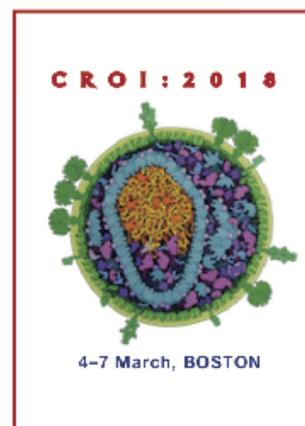


16 April 2018: no.7

*Further reports from CROI 2018*

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## h-tb

### HIV TREATMENT BULLETIN

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## EDITORIAL

### As CROI is a conference that keeps on giving, this issue continues with further reports from this important meeting.

This slim edition of HTB has articles related to pregnancy, paediatric care, drug-drug interactions and side effects of ART.

New results on the use of TB prophylaxis during pregnancy are important enough to recommend re-evaluating current guidelines.

A drug-drug interaction study suggests efavirenz might reduce the effectiveness of a contraceptive vaginal ring.

Plus, two studies providing data on TAF in adolescents showing similar results to adults, including one using bictegravir.

Finally, two reports by guest writer Dr Satyajit Das who reviews several studies on management of cardiovascular risk and a poster looking at the role of the M184V mutation in 3TC-containing dual therapy.

The next issue will include news from the BHIVA/BASHH joint conference being held in Edinburgh from 17 to 20 April 2018.

### Subscriptions

To join the email list for HTB please register free online:

<http://i-base.info/htb/about/subscribe>

### i-Base 2018 appeal: we still need your help...

Last year we launched a funding appeal to help i-Base continue to provide free publications and services.

Your help has been inspiring – and we hope this support will continue during 2018. If 1000 people support us with £5 a month we will be on course to meet our shortfall.

HTB is the UK's longest running activist HIV treatment publication - starting as DrFax from 1996-2000 and relaunched as HTB from 2000-2018.

We are the only HIV organisation to provide free booklets to NHS clinics on HIV treatment. All support is appreciated.

<http://i-base.info/i-base-appeal-we-need-your-help>



## IN MEMORY

### Professor David Cooper

**It is with great sadness that we report the death of Professor David Cooper, one of the leading HIV doctors in Australia, and who was internationally respected for his impact on HIV care over many decades.**

David had been involved with HIV since the first HIV cases in the early 1980s and he went on to found and lead the Kirby Institute in Sydney.



*Professor David Cooper*

He was closely linked to many global research initiatives including cofounding the HIV-NAT initiative for research for south-east Asia and he was president of the International AIDS Society from 1994 to 1998.

His group conducted several important ART optimisation studies including START, ENCORE-1 and SECOND-LINE, which continue to influence global guidelines.

David had many friends in the UK (including at i-Base), recently presenting at the BHIVA conference. He was a kind and generous man, committed to the care of HIV positive people, and he will be greatly missed.

With many international tributes, the following links provide insight into David's life and work.

#### *Kirby Institute*

<https://kirby.unsw.edu.au/news/kirby-institute-director-professor-david-cooper-ao-passes-away>

*Sydney Morning Herald: David Cooper, leader in the global fight against HIV*

<https://www.smh.com.au/national/david-cooper-leader-in-the-global-fight-against-hiv-20180327-h0y0r7.html>

*Webcast of David talking about his time leading IAS.*

<http://www.iasociety.org/The-latest/News/ArticleID/182/Remembering-David-Cooper>

## CONFERENCE REPORTS

### Conference on Retroviruses and Opportunistic Infections (CROI 2018)

4–7 March 2018, Boston

#### Introduction

**We continue our reports from CROI 2018, which was held this year from 4 - 7 March in Boston.**

CROI is one of the most important HIV conferences and comprehensive conference material is available free online.

This includes the full programme and abstracts with webcasts from oral presentations. Approximately 1100 new studies were selected for the conference this year.

<http://www.croiconference.org>

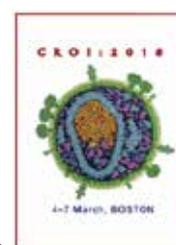
<http://www.croiconference.org/abstracts/search-abstracts> (abstracts and posters)

<http://www.croiwebcasts.org> (webcasts)

Reports from CROI 2018 in this issue include:

- No increased risk of IRIS in people with low CD4 counts receiving raltegravir in the REALITY trial
- Isoniazid preventive TB therapy in pregnancy and postpartum: recommendations now need to be re-evaluated
- Efavirenz could decrease effectiveness of the vaginal contraceptive ring
- Switch to TAF appears safe and effective in adolescents: similar PK to adults
- Doubling raltegravir dose might overcome interaction with rifampicin in children aged 2 to 6
- Twice-daily bictegravir does not overcome drug interaction with rifampicin in adults
- Reducing risk of myocardial infarction (MI) in HIV positive people
- M184V mutation associated with increased risk of viral blip but not viral failure with 3TC-based dual therapy

i-Base reports link to key studies, and hyperlinks take you to the full results. Earlier reports from CROI are included in the March issues of HTB (numbers 5 and 6).

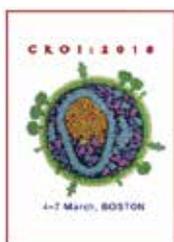


CROI 2018: ANTIRETROVIRALS

## No increased risk of IRIS in people with low CD4 counts receiving raltegravir in the REALITY trial

Polly Clayden, HIV i-Base

**Despite more rapid viral load decline with a raltegravir-intensified regimen compared with a standard one, there was no evidence that this increased the risk of IRIS in people starting ART with advanced HIV. This important finding from the REALITY trial was presented at CROI 2018.**



The REALITY trial, conducted in ART naive adults and children with less than 100 CD4 cells/mm<sup>3</sup> in sub-Saharan Africa, showed that raltegravir (RAL)-intensified treatment led to faster viral load decline but no reduction in mortality or WHO 3/4 events.

