

## november-december 2017

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## EDITORIAL

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### **This last issue of HTB for 2017 leads with conference reports from three meetings.**

EACS 2017 was lively with phase 3 results using the pipeline compound fostemsavir, phase 3 results with D/C/F/TAF (the new FDC just approved in Europe) and numerous tentative studies using dolutegravir/3TC dual ART as maintenance therapy. Although i-Base was not able to attend the 8th HIV and Ageing meeting, we review (and recommend) key webcasts and link to coverage from NATAP.

Finally, from IAS 2017, the last of our reports relating to HIV and pregnancy including using raltegravir.

Other selected contents include two articles by Richard Jefferys that analyse peer reviewed papers estimating the size of the latently infected viral reservoir, and the implications of the CANTOS study using the anti-inflammatory antibody canakinumab on heart disease and cancer for HIV. Plus, a review of a very large database on HIV and cancer – with largely positive results from the impact of ART.

We also feature (see below) additional new resources on PrEP – especially a new booklet for women, developed with the Sophia Forum.

This year has not been easy for i-Base, with funding changes moving HTB to electronic-only distribution. So we would like to extend our appreciation and thanks to our readers who supported the 2017 i-Base appeal.

And yes! This appeal continues for any readers who would like to actively support us in 2018 - likely to be just as financially difficult. This online review of i-Base services has more details about the projects you will be supporting.

[i-base.info/wp-content/uploads/2017/11/i-Base-2017-review.pdf](http://i-base.info/wp-content/uploads/2017/11/i-Base-2017-review.pdf)

With this, thank you to all our readers, supporters and contributors, Everyone at i-Base would like to send early best wishes for a happy and productive 2018.

### **Supplements**

Two new patient guides are supplements to the issue of HTB.

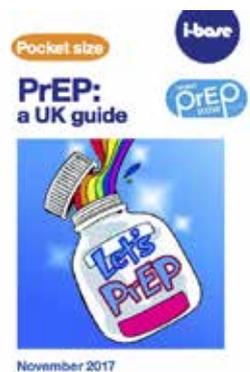
#### **PrEP for women (November 2017)**

A new leaflet about PrEP produced by and for women (with the Sophia Forum).

These small 16-page A7 leaflets were produced to raise awareness of access to PrEP, and to coincide with the launch of the IMPACT trial.

#### **PrEP in the UK (November 2017)**

An updated 16-page A7 pocket leaflet about PrEP in the UK.



## **i-Base 2017 appeal: we need your help....**

**This year, the i-Base 2017 appeal was launched to respond to larger changes in our funding.**

Your regular support can make a big difference.

We could reach our £100,000 target if:

- 500 people support i-Base with £9.00 a month and...
- 1000 people support with £4.50 a month.

**Please become one of our subscribers that help.**

- i-Base continues to provide all services free, including free community publications for all UK clinics.
- The i-Base website gets more than 400,000 users every month. And last year the i-Base Q&A service answered almost 6,000 individual questions from HIV positive people.
- HIV services are being dramatically cut across the UK, and much of the voluntary sector is vulnerable, including i-Base.

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

If you would like to help i-Base in other ways, or would like more information about this i-Base appeal, please contact Suzanne Thompson or Simon Collins at HIV i-Base on 020 8616 2210.



**Thank you for your help.**

## CONFERENCE REPORTS

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### **16th European AIDS Conference**

**25–27 October 2017, Milan**

#### **Introduction**

**The 16th European AIDS Conference (EACS 2017) is being held from 25–27 October 2017 in Milan, Italy.**

This conference is held every two years (alternating with the Glasgow HIV Congress) and always provides a good focus for European HIV research.

This year the conference abstracts are already available online in a searchable database.

<http://www.professionalabstracts.com/eacs2017/iplanner/>

Although PDF files for posters will be added during the meeting, these are not yet linked to the abstract pages. Also, access to abstracts is only available via the iPlanner or App, with no direct URLs to individual abstracts.

Early reports from this meeting will be linked to this page.

- Fostemsavir in highly treatment-experienced participants: 24-week phase 3 results
- D/C/F/TAF: phase 3 naive results and splitting PI-based FDC tablets
- Dolutegravir-based dual therapy as switch option in multiple studies
- Switch study shows F/TAF non-inferior to continuing abacavir/3TC
- Twice-daily tenofovir alafenamide dose might overcome interaction with rifampicin
- No impact on bioavailability of D/C/F/TAF when tablet is split but TAF absorption is reduced if crushed

- Dolutegravir linked to less sleep but not cardiovascular or other CNS side effects, or IRIS
- Dolutegravir use in pregnancy: results from small Belgian cohort
- No transmissions from breastfeeding in Tanzania cohort from mothers with undetectable viral load
- Updated European guidelines launched at EACS 2017
- ABX464 nudges viral reservoir but not time to viral rebound

EACS 2017: ANTIRETROVIRALS

## **Fostemsavir in highly treatment-experienced participants: 24-week phase 3 results**

**Simon Collins, HIV i-Base**

**The most important results at EACS 2017 on new pipeline compounds were the first phase 3 results for the investigational entry inhibitor fostemsavir.**

As with any first drug in a new class, this data will provide hope for people with multidrug HIV resistance and whose combination is failing. For people in this situation, fostemsavir could be a life-saving drug.

This was a randomised, blinded, placebo-controlled international study in 272 treatment experienced participants currently on virologically failing combination and with drug resistance to at least two classes.

The study design included randomisation (3:1) to either fostemsavir 600 mg twice-daily or matching placebo for eight days, while remaining on failing ART, and then optimising the background regimen (OBR), which included the option to add other investigational drugs. The study also enrolled an additional 99 participants to open-label fostemsavir who had no other fully active ARV options, who were allowed to optimise background therapy from day one.

Although the primary endpoint was viral suppression to <40 copies/mL at day 8 in the randomised group, all participants had 24-week results for secondary efficacy and safety endpoints. In addition to allowing other investigational drugs during the optimisation phase, follow-up is planned to weeks 48 and 96, and to then continue until the next pipeline drug becomes available.

This was an advanced patient group with CD4 count at screening less than 200 cells/mm<sup>3</sup> in 72% and 50 cells/mm<sup>3</sup> in 41% of the group. Previous use of integrase inhibitors and protease inhibitors were reported for 80% and 96% respectively.

Baseline characteristics for the randomised group included median age 44 years (range 18 to 73) and approximately 30% were women. Median (range) CD4 and viral load were approximately 100 cells/mm<sup>3</sup> (0 to 1160) and 4.7 log copies/mL (1.6 to 6.9), respectively. Approximately 10% had no fully active drugs in the OBR, with 40-50% having either 1 or 2 fully active drugs.

Baseline characteristics were similar for the open-label group, with the important exception that 80% had no active drugs in the OBR and 20% had only one active drug. In this group, >95% had integrase experience and 70% had used T-20. Of the 19 people with sensitivity to one drug, 13/19 used the investigational mAb ibalizumab (See Table 1)

At day 8, mean viral reductions were 0.79 vs 0.17 log copies/mL for fostemsavir vs placebo arms respectively, (difference: -0.625; 95%CI: -0.810 to -0.441, p< 0.0001). By intent-to-treat (ITT) analysis 65% had >0.5 log reductions and 46% had >1 log reductions. In sub-group analysis of participants with baseline viral load >1000 copies/mL, the median viral load decline was -1.0 log copies/mL.

By week 24, viral suppression was reported for 54% of participants, with 71% and 77% using <200 and <400 copies/mL cut-offs respectively.

In the open-label group, 36% reported viral load <40 copies/mL at week 24. These rates were 49% and 53% using <200 and <400 copies/mL thresholds. For 80% of this group fostemsavir was the only active drug. Median viral reduction were -0.63 log copies/mL (95%CI: -0.81 to -0.44).

Mean CD4 counts increased by 90 and 41 cells/mm<sup>3</sup> in the randomised and open-label groups respectively.

Side effects were generally mild and manageable but serious complications reflected how advanced HIV was in this population. Although 91% of participants reported side effects (mostly grade 1-2), 30% experienced a serious event, including 13 people with pneumonia. Side effects leading to discontinuation were reported by 12 (4%) participants in the randomised group vs and 9 (9%) in the open-label group.

The urgency of treatment for this group with advanced HIV was shown by 17 participants who died, with 12/17 deaths due to AIDS/IRIS-related events and acute infections.

Fostemsavir is being developed by Viiv Healthcare from a compound that was acquired from BMS (BMS-663068).

**Table 1: Baseline characteristics for fostemsavir phase 3 study**

	Randomised cohort		Open label cohort
	Placebo BID (N=69)	Fostemsavir 600 mg BID (N=203)	Fostemsavir 600 mg BID (N=99)
Mean age, years, (range)	43 (19 to 66)	45 (18 to 73)	48 (17 to 72)
Sex; Male [n (%)]	57 (83)	143 (70)	89 (90)
Median CD4 count (range)	100 (0 to 915)	99 (0 to 1160)	41 (0 to 641)
Median viral load (range)	4.5 (1.6 to 6.9)	4.7 (1.6 to 6.4)	4.3 (1.6 to 6.6)
No. fully active drugs in OBT	0	5 (7%)	21 (10%)
	1	28 (41%)	103 (51%)
	2	36 (52%)	79 (39%)
			80 (81%)
			19 (19%) *
			0

\* 13/19 participants used ibalizumab

**C O M M E N T**

**Although the current number of people with multidrug resistance is relatively low, this is a group in the highest need.**

**It is therefore essential that research companies invested in compounds in new drug classes.**

**As integrase inhibitors become more widely used, multidrug resistance is likely to increase, further emphasising the need for future options.**

Reference

Lataillade M et al. Phase 3 study of fostemsavir in heavily treatment experienced HIV-1 infected subjects: day 8 and week 24 primary efficacy and safety results (BRIGHTE Study, Formerly AI438-047). 19th EACS, 25 - 27 October 2017. Oral abstract PS8/5.

**D/C/F/TAF: phase 3 naive results and splitting PI-based FDC tablets**

**Simon Collins, HIV i-Base**

**Two oral presentations at EACS 2017 included new data on the fixed dose combination (FDC) of D/C/F/TAF: darunavir (800 mg), cobicistat (150 mg), emtricitabine (200 mg) and tenofovir alafenamide (10 mg).**

**Phase 3 AMBER study: 48-week results**

48-week results from the phase 3 AMBER study in treatment-naive were presented by Chloe Orkin from Barts NHS Trust, London. [1]

This was an international, double-blind, active-controlled study that randomised 725 treatment-naive patients to either the single tablet D/C/F/TAF or a control group taking darunavir/cobicistat plus tenofovir DF/FTC.

This was a non-inferiority study (defined using 10% lower margin for the 95%CI) with a primary endpoint of viral suppression (<50 copies/mL) at week 48, and follow-up to week 96.

This was a generally young cohort, in early infection, reflecting earlier diagnosis in many countries. Baseline characteristics included median age 34 years (IQR: 27 to 42), 88% male, 82% white. Median CD4 count was 453 cells/mm<sup>3</sup> (IQR: 333 to 601) with 7% <200 cells/mm<sup>3</sup> and viral load was 4.5 log copies/mL (IQR: 4.1 to 4.9) with 17% >100,000 copies/mL. Baseline renal function was also high with median eGFR of 119 mL/min (IQR: 104 to 136).

