potential for drug-drug interactions with concomitant medications. Levonorgestrel is primarily metabolised by cytochrome P450 3A4, because of this, manufacturers and guidelines recommend avoiding co-administration with medications known to induce this pathway. So perhaps the results are not surprising.**

**That the proposed threshold for levonorgestrel efficacy (180 pg/mL) was inadequate in this study population is particularly worrying.**

**These data support a previous retrospective study of unintended pregnancies with levonorgestrel use in a low-income country: 12.4% (15/121) in women receiving EFV-based ART vs 0% (0/208) in those receiving NVP-based. [4]**

**Dr Scarsi rightly remarked: “Effective contraception for women on EFV-based ART is a public health priority.” She recommended that health workers discuss the risk of unintended pregnancy with women in this situation and other methods of contraception in the short term.**

**But she noted that sub-dermal implant use is continuing to rise: in sub Saharan Africa the procurement increased from 1 million to 5 million purchases in 2013.**

**It is vital that novel sub-dermal dosing strategies to use with EFV are explored as it is likely that similar effects on levonorgestrel levels might be observed with lower doses of EFV (e.g. 400 mg OD). However, more data to confirm this are warranted.**

**This serious interaction is another reason to consider alternatives to EFV first line and appropriate trials must be designed and funded to generate sufficient data to support future guideline changes for low-income countries (particularly with dolutegravir-based regimens).**

#### References

1. Scarsi K et al. Levonorgestrel implant + EFV-based ART: unintended pregnancies and associated PK data. CROI 2015. Seattle, Washington. 23-26 February 2015. Oral abstract 85LB.  
<http://www.croiconference.org/sessions/levonorgestrel-implant-efv-based-art-unintended-pregnancies-and-associated-pk-data>
2. Scarsi K et al. Efavirenz- but not nevirapine-based antiretroviral therapy decreases exposure to the levonorgestrel released from a sub-dermal contraceptive implant. HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Oral abstract 0131. Journal of the International AIDS Society 2014, 17(Suppl 3):19484.  
<http://www.jiasociety.org/index.php/jias/article/view/19484>
3. Clayden P. Efavirenz decreases exposure to hormonal contraceptive implant. HTB. 1 December 2014.  
<http://i-base.info/htb/27624>
4. Perry SH et al. Implementing the Jadelle implant for women living with HIV in a resource-limited setting: concerns for drug interactions leading to unintended pregnancies. AIDS. 2014;28:791-793.

CROI 2015: PMTCT

## Three drug ART best for preventing vertical transmission to infants: results from the PROMISE study

**Polly Clayden, HIV i-Base**

**Taking a three-drug ART combination in pregnancy was more effective in preventing mother-to-child transmission than taking one drug during pregnancy, another in labour and two after delivery.**

**This was reported from the PROMISE (Promoting Maternal-Infant Survival Everywhere) study presented at CROI 2015. [1]**

These initial findings were reported in a US National Institutes of Health press release on 17 November 2014 after a scheduled interim review by the data and safety monitoring board (DSMB). [2]

PROMISE is a multinational trial conducted by the IMPAACT Network [3], which has been ongoing since 2010. Mary Glenn Fowler presented the data on behalf of the trial investigators. She summarised the goals of PROMISE:

- 1) Maximise prevention of mother-to-child HIV transmission (PMTCT) and optimise maternal/child health and survival.
- 2) Assess the relative safety and efficacy of triple antiretroviral treatment compared to other PMTCT regimens in women who did not require antiretroviral treatment, and their infants.
- 3) Conduct the study in the context of standard of care (SOC) for adult HIV treatment and infant feeding – Breastfeeding (BF) and Formula Feeding (FF).

PROMISE is multinational and includes sites in the following resource-limited countries: India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe.

Asymptomatic women with  $>350$  cells/mm<sup>3</sup> (or above local threshold for starting treatment) were enrolled. The trial has three randomisations:

**Antepartum** (14 weeks term) Arm A – AZT plus single-dose nevirapine (NVP) at delivery plus tenofovir (TDF)/emtricitabine (FTC) till vs Arm B – AZT-lamivudine (3TC) plus lopinavir/ritonavir (LPV/r) vs Arm C – TDF/FTC plus LPV/r.

**Postpartum** (duration of breastfeeding) uninfected infant, triple antiretroviral prophylaxis vs nevirapine prophylaxis.

**Maternal health** mothers receiving ART, after stopping BF, continue vs stop ART.

At the interim review, the DSMB reported that the pre-specified efficacy boundary for the antepartum part of the trial was crossed and there were safety differences between arms. The DSMB recommended: dissemination of the antepartum results to 14 days postpartum; continue follow-up for protocol-specified duration to obtain longer term efficacy/safety data and achieve the postpartum and maternal health objectives; and women who were still pregnant were advised to switch to ART arm.

Antepartum data to 14 days postpartum were presented at the conference.

Efficacy analyses compared vertical transmission in Arm A to the pooled triple ART arms. Safety analyses compared all three arms. Dr

Fowler noted that Arm C was only open to all women in a later version of the protocol (V3) because of concerns about the safety of TDF in pregnancy. So comparisons of Arms A and B included all women, but comparisons with Arm C only included those randomised under V3, when there was more TDF safety data available.

Data from 3523 pregnant women were available for analysis. At baseline, the women were a median age of 26 years; 97% were black African; median enrolment gestational age was 26 weeks; median CD4 was 530 cells/mm<sup>3</sup>; and 97% of women had not previously received antiretrovirals for PMTCT.

The rate of vertical transmission at 14 days postpartum was significantly lower in the pooled triple ART arms: 0.56% (9/710) vs 1.8% (25/1,326). This gave a difference in transmission risk of -1.28% (95% CI: -2.11 to -0.44).

There were no maternal deaths. There were significantly higher rates of Grade 2-4 adverse events (mostly LFTs) in both triple ART arms. Moderate but not severe adverse pregnancy outcomes were also higher with triple ART. Severe pregnancy outcomes were greater in Arm C: any, 4 vs 9%,  $p=0.02$ ; preterm delivery < 34 weeks, 3 vs 6%,  $p=0.04$ , respectively B vs C.

There were no significant differences in infant signs/symptoms and laboratory adverse events across arms for all infants and for V3 only infants. There were 60 early infant deaths by 14 days; 28 occurred in V3 infants. In V3, there was a significantly lower risk of infant death for Arm B vs C: -0.6% (2/346) vs 4.4% (15/341),  $p=0.001$ . The difference was mostly in deaths in preterm infants <34 weeks gestation.

There was significantly higher HIV-free survival in Arm B vs C at 14 days,  $p=0.002$ .

Dr Fowler concluded that the results support the 2013 WHO recommendations for use of triple maternal ART regimens in pregnancy (Option B or B+). She noted that antepartum triple ART regimens were associated with higher risk of moderate but not severe adverse maternal and pregnancy outcomes, including preterm birth and low birth weight, and that this will require follow up of 12 month infant mortality.

She also added that the difference in risk of early infant deaths in the FTC/TDF triple ART arm compared to the 3TC/AZT one was unexpected and requires further investigation.

The other parts of the study will remain unchanged and continue.

## COMMENT

**We previously reviewed these findings after the NIH press release in January. [4]**

**We wrote then that the regimen used in PROMISE included lopinavir/ritonavir. And that a recent report found approximately 30% increases in tenofovir AUC in a literature search to determine the effects of boosted antiretrovirals on tenofovir plasma concentrations.**

**The authors of the report noted that tenofovir toxicity might be overestimated in clinical trials where it is only combined with boosted antiretrovirals. Andrew Hill, the lead author, made the same observation in questions after the PROMISE presentation. He suggested that a reduced dose of TDF might be appropriate with lopinavir/ritonavir.**

**The PROMISE investigators plan to look at drug levels.**

## References

1. Fowler MG et al. PROMISE: Efficacy and safety of 2 strategies to prevent perinatal HIV transmission. CROI 2015. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Oral abstract 31LB.  
<http://www.croiconference.org/sessions/promise-efficacy-and-safety-2-strategies-prevent-perinatal-hiv-transmission>
2. National Institutes of Health press release. NIH-sponsored study identifies superior drug regimen for preventing mother-to-child HIV transmission. 17 November 2014.  
<http://www.nih.gov/news/health/nov2014/niad-17.htm>
3. International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) .  
<http://www.impaactnetwork.org/studies>
4. Clayden P. Three drug regimen superior for preventing vertical transmission in the PROMISE study. HTB, January/February 2015.  
<http://i-base.info/htb/27716>
5. Hill A et al. Should the dose of tenofovir be reduced to 200-250 mg/day, when combined with protease inhibitors? HIV Drug Therapy Glasgow Congress, 2-6 November 2014. Poster abstract P-51. Journal of the International AIDS Society 2014, 17(Suppl 3):19583 .  
<http://www.jiasociety.org/index.php/jias/article/view/19583>

## 3 in 5 breastfeeding women with HIV viral load >1000 copies/mL are undiagnosed in Kenya, Malawi and South Africa

**Polly Clayden, HIV i-Base**

**A large proportion of pregnant and breastfeeding women with high viral load were undiagnosed in a study conducted in Kenya, Malawi and South Africa. David Mamen from Médecins sans Frontières presented these findings at CROI 2015.**

Dr Mamen pointed out that although maternal viral load is a strong predictor of vertical transmission, few studies have investigated population viral load and cascade of care in pregnant/breast feeding women.