As integrase inhibitors are steadily replacing NNRTIs first-line, there is concern that rapid viral load reduction might increase rates of immune reconstitution inflammatory syndrome (IRIS) in people starting ART with very low CD4 – which is still common in low- and middle-income countries.

Diana Gibb presented an evaluation of rates of IRIS events among people receiving treatment intensified with RAL versus standard ART on behalf of the REALITY investigators.

Participants were randomised to start ART of 2NRTI + NNRTI with 12 weeks RAL (standard of care; SoC + RAL) vs without (SoC). A blinded endpoint review committee adjudicated serious adverse and WHO grade 3/4 events, causes of death and compatibility with IRIS. Predictors of time to first fatal/non-fatal IRIS-compatible event were identified using backwards elimination (exit  $p=0.05$ ) treating death from other causes as a competing risk.

Overall 1805 participants with median age of 36 years (4% were 5–17 years), CD4 37 cells/mm<sup>3</sup> and viral load 249,770 copies/mL – almost three quarters of whom had 100,000 copies/mL or more – were randomised to SoC + RAL ( $n=902$ ) vs SoC ( $n=903$ ).

Approximately 90% of participants received an efavirenz-based SoC regimen and 80% an TDF/FTC NRTI backbone.

At week 4 from starting ART the percentage of participants with viral load <50 copies/mL was 41.0% vs 13.4% in the SoC + RAL vs SoC arms respectively; at week 12 these values were 71.9% vs 51.7% (both  $p<0.0001$ ). By weeks 24 and 48 percentages were similar in both arms, approximately 75% and 80% respectively. Mean change in log<sub>10</sub> viral load at week 4 was -3.4 in SoC + RAL and -2.7 in SoC ( $p<0.001$ ).

All-cause mortality at 24 weeks was similar in both arms: 10.9% vs 10.2% in SoC + RAL vs SoC. Fatal IRIS was seen in 36 (4.0%) vs 31 (3.4%) in SoC + RAL vs SoC ( $p=0.54$ ) occurring a median 4.4 (IQR 2.6– 9.4) weeks after starting ART. Overall fatal/non-fatal IRIS events occurred in 89 (9.9%) vs 86 (9.5%) in SoC + RAL vs SoC ( $p=0.79$ ). Over half of the fatal and non-fatal IRIS events in both arms were TB IRIS.

Risks of fatal/non-fatal IRIS were independently higher in participants with lower pre-ART CD4 ( $p<0.001$ ), older people ( $p=0.004$ ) and those with TB when starting ART ( $p=0.01$ ).

Enhanced prophylaxis of cotrimoxazole + 12 weeks isoniazid/B6 + 12 weeks fluconazole + 5 days azithromycin + single dose albendazole (also evaluated as a factorial in the REALITY trial) was protective of IRIS vs standard cotrimoxazole alone. Fatal/non-fatal IRIS compatible events occurred in 67 (7.4%) vs 108 (12.0%) in the enhanced vs standard prophylaxis groups ( $p=0.001$ ).

### COMMENT

**These raltegravir data can likely also be applied to dolutegravir as rapid viral load reductions are similar with all integrase inhibitors. The results provide reassurance that the current transition to ART with dolutegravir first-line will not result in increased IRIS.**

**Pre-ART CD4 is still needed to identify people with advanced HIV at high mortality and IRIS risk for whom enhanced prophylaxis would be helpful.**

Reference

Gibb D et al. Impact of raltegravir intensification of first-line ART on IRIS in the REALITY trial. 25th CROI, 4-7 March 2018, Boston. Oral abstract 23.

<http://www.croiconference.org/sessions/impact-raltegravir-intensification-first-line-art-iris-reality-trial> (abstract)

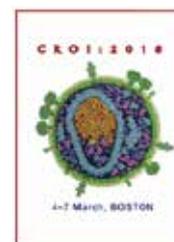
<http://www.croiwebcasts.org/console/player/37060> (webcast)

CROI 2018: PREGNANCY

## Isoniazid preventive TB therapy in pregnancy and postpartum: recommendations now need to be re-evaluated

Polly Clayden, HIV i-Base

**Isoniazid preventive therapy during and pregnancy and postpartum in HIV positive women receiving ART in high-burden TB settings led to serious adverse events with no reduction in TB cases, according to findings from IMPAACT P1078/TB APPRISE.**



Adverse pregnancy outcomes were higher among women starting isoniazid (INH) preventative therapy (IPT) in pregnancy compared with postpartum in the study. These data were presented as a late breaker by Amita Gupta at CROI 2018.

IPT is currently recommended by WHO for people with HIV who are at high risk of TB with strong evidence, based on over 10 randomised trials. IPT is also recommended for pregnant HIV positive women but informed by weak evidence as not a single IPT trial included them. Previous data has found INH to

be associated with increased liver damage in pregnant and postpartum women.

The IMPAACT P1078 investigators hypothesised that IPT can be safely started during pregnancy in HIV positive women.

This was a phase 4 double-blind, placebo-controlled, non-inferiority trial that randomised women to start IPT for 28 weeks either in pregnancy (immediate arm) or at 12 weeks postpartum (deferred arm) in HIV positive women from TB-endemic areas in Africa, Asia, and Haiti. There were 13 sites across eight countries.

Women were randomised 1:1 to either INH (300mg daily) for 28 weeks followed by placebo or to placebo until week 12 postpartum then INH for 28 weeks. Mother-infant pairs were followed to week 48 postpartum. Safety evaluations were every four weeks.

The primary endpoint was treatment-related maternal adverse events grade 3 or higher/permanent drug discontinuation due to toxicity. Secondary outcomes were maternal hepatotoxicity, maternal/infant death, TB, adverse pregnancy outcomes, and infant adverse events.

The non-inferiority margin was an incidence rate of 5/100 person-years (PY), assuming a 5/100 PY incident rate in the deferred arm (based on data in non-pregnant HIV positive adults).