At week 48, viral suppression <50 copies/ml was reported in 91% vs 88% of the FDC vs control group respectively (difference: 2.6%; 95%CI: -1.6 to +7.1), meeting criteria for non-inferiority. Viral load was >50 copies/mL in 4% vs 3% and discontinuations/missing data accounted for 4% vs 8%, all FDC vs control. Discontinuations due to side effects were lower for the FDC (2.2% vs 4.4%).

No significant differences in viral outcome were reported by sub group analysis (by age, gender, race, and baseline CD4 and viral load). Although the percentage differences generally favoured D/C/F/TAF, the low numbers for some groups

generated wide confidence intervals. For example, for the key viral load stratification, response rates were higher with D/C/F/TAF (90% vs 80%; 95%CI: -3 to + 22) in participants with viral load above 100,000 copies/mL. For the subgroup with CD4 counts <200 cells/mm<sup>3</sup> however, results favoured the control arm (72% vs 86%; 95%CI: -37 to +8).

Side effects were generally mild and similar between groups and no grade 3/4 events occurred in more than 5% of participants. eGFR based on serum creatinine dropped during the first two weeks, significantly more in the control arm – by approximately 5.0 vs 8.0 mL/min/1.73m<sup>2</sup> (p<0.0001) and then remained stable to week-48 in both groups. When eGFR was estimated by serum cystatin C, both arms increased over 48 weeks. Reductions in bone mineral density (BMD) at the spine occurred in both groups but were lower in the control arm only, as expected with tenofovir-based ART. BMD at the hip only reduced in the control arm, by -1.7% at week-24 and -2.7% at week 48.

Fasting lipids (TC, LDL, HDL and TG) increased between baseline and week 48 in both arms but were significantly greater in the FDC arm, with small absolute differences that were unlikely to have clinically relevant for most people. Although a marker of patients management rather than drug effect, and not protected by randomisation or study protocol, lipid lowering drugs were started by 2 (0.6%) vs 6 (1.7%) of the FDC vs control group (p=0.18 NS).

### PK for whole, split and crushed tablet

The second presentation, by Kimberley Brown from Janssen, reported on bioavailability results from splitting and crushing the D/C/F/TAF tablet, with broadly comparable drug exposures for the split tablet but not the crushed version. [2]

This was a randomised, open-label, cross-over study in 30 HIV negative volunteers, using a single dose, taken 30 minutes after a standard breakfast, as (i) a complete tablet, (ii) two halves of a pill=cutter split tablet, or (iii) as a crushed tablet with the powder mixed in apple sauce.

Overall, plasma concentrations over 24 hours for each method of administration were closely similar at all timepoints for darunavir, cobicistat and FTC, with 90% confidence intervals (CI) for the mean difference falling within the 80% to 125% routinely used to show bioequivalence.

Although the mean difference in AUC for TAF was bioequivalent for the whole vs split tablet (mean ratio 97%; 90%CI 90 to 105) the crushed tablet resulted in approximately 20% reduced AUC (mean ratio 81%; 90%CI 47 to 88).

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### C O M M E N T

**D/C/F/TAF has already been approved in the EU (in September 2017) and is currently filed with the US FDA.**

**In the questions after the presentations, the generally healthy cohort in AMBER was referred to several times. For example, in producing the highest viral response rates for darunavir than seen in earlier randomised phase 3 studies. This linked to questions about tolerability results in participants who had poorer baseline markers of higher risks for cardiovascular and renal disease.**

**Nevertheless, the results of this new formulation broadly reflected the individual component drugs.**

**The pharmacokinetic study results from splitting the single tablet in half are encouraging for people who need to take smaller pills. The lower AUC with the crushed tablet, however, means this should not be recommended until validated with further studies, even though TAF generally reaches concentrations that are well above the IC95.**

#### References

1. Orkin C et al. Week 48 results of AMBER: A phase 3, randomised, double-blind trial in antiretroviral treatment (ART)-naïve HIV-1-infected adults to evaluate the efficacy and safety of the once-daily, single-tablet regimen (STR) of darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide (D/C/F/TAF) versus darunavir/cobicistat (DRV/c) plus emtricitabine/ tenofovir disoproxil fumarate (FTC/TDF). 16th European AIDS Conference (EACS 2017), 25–27 October 2017, Milan. Oral abstract PS8/2.
2. Brown K et al. Relative bioavailability of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen when administered as a whole, split, or crushed tablet. 16th European AIDS Conference (EACS 2017), 25–27 October 2017, Milan. Oral abstract PS8/3.

## Dolutegravir-based dual therapy as switch option in multiple studies

Simon Collins, HIV i-Base

**Two oral presentations and numerous posters included new data on using dolutegravir-based dual ART (many with 3TC) as a switch option for people currently on stable three-drug ART.**

Esteban Martinez from University of Barcelona presented 24-week results from the first phase of the open-label DOLAM study that randomised 91 participants (1:1:1) to dolutegravir plus 3TC, dolutegravir monotherapy or to a control group continuing on standard three-drug ART. [1]

Entry criteria included having an undetectable viral load (<50 copies/mL) for ≥12 months, CD4 nadir >200 cells/mm<sup>3</sup>, no history of viral failure or resistance mutations to 3TC/FTC or integrase inhibitors and HBsAg negative.

Baseline characteristics included mean age 46 years, 86% men, 76% MSM, and mean CD4 count 739 cells/mm<sup>3</sup> (SD +/- 303).

By week 24, there were three discontinuations due to viral failure (one on dual therapy at week 12 and two on monotherapy at week 24) and the monotherapy arm was discontinued early following a recommendation by the DSMB due to higher rates for viral rebound. Importantly, both participants in the monotherapy arm developed integrase associated drug resistance.

The participant who discontinued in the dual arm due to low level viral rebound had no resistance and an additional participant in this arm also report low level viral blip (resuppressed without change or treatment).

Enrolment into the two remaining arms of the DOLAM study will expand to 129 participants in each arm. This will be powered for 8% margin for non-inferiority (rather than new FDA definition of 4% for studies looking for new licensing indication).

The second oral study was a meta-analysis presented by Marta Buzzi and colleagues from University Hospital Geneva, and reported low rates of viral failure in participants switched to dolutegravir-based dual therapy. From six studies, only 3/835 participants reported virological failure at 48 weeks (0.4%, 95% CI: 0.1 to 1.3). Of these, only one developed drug resistance: a person using rilpivirine plus dolutegravir developed NNRTI drug resistance (K101K/E).

The same study reported that dolutegravir monotherapy was associated with significantly higher risk of viral rebound. In 212 participants from six monotherapy switch studies, the rate of viral rebound was 3.3% (95%CI: 1.6 to 6.8) at 24 weeks and 8.9% (95%CI: 4.7 to 16.2) at 48 weeks. However, emergent drug resistance developed in 7 (3%) participants on DTG-monotherapy.

The authors reported dolutegravir-based dual therapy is a promising simplification strategy for people with stable HIV suppression on ART and that large trials are already ongoing.

### Posters using dolutegravir/3TC dual therapy

Additionally, numerous poster presented result from the dual combination of dolutegravir plus 3TC, some of which had been included in the above meta-analysis by Buzzi et al described above. [5, 6, 7, 8, 9, 10]

Babafemi Taiwo and colleagues from Northwestern University, Chicago, randomised 89 participants on stable ART to switch to dolutegravir plus 3TC (n= 44) or remain on current ART (n=45). The primary endpoint of viral suppression <50 copies/mL at week 24 was maintained in 93% (41/44) vs 91% (41/45) in the dual vs control groups (difference 2%; 95%CI: -11% to 15%) at week 24. At week 48, this was extended to 91% versus 89%, showing dual therapy to be non-inferior. [5]

Véronique Joly and colleagues from the French ANRS 167 LAMIDOL study reported on 110 participants in an open-label, single-arm, multicenter trial that switch people on stable ART (<50 copies/mL for >2 years, with no drug resistance). For the first eight weeks the third component of ART was switched to dolutegravir, changing to using only 3TC as background NRTI (if there were no earlier complications).

Six participants did not enter the second phase (n=3 due to dolutegravir side effects and n=3 due to viral load >50 copies/mL). At week 48, viral suppression was maintained by 101/104 participants with three therapeutic failures due to 1 x lost to follow-up, 1 x interruption of strategy, and 1 x viral failure (rebound to 77 copies/mL at week 4). [6]

A small study presented by Luba Tau and colleagues from Tel Aviv compared outcomes of 72 participants switched to dolutegravir plus 3TC compared to a historical cohort of 86 patients on non-dolutegravir containing ART. After 96 weeks, viral load <50 copies/mL was reported for approximately 97% in each group, with higher rates of blips >200 copies/mL in the control group (n=1 vs 6, p=0.08 NS). [7]

A larger prospective Italian cohort of 203 participants on stable ART (> 6 months) switched to dolutegravir plus 3TC was presented by Franco Maggiolo and colleagues. [8]

At switch, participants had been on ART for a median of 10.3 years (IQR: 5.5 to 17.6) and had been virally suppressed for a median of 72 (IQR: 33 to 121) months. No cases of viral failure were reported over 295 patient years of follow up. The 12 discontinuations (5.9%) were due to death (n=3; 2 x neoplastic disease and 1 x cirrhosis), intolerance (n=5: 2 x muscle pain/stiffness, 1 x headache, 1 x dizziness and 1 x increased AST/ALT) or patient decision (n=2) and lost to follow-up (n=2).

From Spain, Carmen Hidalgo-Tenorio and colleague presented retrospective results on 105 participants in a multicentre observational cohort on ART (96% with viral load <50 copies/mL) who switched to dolutegravir plus 3TC for simplification (39%) or toxicity (45%). In 84 patients with viral load results after switch (after a median of 23 weeks of follow up), 97% (82/84) maintained viral load <50 copies/mL. Two results were >50 copies/mL, both pending confirmation, of 55 and 239 copies/mL. [9]

Again from Italy, Alberto Borghetti presented retrospective results from a single centre in Rome of 494 treatment experienced patients switching to investigator choice of one of three simplified dual combinations of 3TC with dolutegravir (n=183), darunavir/r (n=170) or atazanavir/r (n=141). [10]

Viral failure occurred in 3, 6 and 4 cases with dolutegravir, darunavir/r and atazanavir/r respectively. The percentages of people remaining on switch treatment at weeks 48 and 96 were: 88% and 82% with dolutegravir, 80% and 48% with darunavir/r, and 87% and 71% with atazanavir/r ( $p < 0.001$ ).

Although viral responses were similar between arms, dolutegravir/3TC had fewer discontinuations due to tolerability.

### Dolutegravir-based dual therapy with darunavir/b

Finally, one small study paired dolutegravir with darunavir/r QD. [11]

A retrospective analysis from Navarro and colleagues reported on 27 highly treatment-experienced patients who were switched to dual therapy using dolutegravir with once-daily boosted darunavir. Median time with undetectable viral load before the switch was 44 months (IQR: 18 to 104) but treatment history included a median of 8 (IQR: 4 to 11) ART combinations with a median of 5 (IQR: 2 to 8) viral failures. Historical genotype primary mutations included: 96% (n=27) to NRTIs, 78% (n=21) to NNRTIs and 41% (n=11) to PI, of whom 6 had DRV-associated mutations. Importantly no participants had integrase mutations.

At week 48, viral load was  $<50$  copies/mL in 93% (n=25) participants. There was one viral rebound without resistance emergence and one patient died due to bacterial peritonitis.