The study was a secondary analysis of three large population surveys of participants aged 15-59 in randomly selected households in Ndhiwa (Kenya), Chiradzulu (Malawi) and Mbolongwane/Eshowe (South Africa). The surveys were conducted between September 2012 and November 2013.

There were 12,461 eligible women and 11,550 (92.7%) consented to be included in the study. Women answered a questionnaire, which included questions on HIV testing, pregnancy, birth, breastfeeding and antenatal attendance. They were then tested for HIV with a rapid test. HIV positive women had their status confirmed by ELISA and negative women by NAT. Positive women were given CD4 and viral load testing. The investigators also measured incidence using recent infection assays.

At the time of the study, Kenya was implementing WHO PMTCT Option A, Malawi Option B+ and South Africa Option B.

The proportion of women who were pregnant or breastfeeding was higher in Kenya, 37.8% (1413/3760) and Malawi, 33.8%, (1444/4275) than in South Africa, 12.5% (439/3515). Among them, HIV prevalence ranged from 13.4% in Malawi to 22.2% in Kenya and 23.0% in South Africa. Dr Mamen added that when they looked at women aged 15-29 years, this proportion reached 50% in Kenya and Malawi.

The median age of women across all sites was about 25 years of age. HIV prevalence was higher in Kenya (22.2%) and South Africa (23.0%), than Malawi (13.4%).



A high proportion of women attended at least one antenatal clinic: 94.0%, 98.8% and 96.4% in Kenya, Malawi and South Africa, respectively. Fewer women attended at least three antenatal clinics: 75.5%, 86.1% and 73.1%, respectively. Most received an HIV test at their antenatal visit: 85.0%, 89.8% and 93.2%, respectively.

Although the proportion of women tested for HIV was similar across sites, the proportion diagnosed varied greatly from above 80% in Malawi to just over 50% in Kenya. In sites where Option B and B+ were implemented there was less loss at all stages of the cascade of care: diagnosis, link to care, in care, on ART and viral load <1000 copies/mL. The proportion of pregnant or breastfeeding women with viral load <1000 copies/mL was much higher in Malawi (72.3%) and South Africa (63.4%), than Kenya (27.3%). But, even in Malawi, 12% of pregnant or breastfeeding women had viral load >100,000 copies/mL.

Of the breastfeeding women with viral load >1,000 copies/mL (n=220), 58.6% were undiagnosed at the time of the survey, despite the majority (37.8%) testing negative at a routine antenatal visit. The proportion was similar across sites.

Overall 4.1% of breastfeeding women were infected during pregnancy or breastfeeding. The proportion was higher in Kenya (7.4%) than in South Africa (4.9%) and Malawi (2.1%).

HIV incidence among breastfeeding women aged 15-29 years, using incidence (recent infection) assays was: 3.8, 0.9 and 3.2 per 100 person years in Kenya, Malawi and South Africa, respectively.

## COMMENT

**The study investigators recommended implementing Option B+ and following the WHO guidelines as far as possible. Dr Maman added that Option B+ might not be enough and that a successful programme must also reduce HIV incidence among young women though strategies such as treatment as prevention and PrEP. “A bolder approach to PMTCT is required”, he said.**

**He called for programmes to: “Diagnose women and infants where they are”. HIV tests need to be repeated in women at antenatal visits and delivery. Infants need to be tested whenever they visit a health facility not just within PMTCT programmes.**

### Reference

David Maman D et al. Most breastfeeding women with high viral load are still undiagnosed in Sub-Saharan Africa. CROI 2015. Seattle, Washington. 23-26 February, 2015. Oral abstract 32.

Abstract: <http://www.croiconference.org/sessions/most-breastfeeding-women-high-viral-load-are-still-undiagnosed-sub-saharan-africa>

Webcast: <http://www.croiwebcasts.org/console/player/25552>

## Point of care HIV PCR test for infant diagnosis: good performance but poorer results in youngest age group

### Polly Clayden, HIV i-Base

**A point of care (POC) assay performed well in infant diagnosis in a large laboratory study. But its error rate of 6% has implications for implementation and its newborn performance requires further evaluation.**

Nei-Yuan Hsiao from the University of Cape Town presented these findings at CROI 2015.

The study evaluated the Alere q HIV1/2, a qualitative POC, nucleic acid test for HIV designed for use in the clinic that does not require a laboratory or extensive training. The test is real-time PCR, targeting unspliced HIV RNA, cartridge based, requiring a 25 uL blood sample with turnaround time of approximately 55 minutes.

Samples were routinely collected from HIV-exposed infants in the Western Cape from December 2013 to August 2014 from: primary care facilities (infants); maternity services (newborns < 7 days) and tertiary hospitals (infants and newborns).

The performance of the POC assay was compared with the local standard-of-care (SOC), Roche CAP/CTM HIV-1 V1 qualitative PCR in a laboratory setting and to the final infant HIV status (positive on two different PCR assays or two positive PCR assays on two different samples).

The investigators tested 1131 samples from 1098 infants with a median age of 47 days (IQR: 42–117); 90 were newborns. The majority of samples were from primary facilities (74%), the remainder were from tertiary paediatric services (19%) and maternity services (7%).

There were error results in 60 samples (6%) with the first test of which, 70% were resolved with a repeat test, and >90% were assay or sample related. Errors are more common with newborns.

Excluding retest or errors, sensitivity of Alere q was 95.5% (95% CI: 91.7 to 97.9) and specificity was 99.8% (95% CI: 99.1 to 100%). See Table 1 for results.

**Table 1: POC performance against SOC assay**

Alere q first test	Roche CAP/CTM HIV-1 PCR		
	Positive	Negative	Total
Positive	192	2	194
Negative	9	832	841
Error	11	52	63
Total	212	886	1098

Dr Hsiao noted that with re-test, sensitivity improved but specificity remained the same.

False negative samples had a median cycle threshold (CT) value of 33 on the SOC assay, higher than the true positives and errors, both  $p < 0.001$ . This was possibly due to lower levels of circulating virus during early infection.

Performance against the final infant HIV test result, excluding indeterminate status and Alere q errors: sensitivity 96.9% (95% CI: 93.4 to 98.9) and specificity 100% (lower 95% CI: 99.6)

Stratified by age group, the investigators found the performance was worse in younger infants: 6-10 weeks, sensitivity 96%, specificity 100%, error rate, 4%; newborns <7 days, sensitivity 93%, specificity 100%, error rate 10%.

### Reference

Hsiao N et al. Evaluation of the Alere q for point-of-care early infant HIV diagnosis in South Africa. CROI 2015. Seattle, Washington. 23-26 February 2015. Oral abstract 34.

<http://www.croiconference.org/sessions/evaluation-alere-q-point-care-early-infant-hiv-diagnosis-south-africa>

## CROI 2015: PAEDIATRIC STUDIES

## Weekend off ART is non-inferior to continuous ART in young people taking efavirenz-based regimens: results from BREATHER study

Polly Clayden, HIV i-Base

**Viral load suppression taking ART five days on and two days off (short cycle therapy) was non-inferior to that achieved with continuous therapy in young people receiving efavirenz-based first line treatment, at 48 weeks. These results from the BREATHER trial were presented as a late breaker at CROI 2015.**

Young people have reported difficulties with adherence during weekend, especially when socialising. BREATHER was designed to exploit the pharmacokinetics of long acting drugs such as efavirenz and look at whether a weekend off treatment strategy was feasible in this population.

Karina Butler from Our Lady's Children's Hospital, Dublin, Ireland presented the results on behalf of the BREATHER investigators.

BREATHER is a randomised, Phase 2, multicentre, non-inferiority trial conducted in 11 countries. Young people 8 to 24 years of age were eligible if they had a stable viral load <50 copies/mL and no previous virological failure, CD4  $\geq$  350 cells/mm<sup>3</sup> and were receiving efavirenz plus two NRTIs. They were randomised to continue daily ART or change to short cycle therapy.