Of 956 women enrolled (477 immediate and 479 deferred arms), 93% were black and 7% Asian. Median age was 29 years and CD4 493 cells/mm<sup>3</sup>. Almost all (955) were on ART (85% efavirenz-based) and 63% had undetectable viral load. Approximately a third had latent TB. Approximately two thirds of women were enrolled at 24 to 34 weeks gestation and the remainder at 14 to 24 weeks. Median follow-up was 58.6 weeks.

In intent to treat analysis, 147 women (15%) reached the primary endpoint: 74 and 73 in the immediate and deferred arms respectively. Incidence rates were 15.4 and 14.9 per 100PY, respectively: IRD 0.5 (95% CI: -4.4 to +5.4).

Grade 3 and above maternal adverse events occurred in 145/477 (30.5%) and 136/479 (28.4%): IRD 4.2 (95% CI: -3.6 to +12.0).

Overall, 45 women permanently discontinued due to toxicity: 35 protocol-defined toxicity; nine non protocol-defined low-grade toxicity and one woman died due to toxicity. Almost all were liver function adverse events.

There were six maternal deaths (two in the immediate and four in the deferred IPT arms). All occurred after delivery (at 5, 5, 7, 12, 19 and 40 weeks). Four deaths were due to hepatotoxicity, two were judged to be related to INH. All women were receiving efavirenz-based ART.

After a review of the first two deaths, the DSMB requested a participant letter providing explicit information about signs and symptoms of hepatotoxicity and the risk of death from INH and ART. This led to 77 (8%) women withdrawing consent before the study was completed.

Overall, adverse pregnancy outcomes were significantly higher in the immediate vs deferred arm: 23% vs 17%,  $p=0.009$ . These were largely driven by foetal death and low birth weight.

A total of 380 infants (42%) had grade 3 or 4 adverse events with no significant differences by treatment arm.

Maternal and infant TB incidence were very low: 0.6% and 0.2% respectively, with no significant differences by treatment arm.

Dr Gupta concluded that adverse events were higher than expected, at least possibly attributed to INH in both arms. The non-inferiority margin was not reached for the primary maternal safety endpoint, so the investigators could not confirm that INH is safe for the mother. She noted that they did not find significant differences in maternal hepatotoxicity, grade 3 and above infant adverse events or maternal infant death between immediate and deferred IPT.

But adverse pregnancy outcomes were more frequent with IPT during pregnancy. And timing of IPT did not affect TB risk. The conclusions included a suggestion that current WHO guidelines on IPT in pregnancy for HIV positive women receiving ART now need re-evaluation to weigh the risks and benefits.

## C O M M E N T

**This is a cautionary tale.**

**Although IPT is recommended for this population, IMPAACT P1078 is the first randomised trial of TB prevention in HIV positive pregnant and postpartum women at high risk of TB.**

**Once again these findings highlight the importance of earlier inclusion of pregnant women in clinical trials. Not doing so can lead to risky recommendations or delayed roll out of potentially beneficial new treatments to the general population – as we are seeing with dolutegravir.**

Reference

Gupta A et al. Randomised trial of safety of isoniazid preventive therapy during or after pregnancy. 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. Oral abstract 142LB.

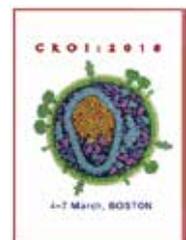
[www.croiconference.org/sessions/randomized-trial-safety-isoniazid-preventive-therapy-during-or-after-pregnancy](http://www.croiconference.org/sessions/randomized-trial-safety-isoniazid-preventive-therapy-during-or-after-pregnancy) (abstract)

[www.croiwebcasts.org/console/player/37314](http://www.croiwebcasts.org/console/player/37314) (webcast)

## Efavirenz might decrease effectiveness of the vaginal contraceptive ring

**Polly Clayden, HIV i-Base**

**Efavirenz and atazanavir/ritonavir both alter hormone exposure from the vaginal ring in HIV positive women. But, unlike efavirenz, atazanavir/ritonavir is not expected to have an impact on the ring's effectiveness. This phenomenon is similar or greater to that previously reported with oral hormonal contraceptives.**



These findings from the ACTG 5316 pharmacokinetic (PK) study were presented by Kimberly Scarsi of University of Nebraska Medical Center at CROI 2018.

The vaginal ring (Nuvaring) contains etonogestrel/ethinyl estradiol (ENG/EE) 120/15 mcg/day and provides a month of hormonal

contraception. Contraceptive hormones delivered in this way achieve lower concentrations than those with oral or injectable methods but sufficient levels to provide contraception.

Drug-drug interactions (DDI) occur with oral hormonal contraceptives and some antiretroviral therapy (ART). But the impact of ART on hormone exposure from a vaginal ring is unknown.

ACTG 5316 was a phase 2 multicountry, multicentre, non-randomised, parallel group, PK assessment of HIV positive women 16 years old and above with sites in Africa, Asia, South America and North America.

The study evaluated three groups of participants: women not yet receiving ART (control group; n=25); receiving efavirenz (EFV)-containing ART 600mg daily (n=25); and receiving atazanavir/ritonavir (ATV/r)-containing ART 300/100 mg daily (n=24). Women in the control group had CD4 above 350 cells/mm<sup>3</sup>, the threshold for starting ART at the time the study was conducted. All women consented to use an additional method of contraception during the evaluation.

Participants were approximately 35 years of age (women in the control group were slightly younger than in the two ART groups), 50% black, and 35% Hispanic.

Single PK measurements of ENG and EE were taken on days 7, 14, and 21. Plasma hormone PK exposure was compared between each ART group and the control group.

Compared to the control group, participants in the EFV group had 76–79% lower ENG and 53–57% lower EE over 21 days (all comparisons p<0.001).

Participants in the ATV/r group had 71–79% higher ENG (all p<0.001), but 29–35% lower EE (p=0.066, 0.032 and 0.004 at days 7, 14 and 21, respectively) over 21 days compared to the control group.