**Table 1: Key dolutegravir-based dual therapy studies at EACS**

	Design	N		Ref.
Blanco JL et al.	RCT: DTG+3TC vs mono vs 3-drug ART.	n=91.	Monotherapy stopped with 2 VF at week 24m (vs 1x VF in dual. Dual vs triple arms continue with expanded enrolment.	[1]
Buzzi M et al.	Meta analysis and reanalysis of six studies with DTG+3TC.	n=835 on DTG-based dual.	1/835 report viral failure at week 48 (using dolutegravir + rilpivirine). VF with NNRTI resistance.	[2]
Taiwo BO et al.	RCT: switch to DTG+3TC vs current ART.	n=89.	VL $<50$ in 93% vs 91% in dual vs control at week 24 and 91% vs 89% at week-48.	[5]
Joly V et al.	Single-arm, prospective, open-label ANRS167 switch study.	n=104.	101/104 $<50$ copies/mL at week 48. Only one case of viral rebound (to 67 copies/mL).	[6]
Tau L et al.	Prospective open-label switch to DTG+3TC compared to historical control.	n=72 dual vs 86 control.	At 96 weeks, viral load $<50$ copies/mL in 97% of each group. higher numbers of blips $> 200$ copies/mL in the control group (n=1 vs 6, NS).	[7]
Maggiolo F et al.	Single-arm, prospective, open-label switch study to DTG + 3TC.	n=203.	No viral failures during 295 patient-years of follow-up. 12 discontinuations were due to intolerance, clinical complications or loss to follow-up.	[8]
Hidalgo-Tenorio C et al.	Retrospective results in people switched to DTG + 3TC.	n=105,	82/84 pts with results had viral load $<50$ copies/mL after median 23 weeks. Two rebound results to 55 and 239 copies/mL.	[9]
Borghetti A et al.	Retrospective results after switch to 3TC dual with DTG, darunavir or atazanavir.	n=494; (DTG: 183, DRV: 170, ATZ: 141).	Viral failure in 3 vs 6 vs 4 with DTG vs DRV vs ATV. At weeks 48/96: 88%/82% with DTG, 80%/48% with darunavir/r and 87%/70% with atazanavir/r.	[10]
Navarro J et al.	Single-arm, open-label switch to DTG + darunavir/b QD in experienced pts.	n=27.	VL $<50$ c/mL in 25/27 (93%) at week 48. Only 1 x VF with no resistance.	[11]

### C O M M E N T

**Both the Blanco et al and Buzzi et al studies rightly emphasised that dolutegravir monotherapy should no longer used due to the unpredictable risk of viral rebound with integrase inhibitor resistance. Two posters presented detailed case reports of viral rebound with dolutegravir monotherapy. [3, 4]**

**Although the numerous poster studies are broadly encouraging, the results from larger randomised studies that are currently ongoing will clearly be important.**

**The Gemini 1 and 2 studies that compare dolutegravir/3TC to dolutegravir plus TDF/FTC are already enrolled with results due in mid-2018.**

## Reference

Unless stated otherwise, references are to the programme and abstracts of the 16th European AIDS Conference (EACS 2017), 25–27 October 2017, Milan. Abstracts are available from the online conference planner:

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## Switch study shows F/TAF non-inferior to continuing abacavir/3TC

Simon Collins, HIV i-Base

**Results from the first randomised study comparing FTC/tenofovir alafenamide (F/TAF) to continuing on abacavir/3TC showed little significant differences between the newer vs older dual NRTI combinations, but also no risk from switching.**

This was a randomised, double-blind, placebo controlled switching study in 556 participants on ABC/3TC-based ART, sponsored by Gilead. Week-48 primary endpoint results were presented by Alan Winston from Imperial College, London. Entry criteria included viral suppression <50 copies/mL on ABC/3TC-based ART for > 6 months and CrCl > 50 mL/min.

Baseline criteria included median age 52 years (range: 20 to 79). 18% women, 73% white, with high CD4 counts (median >650 cells/mm<sup>3</sup>). Although renal function was good, with median eCrCl 100 mL/min (IQR: 83 to 123), approximately half the cohort had hyperlipidaemia, 40% had hypertension, 12% had diabetes and 6% were defined as having cardiovascular disease. Participants had been taking abacavir/3TC for a median of 8 years (IQR: 3 to 11). The third component of ART was an NNRTI for 50%, with 30% using PI and 20% integrase-based ART.

By week-48, there were fewer overall discontinuations in the abacavir/3TC arm (n=18 vs 31; 7% vs 11%), mainly due to higher loss to follow-up or investigation decision (both n= 0 vs 3).

Viral efficacy <50 copies/mL at week-48 was also higher for the abacavir/3TC group at 93% vs 90% (difference –3.0%; 95%CI: –8.2 to +2.0) but this met the criteria for non-inferiority (based on lower margin of –10% cut off).

Side effects were generally low incidence and grade and closely similar in both groups. Laboratory abnormalities were also similar, including lipid changes.

However, although changes in estimated creatinine clearance favoured F/TAF (–1.1 vs +1.3 mL/min; p=0.05), there were no significant differences in renal tubular biomarkers or bone mineral density. Small differences in some lipid parameters didn't result in a significant difference in TC:HDL ratio or in new use of lipid lowering drugs.

The single death was sudden cardiac event in the F/TAF arm that was not judged linked to ART.

### C O M M E N T

**Given the contraindication in people with high Framingham score it was unclear why people with significant cardiovascular risk were still using abacavir/3TC.**

**This randomised dataset is interesting, even with no expected benefits in renal and bone markers. Further follow-up will continue to week-96.**

**The difference in cost (approximately 4000 vs 500 Euros a year) was raised in the Q&A session afterwards as likely to limit widespread switching in clinical practice, unless there is concern for cardiovascular risk.**

Reference

Winston A et al. Phase 3 randomized controlled trial of switching to emtricitabine/tenofovir alafenamide (F/TAF) from abacavir/lamivudine (ABC/3TC) in virologically suppressed adults: week 48 results. EACS 2017, Milan. Oral abstract PS8/4.

## Twice-daily tenofovir alafenamide dose might overcome interaction with rifampicin

**Polly Clayden, HIV i-Base**

**Twice-daily tenofovir alafenamide (TAF) plus rifampicin (RIF) provided similar exposures to once-daily TAF in pharmacokinetic (PK) study. This strategy might be a suitable option for people with HIV/TB coinfection.**

TAF and tenofovir disoproxil fumarate (TDF) are prodrugs of tenofovir (TFV). TAF is more stable in plasma compared with TDF and gives about 90% lower plasma TFV exposures.

TAF is a substrate of drug transporters and RIF is a potent inducer and associated with drug-drug interactions and in turn lower drug exposures. The interaction between TAF and RIF has not previously been evaluated. Currently TDF is indicated for use with RIF but once-daily TAF is not.

Gilead Sciences, the originator company of TDF and TAF, conducted a PK study to look at twice-daily TAF co-administered with once-daily RIF. [1] The results were presented at EACS 2017.

The study aims were to evaluate the steady state PK of TAF, the active intracellular moiety tenofovir-diphosphate (TFV-DP), and the TAF major metabolite TFV, after co-administration of twice-daily TAF with once-daily RIF 600 mg, compared with once-daily TAF. It was a phase 1, open label, parallel design, multiple dose, single centre study in HIV/TB negative volunteers.

Participants were enrolled into two cohorts (26 in each cohort). TAF was given in the fixed dose combination (FDC) tablet bictegravir/emtricitabine/TAF (B/F/TAF 50/200/25 mg).

Cohort 1 received B/F/TAF once daily and cohort 2 B/F/TAF twice daily plus RIF 600 mg once daily, both two hours after food, for 28 days. Plasma and intracellular peripheral blood mononuclear cell (PBMC) PK was assessed on days 1 and 28.

Statistical comparisons used geometric least-square mean (GLSM) ratios and 90% confidence intervals (CI). Cohort 2 was the test regimen and cohort 1 was reference.

The evaluation revealed that with twice-daily administration of TAF plus RIF, exposures over 24 hours of TAF total plasma, overall systemic plasma TFV and intracellular PBMC-associated TFV-DP are expected to be reduced by <15%, about 20%, and about 24%, respectively, compared with once-daily TAF. See results Table 1.

Notably, after twice-daily administration of TAF plus RIF, the mean (%CV) steady-state trough concentration of TFV-DP was 359 (58) fmol/10<sup>6</sup> cells, which is above the historical steady state TFV-DP concentrations achieved with TDF 300 mg.

**Table 1: TAF twice daily + RIF vs TAF once daily PK**

Mean (%CV)		TAF once daily	TAF twice daily + RIF	GLSM ratio (90% CI)
Plasma TAF PK 0–24 (ng*h/mL)	AUC	345 (52)	290 (48)	85.8 (69.7 to 106)
Plasma TFV PK 0–24 (ng*h/mL)	AUC	348 (20)	277 (19)	79.9 (73.1 to 87.3)
Intracellular TFV-DP AUC 0–24 (fmol*h/10 <sup>6</sup> cells)				76.3 (58.7 to 99.2)

### C O M M E N T

**TAF has the potential to replace TDF as part of an optimised generic first-line regimen for low- and middle-income countries (LMICs).**

**Due to TAF's low milligram dose (and lower amounts of active product ingredients) compared with TDF, this could reduce the annual cost per person from the recently agreed US \$75 (for a fixed dose combination of TDF/lamivudine [3TC]/dolutegravir [DTG]/ or TLD) further still. [2] Approval of two generic FDCs of TAF/3TC/DTG is expected by mid-2019.**

**TAF is not yet recommended in WHO or any national guidelines in LMICs as there are insufficient data on its use in pregnancy and in people with HIV/TB coinfection.**

**Previous investigations by Gilead showed co-administration with carbamazepine leads to a 55% decrease in TAF in plasma and results from modelling to predict the interaction with RIF suggested this reduction would be 73% in plasma. [3]**

**Results from the PK study described above are welcome and provide preliminary evidence for adjusting the TAF dose to twice daily with RIF. But the parallel design is a limitation, and there is no concurrent TDF comparison.**

**Further evidence will be available early 2018 from the RIFT study that is currently evaluating the effect of RIF on plasma PK of emtricitabine (FTC) and TAF and TFV-DP and FTC-triphosphate (FTC-TP). [4]**

**If, as the results above suggest, dosing TAF twice daily is the solution to co-administration with RIF this will potentially make HIV/TB co-treatment easier in for programmes in LMICs as twice-daily DTG also looks promising. Botswana is already using this strategy and results from INSPIRING [5] – looking at DTG and efavirenz-containing ART regimens in people with HIV/TB co-infection – will also be available early next year.**

**The TAF/3TC/DTG could be given twice daily – which is not possible with the TDF-containing FDC that requires giving the extra DTG as a single tablet.**

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## **No impact on bioavailability of D/C/F/TAF when tablet is split but TAF absorption is reduced if crushed**

**Polly Clayden, HIV i-Base**

**There was no clinically relevant effect on the bioavailability of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) components when given as a split tablet compared with a tablet swallowed whole. [1] Crushing the tablet led to a modest decrease in TAF bioavailability.**

Whether or not antiretroviral tablets, including fixed dose combinations (FDCs), can be split or crushed for people who are unable to swallow pills and sometimes for paediatric HIV is important to know.

The originator company, Janssen, previously evaluated the stability of D/C/F/TAF in vitro and found that the individual components remained stable: after splitting the tablet in half; and after crushing the tablet and exposing to liquids (water, orange juice, cranberry juice and apple sauce). The components also did not absorb to PVC or silicone feeding tubes.

The company then assessed the relative bioavailability of D/C/F/TAF as a split or crushed tablet after oral administration compared with a whole tablet. These data were presented at EACS 2018.