Follow up was for a minimum of 48 weeks, with study visits at 0, 4 and 12 weeks, then 12-weekly. The primary outcome was the difference between arms in proportion with viral load >50 copies/mL at 48 weeks, using Kaplan-Meier estimation method adjusted for region and age. The non-inferiority margin was 12%.

A total of 199 young people were randomised: 99 to short cycle and 100 to continuous therapy. They were regionally diverse: 35% Uganda, 18% Thailand, 6% Argentina and 41% Europe and US.

Because of concerns about the trial there was a pilot phase with 32 participants and more intensive monitoring, including viral load testing on Monday mornings, before resuming ART.

The median age of the participants was 14.1 years (IQR: 11.9–17.6); 90% were vertically infected; 56% were black, 21% white and 19% Asian. Their median CD4 was 735 cells/mm<sup>3</sup> (IQR: 575.5–967.5). One fifth of the population was over 18 years of age: 39%, 8 to 13; 40%, 13 to 18; and 21%, 18 to 24.

Median follow up was 85 weeks, with >98% of clinic visits attended up to week 48. Only one participant was lost to follow up by week 48.

Participants reported taking >95% of scheduled drugs in an adherence questionnaire – and this also revealed 27% decreased drug exposure in the short cycle therapy arm. A substudy using MEMs caps in 61 participants (but only 46 by week 48 - MEMs caps were not popular) showed median weekly cap openings of 5 and 7 in the short cycle and continuous therapy arms, respectively.

At 48 weeks, 6 vs 7 participants in the short cycle and continuous therapy arms had detectable viral load >50 copies/mL. This gave a difference of -1.2% (90% CI, -7.3 to 4.9) in favour of short cycle therapy. The upper bound of difference between Kaplan Meier survival curves of 4.9% was inside the non-inferiority margin of 12%.

There were 4 vs 11 changes in ART regimen in the short cycle

vs continuous therapy arms,  $p=0.1$ , NS. The changes were: 8 for toxicity, 4 for simplification, 2 for adherence and 1 for viral failure.

There were no differences in clinical, immunologic or virologic parameters, inflammatory markers, or resistance among participants with virologic failure.

Short cycle therapy was popular in a qualitative substudy: 74% of participants said this strategy made things a lot easier and the remainder a little easier. Notably the participants reported fewer side effects at weekends and these had often not previously been disclosed to caregivers.

Pre- and post-trial questionnaires comparing the two strategies showed modest improvement in most things participants found difficult with continuous ART. Only "going out with friends" was statistically significant,  $p=0.001$ .

Most participants are continuing follow up for an additional two years.

### COMMENT

**During the presentation and at the press conference following, it was emphasised that this study was conducted in a carefully selected group of participants. This included a previous history of viral suppression on their first regimen and close to 100% adherence on weekdays. This is not likely to be suitable for everyone.**

**It is notable that not all the participants were on tenofovir containing regimens – which also has a long half-life. A considerable proportion, particularly in Uganda, received AZT.**

#### Reference

Butler KM et al. ART with weekends off is noninferior to continuous ART in young people on EFV+2NRTI. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Oral abstract 38LB.

Abstract: <http://www.croiconference.org/sessions/art-weekends-noninferior-continuous-art-young-people-efv2nrti>

Webcast: <http://www.croiwebcasts.org/console/player/25558>

## Increased cardiovascular risks in HIV positive children in Uganda and Zambia partially reversed by ART

Polly Clayden, HIV i-Base

**ART naive children had functional and structural cardiovascular changes compared with HIV negative controls but ART can reverse some of these changes caused by HIV, according to data shown at CROI 2015.**

Julia Kenny from University College London presented findings from the CHAPAS 3 trial on behalf of the cardiovascular sub study investigators. She explained that HIV positive adults are at increased risk of cardiovascular disease. Although this has not been described in HIV positive children, there is accumulating evidence of accelerated atherosclerosis in this population.

Two ways of looking at cardiovascular structure/function are used: carotid intimal medial thickness (cIMT) and pulse wave velocity (PWV). Both are impaired in HIV positive children from high-income countries. Few data are available: only one study from Africa (with no controls) and mostly small studies in older children without longitudinal follow up.

CHAPAS 3, conducted in 2010 – 2013, looked at d4T vs AZT vs

abacavir-based first-line ART in treatment naive and experienced children in Uganda and Zambia.

In the substudy—conducted at two sites, one in each country—children had cIMT and PWV measured at baseline, 48 and 96 weeks. Age matched HIV negative controls had a single assessment.

The investigators evaluated baseline differences between ART-naïve and -experienced children vs controls, and compared longitudinal changes in children (using two-sample and paired t-tests respectively).

In 208 ART-naïve children with median age 2.9 years (range 0.3 – 13.6), mean CD4 percent 17% (SD: 8), and 209 HIV negative controls with median age 3.0 years (range: 0.1 – 12.8), mean cIMT was 0.46 (SD: 0.04) vs 0.44 (SD: 0.04) mm respectively,  $p=0.0001$ ; PWV was 5.85 (SD: 0.8) vs 5.67 (SD: 0.74) m/sec respectively,  $p=0.04$ .

In 74 ART-experienced children (receiving treatment for mean 3.7 years) with median age 6.9 years (range: 5.1 – 12.3), median CD4 percent 34% (SD: 10) and 75 HIV negative controls with median age 6.7 years (range: 3.9 – 11.8), mean cIMT was 0.46 (SD: 0.05) vs 0.45 (SD: 0.04) mm respectively,  $p=0.09$ ; PWV was 5.63 (SD: 0.61) vs 5.69 (SD: 0.69) m/s respectively,  $p=0.57$ .

In ART-naïve children at week 96 of ART significant improvement was seen in both parameters: mean cIMT -0.02 (SD: 0.04)mm, PWV -0.38 (SD: 0.83)m/s, both comparisons  $p<0.0001$ .

In ART-experienced children, although cIMT had significantly reduced by mean -0.2 (SD: 0.06) mm,  $p=0.01$ , at week 96 PWV increased by 0.35 (SD: 0.63) m/s,  $p<0.0001$ . Dr Kenny noted that an increase in PWV is expected, as children get older and was also seen in the HIV negative controls.

Despite concerns about abacavir and cardiovascular risk, there was no significant difference between the three randomised treatment arms at 96 weeks in either cIMT or PWV.

## COMMENT

**This is the largest study worldwide of preclinical cardiovascular changes in HIV positive children and the only longitudinal African data. It is also the first time that these techniques have been used in children less than five years old.**

**The study suggests that ART-naïve children have poorer cIMT and PWV compared with controls but that ART can reverse some of the functional and structural changes caused by HIV. One question after the presentation was whether or not all the increase in PWV was fully accounted for by age – Dr Kenny remarked that when they looked at this the confidence intervals overlapped and there was nothing unexpected.**

**These data add weight to the argument that ART in early life might reduce the cardiovascular risk of HIV positive children when they become adults. Longer-term follow up of children who start ART at an early age is important.**

### Reference

Kenny J et al. Structural cardiovascular changes are reversible in HIV-infected children in Zambia and Uganda. CROI 2015. Seattle, Washington. 23-26 February 2015. Oral abstract 37.

Abstract: <http://www.croiconference.org/sessions/structural-cardiovascular-changes-are-reversible-hiv-infected-children-zambia-and-uganda>

Webcast: <http://www.croiwebcasts.org/console/player/25557>

## Lopinavir/ritonavir in young children is superior to nevirapine after five years: results from long term follow up of IMPAACT P1060

Polly Clayden, HIV i-Base

**Long-term virologic suppression was superior in children receiving lopinavir/ritonavir (LPV/r)-based ART compared with nevirapine (NVP)-based regimens at five-year follow up in the IMPAACT 1060 trial. Early modest gains in CD4 percentage and growth with NVP were no longer statistically significant beyond one year after starting ART.**

Linda Barlow-Mosha presented these findings at CROI 2015 on behalf of the IMPAACT P1060 trial Investigators.

The trial was conducted in six African countries and India. It showed short-term superiority of LPV/r-based ART compared with NVP in HIV positive infants and children for the primary endpoint: stopping randomised treatment, virologic failure or death at 24 weeks. The results were regardless of NVP exposure at birth. Participants receiving NVP had slightly superior improvements in CD4 percentage and weight and height z-scores.

Results from long-term follow up of IMPAACT P1060 in a five-year, observational cohort, were shown.

Infants and children aged 2 months to 3 years were enrolled into two cohorts (exposed or unexposed to NVP through PMTCT) and randomly assigned to start NVP or LPV/r in regimens with AZT and 3TC.