Approximately 25% of women experienced mild or grade 2 adverse events – these were mostly abnormal vaginal discharge or menstrual irregularities.

The investigators concluded that ATV/r-based ART is unlikely to have an impact on the effectiveness of the vaginal ring but EFV lowered both ENG and EE and might decrease its effectiveness.

#### C O M M E N T

**The effect of EFV on other methods of hormonal contraception has been well characterised previously – including by excellent work from Dr Scarsi's group. This inconvenient aspect of EFV is not always considered enough in discussions of optimum ART regimens.**

**This study highlights the importance of understanding DDI of drugs given by vaginal ring which should be looked at routinely during the development of new technologies.**

Reference

Scarsi K et al. Vaginal contraceptive hormone exposure profoundly altered by EFV- and ATV/r-based ART. 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. **Oral abstract 141.**

<http://www.croiconference.org/sessions/vaginal-contraceptive-hormone-exposure-profoundly-altered-efv-and-atvr-based-art> (abstract).

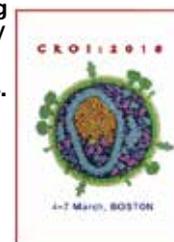
<http://www.croiwebcasts.org/console/player/37313> (webcast)

CROI 2018: PAEDIATRICS

## Switch to TAF appears safe and effective in adolescents: similar PK to adults

Polly Clayden, HIV i-Base

**Pharmacokinetics, safety and efficacy of tenofovir alafenamide (TAF) in adolescents receiving the coformulation with emtricitabine (FTC/TAF) was similar to adults at 24 weeks, according to data presented at CROI 2018. [1]**



Coformulated FTC/TAF is approved for adolescents aged 12 to 18 years in the US and EU and is a recommended first-line NRTI backbone for adolescents in the US.

FTC/TAF was developed with two versions: 200/10 mg and 200/25 mg for administration with boosted and unboosted agents respectively. FTC/TAF 200/25 mg is the only dose strength approved by the FDA.

Safety and efficacy of TAF in adolescents has been shown in studies of elvitegravir/cobicistat/FTC/TAF and bicittegravir/FTC/TAF. Safety, pharmacokinetics (PK), and efficacy of other FTC/TAF-containing regimens in adolescents have not been reported. These data are the first to be presented on FTC/TAF with other with non-Gilead third agents in HIV positive adolescents.

This was a phase 2/3, open-label, multicentre, single arm switching study in 28 virologically suppressed adolescents aged 12 to 18 years weighing at least 35 kg.

Participants were a median age 14 years (range 12 to 17) and weight 45 kg (range: 35 to 62); 57% male and 43% black. Median CD4 count was 909 cells/mm<sup>3</sup>. Third agent was efavirenz or lopinavir/ritonavir.

Exposures of TAF and TFV were consistent with those of adults regardless of third agent.

Most common adverse event (AE) was viral upper respiratory infection (32%) followed by headache (25%). Two participants had serious, unrelated AEs. Five had TAF-related AEs; no participant discontinued study drug due to an AE.

Mean % change from baseline in BMD at week 24 was +3.56% for spine and +1.57% for total body less head (TBLH). Mean change in BMD height-age adjusted z-score was 0.00 for spine and -0.03 for TBLH. Mean (SD) estimated change in glomerular filtration rate was 2.0 (20.95) mL/min/1.73 m<sup>2</sup>.

The majority of participants (92.9%, 26/28) maintained viral load <50 copies/mL. Mean reductions in CD4 count and CD4% from baseline were -130 cells/mm<sup>3</sup> and -0.2%.

#### C O M M E N T

**CROI 2018 also showed the first data from the fixed dose combination of bictegrovir/FTC/TAF in 24 virologically suppressed adolescents. [2]**

**At week 24 PK, safety and efficacy of all the component agents were also similar to those reported in phase 3 trials in adults.**

**There were no grade 3/4 AEs. One participant experienced grade 1 vomiting, judged related to study drug that resolved on the same day with no adjustment to the regimen.**

**This fixed dose combination is a considerably smaller tablet than those currently most commonly prescribed (as will generic versions of dolutegravir/FTC/TAF for low- and middle-income countries) – its shape and size were reported to be acceptable.**

#### References

- Chen J et al. Safety, PK, & efficacy of FTC/TAF in HIV-infected adolescents (12–18 yrs). 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. Poster abstract 843. <http://www.croiconference.org/sessions/safety-pk-efficacy-ftctaf-hiv-infected-adolescents-12-18-yrs> (abstract and poster)
- Guar A et al. Bictegrovir/FTC/TAF single-tablet-regimen in adolescents: week 24 results. 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. Poster abstract 844. <http://www.croiconference.org/sessions/bictegrovirftctaf-single-tablet-regimen-adolescents-week-24-results> (Poster and abstract)

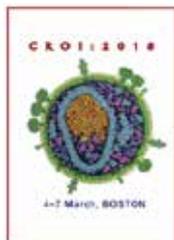
## Doubling raltegravir dose could overcome interaction with rifampicin in children aged 2 to 6

Polly Clayden, HIV i-Base

**Doubling the dose of raltegravir for children aged two to six years with HIV/TB coinfection who were taking rifampicin achieved adequate concentrations and was found to be safe. Results from IMPAACT P1101 were presented at CROI 2018.**

A dose of 12 mg/kg of raltegravir (RAL) can be used for TB-HIV co-infected children taking rifampicin in this age group.

IMPAACT P1101 is a phase 1/2 dose finding study of RAL for HIV positive children receiving rifampicin (RIF)-containing TB treatment for at least one week. The study has three age cohorts: cohort 1: 2 to <6 years (results shown here), cohort 2: 6 to <12 years of age and cohort 3: 4 weeks to <2 years. Each cohort needs 12 participants for pharmacokinetic (PK) and safety evaluations.



Participants start a three-drug ART regimen at enrolment, including chewable RAL formulation at 12 mg/kg/dose twice daily (twice the recommended paediatric dose).