This assessment was a phase 1, randomised, open-label, 3-period, 3-treatment, crossover study of a single dose of D/C/F/TAF (800/150/200/10 mg) given as a split or crushed tablet versus a whole tablet.

Thirty HIV negative adults aged 18–55 years were enrolled and the dose was given within 30 minutes of a standard breakfast. Tablets were: swallowed whole (reference); split with a tablet cutter (both halves swallowed); or crushed and mixed with apple sauce.

Full pharmacokinetic (PK) profiles were determined up to 72 hours (darunavir, cobicistat and emtricitabine), and 8 hours for TAF. Primary PK parameters were C<sub>max</sub> and AUC. Treatments were compared using a linear mixed effects model.

The assessment found no relative impact on the bioavailability of D/C/F/TAF components when given as split compared with whole tablet (least squares means ratio confidence intervals all within 80 to 125% boundaries).

There was no relevant impact on the bioavailability of darunavir, cobicistat and emtricitabine when given as a crushed tablet but approximately 20% decrease in the bioavailability of TAF.

The investigators noted that the clinical relevance of the decrease has not been assessed but it is expected to be minimal because of the wide therapeutic window for TAF.

C O M M E N T

**It is good to have data to inform whether or not tablets can be split in half for people who have difficulties swallowing them whole.**

**The results for darunavir/cobicistat contrast with those for lopinavir/ritonavir for which crushing significantly reduced exposure of both components with a decrease in AUC by 45% lopinavir and 47% ritonavir in a study in older children. [2]**

References

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EACS 2017: SIDE EFFECTS

## **Studies on dolutegravir and sleep, cardiovascular and CNS side effects, and risk of IRIS**

**Polly Clayden, HIV i-Base**

**A meta-analysis of randomised trials presented at EACS 2017 found a slightly higher risk of insomnia for dolutegravir (DTG) compared with other antiretrovirals (ARVs). But no difference for other CNS side effects.**

There was also no significant difference in the risk of cardiac serious adverse events (SAEs) between DTG and other ARVs. The risk of IRIS was low but the main trials excluded people with CDC stage C disease.

Observational data suggest higher risks of CNS adverse events for DTG, compared with other ARVs. There have been two case reports of myocarditis in people receiving DTG. And integrase inhibitors have been associated with IRIS in two cohort studies.

In response to these signals, Andrew Hill and Nikkita Mitchell from Liverpool University and Imperial College London, performed a meta-analysis to compare rates of each adverse event for DTG versus other ARVs – stratified by trial. They compared suicidality between DTG and efavirenz (EFV) and non-EFV controls in two separate analyses. This meta-analysis of randomised trials included 6,647 patient-years of follow-up.

For cardiac SAEs, the authors included trials: SINGLE, SAILING, FLAMINGO, SPRING-1, SPRING-2, ARIA, STRIVING and NEAT SSAT 060. The analysis revealed 15/2,202 (0.7%) participants with cardiovascular SAEs receiving DTG compared with 8/2,215 (0.4%) receiving other ARVs (RR=1.69, NS). Only 1/25 (4%) cardiac SAE in SPRING-1 was considered to be related to DTG; 1 other cardiac SAE in the same trial was considered unlikely to be related. There was additional case information available for 19/23 participants with cardiac SAEs. Of these 17/19 (89%) had underlying cardiac risk factors.

When the authors looked at suicidality in the SINGLE and SPRING-1 trials, there were 5/465 participants with reported SAEs receiving DTG (1.1%) compared with 6/469 (1.3%) receiving EFV (RR=0.87, NS). In the SAILING, FLAMINGO, SPRING-2, ARIA, STRIVING, SWORD and NEAT SSAT 060 trials, suicidality SAEs were reported for 15/2,250 participants receiving DTG (0.7%) compared with 9/2,257 receiving other ARVs (0.4%) (RR=1.58, NS). The authors found no significant differences in other CNS endpoints between DTG and other ARVs.

The risk of grade 1–4 insomnia was higher for DTG compared with other ARVs: 165/2,716 (6.1%) vs 124/2,727 (4.5%) (RR=1.30, p=0.02).

IRIS was seen in 1/414 participants receiving DTG compared with 2/419 participants receiving EFV in SINGLE, 6/354 receiving DTG compared with 3/361 receiving raltegravir (RAL) in SAILING, and 1/411 DTG compared with 0/411 receiving RAL in SPRING-2. No cases of IRIS were reported in SPRING-1, FLAMINGO, STRIVING or NEAT SSAT 060. Although there was no significant difference in the risk of IRIS between DTG and other ARVs, none of the randomised trials included people with low CD4 counts where the risk is likely to be elevated.

Importantly the authors reported that the overall risk of adverse events was lower for DTG than EFV in the SINGLE trial, darunavir/ritonavir (DRV/r) in FLAMINGO, and atazanavir/ritonavir (ATV/r) in ARIA.

They added that other completed randomised DTG trials should be included in new safety analyses: DAWNING (n=627), SWORD 1 and 2 (n=1024), Gilead trial 1489 (n=629) and Gilead trial 1490 (n=645). And they stressed the importance of continued pharmacovigilance with regular meta-analysis to monitor safety.

C O M M E N T

The importance of continual monitoring of new ARVs cannot be emphasised more. This is particularly important for DTG, which will be used to treat millions of people in low- and middle-income settings, in programmes that have already begun or will do so in the next couple of years.

Overall these data are reassuring – particularly learning from the authors that the non-significant relative risk for suicidality was way off  $p=0.05$  (Test for overall effect:  $Z=0.53$ ,  $p=0.6$ ).

The risk of IRIS was low, but event rates were low and the main trials excluded those at greatest risk. Data from ongoing closer-to-real-life trials such as ADVANCE and NAMSAL in South Africa and Cameroon will provide more information on IRIS risk with DTG.

This group will continue to re-evaluate DTG safety as data from completed randomised trials becomes available.

Of note, many posters at EACS reported lower rates of dolutegravir-related side effects with fewer differences to other integrase inhibitors.

The Dutch ATHENA cohort reported no differences in discontinuations between dolutegravir and elvitegravir. [2]

The Italian ICONA cohort of 1057 patients (approximately 600 were naive) reported 2.5% discontinuations due to side effects at one year. [3]

A UK study reported a discontinuation rate of 2.2% out of 181 (50 naive) using dolutegravir, with sleep changes managed by changing the timing of dosing. [4]

A German cohort of over 400 people starting dolutegravir-based ART reported 5.8% discontinuations linked to side effects at 27 months. [5]

Also, an intensive six-month dolutegravir sleep study in older participant (>60 years), was presented at the PK workshop earlier this year by Marta Boffito and colleagues. This study reported that higher dolutegravir C<sub>max</sub> and AUC were associated with reduced sleep time, there were no significant changes in sleep scores over the first 28 days after switching to dolutegravir/abacavir/3TC. [6]

Unlike with CNS side effects with efavirenz, taking dolutegravir in the morning anecdotally may overcome difficulties with insomnia, without causing additional problems during the day.

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Unless stated otherwise, references are to the programme and abstracts of the 16th European AIDS Conference (EACS), 25–27 October 2017. Milan.

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EACS 2017: PREGNANCY

## Dolutegravir use in pregnancy: results from small Belgian cohort

Polly Clayden, HIV i-Base

**There were no vertical transmissions, obstetrical complications or birth defects among 11 dolutegravir (DTG)-exposed pregnancies at a Brussels-based centre between November 2015 and June 2017.**

Preliminary data from a prospective observational study of pregnant women and their children exposed to DTG at Hôpital Erasme were presented at EACS 2017.

The women were a median of 33 years old and were all ART-experienced before pregnancy. Eight women were receiving a DTG-containing regimen at conception and already virologically suppressed. The remaining three started a DTG-containing regimen during pregnancy (14, 16 and 26 weeks gestation).

Of 11 women, two experienced blips during pregnancy at nine and 32 weeks gestation: 66 and 1743 copies/mL respectively. All women had viral loads <40 copies/mL at delivery.

There was one twin pregnancy and no obstetrical or peri-partum complications.

All infants received four weeks AZT prophylaxis and remained HIV negative at 0, 1, 2 and 3 months (PCR DNA and RNA testing). Long term follow up of the infants is ongoing.

#### Reference

Henrard S et al. Clinical outcome of 11 pregnancies with a dolutegravir containing regimen. 16th European AIDS Conference. 25–27 October 2017. Milan. Poster abstract PE9/66.

## **No transmissions from breastfeeding in Tanzania cohort from mothers with undetectable viral load**

**Polly Clayden, HIV i-Base**

**No HIV exposed infants who were negative at birth, whose mothers started ART before delivery, had suppressed viral loads and exclusively breastfed, were HIV positive after breastfeeding, in a rural African cohort.**

These findings from the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), Tanzania were presented at EACS 2017.

This study included infants born between January 2013 and May 2016 to mothers enrolled in KIULARCO who started ART before delivery, exclusively breastfed for five months or more, and whose infants had a negative viral load test at age 4–12 weeks.

The mothers' viral loads were measured once or twice up to 11 months after delivery. Infants testing was according to national guidelines.

Of 215 mothers with 219 pregnancies and 229 infants (10 twins), the median age at delivery was 33 years (IQR 29–36) and time since starting ART was 23 months (IQR 4–52).

Of the total mothers, 180 (84%) were in care, 2 (1%) died, 24 (11%) were lost to follow up and 9 (4%) transferred out.

A total of 335 viral load samples were tested from 219 post-partum in 215 women; 114 women had two samples.

During the breastfeeding period, 91% of mothers had viral <1000 copies/mL, with 75% <100 copies/mL.

As of 30 June 2017, of 229 infants 10% were lost to follow-up, 2% were transferred and 8% died 2% were still breastfeeding. Of 181 (79%) infants with final HIV status, 2 (1%) were infected through breastfeeding.

One HIV positive infant was born to a mother with high viral load (144,111 copies/mL) at one month post-delivery and the other to a mother who stopped ART during breastfeeding.

There was no vertical transmission through breastfeeding among mothers with suppressed viral load in this cohort, suggesting that this is very low risk. But loss to follow up and adherence problems can threaten the success of interventions to reduce vertical transmission through breastfeeding.

“Viral load monitoring during pregnancy and breastfeeding and strategies to trace back those lost to follow up should be a priority” the investigators recommended.

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Luoga E et al. HIV transmission from mothers on antiretroviral therapy to their infants during breastfeeding in rural Tanzania. 16th European AIDS Conference (EACS 2017), 25–27 October 2017, Milan. Oral abstract PS5/5.

EACS 2017: GUIDELINES

## Updated European guidelines launched at EACS 2017

**Simon Collins, HIV i-Base**

As with previous years, the conference was used to launch the 2017 update for the EACS guidelines.

The English edition (Version 9.0) are now available in print, online and as a n App.

Translations into Chinese, French, German, Portuguese, Russian and Spanish will be available shortly.

These practical guidelines on the management of HIV infection are based on easy-access look-up tables and summaries of key topics that are organised into five main sections: Initial assessment, ART, comorbidities, hepatitis B and C coinfection and opportunistic infections.

The 200-page handbook is also supplemented with additional content that is only available online.

Main changes in this edition are also summarised at the beginning of the guidelines and include:

- Updating references to newer drugs (TAF) and removing older drugs (lopinavir/r)
- New sections on NAFLD, chronic lung disease, prescribing in elderly patients and solid organ transplant (SOT)
- Drug interaction tables are updated.
- Updated sections on monitoring for management of hypertension, diabetes, lipid management, STIs and HPV vaccination.
- Updated HBV and HCV sections.
- Updates for management of cryptococcal infections and TB.