Due to superiority of the LPV/r arm for the primary endpoint, the DSMB recommended stopping enrolment and unblinding the cohort with NVP-exposed participants in 2009 followed by the unexposed cohort in 2010. All participants were eligible to switch regimens and continue in observational follow up. Randomised and observational data were combined in the analyses presented.

There were 229 participants randomised to NVP and 222 to LPV/r based ART. At baseline, median age was 1.2 years and 55% were older than one year. By January 2014, 75% were still in follow up for a median 4.6 years [IQR: 3.7-5.7] and 92% had viral load <400 copies/mL.

From the original randomisation, 84% of participants receiving LPV/r remained on treatment compared with 52% receiving NVP. Median time on randomised treatment was: 54 vs 19 months in the LPV/r and NVP arms respectively.

There was 14% higher virologic failure in the NVP arm. For the combined endpoint of time to virologic failure and death the adjusted hazard ratio was 1.9 (95% CI: 1.4 to 2.7).

The initial gains in CD4 percent with NVP vs LPV/r (12-month difference ITT adjusted 1.52 [95% CI: 0.13 to 2.92],  $p=0.03$ ) were not statistically significant by the second year. The participants in the NVP arm continued to have higher weight for age z-scores throughout the study (36-month difference ITT adjusted 0.22 [95% CI: 0.05 to 0.38],  $p=0.01$ ). Height for age z-score was only higher in the NVP arm early on (6-month difference ITT adjusted 0.2 [95% CI: 0.01 to 0.39],  $p=0.04$ ).

## COMMENT

**These results support the WHO recommendations of LPV/r-based regimens for first line ART in infants and young children less than 3 years of age.**

In reality the problems with the LPV/r liquid formulation remain (it is unpalatable, requires cold chain, and is expensive) and coverage is poor outside South Africa.

Cipla has submitted a solid “pellet” formulation of LPV/r to the FDA (and Mylan is also developing one) – but the taste masking is still not ideal. Cipla in partnership with the Drugs for Neglected Diseases initiative (DNDi), and Mylan are developing 4-in-1 fixed dose combinations of LPV/r granules (finer than pellets with better taste masking), with abacavir or AZT plus 3TC.

Until these formulations are available, the practical challenges associated with giving LPV/r to infants and young children in low-income countries are still with us.

#### Reference

Barlow-Mosha L et al. Long-term outcomes of HIV-infected children initiating NVP vs LPV/r-based treatment. CROI 2015. Seattle, Washington. 23-26 February, 2015. Oral abstract 36.

Abstract: <http://www.croiconference.org/sessions/long-term-outcomes-hiv-infected-children-initiating-nvp-vs-lpv-r-based-treatment>

Webcast: <http://www.croiwebcasts.org/console/player/25556>

## Long-term safety and efficacy of tenofovir in children

### Polly Clayden, HIV i-Base

**Tenofovir was well tolerated in children for up to 336 weeks, according to preliminary efficacy and safety data presented at CROI 2015.**

There are concerns about long-term bone and renal safety among children receiving tenofovir disoproxil fumarate (TDF), for which data are limited. It is approved in children and adolescents age 2 – 18 years in the US and EU. Paediatric formulations (150, 200 and 250 mg tablets and a 40 mg/g powder) are available.

Results from the extension to the GS-US-104-352 study, conducted in the US and Panama, were shown in a poster presentation. GS-US-104-352 was a Phase 3, randomised, open-label, non-inferiority study, comparing the safety of switching d4T or AZT to TDF vs continuing d4T or AZT in children 2 – 16 years of age. At week 48, 40/48 (83.3%) vs 45/49 (91.8%) in the TDF and d4T/AZT arms respectively had viral load <400 copies/mL: difference -8.5 (95% CI: -21.5 to 4.5),  $p=0.23$ . All participants who received d4T/AZT in the randomised phase were switched to TDF in the open label extension (OLE) phase.

Overall, 89 participants received TDF: median age 8 years (range 2 -15), 49.4% boys, median CD4 1095 cells/mm<sup>3</sup> and median CD4 percent 34%. Twenty-four children were in the 2 – 6 years age group, 59 were 6 – 12, and 6 were 12 years and above.

The median duration of TDF was 302 weeks; 79 participants received TDF in OLE extensions; and 48 participants completed 336 weeks.

At week 336, 80% of participants had viral load <50 copies/mL, see Table 1.

Nine participants discontinued OLE TDF for adverse events: 3 hypophosphatemia, 2 proteinuria, 2 arthralgia, 1 brain neoplasm and 1 glycosuria. Six discontinuations were related to renal toxicity (hypophosphatemia; proteinuria and glycosuria).

Overall, 13/86 (15.1%) participants had  $\geq 4\%$  decline in bone mineral

**Table1: Virologic response rates in all TDF group by visit OLE (missing=failure)**

Week	Participants with viral load <50 copies/mL	
	n ( %)	95% CI
48	61/89 (68.5)	57.8 – 78.0
96	57/79 (72.2)	60.9 – 81.7
144	54/78 (68.2)	57.8 – 79.2
192	53/74 (71.6)	59.9 – 81.5
240	51/71 (71.8)	59.9 – 81.9
288	45/64 (70.3)	57.6 – 81.1
336	32/40 (80.0)	64.4 – 90.9

density (BMD) in the spine or total body (less head) at one post baseline visit; 3 had  $\geq 4\%$  decline in BMD at >1 visit. Bone fractures were reported in 3 participants but were trauma-related and none were considered related to study drug.

One participant developed K65R at week 4 (suggesting it might be archived from previous treatment).

#### Reference

Saez-Llorens X et al. Efficacy and safety of long-term tenofovir DF (TDF) therapy in HIV-infected children. 2015 CROI, 23-26 February 2015. Poster abstract 954.

Abstract: <http://www.croiconference.org/sessions/efficacy-and-safety-long-term-tenofovir-df-tdf-therapy-hiv-infected-children>

CROI 2015: CURE RESEARCH

## UK case of HIV remission: ten years off-ART in patient with prior progression and treated during seroconversion

### Simon Collins, HIV i-Base

**An interesting case study was reported as a poster at CROI 2015, of a UK patient whose viral load has remained undetectable for more than ten years since stopping ART in 2004. This was despite viral failure on earlier ART and persistence of a detectable viral reservoir. [1]**

This case is of a 23 year old African woman who was diagnosed in 1997 with subtype C, following three weeks of acute and severe seroconversion symptoms, during which her CD4 count was confirmed <200 cells/mm<sup>3</sup> and viral load was >750,000 copies/mL.

Initial treatment was with AZT/3TC/indinavir, switched after two weeks to AZT/3TC/ritonavir (600mg BD) but viral load remained detectable until treatment was changed again (at 94,000 copies/mL) in April 1999. Viral load then became suppressed and remained undetectable until January 2004 when treatment was stopped.

HIV viral load has remained consistently undetectable off-ART since 2004.

In 2014, a detectable viral reservoir was confirmed with total HIV-1 DNA, integrated HIV-1 DNA and 2-LTR circles at 148.93 (95% CI: 76.99 to 229.64), 134.31 (95% CI: 56.47 to 304.39) and 3.89 (95% CI: 0 to 9.15) HIV-1 copies/million PBMCs, respectively.



The extended period of viral control has not been explained by HLA genotype. Moderately potent CD8 T cell responses were similar to clade-matched responses similar to that seen in treatment-naïve patients whose viral set-point is <10,000 copies/mL.

However, unusually broad Gag-specific IFN-gamma CD4 responses were detected that targeted multiple regions of Gag that are associated with viral control.