Intensive RAL PK sampling is performed one week after ART is started and then a fourth ARV is added to the regimen – standard of care with TB treatment, usually efavirenz or lopinavir/ritonavir.

RAL is stopped when TB treatment is completed and participants followed for a further three months. PK targets are a geometric mean (GM) AUC<sub>12h</sub> of 6–20 mgxh/L (14–45 uMxh) and GM C<sub>12h</sub> ≥ 33 ng/mL (≥75 nM). The study defines virologic success as at least 1 log<sub>10</sub> copies/mL reduction from baseline or viral load ≤400 copies/mL at week 8.

The 12 participants were 7 (58%) male, 100% black and median age of 3 years (IQR: 2 to 5). Median baseline viral load 4.91 log<sub>10</sub> copies/mL (IQR: 4.42 to 5.42), CD4 count 559 cells/mL (IQR: 390 to 1185) and CD4 per cent 15% (IQR 9–24). Median follow up was 33 weeks (IQR: 28 to 37). The majority of participants (11/12) received efavirenz as the fourth drug and one participant received lopinavir/ritonavir.

At week 1 GM AUC<sub>12h</sub> was 12.8 mgxh/L (28.8 uMxh; CV 50%) and GM C<sub>12h</sub> was 102 ng/mL (230 nM; CV 76%).

Median CD4 change from baseline was 101 cells/mm<sup>3</sup> and 6.1%.

One participant had grade 3 AST and grade 3 ALT elevations at week 4 judged possibly related to RAL. RAL/ART was temporarily stopped for 21 days and then restarted, with no recurrence.

At week 8 11/12 (92%) participants achieved virologic success and 9/12 (75%) viral load <50 copies/mL; 10/11 remained <400 copies/mL through week 24. The participant who did not achieve virologic success was the same one that stopped ART temporarily.

#### C O M M E N T

**These data are welcome as options for treating children with coinfection are scarce.**

**Results from cohorts 2 and 3 are needed before the double dose of RAL can be recommended for all infants and children with HIV/TB coinfection who are treated with rifampicin.**

#### Reference

Myers T et al. P1101: phase I/II study of raltegravir containing regimen in HIV-TB cotreated children. 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. Poster abstract 845.

<http://www.croiconference.org/sessions/p1101-phaseiii-study-raltegravir-containing-regimen-hiv-tb-cotreated-children> (abstract and poster)

CROI 2018: DRUG INTERACTIONS

## Twice-daily bictegrovir does not overcome drug interaction with rifampicin in adults

Polly Clayden, HIV i-Base

**Twice daily dosing of bictegrovir is not sufficient to mitigate the induction effect of rifampicin and still achieve adequate bictegrovir concentrations.**

Results from a drug-drug interaction study of bictegrovir (BIC) and rifampicin (RIF) conducted in HIV negative participants were included in an oral presentation at CROI 2018.

BIC is primarily eliminated by the drug metabolising enzymes CYP3A and UGT1A1. RIF is well-known to be a potent inducer of metabolising enzymes.

A previous study looking at once daily coadministration of the two drugs showed a reduction in BIC concentrations of approximately 75%. This study evaluated the pharmacokinetics (PK) of BIC given twice daily with RIF.

The was a phase 1, open label study with a parallel design. Participants were enrolled into one of two cohorts – 26 per cohort.

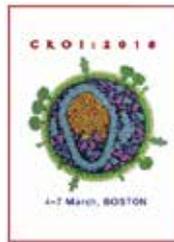
Cohort 1 participants received the fixed dose combination BIC/emtricitabine/tenofovir alafenamide (B/F/TAF) 50/200/25 mg once daily for 28 days. Cohort 2 participants received B/F/TAF twice daily plus RIF 600 mg once daily, for 28 days.

Intensive sampling was performed on day 28. Statistical comparisons for BIC used geometric least squares mean (GLSM) ratios and associated 90% confidence intervals with B/F/TAF once daily as reference.

This evaluation found BIC AUC<sub>0-24h</sub> and C<sub>max</sub> were decreased approximately 61% and 47%, respectively, versus B/F/TAF once daily alone.

BIC C<sub>trough</sub> GLSM was approximately 80% lower, as compared with that with B/F/TAF once daily.

These findings showed that twice daily administration of B/F/TAF with RIF does not mitigate the induction effect sufficiently to give BIC C<sub>trough</sub> concentrations associated with the B/F/TAF registrational phase 3 studies.



Reference

Custodio JM et al. Pharmacokinetics of bictegrovir administered twice daily in combination with rifampin. 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. Oral abstract 34.

<http://www.croiconference.org/sessions/pharmacokinetics-bictegrovir-administered-twice-daily-combination-rifampin> (abstract)

<http://www.croiwebcasts.org/console/player/37074> (webcast)

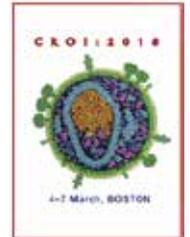
CROI 2018: SIDE EFFECTS &amp; COMPLICATIONS

## Reducing risk of myocardial infarction (MI) in HIV positive people

Satyajit Das, HIV i-Base

**Platelets, leucocytes and thrombosis**

**Several research groups have tried to explain the potential mechanism for the association of increased MI risk and abacavir use reported by the D:A:D study and others.**



This year at CROI 2018 a few studies tried to explore possible mechanisms

Patrick Mallon et al, in an oral presentation and related poster, reported improved platelet activity after switching away from ABC to TAF or TVD use. [1, 2]

Glycoprotein VI (GPVI) is platelet membrane receptor that regulates platelet activation in response to collagen exposure. Activity mediated through cleavage from the platelet surface by metalloproteinase, resulting in soluble GPVI (sGPVI), which can be measured in blood. Low level of this protein can be associated with acute coronary events.