<http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html>

[http://www.eacsociety.org/files/guidelines\\_9.0-english.pdf](http://www.eacsociety.org/files/guidelines_9.0-english.pdf) (PDF)

EACS 2017: CURE RESEARCH

## ABX464 nudges viral reservoir but not time to viral rebound

**Simon Collins, HIV i-Base**

**New data presented at EACS 2017 suggested that the investigational REV inhibitor ABX464 might reduce the viral reservoir in a study that included a treatment interruption. [1]**

The ABX464-004 study randomised (3:1) 30 participants on stable ART (CD4 nadir >350) who had been taking boosted darunavir monotherapy for at least 8 weeks to either add ABX464 (mainly 150 mg) or matched placebo for 28 days, after which all treatment was stopped. Full ART was restarted if viral load rebounded to >1000 copies/mL.

The impact on viral reservoir was measured by total HIV DNA in PBMCs with response defined as minimum reduction of 50 copies/million PBMCs and >25% decrease in HIV DNA copies.

Baseline characteristics included median duration of HIV infection of 10.2 years with median 5.6 years on ART.

In the 15 subjects with validated viral DNA results, 8/15 (53%) of the active group reported significant reductions (mean change of -38% (95%CI: -27% to -67%), with a mean decrease of 185 copies/million PBMCs (95%CI: -434 to -82) compared to no responders in the placebo group (0/4).

However, there were no differences between groups in time to viral rebound after stopping ART: mean 13 vs 14 days for ABX464 vs placebo groups respectively.

Tolerability was good with no serious side effects reported in the treatment group.

ABX464 blocks the end stages of viral assembly. Results on antiviral efficacy from an earlier phase 2a dose-ranging study in 80 treatment-naive participants in Thailand reported modest antiviral activity (~0.5 log copies/mL) but only in 4/6 people using the highest 150 mg dose (with no responses in 2/6). [2]

Future studies are planned to use ABX464 with triple therapy ART using longer treatment with ABX464 (64 days) (study 005), in people suppressed in chronic infection (study 006) and those treated in acute infection (study 007).

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## CONFERENCE REPORTS

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### 8th International Workshop on HIV & Ageing

2–3 October 2017, New York

#### Introduction

**This annual workshop is important for providing a focus for the key issue of HIV and ageing.**

Importantly, the meeting includes a good online selection of webcasts and PDF file presentations afterwards.

Presentations

<http://www.infectiousdiseasesonline.com/8th-hiv-aging-presentations>

Webcasts

<http://www.infectiousdiseasesonline.com/8th-hiv-aging-presentations/8th-hiv-aging-video/>

A useful report from the meeting by Mark Mascolini is also available online:

<http://regist2.virology-education.com/2017/8Ageing/MeetingReport.pdf> (PDF)

As i-Base wasn't able to attend this event, we have included a review of the excellent webcasts and links to reports at [natap.org](http://natap.org).

- Selected webcasts from the 8th HIV and ageing workshop
- HIV and Ageing Workshop reports at [natap.org](http://natap.org)

### Selected webcasts from 8th HIV and ageing workshop

Simon Collins, HIV i-Base

**The following selected web coverage includes selected talks and perspectives from this workshop.**

#### The community perspective - Jules Levin

<https://vimeo.com/album/4819995/video/239090686>

The best introduction to this workshop is to watch the short talk by HIV activist Jules Levin who has been leading the demands for increasing appropriate funding and research on HIV and ageing.

Informed by personal experience of living with HIV, the talk sideswipes, cure research, treatment interruptions and activist priorities – you are unlikely to agree with every opinion – but the talk is driven by the urgency of needing to address the realities of HIV and ageing.

In the US, as in the UK, the complexity of managing multiple co-morbidities is not possible with financial contracts that results in ever-shorter consultations and having to see multiple doctors who rarely talk to each other. Stigma continues, social isolation is widespread - and this is a growing population where the majority of people living with HIV are already older than 50.

### **New research approaches to treatments for Alzheimer's disease - Mashav Thambisetty**

With few current treatments - mainly palliative for symptom relief – and nothing since 2003. The current pipeline are also based on few therapeutic targets, with limited proof of concept data, and a history of risk of potential harm in addition to lack of benefit.

Successes in animal models and pre-clinical promise are so-far not matched in human studies. this includes working with a larger cohort of longitudinal samples from people with dementia, pre-dementia and unaffected controls to identify biomarker metabolites on the phenotypic pathway.

<https://vimeo.com/album/4819995/video/239089559>

### **Potential role of metformin research in targeting ageing - Jamie James**

Plans for future research using the antidiabetic drug metformin for it's potential impact on the ageing processes to delay or prevent chronic diseases collectively, rather than one at a time. Although metformin is a widely-used insulin sensitiser it also has significant off-target effects that include extending lifespan and healthspan in animal studies.

Primary outcomes for the proposed randomised, placebo-controlled TAME study is likely to involve multiple morbidity composite endpoints including cardiovascular, cancer dementia and mortality. It is expected to need 3000 participants followed for 3 to 4 years.

<https://vimeo.com/album/4819995/video/239089805>

See also: Barzilai N et al. Metformin as a Tool to Target Aging. Cell Metabolism, 23(6):1060–1065, doi: 10.1016/j.cmet.2016.05.011. (14 June 2016).

<http://dx.doi.org/10.1016/j.cmet.2016.05.011>

### **Exercise and ageing - Wendy Kohrt**

An overview on the role of exercise on healthy and successful ageing - and the disconnect with normal ageing including a biological component to exercise that might drive lower activity levels as we age.

Currently, even a low bar of 150 minutes of moderate physical activity a week, is only met by around 50% of 18–25 year olds and 30% of those older than 65 with 50% of the older group reporting no activity (based on bouts of 10 minutes or more). This includes burning less calories as we age, at similar levels of activity and the impact of testosterone and estradiol on activity.

It also includes an outline of the planned US MoTrPAC study looking at benefits of exercise in 3000 mostly sedentary adults but also with a children's cohort and physically active control group ([www.motrpc.org](http://www.motrpc.org)).

<https://vimeo.com/album/4819995/video/239091076>

### **Biology of superagers - Nir Barzilai**

How ageing itself is the highest risk for all serious complications – approximately 1000-fold at >80 years old compared to being 20. This talk reviewed research in longevity from a cohort of >670 centenarians. These people not only live longer, but live disease-free with low health costs for most of this time.

However, as a population, lifestyle factors including obesity, smoking, alcohol and exercise etc were broadly similar to general US population. Also, genetic patterns commonly included pathogenic SNPs: longevity in centenarians is not explained by having fewer pathogenic genes. Although protective lipid-related genes (APOC3 and adiponectin) were present at higher levels, diminished IGF-1 and growth hormone was discussed as a pathway supported by human data with the potential for IGF-receptor antibodies as treatment.

<https://vimeo.com/album/4819995/video/239090065>

### **Current reality: the New York experience - Eugenia Seigler**

Examples of a HIV practice that includes a geriatrician in the team - while recognising that this also involved a broad range of needs for older HIV positive people than just assessment tools. The role of comprehensive geriatric assessment and whether this can help meet such complex psychosocial and long-term care needs.

<https://vimeo.com/album/4819995/video/239090442>

### **The research perspective - Phyllis Tien**

Review of how two large prospective cohort studies - especially MACS and WYSE - can inform issues relating to HIV and ageing.

<https://vimeo.com/album/4819995/video/239122407>

## **HIV and Ageing Workshop reports at natap.org**

**Mark Mascolini, natap.org**

The 8th International Workshop on HIV & Aging offered reports on new research in three broad areas—exercise and aging, the central nervous system and aging, and epigenetic (or biological) aging.

Under those broad umbrellas, attendees heard new data from rigorously planned studies on metformin suppression of cytomegalovirus, cognitive impairment in HIV-positive people over 60, declining lean mass in adults aging with HIV, step count as a predictor of health outcomes in an older HIV group, and an array of other topics.

The following reports by Mark Mascolini were published by natap.org.

### **Hearing loss and quality of life in middle-aged with or without HIV**

[www.natap.org/2017/AGE/AGE\\_10.htm](http://www.natap.org/2017/AGE/AGE_10.htm)

### **Subjective and objective fatigue greater in older group with vs without HIV**

[www.natap.org/2017/AGE/AGE\\_07.htm](http://www.natap.org/2017/AGE/AGE_07.htm)

### **Adherence to recommendations from comprehensive geriatric assessment in an HIV+ population**

[www.natap.org/2017/AGE/AGE\\_06.htm](http://www.natap.org/2017/AGE/AGE_06.htm)

### **Cognitive impairment in symptomatic HIV over age 60**

[www.natap.org/2017/AGE/AGE\\_05.htm](http://www.natap.org/2017/AGE/AGE_05.htm)

### **Limited evidence of biological aging in early-treated HIV positive children**

[www.natap.org/2017/AGE/AGE\\_04.htm](http://www.natap.org/2017/AGE/AGE_04.htm)

### **Lean mass declines consistently over 10 years in HIV positive adults on antiretroviral therapy, with patterns differing by sex**

[www.natap.org/2017/AGE/AGE\\_03.htm](http://www.natap.org/2017/AGE/AGE_03.htm)

### **Metformin suppresses human CMV infection**

[www.natap.org/2017/AGE/AGE\\_02.htm](http://www.natap.org/2017/AGE/AGE_02.htm)

### **Antiretroviral therapy does not dial back advanced epigenetic age with HIV**

[www.natap.org/2017/AGE/AGE\\_01.htm](http://www.natap.org/2017/AGE/AGE_01.htm)

### **Current reality: the San Francisco experience / SF ageing clinic: reality switch from 1990 to 2018 / a crisis ignored by many**

[www.natap.org/2017/AGE/AGE\\_11.htm](http://www.natap.org/2017/AGE/AGE_11.htm)

## CONFERENCE REPORTS

### 9th IAS Conference on HIV Science

23-26 July 2017, Paris

#### Introduction

**The 9th IAS Conference on HIV Science (IAS 2017) was held from 23–26 July 2017.**

As with all IAS conferences, many of the key presentations are available online after the meeting.

All abstracts are also posted online, with full versions of the posters and presentations often also available from the conference website.

<http://www.ias2017.org>

Webcasts are published to three different webpages:

The main IAS 2017 youtube channel includes most oral abstract presentations and some plenary sessions.

IAS 2017 on youtube.com

Live broadcasts for opening and closing ceremonies, and some press conferences are at this link on the conference website. Currently the link to the closing ceremonies with rapporteur summaries and the community speech is not available.

<http://www.ias2017.org/Get-Involved/IAS-2017-Live>

Press conferences and other webcasts are online on a different IAS youtube channel.

IAS 2017 press conference webcasts

Articles in this issue are:

- Reassuring French data using raltegravir during pregnancy
- Earlier ART reduces infant mortality in South Africa but risk of death and loss to follow up still high
- Screening HIV positive pregnant women for TB in South Africa increased detection by 10-fold



### Reassuring French data using raltegravir during pregnancy

Polly Clayden, HIV i-Base

**A presentation from the French Perinatal Cohort at IAS 2017 reported reassuring safety data on raltegravir-exposed pregnancies – including first trimester exposure. [1]**

This large prospective cohort of children exposed to raltegravir (RAL) in utero found no significant association between first trimester exposure and birth defects.