## COMMENT

**This interesting case study highlights how much we still have to learn about the HIV reservoir and immune control of HIV replication. It is important that these and similar cases are presented and published to connect collaborative research.**

**Do individuals such as this accumulate functional HIV-specific CD4 memory responses that are able to mediate control (rather than succumb to infection). If so, is this due to a bias to produce chemokines that make the CD4 T cells relatively resistant to HIV? [2] This phenomenon has been reported in CMV-specific CD4 T cell responses. [3]**

**Are these CD4 cells biased toward a cytotoxic phenotype which has been associated with control? [4] Or are they expressing restriction factors? Or are NK cells involved, with the CD4 responses more of an effect than a cause? Lots of questions...**

**Finding out whether immunological factors contribute to or determine viral control in such single cases involves detailed, longitudinal assessments. In this case, broadly cross-neutralising antibodies in plasma could be assessed at multiple time points, in addition to the T cell responses already described.**

**However, the neutralising response against heterologous virus was not particularly strong when tested a few years ago.**

**While the authors report the detection of pro-viral DNA, RNA and 2-LTR circles, it would be surprising if at least some of these were not present in a person with a history of high viraemia. The continued existence or not, of a replication-competent reservoir could be demonstrated with viral outgrowth assays. This might explain whether persistent aviraemia is a feature of a defective reservoir or ongoing effector immune responses, or both.**

**For HIV positive people, these examples are hopeful, although their rarity emphasises that this is not yet something to try at home.**

## Reference

1. Kinloch SI et al. Aviremia 10-year post-ART discontinuation initiated at seroconversion. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Poster abstract 377. Abstract: <http://www.croiconference.org/sessions/aviremia-10-year-post-art-discontinuation-initiated-seroconversion>
2. Walker WE et al. Increased levels of MIPs result in resistance to R5-tropic HIV-1 in a subset of elite controllers. J. Virology, posted online 4 March 2015, doi: 10.1128/JVI.00118-15. <http://jvi.asm.org/content/early/2015/02/26/JVI.00118-15.abstract>
3. Casazza JP et al. Autocrine production of Beta-chemokines protects CMV-specific CD4+ T cells from HIV infection. PLoS Pathogens, 30 October 2009. DOI: 10.1371/journal.ppat.1000646. <http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1000646>
4. Soghoian DZ et al. HIV-specific cytolytic CD4 T cell responses during acute HIV infection predict disease outcome. Sci Transl Med. 2012 Feb 29;4(123):123ra25. doi: 10.1126/scitranslmed.3003165. <http://www.ncbi.nlm.nih.gov/pubmed/22378925>

## CONFERENCE REPORTS

### XXIV International HIV Drug Resistance Workshop

**21-22 February 2015, Seattle, Washington**

#### Introduction

**This was the first year that the International Drug Resistance Workshop has been held before CROI and the programme has returned to focus on HIV drug resistance, having for several previous years covered both HIV and hepatitis.**

Importantly, the meeting continues to focus implications of drug resistance globally, especially in the context of resource-limited settings where treatment options are fewer, access to viral load testing is limited and resistance testing is only generally only available in a research setting.

These brief reports include a selection of short summaries that related to clinical implications of drug resistance.

Abstract are published as a supplement in Global Antiviral Journal, Volume 11, Supplement 1 and the abstract book is available to download free in PDF format:

[https://www.informedhorizons.com/resistance2015/pdf/RW2015\\_Book.pdf](https://www.informedhorizons.com/resistance2015/pdf/RW2015_Book.pdf) (PDF)

PowerPoint slides from many of the oral presentations are also available:

<https://www.informedhorizons.com/resistance2015/presentations.html>

Reports included in this issue of HTB are:

- Prevalence of transmitted drug resistance globally: highest in Australia, US and some European countries but between-country differences in all regions
- Higher rates of K65R in non-B subtype in large UK cohort and implications of tenofovir resistance in resource-limited settings
- Drug resistance and integrase inhibitors: potential impact of HIV subtype
- Drug resistance in children after PMTCT and early treatment

### Prevalence of transmitted drug resistance globally: highest in Australia, US and some European countries but between-country differences in all regions

**Simon Collins, HIV i-Base**

**The XXIV International Drug Resistance Workshop provided a focus for many reports on the prevalence of transmitted HIV drug resistance (TDR) in different countries, although the size and approach to collecting this data varied considerably between studies.**

Some of the highest rates reported were in the US, Europe and Central America. Within all regions, including countries in sub-Saharan Africa, wide difference were reported.

Global differences in TDR, together with the disparity in access to resistance testing, was highlighted in a study of baseline data from 4,685 participants enrolled from 2009-2013 in the international START study. [1] START has already randomised 4600 treatment-naïve individuals with CD4 counts >500 cells/mm<sup>3</sup> to either immediate ART or deferred ART (when CD4 count drops to 350 cells/mm<sup>3</sup>).

The overall prevalence of TDR from samples tested was 10.1%, most commonly to NNRTIs (4.5% and NRTIs (4%) and was higher in Australia (17.5%) and the US (12.6%) than Europe (8.8%), but within Europe, differences ranged from 16.7% in France and 12.6% in Spain to 4.7% in the UK. Given surveillance studies in the UK have consistently report rates that are at least twice as high, this low percentage has yet to be explained.

However, access to resistance testing varied considerably: 89% in Australia, 86% in Europe, 81% in the US, 22% in Asia, 1.8% in South America and 0.1% in Africa.

This highlights the importance of the range of national studies on transmitted drug resistance that were presented at the workshop from other global regions.

In Africa, some countries, with established access to ART for a decade or longer, reported relatively low levels of TDR - defined by the WHO as less than 5% - including Uganda, Mozambique and South Africa.

A study from the Rakai cohort in Uganda in 76 people with recent HIV infection reported that only two people had a single NNRTI mutation each (K101E and K103N), and one individual had a single PI mutation (M46I). Free ART has been widely available in Uganda since 2004. [2]

A surveillance review in antenatal clinics in Maputo and Beira in 2007, 2009 and 2011 reported that transmitted drug resistance was below WHO surveillance threshold of 5%, although details of the numbers of people tested and the incidence of class resistance was not reported. The study concluded that transmitted drug resistance may be declining over time. By 2011, more than 270,000 people were on ART. [3]

In South Africa, several studies presented different results from this country that now has more than two million people on ART.

A national surveillance study from all nine provinces provided an analysis of TDR in 2012. This group tested 770 samples from women younger than 21 years old during their first pregnancy, 532 of which (69%) were successfully genotyped. Overall, the prevalence (95% CI) of resistance by drug class was estimated at 5.4% (3.7 to 7.6%) for the NNRTI, 1.1% (0.5 to 2.4%) for NRTI and 0.9% (0.3 to 2.6%) for PI associated drug resistance. However, four provinces had a prevalence of NNRTI resistance that was greater than 5%. [4]

Results were also reported from three rounds of an annual population based HIV surveillance programme in rural KwaZulu-Natal from 2010-2012. The 701 treatment-naïve participants were estimated to have been HIV positive for at least two years. Prevalence of any significant drug resistance was 5% (36/701). These were predominantly NNRTI (n=35): K103N (n=27), V106M (n=3) and G190A (n=2). NRTI mutations were detected in 11 (1.6%) of the participants, 9 of whom had only one NRTI mutation. TDR was increasing over time (p=0.02). [5]

The clinical importance of TDR was highlighted in a study from six African countries including South Africa that looked at 2-year and 3-year treatment outcomes from treatment-naïve patients at 13 clinic sites. Genotype results from 2,579 participants (94% of the cohort) showed TDR in 5% (n=139). [6]

Pretreatment resistance increased the risk of three categories of treatment failure.

- 1) Switching with drug resistance (HR 7.8 (95% CI: 3.9 to 15.6) during 3 years.

- 2) Virologic failure (OR 2.9 (95% CI: 1.4 to 5.8) after 2 years and 2.8 (95% CI: 1.1 to 7.2) after 3 years.

- 3) Acquired drug resistance (OR 2.5 (95% CI: 1.2 to 5.4) after 2 years and OR 5.0 (95% CI: 1.8 to 14.3) after 3 years of first-line ART.

Although pretreatment drug resistance was not associated with mortality or new AIDS events, this may be a marker of relatively short follow up.

In a small study from Ethiopia where ART has been available in public health programmes since 2003, rates of TDR were higher and have been rising. Genotype results were available for 38/48 newly-diagnosed treatment-naïve individuals at a single clinic in the city of Gondar (24/38 were recently infected). Major mutations were found in 4 (11%) people (PRO 46I, 82L; RT 106M, 190A) and 8 additional patients (22%) had other significant mutations (PR 10I/V, 35G, 58E; RT 62V, 108I, 103E, 138A). The authors concluded that the 17% resistance from samples in 2013 compared to 6% in 2008/9 and only 2% in 2003. [7]

In a cohort of 553 treatment-naïve adults in Kenya, 75/553 (14%) had pre-treatment drug resistance detected at baseline. Of these 75 participants with resistance, 97% had resistance to NNRTIs (75% with K103N, 22% with Y181C, 13% with G190A), and 17% with resistance to 3TC (M184V). In the multivariate analysis, younger age was associated with higher relative risk of resistance (16% per 5 year decrease). [8]

When looking at drug resistance in people on treatment, several studies reported high levels of drug resistance, associated with limited access to viral load testing. This has been a long standing concern for all settings where lack of viral load testing means that first-line combination is continued until clinical failure.