This double blind placebo controlled trial randomised 61 participants with viral suppression on abacavir/3TC to either switch to TAF/FTC or remain on ABC/3TC. All participants continued with their third drug. Platelet aggregation assay and platelet surface markers (sGP VI) were measured at week 4, and 12 by exposing the plasma sample with five different platelet agonists. Participants in the abacavir arm had lower levels of platelet aggregation and sGP VI and switching to TAF regimen improved sGPVI and reduced platelet activity to one platelet agonist at week but not to all others at follow up of 12 weeks.

An in vitro study reported similar result with abacavir use [3]. Platelets isolated from HIV negative donors were incubated with abacavir and TDF. After challenged with platelet activators like collagen or ADP, activation was more marked with abacavir. Abacavir significantly enhanced expression of platelet activation markers whereas TAF and TDF had no effect. The increased degranulation in platelets after incubation with abacavir might indicate enhanced platelet activation and potentially a pro-thrombotic impact.

### C O M M E N T

**Simple HIV and TB co-treatment is essential for low- and middle-income countries so if BIC cannot be administered with RIF this is one reason to suggest this is not good candidate for optimised ART.**

Unlike earlier clinical studies, these observations were made in the absence of HIV infection, allowing assessment of direct pharmacological impacts of abacavir and TDF or TAF on platelets.

One further poster showed that an abacavir-induced pro-thrombotic effect is leucocyte mediated [4] This was a study in mice who were pretreated with abacavir or rofecoxib (which is known to cause vascular thrombi). Abacavir induced dose-dependent vessel occlusion in non-leukopenic mice was of same magnitude as rofecoxib.

However, while the pro-thrombotic effects of rofecoxib were maintained in leukopenic mice, those of abacavir were absent. The researchers concluded that pro-thrombotic effect of abacavir in vivo depends on the presence of leukocytes, thus demonstrating a key role of these cells in the deleterious vascular effects of this drug.

#### C O M M E N T

**Many of these studies did not seem adequately powered to produce conclusive evidence and it is also not clear what magnitude of difference could be clinically significant. Previous MI was an exclusion criteria and it is not known whether participants went on to develop MI or not.**

**Although there has not been increased reports of MI with wider abacavir use in the fixed dose combination with dolutegravir and 3TC, but this might be because prescribing guidelines are being closely followed.**

#### Switching from abacavir to reduce CVD risk

The D:A:D study and other studies have previously shown an increased risk of myocardial infarction (MI) with abacavir use in HIV positive people who are already at high cardiovascular risk.

A poster from Priscilla Hsue and colleagues modelled the impact of interventions that address traditional risk factors on predicted MI rates, including switching from abacavir. The study used a 10-year decision tree model using evidences from published data on MI incidences after modification of potential risk factors. [5]

Assumptions about the effectiveness of interventions were based on publications from the HIV positive or general population, all adjusted for sex, age, and presence of the four risk factors (abacavir use, dyslipidaemia, hypertension and smoking).

The base case used a 50 year old HIV positive man on an abacavir-containing regimen who is also a smoker, with hypertension and hyperlipidaemia.

In this model, replacement of abacavir had the biggest impact, with a 45% reduction in the MI rate compared to those who continued abacavir.

Men who are counselled and treated for smoking cessation which resulted in an 11% MI rate reduction versus those who did not attempt smoking cessation in 10 years.

Treating hypertension and hyperlipidaemia resulted in 19% and 31% reductions in MI risk, respectively. The researcher suggested that abacavir replacement in many cases can potentially reduce the risk of MI more than modifying the traditional risk factors.

#### C O M M E N T

**There is no alternative of reducing the traditional risk factors such as smoking cessation, lowering BP and correcting dyslipidaemia. All are still essential validated health interventions. However, this decision tree model tried to show that MI risk reduction by abacavir substitution can have a significant impact.**

**This should not change current practice in the UK as BHIVA guidelines already recommend against using abacavir in patients who have a high risk of CVD.**

**This study might additionally have selection bias (not discussed in the poster). Although the papers were referenced, the method of paper selection was not discussed.**

#### References

Unless stated otherwise, all references are to the Programme and Abstracts of the 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4-7 March 2018, Boston.

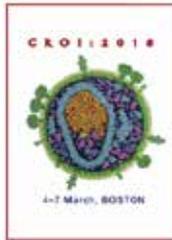
<http://www.croiconference.org>

- Mallon P et al. Platelet function upon switching to TAF vs continuing ABC: a randomized substudy. 25th CROI, 4-7 March 2018, Boston. Oral abstract 80.  
<http://www.croiconference.org/sessions/platelet-function-upon-switching-taf-vs-continuing-abc-randomized-substudy> (abstract)  
<http://www.croiwebcasts.org/console/player/37179> (webcast)
- Mallon P et al. Change in soluble glycoprotein VI (SGPVI) when switching from ABC/3TC to TAF/FTC. 25th CROI, 4-7 March 2018, Boston. Poster abstract 677LB  
<http://www.croiconference.org/sessions/change-soluble-glycoprotein-vi-sgpvi-when-switching-abc3tc-taftc> (abstract and poster)
- Kirk A Taylor et al. Comparative impact of antiretrovirals on human platelet activation. 25th CROI, 4-7 March 2018, Boston. Poster abstract 673.  
<http://www.croiconference.org/sessions/comparative-impact-antiretrovirals-human-platelet-activation> (abstract and poster)
- Victor Collado-Diaz. Leukocytes are key to the pro-thrombotic effects of abacavir. 25th CROI, 4-7 March 2018, Boston. Poster abstract 674.  
<http://www.croiconference.org/sessions/leukocytes-are-key-pro-thrombotic-effects-abacavir> (abstract and poster)
- Hsue P et al. Comparing strategies for reducing myocardial infarction rates in HIV patients. 25th CROI, 4-7 March 2018, Boston. Poster abstract 692.  
<http://www.croiconference.org/sessions/comparing-strategies-reducing-myocardial-infarction-rates-hiv-patients> (abstract and poster)

## M184V mutation associated with increased risk of viral blip but not viral failure with 3TC-based dual therapy

Satyajit Das, HIV i-Base

**Although dual therapy is not recommended in treatment guidelines, this strategy is sometimes used when the option to use a dual NRTI backbone is contraindicated. The impact of the 3TC-associated M184V mutation on viral outcome is unclear, given the resulting impact on reducing viral fitness.**



A retrospective analysis from the Italian Antiviral Resistance Cohort Analysis (ARCA) database looked at risk of viral rebound in people who switched to 3TC-based dual ART when viral load was <50 copies/mL on their current ART.