There is currently no published literature on RAL and birth defects. The largest report is from the Antiretroviral Pregnancy Registry (APR) to January 2017. The APR reports 7 birth defects out of 263 first trimester exposures (2.7%) and no difference with second/third trimester exposure (8/250, 3.2%). [2]

The French Perinatal Cohort (EPF) is a multicentre ongoing, prospective, national cohort, which enrolls pregnant HIV positive women delivering in 90 centres throughout France. Children are then followed until they are two years old.

The EPF evaluation included all RAL-exposed pregnancies between 2008 and 2015. Birth defects were defined using the EUROCAT classification.

There were 479 RAL-exposed pregnancies of which 6 (1.3%) resulted in stillbirths and 2 late miscarriages (0.4%). There were 68 (14.2%) preterm deliveries and 10 (2.1%) twin pregnancies. No pregnancies were terminated for birth defects.

Earliest RAL-exposure was in the first trimester for 140 (29.2%) and second/third trimester for 339 (78.8%).

There were 20/479 birth defects for all births: 4.2% (95% CI 2.4 to 6.0%). And 20/471 among live births: 4.2% (95% CI 2.4% to 6.1%). The investigators noted that this incidence was similar to that reported in a previous study in EPF for live births exposed to any antiretroviral: 4.4% (95% CI 4.0 to 4.7%).



The was no significant difference in overall birth defect rates between first trimester and second/third trimester exposure to raltegravir: 5.7% vs 3.5%; OR 1.6 (95% CI 0.7 to 4.1),  $p=0.29$ .

The anomalies did not follow a pattern: 7 heart defects, 5 polydactyly, and 8 other defects.

Follow-up was complete to 24 months for 63% of children at time of analysis.

#### References

1. Sibiude J et al. Evaluation of the risk of birth defects among children exposed to raltegravir in utero in the ANRS-French Perinatal Cohort EPF. IAS 2017. 23–26 July 2017. Paris. MOAB0204  
<http://programme.ias2017.org/Abstract/Abstract/3037>
2. Antiretroviral Pregnancy Registry (APR) international interim report. 1 January 1989 to 31 January 2017.  
[http://www.apregistry.com/forms/interim\\_report.pdf](http://www.apregistry.com/forms/interim_report.pdf)

## Earlier ART reduces infant mortality in South Africa but risk of death and loss to follow up still high

Polly Clayden, HIV i-Base

**Infants are starting ART earlier, with less disease progression and declines in mortality according to findings from the leDEA-SA collaboration. But mortality and loss to follow up among infants starting ART remains unacceptably high.**

Over the past few years there has been a significant expansion of universal ART for HIV positive children less than five years old. WHO recommendations have expanded the eligibility to “treat all” in this age group – from only those less than one year in 2008, to all children less than five years old in 2013.

There has also been a shift towards early infant diagnosis (EID) and early infant ART (EIART) but little is known about the outcomes of children starting ART in the context of changing paediatric HIV testing and treatment guidelines.

Investigators from the leDEA-SA showed results from an evaluation conducted to describe temporal trends in characteristics of infants starting ART in South Africa and six month outcomes. These data were presented at IAS 2017.

The analysis included infants starting ART less at less than three months old and described characteristics and outcomes over three guideline periods: 2006–2009, 2010–2012 and 2013 and after.

The median age at ART initiation of 1380 eligible infants was 56 days (IQR: 27 to 73). Median log viral load at ART initiation declined from 5.9 (IQR: 5.4 to 6.4) in 2006–2009 to 5.4 (IQR: 3.9 to 6.3) in 2013+. Median absolute CD4 count increased progressively from 888 cells/mm<sup>3</sup> (IQR: 380 to 1703) in 2006–2009 to 1526 (IQR: 659 to 2231) in 2013+, (both  $p<0.001$ ).

After six months on ART, 78 (5.7%) children died overall. Mortality declined from 9.7% in 2006–2009 to 4.8% in 2013+ ( $p<0.001$ ). Loss to follow up was 225 (17.6%) overall, declining from 22.4% in 2006–2009 to 14.4% in 2013+ ( $p=0.004$ ).

Among the children lost to follow up, 72% had no visit after starting ART and 28% after at least one subsequent visit on ART.

In multivariate analysis, neither age, CD4 count, weight for age z-score nor ART initiation period were predictors for mortality.

The investigators concluded that children are starting ART earlier, with less advanced disease and decline in mortality. But about 40% still start ART with advanced disease and mortality estimates remain unacceptably high. Loss to follow up also remains high overall.

“Innovative approaches are required to ensure HIV infected infants have optimal treatment outcomes”, the investigators wrote.

#### Reference

Iyun V et al. Earlier treatment and lower mortality in infants initiating antiretroviral therapy at < 12 weeks of age in South Africa: The International epidemiologic Databases to Evaluate AIDS Southern Africa (leDEA-SA) Collaboration. 9th IAS Conference on HIV Science. 23–26 July 2017. Paris. Poster abstractTUPDB0206LB

<http://programme.ias2017.org/Abstract/Abstract/5641> (abstract)



## Screening HIV positive pregnant women for TB in South Africa increased detection by 10-fold

Polly Clayden, HIV i-Base

**Universal TB screening of all HIV positive pregnant women increased case detection and was associated with reduced early infant mortality in a South African study presented at IAS 2017.**

TB is a leading cause of maternal and infant morbidity and mortality in HIV positive pregnant women. Currently-recommended symptom-based screening of HIV positive pregnant women may not be sensitive enough.

Investigators from the Perinatal HIV Research Unit, University of the Witwatersrand and Johns Hopkins University, Baltimore conducted a cluster-randomised trial to compare universal sputum TB testing with standard symptom-based testing in this population.

The trial was conducted across 16 public-sector antenatal clinics in two health districts that were randomised to either strategy. HIV positive pregnant women without currently diagnosed TB were eligible.

In universal testing clinics, all women were asked to produce a sputum sample. In symptom clinics, only those with WHO criteria for TB testing (cough, fever, night sweats, or weight loss) were asked to.

Samples were tested using Xpert MTB/RIF. Halfway through the study liquid MGIT culture was added. Follow up of women and infants was two months postpartum.

During the study period (May 2015 to March 2017), 941 and 1100 HIV positive pregnant women were enrolled in the universal and symptom clinics, respectively. In both arms, median age was approximately 30 years, median gestational age 25 weeks, 8% had TB before, 99% were on ART, and CD4 count was 440 cells/mm<sup>3</sup>.

In universal and symptom clinics, respectively, 34/941 and 4/1100 women were diagnosed with TB during pregnancy. Universal clinics prevalence 3.6% (95% CI: 1.2 to 6.0) and symptom clinics 0.36% (95% CI: 0.0 to 1.1),  $p=0.01$ .

At two months post-partum, infant mortality in universal clinics was 1% compared with 2.2% in symptom clinics,  $p=0.134$ . Maternal death was 0.1% compared with 0.3%, respectively. Miscarriages and stillbirths were similar in both arms.

MGIT culture identified more TB than Xpert: 5.1% were MGIT positive compared with 1.4% Xpert positive,  $p<0.05$ .

The investigators concluded that universal TB screening of all HIV positive pregnant women increased case detection 10-fold and halved early infant and maternal deaths (but this was not statistically significant). Xpert detected one third the rate of TB compared with MGIT.

### Reference

Martinson N et al. Universal sputum testing vs symptom-based testing for tuberculosis (TB) in HIV infected pregnant women: a cluster-randomised implementation trial in South Africa. 9th IAS Conference on HIV Science. 23–26 July 2017. Paris. Poster abstract TUPDB0204LB. <http://programme.ias2017.org/Abstract/Abstract/5746> (abstract)



## ANTIRETROVIRALS

### Coformulated dolutegravir plus rilpivirine approved in US (Juluca)

Simon Collins, HIV i-Base

**On 21 November 2017, the US FDA approved the first two-drug, single tablet, fixed dose combination (FDC). [1]**

The FDC includes dolutegravir (50 mg) and rilpivirine (25 mg) and has an indication as switch therapy in HIV positive people who have been on stable ART for more than six months with no history of drug resistance. The pharmacokinetic importance of food for boosting rilpivirine means this FDC needs to be taken with food.

Approval is based on results from the phase 3 SWORD 1 and 2 studies. Please see prescribing information for more details. [2]

This FDC is marketed by ViiV Healthcare with the brand name Juluca.

Reference

1. ViiV Healthcare press statement. dolutegravir and rilpivirine (Juluca) approved in US as first 2-drug regimen once-daily single pill - a complete regimen for the maintenance treatment of virologically suppressed HIV-1 infection (21 November 2017).  
<https://www.viivhealthcare.com/media.aspx>
2. ViiV Healthcare. **Highlights of prescribing information (Juluca). November 2017.**  
[https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing\\_Information/Juluca/pdf/JULUCA-PI-PIL.PDF](https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Juluca/pdf/JULUCA-PI-PIL.PDF) (PDF)

## **Darunavir-based single pill FDC approved in EU (Symtuza)**

**Simon Collins, HIV i-Base**

**On 27 September 2017, the first protease inhibitor-based fixed-dose combination (FDC) was approved in Europe by the European Medicines Agency (EMA). [1]**

The once-daily FDC combines darunavir 800 mg, cobicistat 150 mg and emtricitabine/tenofovir alafenamide 200 mg/10 mg fixed-dose combination (D/C/F/TAF). The indication is for HIV positive adults and adolescents aged 12 years and older.

Symtuza needs to be taken once-daily with food. Approval is based on phase 3 studies showing bioequivalence to the individual components being taken separately.

For full details see the SPC and patient information on the EMA website. [2]

This FDC is marketed by Janssen-Cilag with the brand name Symtuza.

Reference

1. Janssen press statement. **European Commission approves Symtuza for the treatment of HIV-1 in adults and adolescents in Europe. (27 September 2017).**  
<http://www.investor.jnj.com/releases.cfm>
2. European Summary of Product Characteristics (SPC) for Symtuza. (September 2017).  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004391/human\\_med\\_002165.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004391/human_med_002165.jsp&mid=WC0b01ac058001d124)

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## PAEDIATRIC CARE

### **Long-acting ART for children is a deferred priority despite achievable dosing**

**Polly Clayden, HIV i-Base**

**Optimal doses of long-acting injectable antiretrovirals cabotegravir and rilpivirine were predicted for different weight bands in children and adolescents.**

Long-acting injectable antiretrovirals could be future alternatives to oral formulations and might help to address adherence. There is great interest in the potential use of these formulations in the treatment of paediatric HIV.

Clinical trials of new drugs in children and adolescents are delayed by both ethical and logistical barriers complicating the identification of appropriate doses. Physiologically-based pharmacokinetic (PK) modelling can inform dose finding before clinical trials are conducted.

Researchers from the University of Liverpool and Johns Hopkins conducted a study to simulate potential dosing strategies of long-acting injectable depot formulations of cabotegravir and rilpivirine in children and adolescents (aged 3 to 18 years) using such modelling.

The researchers developed whole-body physiologically-based PK models to act as the anatomical, physiological and molecular processes as well as age-related changes in children and adolescents using allometric equations.

The models were validated for the two long-acting injectable intramuscular agents in adults. The characteristics of children and adolescents were validated using available literature.

PK data generated through the physiologically-based PK simulations were similar to that observed in adult clinical data.

The researchers predicted optimal doses of long-acting injectable cabotegravir and rilpivirine using the release rate for existing clinical formulations, for different weight groups of children and adolescents.