In Ghana, in a cohort of 175 patients receiving long-term NNRTI-based ART, one third were found to have detectable viral load. This was detectable below vs above 1000 copies/mL in 19% vs 4%, respectively, with drug resistance in 18% (2/11) vs 83% (19/23). Almost all patients with viral load above 1000 copies/mL (median 4.1 log; IQR: 3.8-4.3) also had dual NRTI/NNRTI resistance. In the 151 people with low or undetectable viral load, viral rebounded to >1000 copies/mL in 11% of people over 20 months, by which time the majority of these patients also acquired dual NRTI and NNRTI resistance. [9]

In the first study of drug resistance in Liberia, out of 90 patients at a single clinic in Monrovia on first-line NNRTI-based treatment for median 42 months (IQR: 22-55 months), only 27% had undetectable viral load <50 copies/mL. In those with detectable viral load, 63% had NRTI, 70% had NNRTI and 60% had dual class resistance. Two people had PI mutations (M46L and D30N). [10]

A multinational study of six countries in Central America reported rates of TDR in more than 3600 people who were recently diagnosed between 2010-2014 in Mexico (n=1476), Guatemala (n=1180), Panama (n=238), Nicaragua (n=222), Honduras (n=294) and Belize (n=100). Belize showed the highest prevalence (19.0%), followed by Nicaragua (14.9%), Panama (12.2%), Honduras (9.9%), Mexico (7.7%) and Guatemala (7.1%). In all countries, resistance was generally highest to NNRTIs, then NRTIs with lower rates of PI-associated mutations. [11]

One of the highest rates of TDR however was reported from the US National Surveillance System in a recent study of 9,629 MSM diagnosed from 2010-12 in eight sites (Colorado, Connecticut, Los Angeles county, Michigan, New York, South Carolina, Texas, and Washington). [12]

In this analysis, 18.9% men had TDR to any class: 16.2% to 1 drug class, 2.3% to 2 drug classes, and 0.4% to 3 drug classes. TDR by class was NNRTI (9.9%), NRTI (6.8%) and PI (5.3%).

Men aged 20–29 years accounted for 40% of TDR (with a prevalence of 19.4%). However, younger men aged 13–19 years, who accounted for only 6.6% of infections, had the highest prevalence of 23.4%. Although TDR was significantly different by race/ethnicity these rates were 20.1% for black MSM, 18.5% for Hispanic/Latino and 17.5% for white MSM.

## COMMENT

**Taken together these studies highlight the need to know (1) the prevalence of transmitted drug resistance in various populations in different countries and regions and (2) the prevalence of developed drug resistance in different regions. The results then need to relate to aspects of care such as availability of viral load testing and frequency of follow up visits.**

**The studies give a limited view, with different sampling rates and sizes and little information on the populations studied. They highlight the importance of increasing availability to viral load testing. It would be of interest to have more results from people who have advanced clinically.**

### References

Unless stated otherwise, references are to the Programme and Abstracts of the XXIV International HIV Drug Resistance Workshop, 21–22 February 2015, Seattle, Washington.

1. Baxter JD et al. Global HIV-1 transmitted drug resistance in the INSIGHT Strategic Timing of AntiRetroviral Treatment Study. Abstract 67.
2. Reynolds SJ et al. Low rates of transmitted drug resistance among newly identified HIV-1 seroconverters in rural Rakai, Uganda. Abstract 60.
3. Bila D et al. Three consecutively surveillance rounds reveal a decrease in transmitted drug resistance in Mozambique. Abstract 56.
4. Hunt G et al. National surveillance of HIV-1 transmitted drug resistance in South Africa in 2012. Abstract 77.
5. Manasa J et al. Increase in HIV primary drug resistance in a demographic surveillance area in Rural KwaZulu- Natal South Africa. Abstract 73.
6. Boender TS et al. Pretreatment HIV drug resistance increases regimen switch in Sub-Saharan Africa. Poster abstract 3.
7. Olshtain-Pops E K et al. High HIV drug resistance in naive, recently diagnosed patients in Gondar. Abstract 23.
8. Silverman RA et al. Higher risk of pre-treatment HIV drug resistance among younger ART-naïve Adults in Kenya. Abstract 86.
9. Beloukas A et al. Prevalence of resistance-associated mutations at viral load below 1000 copies/mL during long-term first-line NNRTI-based antiretroviral therapy in Ghana. Poster abstract 2.
10. Loubet P. High level of acquired HIV drug resistance in patients failing on first-line regimen in Liberia. Abstract 15.
11. Avila-Rios S et al. HIV drug resistance in antiretroviral treatment-naïve individuals in the Mesoamerican Region, 2010–2014. Abstract 65.
12. Ofcemia MCB et al. Epidemiology of HIV-1 transmitted drug resistance among men who have sex with men in the United States. Oral abstract 81.

## Higher rates of K65R in non-B subtype in large UK cohort and implications of tenofovir resistance in resource-limited settings

**Simon Collins, HIV i-Base**

**Given the cost pressures on universal access to HIV medicines in resource-limited settings, it is a considerable achievement that global use of tenofovir has largely - and rightly - replaced use of d4T which was initially much cheaper but also associated with more serious toxicity.**

There is a caution that some subtypes, notably subtype C, might be

more susceptible to the key K65R tenofovir-associated mutation (due to differences in the template at RT 64–66), especially in the context of use in settings without routine viral load monitoring. Several groups reported on this at the meeting.

Data from the UK HIV Drug Resistance Database reported higher rates of K65R with subtype C compared to subtype B. The analysis included samples from 4,242 patients on failing treatment, collected from 1996–2013, irrespective of drugs used or treatment combination. Of these 3,439 were subtype B (77% MSM) and 803 subtype C (82% heterosexual). [1]

Prevalence of K65R was related to subtype and exposure to the NRTIs that select for this mutation (tenofovir, abacavir, ddI and d4T). Overall, K65R was detected in 7.8% subtype B patients after a median 5.0 years (IQR: 1.6–7.8) from initiating ART, compared with 14.5% in patients with subtype C at a median of 2.5 years (IQR: 0.8–5.1) after starting ART.

The subtype difference in K65R prevalence was observed irrespective of NRTI exposure. K65R was frequently seen in patients with no previous exposure to tenofovir. Although prevalence of thymidine analogue mutations was similar, K65R was significantly more common in subtype C (OR 1.95; 95% CI: 1.51 to 2.51,  $p < 0.001$ ).

Although associations can not show causation, this study is important for its size, together with the significant differences observed in the prevalence of K65R and time to develop resistance.

In a study from Kenya, the prevalence of K65R was reported from a cohort of 332 people who had been on tenofovir plus NNRTI-based ART for >6 months. Of these, 216 were treatment-naïve when starting tenofovir and 116 had switched to tenofovir when already on treatment. [2]

Overall, viral load was detectable in 17% of patients and in 10% of patients it was >1000 copies/mL. However, viral failure was 23% in the previously naïve patients (after a median 20 months on ART) compared to 7% in those who switched (after a median 24 months on TDF and 47 months on prior ART). This difference was significant ( $p < 0.001$ ).

Genotype results were available for 35 patients showed that high levels of NNRTI (89%), RT (89%), dual class (83%) and RT K69R (69%). HIV subtype (69% A, 12% C, 11% D, 9% A/D) was not statistically significant ( $p = 0.22$ ) and RT region 64–66 were similar to subtype B indicated this was not due to higher subtype susceptibility in this cohort. Higher failure rates were associated with tradition reasons for virologic failure, including lower CD4 count ( $p = 0.02$ ), higher WHO stage ( $p = 0.004$ ) and higher RT resistance ( $p < 0.001$ ).

In this case, the results are important for showing that switching to tenofovir was not associated with higher risk of treatment failure due to drug resistance.

A study from South Africa looked at the prevalence of K65R in 86 patients with treatment failure using a tenofovir-including combination. The group also looked at low frequency K65R variants using deep sequencing with a 1% threshold. [3]

Using Sanger sequencing, 79/86 samples were amplified and 47/79 (60%) had K65R. Deep sequencing identified K65R in a further 8/27 samples (5 were not available) at frequencies ranging from 1% – 32%. Taking the results together the researchers concluded a conservative prevalence of 70%. Deep sequencing in these 27 patients also identified high rates of NNRTI mutations that were missed by Sanger, changing the interpretation of drug sensitivity in 16/27 (60%) cases.

An analysis of 101 treatment-experienced patients in Cameroon with first-line combinations of d4T with or without AZT in various NNRTI-based combinations concluded that the complexity of cross-resistance of thymidine analogue mutations required genotypic resistance testing to be able to select fully active NRTIs for second-line therapy.

Unfortunately, much of the rest of the workshop emphasised how far away this need was from reality.