The analysis included 436 participants, of which 87 had the M184V mutation in a previous resistance test. Patients were followed from the time of switching to the time of virological failure (VF), defined as two consecutive viral load results >50 copies/mL or single result > 200 copies/mL, or discontinuation. The primary aim was to find out the time to virological failure with or without M184V mutation. The secondary aim was to find out the time to virological blips (VB), defined as a single viral result of 50 to 199 copies/mL, and predictors of virological failure and blips between the two groups.

Factors with strongest association of having M184V included older age, longer duration of HIV, longer time to ART and duration of viral suppression, lower CD4 at nadir, HCV coinfection and reduced genotypic sensitivity to the second ART component (all  $p < 0.001$ ).

During 693 person-years of follow-up (PYFU) the incidence of VF was 5.1/100 vs 3.1 per 100 PYFU in M184V positive vs negative groups respectively. Time to VF did not differ between groups and the only predictors of VF in multivariate analysis were higher ( $p=0.035$ ) zenith virological value and HBsAg positivity ( $p=0.005$ ).

In participants with previous viral suppression for more six years, the three year probability of remaining free from VF was 82% vs 92% in the M184V positive vs negative groups respectively (NS,  $p=0.080$ ). The probability of remaining free of VB was 69% vs 91%, respectively, ( $p < 0.001$ ).

M184V was not associated with a higher risk of VF when 3TC was used with a boosted PI or dolutegravir, but there was a higher probability of VB. In participants with M184V, a shorter time of viral suppression appeared to increase the risk of VF and of VB. There were no cases of viral failure in 21 participants with the M184V mutation using dolutegravir plus 3TC, after a median follow-up of 10 months.

The study concluded that prior selection of M184V did not seem to play a significant role on virological efficacy with 3TC+boosted PI or dolutegravir with 3TC as a switch regimen.

Nonetheless, a virological signal was seen for previous M184V and higher probability of viral blips and shorter time of prior viral suppression appearing to increase the risk of virological failure and of virological blips in this group.

### C O M M E N T

**Limitations for this study include retrospective observational design, limited statistical power, no data about adherence, and significant different baseline characteristics of the two groups.**

#### Reference

Gagliardini R et al. Impact of previous M184V on virological outcome of switch to 3tc-based dual therapies. 5th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. Poster abstract 498.

<http://www.croiconference.org/sessions/impact-previous-m184v-virological-outcome-switch-3tc-based-dual-therapies> (abstract and poster)

## PREVENTION

### PrEP engagement workshops

Linked to the ongoing UK PrEP IMPACT trial (see HTB issue 6 for last update), six engagement workshops are planned for community health workers.

The workshops aim to engage with service providers who work with people at risk of HIV, especially from Black and Minority Ethnic (BAME) communities, outside of the sexual health clinic setting. These include:

- GPs in areas of high HIV prevalence.
- Family planning and reproductive health services, including abortion services providers.
- Trans service providers including Gender Identity Clinics.
- Sex worker organisations.
- Youth workers organisations – especially those working with vulnerable youth.
- Migrant support organisations.

The aims of the engagement events include to:

- To increase knowledge about the PrEP IMPACT trial to networks, organisations, and individuals who engage with and are in contact with individuals or groups who might benefit from participation in the trial;
- To identify and map activities that participants in the above events identify as being key to further engagement with other organisations in their networks, and with their target groups;
- To identify the support and communication needs of event participants about the trial and the information they need to inform their target groups about the trial;
- To bring together those with an interest in the trial and share good practice, learning and experiences from those who have successfully recruited diverse populations. All workshops are from 2 pm to 5 pm.

17 April: Bristol - Mercure Grand Hotel, Broad Street, BS1 2EL

23 April: Leeds - Cosmopolitan Hotel 2 Lower Briggate, LS1 4AE

30 April: Leicester - Orange Room, Voluntary Action Leicestershire, 9 Newark Street, LE1 5SN

02 May: Brighton - Brighthelm Centre, North Road, Brighton, BN1 1YD

08 May: Croydon - The Business Xchange Hub, 3-5 Marco Polo House, Lansdowne Road, CR0 2BX

14 May: London - St Stephen's Centre, Mansfield Room, 4th Floor, Chelsea and Westminster Hospital, SW10 9NH

For further details please email:

england.voice-crg@nhs.net

## ON THE WEB

### Legal Aide - an app for people arrested for minor drug possession

#### Release

**The drug charity Release has produced a free app, called Legal Aide, to help people who are arrested for personal possession of drugs. It is a step-by-step guide on how to deal with a drug possession offence.**

The app is for both Apple and Android also available as a PDF download.

This is a guide to your rights, including self-representation, after an arrest for personal possession of drugs under the Misuse of Drugs Act 1971 ('MDA'). This guide will take you through the process step-by-step and explain all possible outcomes as clearly as possible. The aim is to get the best possible result for you, in your personal situation. This might mean getting a cannabis warning instead of a caution, or getting the case sent back to the police for a caution instead of having to go to court.

The guide and app are aimed at people who accept that they are guilty of the offence of possession of a controlled drug and provides them with information on how to navigate the criminal justice system to get the least punitive penalty possible. The majority of the people who are caught in possession of drugs plead guilty to the offence or admit their guilt in order to get an out of court disposal, for example, a cannabis warning or a caution.

If you have been arrested or charged with the offence of possession, but are not guilty of the offence, then you should call us for advice on 020 7324 2989. You can also call us if you need more help, or aren't sure about anything in the guide.