They found the intramuscular loading dose and maintenance dose of cabotegravir across various weight bands in children weighing from 15–70 kg ranged from 200–600 mg and from 100–250 mg, respectively. For rilpivirine these ranged from 250–550 mg and from 150–500 mg, respectively.

“The reported findings represent a rational platform for the identification of suitable dosing strategies and can inform prospective clinical investigation of long-acting injectable formulations in children and adolescents” the researchers wrote.

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#### C O M M E N T

**The paediatric investigation plan for these long-acting drugs includes their use in both treatment and prevention.**

**However, there is a waiver for young children less than two years (for treatment) and less than 12 years for prevention. But there is a deferral for children that are two years and above.**

**This means that these agents will only potentially be available for use in the paediatric population many years after they are likely to be approved for adults.**

#### Reference

Rajith K et al. In silico dose prediction for long-acting rilpivirine and cabotegravir administration to children and adolescents. *Clin Pharmacokinet.* 24 May 2017. Epub ahead of print.  
<https://www.ncbi.nlm.nih.gov/pubmed/28540638>

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## GUIDELINES

### **Sexual and reproductive health: draft UK guidelines online for comment**

**The BHIVA/BASHH/FSRH guidelines for the sexual and reproductive health of people living with HIV 2017 are open for public consultation.**

<http://www.bhiva.org/SRH-guidelines-consultation.aspx>

Deadline for comments is 17.30 on Friday 8 December 2017.

These are an update to 2007 guidelines.

The guidelines cover:

- Sexually transmitted infections
- Cervical screening
- Pre-conception advice & conception
- Antiretroviral therapy: impact on transmission & conception
- Pre-exposure prophylaxis (PrEP) and pre-exposure-prophylaxis for conception (PrEP-C)
- Investigations in couples affected by HIV, trying to conceive through UPSI
- Contraception for Women with HIV
- Hormonal contraception and antiretroviral drug-drug interactions
- Contraception and HIV Acquisition, Transmission and Disease Progression
- Management of the menopause in women living with HIV
- Intimate Partner Violence
- Female genital mutilation
- Sexual dysfunction and HIV

The guidelines are aimed at all people involved in the provision of services or advice related to the sexual and reproductive health of PLWH and their partners including: HIV clinics, sexual and reproductive health services, primary care, obstetrics, gynaecology and fertility services, community and peer-led organisations, and appropriate commissioners.

## CURE RESEARCH & BASIC SCIENCE

### Estimating the total size of the HIV reservoir

Richard Jefferys, TAG

**A paper published earlier this month in Nature Medicine by Jake Estes and colleagues addresses the difficult challenge of attempting to define the distribution and total size of the persistent HIV reservoir. [1]**

The researchers employed a variety of tests to measure viral RNA and DNA – including new imaging techniques they have developed named RNAScope and DNAScope [2] – in multiple tissues from untreated or ART-treated macaques (infected with SIVmac251, SIVmac239 or SHIV) as well as lymph node and rectal tissue samples from a cohort of 20 individuals on ART in Kampala, Uganda.

The main findings were that the vast majority (~99.6%) of cells expressing viral RNA – indicating some degree of virus production – were found in lymphoid tissues (lymph nodes, gut, spleen, and lung). ART significantly reduced viral RNA levels, but the researchers estimated a total body burden of as many as seven million cells expressing HIV RNA at any given time in tissues, despite viral load suppression to undetectable levels in the blood.

One suggested explanation for the continued viral RNA expression is ongoing replication due to poorer penetration of ART drugs into tissues (the study reports evidence of suboptimal ART levels in tissues of macaques). But the authors' note that the tests for viral RNA were unable to distinguish between ongoing active viral replication and the production of viruses by reactivated latently infected cells. ART would not be expected to block the latter process; rather, it would prevent any viruses that are produced by reactivated latently infected cells from being able to go on and infect other cells.

The total size of the replication-competent HIV reservoir that persists during ART was estimated as approximately 400 million latently infected cells, based on analyses of viral DNA levels in tissues. The researchers suggest this is broadly consistent with another recent estimate, which, when extrapolated to the whole body, gives a result of 240 million cells. [3]

The paper's abstract states a more conservative ~100 million (it is not clear why there's a difference from the estimate provided within the paper). These numbers are larger than had originally been thought, and underscore the challenge of eliminating latent HIV infection.

The question of whether HIV replication commonly persists in tissues despite ART remains contentious, with many of the authors of this study having previously reported that it does, based on analyses of three people who had been receiving ART for six months (this prior work is cited in the current paper). [4]

But these results were recently challenged by the research group of Mary Kearney, who found no evidence of HIV replication in children who had been on ART with suppressed viral loads for seven to nine years (Kearney's work was initially presented at CROI 2017 and has since been published in the Journal of Clinical Investigation). [5, 6]

Kearney argued that there was a potential problem with the original claims because the Bayesian methodology for assessing HIV evolution was not appropriate for the task.

A recent paper by David Asmuth and colleagues also presents a contrary perspective, finding that ART concentrations in gut-associated lymphoid tissue (GALT) were adequate in almost all cases studied, with no evidence of residual HIV replication. [7]

A recent paper by David Asmuth and colleagues also presents a contrary perspective, finding that ART concentrations in gut-associated lymphoid tissue (GALT) were adequate in almost all cases studied, with no evidence of residual HIV replication. [8]

Resolving the question of whether the HIV RNA that is detectable despite ART derives from ongoing active viral replication or reactivated latently infected cells (or both) will be important, because it has implications for therapeutic approaches to reducing the reservoir.

Source

TAG basic science blog. 30 October 2017.

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<https://academic.oup.com/jid/article-abstract/doi/10.1093/infdis/jix418/4092886>

## SIDE EFFECTS & COMPLICATIONS

### Reducing rates of HIV-related cancer in US from 1996-2012

Simon Collins, HIV i-Base

**A large registry-linked database of almost 450,000 people living with HIV in eight US states and Puerto Rico reported significant reductions in the risk of many cancers over time.**

**These results, published in the November 2017 edition of the *Lancet HIV*, were strongly linked to availability of earlier and better HIV treatment. Importantly, there were no cancers where risks increased over time.**

From 1996 to 2012, the HIV/AIDS Cancer Match (HACM) Study included 21,294 newly diagnosed cancers, from more than three million persons-year of follow-up (PYFU). However, each registry contributed data for different periods: Colorado (1996–2007), Connecticut (2005–10), Georgia (2004–12), Maryland (2008–12), Michigan (1996–2010), New Jersey (1996–2012), New York (2001–12), Puerto Rico (2003–12), and Texas (1999–2009).

Standardised incidence ratios (SIR) were compared to data from the US general population (which would also include HIV positive people), adjusted for sex, age, race or ethnic group, calendar year, and registry. The analysis also compared time with AIDS to only HIV, and used four time periods: 1996–99, 2000–04, 2005–08, and 2009–12. The majority of follow-up cover the last two time periods (each with > 1 million PYFU). Participants in the later periods were also more likely to contribute >10 years of PYFU.

Overall, rates of cancer were approximately 70% higher for HIV positive people (SIR: 1.69, 95%CI: 1.67–1.72,  $p < 0.0001$ ).

Rates of HIV-related cancers (14-fold higher) or those linked to other viruses (5-fold higher) were still significantly higher in HIV positive people compared to rates in the general population ( $p < 0.0001$ ). Rates were also higher for some non-virus-related cancers (notably lung, non-HPV oral), but significantly lower for others (including colon, stomach, female breast, prostate, kidney/renal pelvis). In the cases of lower rates, it is unclear whether, for example, this might be associated with more monitoring in the general population (that might not be accessed by HIV positive people) or a survival bias linked to HIV positive people being vulnerable to other cancers at younger age. For many other cancers, rates were similar, irrespective of HIV status. See Table 1.

There were also a few examples of where the trends of some cancers to reduce over time were not significant: Burkitt's lymphoma ( $p = 0.8944$ ), cervical cancer ( $p = 0.0989$ ) and Hodgkin's lymphoma ( $p = 0.862$ ).

However, the results were also limited by not having access to individual data for HIV positive people, for example for CD4, viral load or ART used etc.

Although the paper comments that earlier ART and wider access to ART might continue to reduce cancer rates – both of which have significantly changed in the five years since the cut-off for data collected in this study – it also notes that ART might not fully reverse the effects of immunosuppression, especially for people who are diagnosed late or who delay ART. Given many cancers take decades to develop, the limited data on HIV and cancer in older people makes continued monitoring vital.

**Table 1: Incidence of selected cancers in HIV positive vs US general population, 1996-2012 (all p<0.0001)**

Cancer type	n	SIR	95% CI
Overall	21,294	1.69	1.67–1.72
AIDS-defining cancers	6,384	13.97	13.63–14.32
Kaposi's sarcoma	2269	498.11	477.82–519.03
Non-Hodgkin lymphoma	3687	11.51	11.14–11.89
Cervix	428	3.24	2.94–3.56
Other virus-related cancers	4144	5.39	5.23–5.55
Anal	1568	19.06	18.13–20.03
Liver	1104	3.21	3.02–3.41
Hodgkin's lymphoma	875	7.70	7.20–8.23
Virus-unrelated	10,200	0.92	0.90–0.94
Lung	2475	1.97	1.89–2.05
Oral (non-HPV)	343	2.20	1.98–2.45
Colon *	477	0.61	0.56–0.67
Stomach *	185	0.74	0.64–0.86
Female breast *	688	0.63	0.58–0.68
Prostate *	1522	0.48	0.46–0.51
Kidney/renal pelvis *	360	0.74	0.66–0.82

• Examples of significantly reduced rates

SIR: standardised incidence ratio; CI: confidence interval

#### C O M M E N T

**These results, although retrospective and only based on US data to 2012, are important for the size of the cohort and are generally very positive.**

**Higher rates of smoking-related cancers emphasis the importance of support for lifestyle changes including smoking cessation.**

#### Reference

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## Effects of the anti-Inflammatory antibody canakinumab on heart disease and cancer: implications for HIV?

Richard Jefferys, TAG

**Inflammation is increasingly recognised as an immunological double-edged sword: it contributes importantly to the response to infection, but can also cause serious collateral damage to the body – particularly when persistent – and has been implicated as potentially contributing to multiple conditions, including heart disease and cancers.**

Researchers have found that the anti-inflammatory effects of statin drugs contribute to their beneficial effects against cardiovascular disease, but because statins also reduce cholesterol it has not been possible to disentangle the relative importance of these two potential mechanisms of action.

To directly address the role of inflammation in cardiovascular disease, the pharmaceutical company Novartis sponsored a 10,061-person randomised trial of their antibody canakinumab, which is designed to reduce inflammation by blocking the cytokine IL1-beta (it is already FDA-approved for the treatment of a number of other conditions).

The trial, named the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), recruited HIV negative individuals who had previously experienced a heart attack and had levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) of at least 2 mg/L. The average age of participants was 61 years old. Three different doses of canakinumab were studied: 50 mg, 150 mg, or 300 mg, administered subcutaneously every three months. The primary endpoint was nonfatal heart attack, nonfatal stroke, or cardiovascular death.

The main results were published in the *New England Journal of Medicine* on August 27, 2017, drawing considerable media attention. [1]

After a median of 3.7 years of follow up, the results showed a slight but statistically significant reduction in the incidence of primary endpoints in the 150 mg dose group: there were 3.86 events per 100 person-years compared to 4.50 events per 100 person-years in the placebo group (an approximately 15% reduction in risk). There was a similar reduction in the 300 mg group (3.90 events per 100 person-years) but it did not meet the criteria for statistical significance. No significant effect was observed in recipients of the 50 mg dose. The most common primary endpoints were heart attacks.