## C O M M E N T

**The K65R findings in the UK supports the by easier selection of drug resistance in subtype C due to the differences in codon utilisation at positions 64 65 and 66.**

**As cohort data, it would be important in the UK setting to know whether different care received by Africans compared to gay men in the UK might contribute to different patterns of adherence and so development of resistance?**

**Outside the UK, it highlights the importance of similar studies being run in countries with predominantly subtype C epidemics as tenofovir is now more widely used as standard of care.**

### References

Unless stated otherwise, references are to the Programme and Abstracts of the XXIV International HIV Drug Resistance Workshop, 21-22 February 2015, Seattle, Washington.

1. Smit E et al. K65R detected more frequently in HIV-1 subtype C viruses at virological failure. Abstract 89.
2. Brooks K et al. Viral failure and high K65R in Kenyan patients on tenofovir-based 1st-line therapy. Poster abstract 5.
3. Casadellà M et al. Limited treatment options after virological failure of first-line tenofovir-based regimens in South Africa. Abstract 39.
4. Fokam J et al. Usefulness of HIV-1 resistance testing in switching patients from first- to second-line antiretroviral regimens in resource-limited settings. Abstract 17.

## Drug resistance and integrase inhibitors: potential impact of HIV subtype

**Simon Collins, HIV i-Base**

**Although dolutegravir and cabotegravir have been notable for the lack of integrase resistance that in integrase-naïve patients, several case studies were presented at the workshop about resistance in this class.**

### Cabotegravir and rilpivirine in the LATTE study

The two drug oral combination of cabotegravir and rilpivirine in a Phase 2b Latte study, designed as a prestudy for later use of long acting injectable formulations of each drug, reported a case of dual integrase and NNRTI resistance. [1]

At week 48 in this dose finding study, 4/243 people had virologic failure (one in each of the 10 mg and 30 mg cabotegravir arms and two in the efavirenz control arm). Treatment-emergent resistance (INI Q148R and NNRTI E138Q) was detected in a single patient in the 10 mg cabotegravir group who had had persistently low drug levels of both drugs (<50% mean C trough). Viral load had been undetectable from week 2 to 40 but rebounded to 18,000 copies/mL at week 48.

The Q148R integrase mutation resulted in a 3.08 fold-change in sensitivity to cabotegravir and 30.0 fold change to raltegravir with impact on replicative capacity of 8.1%. The E138Q mutation resulted in a 1.83 fold change in sensitivity to rilpivirine and changed replicative capacity by 44%.

### Raltegravir resistance very common with virological failure in the NEAT001 study

The NEAT001 study was an open label, Phase 3, treatment-naïve (n=805) study of darunavir/ritonavir with either raltegravir in a nucleoside-sparing combination or with tenofovir/FTC as standard ART. [2] In the primary virological endpoint at 96 weeks presented at CROI 2014, the raltegravir arm was non-inferior but this dual combination was less effective in people with high baseline viral load. [3]

An analysis of the resistance test results presented at the workshop reported high levels of genotypic resistance in the raltegravir arm, with 1 in 4 samples at failure showing integrase mutations. In contrast, no mutations were reported from the tenofovir/FTC arm.

Resistance test results were available for 110/127 patients with virologic failure (defined as confirmed viral load >50 copies/mL or any single viral load >500 copies/mL at or after week 32). This was for 61/69 patients in the raltegravir arm and 49/58 patients in the tenofovir/FTC arm although not all tests were successful.

Of the 14/55 amplified raltegravir group samples with integrase resistance, 12 had N155H alone, 1 had N155H + Q148R and 1 had Y143C. Although these were naïve patients without exposure to NRTIs or PIs, 3/53 had NRTI mutations (M184I, K65R, M41L), and 1/57 had a primary protease mutation (L76V).

The frequency of integrase mutations was associated with higher baseline viral load: 7.1% when <100,000 copies/mL, 21.4% when 100,000-500,000 copies/mL, and 53.8% when >500,000 copies/mL,  $p=0.006$  for the trend). However, viral load at failure was not significantly different in those patients who failed with vs without INI mutations: median 615 copies/mL (IQR: 192 – 14864) vs. 361 copies/mL (IQR: 137 – 990) respectively,  $p=0.27$ . Of note, integrase mutations were detected in four patients with viral load between 50 and 200 copies/mL.

All sequenced viruses at virologic failure remained susceptible to dolutegravir.

### Impact of E157Q on dolutegravir

A case study reported a new raltegravir associated mutation that conferred cross resistance to dolutegravir. [4]

This was in a patient who after five months on initial raltegravir/abacavir/3TC treatment still had viral load at 3.9 log copies/mL. This combination was chosen to minimise drug interactions to immunosuppressant drugs related to a recent kidney transplant.

Raltegravir was switched to dolutegravir 50 mg twice-daily which had no impact on viral load. Retrospective resistance testing showed that the E157Q mutation present at the time of the switch was preexisting at baseline. Phenotypic testing confirmed high level resistance to dolutegravir (with an inhibitory quotient of 37.9). The patient achieved viral suppression with a second switch of dolutegravir to darunavir/ritonavir.

### Subtype B may have higher vulnerability to integrase resistance

Raltegravir and elvitegravir both have a lower genetic barrier to HIV drug resistance and mutations rapidly accumulate in the context of suboptimal viral suppression. This significantly reduces sensitivity to both dolutegravir and cabotegravir. Limited information is available on the role of HIV subtype and susceptibility to integrase resistance as clinical studies were predominantly in patients with subtype B.

A UK study suggested that vulnerability to resistance might be



higher in patients with subtype B compared to non-B subtypes, and this finding might be clinically important in resource-limited settings. The group analysed sequences from 255 people who were raltegravir-experienced, 209/255 of which (82%) were subtype B. Non-B subtypes were predominantly subtype C and CRF02 but included nine other variants including A, D, F, G, CRF01, CRF06, and CRF09. [5]

Overall 113/255 (44%) patients had one or more major integrase mutation: N155H (n=57, 22%), G140S (n=33, 13%), Q148H (n=28, 11%), and Q148R (n=15, 6%). A total of 36/44 (82%) patients with Q148H/R/K also had the G140A/C/S compensatory mutation that restores the fitness of mutations at position 148.

Mutations at both codons 148 and 140 were both significantly more prevalent in subtype B compared to non-B sequences, which resulted in higher predicted cross resistance to dolutegravir, see Table 1. These differences were not explained by slightly higher viral load in subtype B (approximately 3,500 copies/ml (IQR: 1,470-25,700) vs. 1,800 (IQR: 550-11,660), respectively (p=0.33).

**Table 1: Prevalence of major integrase mutations in raltegravir-experienced patients**

	B	non-B	p-value
Q148H/R/K	42/209 (20%)	2/46 (4%, subtypes C and G)	0.009
G140A/C/S	36/209 (17%)	1/46 (2%, subtype G)	0.005
predicted cross-Rx to dolutegravir	42 (20%)	2 (4%) in B vs. non-B	0.009

A second analysis of 533 sequences from samples from raltegravir-naïve patients (subtype B 399/533, 75%) found no major integrase mutations. Analysis of sequences showed that emergence of G140S required a single nucleotide substitution in subtype B but all non-B sequences analysed required two substitutions.

#### C O M M E N T

**The significantly lower rates on resistance in non-B subtypes further emphasises the potential role for use in resource-limited settings where other subtypes are more dominant.**

#### References

Unless stated otherwise, references are to the Programme and Abstracts of the XXIV International HIV Drug Resistance Workshop, 21-22 February 2015, Seattle, Washington.

1. Duda K et al. Characterization of NNRTI and INI resistance mutations observed in a study subject on oral two-drug maintenance therapy with 10 mg cabotegravir + 25 mg rilpivirine. Poster abstract 13.
2. Lambert-Niclot S et al. Analyses of emergent drug resistance from the NEAT 001/ ANRS 143 trial: raltegravir + darunavir/ritonavir vs. tenofovir/emtricitabine + darunavir/ ritonavir. Abstract 21.
3. Raffi F et al. First-line raltegravir (RAL) + darunavir/ritonavir (DRV/r) is non-inferior to tenofovir/emtricitabine (TDF/FTC) + DRV/r: the NEAT 001/ANRS 143 randomised trial. 21st CROI, 3-6 March 2014, Boston. Late breaker oral abstract 84 LB.  
<http://www.croiwebcasts.org/console/player/22164>
4. Danion F et al. Non virological response to a dolutegravir-containing regimen in a patient harboring a E157Q- mutated virus in the integrase region. Abstract 43.
5. Geretti AM et al. HIV-1 Subtype influences the pathways of genotypic resistance to integrase inhibitors. Abstract 75.