*Please note that legal advice here only applies to offences committed in England and Wales.*

Source and further information

Release. Self-Representation Guide for Drug Possession Offences

<https://www.release.org.uk/publications/self-representation-guide-for-drug-possession-offences>

Release is the national centre of expertise on drugs and drugs law. Founded in 1967, Release provides free non-judgmental, specialist advice and information to the public and professionals on issues related to drug use and to drug laws.

<https://www.release.org.uk>

## IAS reviews

### CROI 2018 articles

<https://www.iasusa.org/pub#croi2018-review-articles>

#### **CROI 2018: Epidemic trends and advances in HIV prevention**

Susan Buchbinder and Albert Y. Liu

<https://www.iasusa.org/sites/default/files/uploads/26-1-buchbinder-liu.pdf> (PDF)

#### **CROI 2018: Basic science review**

Mario Stevenson

<https://www.iasusa.org/sites/default/files/tam/26-1-17.pdf> (PDF)

*Check back for the upcoming complete issue.*

#### **CROI 2018: Advances in antiretroviral therapy**

Hong Van Tieu, Barbara S. Taylor, Joyce Jones, Timothy J. Wilkin,

#### **CROI 2018: Neurologic complications of HIV infection**

Serena S. Spudich and Beau M. Ances

#### **CROI 2018: Complications of HIV infection and antiretroviral therapy**

Judith S. Currier and Diane V. Havlir

#### **CROI 2018: Highlights of viral hepatitis**

Anne F. Luetkemeyer and David L. Wyles

## Cure research

### **HIV Infection - Advances toward a Cure**

Daniel Douek

Transcript of a useful overview of cure research from mid-2017.

<https://www.iasusa.org/sites/default/files/tam/25-4-121.pdf> (PDF)

## TAGline Spring 2018

### **TAGline - Spring 2018 newsletter**

#### **Moving Beyond Aching Slow Trends**

Newsletter from Treatment Action Group, NY about activism that successfully defends or advances vital research or policy.

This issue has a focus on some important recent successes and challenges in moving beyond slow trends and sharply bending the curves on new HIV, hepatitis C, and tuberculosis infections, suffering, and deaths.

<http://www.treatmentactiongroup.org/content/spring-2018-tagline>

## FUTURE MEETINGS

### Conference listing 2018

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

#### **4th Joint BHIVA/BASHH Spring Conference**

17 – 20 April 2018, Edinburgh

[www.bhiva.org](http://www.bhiva.org)

#### **International Workshop on Clinical Pharmacology of Antiviral Therapy 2018**

22 – 24 May 2018, Washington

[www.virology-education.com](http://www.virology-education.com)

#### **12th INTEREST**

29 May – 1 June 2018, Kigali

[interestworkshop.org](http://interestworkshop.org)

#### **10th HIV Paediatrics Workshop**

20 – 21 July 2018, Amsterdam

[www.virology-education.com](http://www.virology-education.com)

#### **22nd International AIDS Conference (AIDS 2018)**

23 – 27 July 2018, Amsterdam

[www.aids2018.org](http://www.aids2018.org)

#### **International Workshop on HIV & Ageing**

13 – 14 September 2018, New York, USA.

[www.virology-education.com](http://www.virology-education.com)

#### **Australasian HIV&AIDS Conference 2018**

24 – 26 September 2018, Sidney

[www.hivaidsconference.com.au](http://www.hivaidsconference.com.au)

#### **HIV Glasgow 2018**

28 – 31 October 2018, Glasgow

[www.hivglasgow.org](http://www.hivglasgow.org)

## PUBLICATIONS & SERVICES FROM i-BASE

### i-Base website

**All i-Base publications are available online, including editions of the treatment guides.**

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

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>

### i-Base treatment guides

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

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

- Introduction to ART (September 2016)
- HIV & quality of life: side effects & long-term health (Sept 2016)
- Guide to PrEP in the UK (November 2016)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (February 2015)
- Guide to HIV, pregnancy & women's health (December 2015)

### New pocket guides

A new series of pocket-size concertina folding leaflets that is designed to be a very simple and direct introduction to HIV treatment.

The first five pocket leaflets are: Introduction to ART, HIV and pregnancy, ART and quality of life, UK guide to PrEP and HCV/ HIV coinfection.

We hope these are especially useful as low literacy resources.

The leaflets use simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

### Order publications and subscribe 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>

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Pocket ART      quantity \_\_\_\_\_      Pocket pregnancy      quantity \_\_\_\_\_

Pocket side effects      quantity \_\_\_\_\_      PrEP for women      quantity \_\_\_\_\_

• **Booklets about HIV treatment****ART in pictures: HIV treatment explained** (*June 2017*): 32-page A4 booklet      quantity \_\_\_\_\_**Guide to hepatitis C coinfection** (*April 2017*): 52-page A5 booklet      quantity \_\_\_\_\_**UK Guide To PrEP** (*November 2016*): 24-page A5 booklet      quantity \_\_\_\_\_**Introduction to ART** (*September 2016*): 48-page A5 booklet      quantity \_\_\_\_\_**HIV and quality of life: guide to side effects and long-term health** (*Sept 2016*): 96-page A5      quantity \_\_\_\_\_**Guide to HIV testing and risks of sexual transmission** (*July 2016*): 52-page A5 booklet      quantity \_\_\_\_\_**Guide to HIV, pregnancy and women's health** (*November 2015*): 52-page A5 booklet      quantity \_\_\_\_\_**Guide to changing treatment: what if viral load rebounds** (*Jan 2018*): 24-page A5 booklet      quantity \_\_\_\_\_• **Other resources****HIV Treatment 'Passports'** - Booklets for patients to record their own medical history      quantity \_\_\_\_\_**Phoneline posters (A4)**      quantity \_\_\_\_\_

Please fax this form back, post to the above address, or email a request to HIV i-Base:

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