In a separate paper published in *The Lancet*, another interesting possible benefit was reported against cancer; the analysis was not pre-planned so is considered exploratory, but there was a statistical trend toward a reduction in cancer mortality when recipients of all canakinumab doses were compared to the placebo group. [2]

The result achieved statistical significance in recipients of the 300 mg dose, for whom the risk of cancer mortality was roughly halved compared to placebo. The incidence of lung cancer was also significantly reduced in the 150 mg and 300 mg dose groups, and there was a reduction in lung cancer-related mortality that reached statistical significance in the latter group.

Consistent with the clinical outcomes, canakinumab was associated with dose-dependent reductions in the levels of the inflammatory biomarkers hsCRP (26 to 41%) and interleukin-6 (25 to 43%).

There were distinct downsides to the therapy: fatal infections or sepsis were significantly more frequent among canakinumab recipients (the incidence rates were 0.31 vs. 0.18 events per 100 person-years in the canakinumab and placebo groups, respectively), and this meant that all-cause mortality was similar between the treatment and placebo arms. Neutropenia and thrombocytopenia were also significantly more frequent in the canakinumab groups.

In an editorial commentary in the *New England Journal of Medicine*, Robert Harrington notes that uncertainties about the risk/benefit of canakinumab that will need to be resolved before it can be considered for routine use against cardiovascular disease. [3]

Harrington also highlights the current exorbitant price of the antibody: approximately \$200,000 per year in the United States. More optimistically, he emphasises the importance of the CANTOS trial in confirming that targeting inflammation can produce clinical benefits in cardiovascular disease. Other trials are addressing whether cheaper alternative anti-inflammatories can produce similar or better results, with one example being an evaluation of low-dose methotrexate sponsored by the National Heart, Lung, and Blood Institute. [4]

## Implications for HIV?

Associations between higher levels of inflammatory biomarkers and increased risk of morbidity and mortality (including events resulting from cardiovascular disease and cancers) have been consistently reported in HIV positive people, most notably in analyses of the large SMART and ESPRIT trials. [5]

A paper just published in the *Journal of AIDS* reports that levels of the biomarkers IL-6 and D-dimer were also significantly associated with potentially life-threatening grade 4 events that were not attributable to AIDS, cardiovascular disease, or non-AIDS cancers in these study populations. These results prompt the question of whether canakinumab or other anti-inflammatories might have salutary clinical effects in HIV-positive people. [6]

The researcher Priscilla Hsue at UCSF has conducted a small pilot study of a single 150 mg canakinumab dose in ten HIV positive people on ART – results were described earlier this year at CROI (a webcast of the presentation is available online). Participants were required to be over 40 years old with known cardiovascular disease or at least one risk factor. [7]

Eight weeks after the single dose, there were dramatic declines in levels of hsCRP (41%) and IL-6 (30%), as well as evidence of reduced arterial inflammation. Adverse events included a 28% drop in absolute neutrophil count measured at two and three weeks after canakinumab administration, which recovered to normal by week four. There was also a single case of shingles that may have been related to the study drug, although Hsue noted that no cases were observed in the CANTOS trial.

Hsue is now conducting a larger randomised, placebo-controlled extension of the trial that will administer two doses of canakinumab, at baseline and week 12, and follow participants for 36 weeks. [8]

The study aims to recruit 100 HIV positive individuals and has the same entry criteria as the pilot: over 40 years of age with known cardiovascular disease or at least one risk factor. Results should help discern if canakinumab might have potential in HIV, and it will be interesting to find out if the effects on hsCRP and IL-6 – which dwarf the reductions seen with any other interventions – are sustained in the absence of ongoing repeat dosing.

In terms of other research involving potential anti-inflammatory approaches, the most significant is the large REPRIEVE trial, which is evaluating the clinical effects of pitavastatin in 6,500 HIV positive individuals (aged 40-75) on ART. Substudies will investigate the relationship between effects on inflammatory biomarkers and outcomes. [9]

An AIDS Clinical Trials Group (ACTG) study of low-dose methotrexate in 176 HIV positive ART-treated participants over 40 years of age has been completed and results are pending. [10]

Looming over the research into therapeutic approaches for reducing inflammation in HIV positive people on ART are unresolved questions about the exact causes of the problem. Studies have been consistent in showing a relationship between the magnitude of persistent inflammation and timing of ART initiation: the later in the course of infection that ART is started, the higher the levels of inflammatory biomarkers and vice versa. But even in people who start ART very early, inflammatory biomarkers typically don't drop all the way down to levels that are normal for healthy HIV-negative people, and the exact causes are still unclear.

Some research has posited that the persistence of HIV contributes, but a large ACTG study published earlier this year found no significant relationship between various measures of HIV persistence (e.g. HIV DNA, HIV RNA) and inflammatory biomarkers in individuals on long-term ART. Rather, the levels of inflammation remained significantly associated with pre-ART measures, which led the researchers to conclude that “immune events that occurred before treatment initiation had long-lasting effects despite sustained control of the virus.” [11]

While the study could not answer the question of exactly what the immune events were, the authors write: “Mechanisms consistent with our observations are those that predominate during untreated infection but can exert a long-lasting effect, such as fibrotic damage to lymphatic tissue, increased intestinal permeability leading to elevated microbial translocation, or persistent co-infections in the setting of compromised immune surveillance.” There has been some research into approaches that might address these potential causes, particularly candidates predicted to affect microbial translocation such as sevelamer, mesalamine, rifaximin and various probiotics, but results have been mixed, with little sign of significant anti-inflammatory effects. A trial of the antifibrotic drug losartan is currently ongoing. [12]

Another possible contributor to persistent inflammation might be immune system perturbations such as loss of naïve T cells and inversion of the CD4/CD8 ratio, which tend not to fully normalise even in early-treated individuals. There was intriguing evidence that the cytokine IL-7, which promoted reconstitution of naïve T cells in people on ART, was associated with short-term declines in inflammatory biomarkers, but since the manufacturer went bankrupt several years ago this candidate immune-based therapy appears to be in limbo. [13]

Additional studies on the causative mechanisms of persistent inflammation on ART are clearly needed, in order to better define targets for therapeutic interventions.

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## OTHER NEWS

### MSF secures generic hepatitis C treatment at \$120 per course

#### MSF press release

**On 31 October 2017, on the eve of the World Hepatitis Summit in Sao Paulo, Médecins Sans Frontières (MSF) announced that it had secured deals for generic hepatitis C medicines for as low as US\$1.40 per day, or \$120 per 12-week treatment course for the two key medicines sofosbuvir and daclatasvir.**

In the US, sofosbuvir was launched by Gilead at \$1,000 per pill in 2013, and daclatasvir was launched by Bristol-Myers Squibb (BMS) at \$750 per pill in 2015. This led to the original combined price of \$147,000 for a 12-week combination course.

In 2015, MSF started procuring sofosbuvir and daclatasvir from Gilead and BMS through their 'access programs' at a price of \$1,400 to \$1,800 per 12-week treatment. Today, MSF pays a fraction of that, at \$120, sourced from quality-assured generic manufacturers.

An estimated 71 million people have chronic hepatitis C infection worldwide, 72 per cent of whom live in low- and middle-income countries. Direct-acting antiviral medicines (DAAs) represent a treatment breakthrough for people with hepatitis C, with cure rates of up to 95%, and with far fewer side effects than previous treatments. Yet access to DAAs has remained limited because of unaffordable prices, leading many countries to reserve treatment only for people with the most advanced stages of the disease.

By the end of 2016, three years after sofosbuvir was launched, only an estimated 2.1 million people globally had been treated with the medicines, leaving 69 million people still without access.

These high prices have also put a major strain on health systems in wealthy countries, in particular those enacting universal health care. Treatment is being rationed in countries such as Australia, Canada, Italy and the US, in addition to developing countries, and is a stark reminder of the early days of HIV treatment.

This is a reduced version of the press release that is online in full. [1]

Additional briefing on HCV is also recommended. [2]

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[www.doctorswithoutborders.org/article/msf-secures-generic-hepatitis-c-treatment-120-compared-147000-launch-price-tag](http://www.doctorswithoutborders.org/article/msf-secures-generic-hepatitis-c-treatment-120-compared-147000-launch-price-tag)
2. Not Even Close: This issue brief provides information on currently available HCV diagnostics and treatments, including pricing and registration information from manufacturers of DAAs  
[www.msfacecess.org/hep-c-not-even-close](http://www.msfacecess.org/hep-c-not-even-close)

## ON THE WEB

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### *Conference materials online*

#### **8th International Workshop on HIV & Ageing**

2–3 October 2017, New York

This annual workshop includes a good selection of webcasts, powerpoint presentations.

<http://www.infectiousdiseasesonline.com/8th-hiv-aging-presentations>

<http://www.infectiousdiseasesonline.com/event/workshop/8th-international-workshop-hiv-aging-2017>

#### **International Workshop on Comorbidities and Adverse Drug Reactions in HIV**

**23 – 25 October 2017, Milan**

A selection of 20 slide presentations from this annual workshop on side effects and other complications of HIV are available online.

<https://www.intmedpress.com/comorbidities/default.cfm?itemtypeid=28&title=2017%20presentations>

### *Recent peer-review studies*

**Long-term immune response to yellow fever vaccination in HIV-infected individuals depends on HIV-RNA suppression status: Implications for vaccination schedule.** Olivia Veit et al.

Clinical Infectious Diseases; cix960 (11 November 2017).

<https://doi.org/10.1093/cid/cix960>

Important link between vaccine efficacy and undetectable viral load (rather than just CD4 count).

**The importance of HIV research for transgender and gender non-binary individuals.** Gianella S et al. (08 November 2017).

Clinical Infectious Diseases; cix990

<https://doi.org/10.1093/cid/cix990>

Paper highlighting importance and need for this research.

**Cardiovascular disease (CVD) and chronic kidney disease (CKD) event rates in HIV-positive persons at high predicted CVD and CKD risk: A prospective analysis of the D:A:D observational study**

PLoS Medicine 14(11):e10024 (24 November 2017).

<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002424>

<http://dx.plos.org/10.1371/journal.pmed.1002424.g001>

The importance of monitoring CVD and CKD together.

## FUTURE MEETINGS

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### Conference listing 2018

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.

#### **8th International Workshop of HIV & Women**

2 – 3 March 2018, Boston

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

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

4 – 7 March 2018, Boston

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

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

17 – 20 April 2018, Edinburgh

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

#### **12th INTEREST Workshop**

29 May – 1 June 2018, Kigali

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

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

Tbc May 2018, Washington

[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)

#### **HIV Glasgow 2018**

28 – 31 October 2018

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

## PUBLICATIONS & SERVICES FROM i-BASE

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### **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.

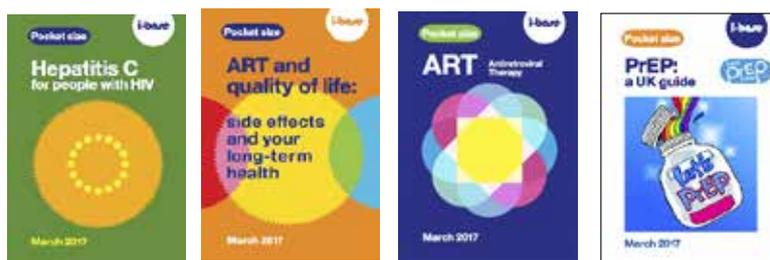
We hope these are especially useful as low literacy resources.

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 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.

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## ***h-tb***

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