## Drug resistance in children after PMTCT and early treatment

**Simon Collins, HIV i-Base**

**With fewer treatment options, especially in resource-limited settings, two studies were notable for highlighting the high rates of drug resistance in young children and that this is often compounded by transmitted resistance.**

Resistance test results were presented for a cohort of children in Burkino Faso and Côte d'Ivoire aged < 2 years who were enrolled from September 2011 to January 2013 on first-line lopinavir/ritonavir based combinations, whose treatment was failing (defined as viral load >1000 copies/mL at 12 months). [1]

Of 156 children enrolled, 28 (18%) had virologic failure. Median viral load was 5 million copies/mL (range 4.4 to 8.2 log copies/mL). All samples were amplified and 21/28 (75%) had resistance to at least one drug. Among those, 11/21 (52%) were primary mutations acquired during therapy and 5 (25%) attributed to PMTCT intervention. The most common mutations were M184 (57%), K103N (18%), Y181C (11%) and E138G (3.6%). One sample had 3-class resistance to NRTI, NNRTI and PI.

The impact of ARV exposure as part of PMTCT on drug resistance in children who became infected was reported in a cohort of children from Mozambique. Results were from dry blood spot samples that had formed their initial diagnosis.

Of 496 samples collected, 429 (86%) were successfully genotyped, 97% were subtype C.

NNRTI resistance (Y181C, E138A and G190A) was present in 52.9% and NRTI resistance in 11.4% (mainly M184V). Maternal use of ART was significantly associated with NRTI resistance, (OR 2.41; p<0.05).

#### C O M M E N T

**A poster from the ARROW study at CROI 2014, [3] joins other studies in older children [4, 5] that suggest perinatally acquired resistance from nevirapine exposure might not necessarily translate into poor response to nevirapine-based treatment.**

#### References

Unless stated otherwise, references are to the Programme and Abstracts of the XXIV International HIV Drug Resistance Workshop, 21-22 February 2015, Seattle, Washington.

1. Toni TA et al. Virologic failure and profiles of resistance after 12 months of antiretroviral lopinavir-based therapy in children early treated before the age of two, in West Africa. Abstract 33.
2. Ismael N et al. Primary drug resistance among children infected with HIV-1 in Mozambique: impact of maternal and neonatal prophylaxis. Abstract 78.
3. Musoke P et al. SdNVP exposure and ART response in children <3 years initiating ART in the ARROW trial. CROI, March 3-6, 2014, Boston. Poster abstract 894.  
<http://www.croiconference.org/sessions/sdnvp-exposure-and-art-response-children>
4. Lindsey JC et al. Predictors of virologic and clinical response to nevirapine versus lopinavir/ritonavir-based antiretroviral therapy in young children with and without prior nevirapine exposure for the prevention of mother-to-child HIV transmission. The Pediatric Infectious Disease Journal 2014 (33):846-854.
5. Musoke P et al. Response to antiretroviral therapy in HIV-infected Ugandan children exposed and not exposed to single-dose nevirapine at birth. Journal of AIDS 2009 (52):560-568.

## ON THE WEB

### *Online video resources*

#### **START study video**

Check out the new video on the International START study, written and recorded by Moses Supercharger, the community advocate from Uganda on the START community Advisory Board.

The video was launched at the START Investigator meeting held just prior to CROI in Seattle.

<http://youtu.be/RXu2u36nY8Q>

Many of the children in the video are HIV positive.

### *Community reports*

#### **NAT report: Young MSM in the UK**

Report from NAT from an online survey of over 1000 young MSM (14-19 years) in the UK about where get information about sex, relationships and HIV and how helpful they find it.

[http://www.nat.org.uk/media/Files/Publications/Boys\\_Who\\_Like\\_Boys.pdf](http://www.nat.org.uk/media/Files/Publications/Boys_Who_Like_Boys.pdf) (PDF)

- Almost a third thought HIV might be caught from kissing
- Nearly three-quarters didn't know about PEP.
- Three quarters had not received any information about same sex relationships at school, with a third not receiving any information on HIV transmission and safer sex.
- Over half (55%) had been bullied at school because of their sexual orientation. Of these, 99% reported this from another pupil and over a third (39%) from a teacher or other adult.

#### **Diabetes and HIV: special issue of RITA**

Highly recommended latest issue of RITA offers a detailed look at diabetes in people with HIV.

The PDF for this issue is available online:

<http://centerforaids.org/pdfs/0215rita.pdf>

#### **Guidance on reporting results of clinical trials**

The multi-regional clinical trials centre at Harvard have produced two very useful resources on reporting research results to community.

**Return of results guidance document and toolkit** (draft February 2015)

[http://mrct.globalhealth.harvard.edu/files/mrct/files/mrct\\_at\\_harvard\\_ror\\_guidance\\_5\\_feb\\_2015b.pdf](http://mrct.globalhealth.harvard.edu/files/mrct/files/mrct_at_harvard_ror_guidance_5_feb_2015b.pdf) (PDF)

[http://mrct.globalhealth.harvard.edu/files/mrct/files/mrct\\_at\\_harvard\\_ror\\_toolkit\\_5\\_feb\\_2015.pdf](http://mrct.globalhealth.harvard.edu/files/mrct/files/mrct_at_harvard_ror_toolkit_5_feb_2015.pdf) (PDF)

## FUTURE MEETINGS

### **Conference listing 2015/16**

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

#### **21st BHIVA Spring Conference**

21 - 24 April 2015, Brighton, UK

<http://www.bhiva.org/AnnualConference2015.aspx>

#### **Towards an HIV Cure Symposium**

18-19 July 2015, Vancouver, British Columbia, Canada

<http://hivcure.ias2015.org>

#### **8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015)**

19-22 July 2015, Vancouver, British Columbia, Canada

<http://www.ias2015.org>

#### **17th International Workshop on Co-morbidities and Adverse Drug Reactions**

Date and venue TBC, but linked to EACS in Barcelona

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

#### **15th European AIDS Conference (EACS)**

21-24 October 2015, Barcelona

<http://www.eacs-conference2015.com>

#### **7th International Workshop on HIV Persistence During Therapy**

8-11 December 2015, Miami

<http://www.hiv-persistence.com>

#### **23rd Conference on Retroviruses and Opportunistic Infections (CROI 2015)**

22-25 February 2016, Boston

<http://www.croiconference.org>

## PUBLICATIONS & SERVICES FROM i-BASE

### **i-Base website: updates for PDA access**

**The i-Base website is designed to meet access standards for PDA, iPad, tablet, Windows 8 and touch screen access.**

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

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

All i-Base publications are available online, including editions of the treatment guides. The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

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

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

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

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

### *Non-technical treatment guides*

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

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

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

- NEW: Introduction to combination therapy (July 2014)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (November 2013)

### *Publications and reports*

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

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

#### **HTB South**

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

#### **HTB Turkey**

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

#### **HTB West Balkans**

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

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

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

#### *Translations of i-Base publications*

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

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

### *Advocacy resources*

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

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

Entry-level curriculum relating to HIV and treatment.

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

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

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

<http://www.ukcab.net>

### *Phoneline and information services*

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

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

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

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

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

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



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

However, any donation that your organisation can make towards our costs is greatly appreciated.

## STANDING ORDER DONATION

## THANK YOU FOR YOUR SUPPORT

Title: \_\_\_\_\_ First Name \_\_\_\_\_ Surname \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_ Postcode \_\_\_\_\_

Email \_\_\_\_\_ @ \_\_\_\_\_

Telephone (s) \_\_\_\_\_

Please pay HIV I-Base £ \_\_\_\_\_ each month until further notice

Please debit my account number \_\_\_\_\_

Name of account (holder) \_\_\_\_\_ Bank sort code \_\_\_\_/\_\_\_\_/\_\_\_\_

Starting on \_\_\_\_/\_\_\_\_/\_\_\_\_ (DD/MM/YY)

Signature \_\_\_\_\_ Date \_\_\_\_/\_\_\_\_/\_\_\_\_ (DD/MM/YY)

To: Manager: (Bank name, branch and address)

\_\_\_\_\_  
\_\_\_\_\_

**Please complete the above and return to: HIV i-Base, 57 Great Suffolk Street, London SE1 0BB**

(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.  
Sort Code: 60-12-14. Account Number: 28007042)

### ONE-OFF DONATION

I do not wish to make a regular donation at this time but enclose a one-off cheque in the sum of £ \_\_\_\_\_.

I wish to make a one of donation (minimum £12.50 inc p&p) for the Treatment Literacy Photogrphay Book £ \_\_\_\_\_.

### GIVE AS YOU EARN

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

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

### REFUNDS FROM THE TAX MAN

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

**However you chose to donate to i-Base,  
we would like to thank you very much for your support.**