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# hiv treatment bulletin

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CONTENTS



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





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# EDITORIAL

**This first issue of HTB for 2017 comes slightly late in the month to be able to include rapid reports from CROI 2107.**

As usual, this major scientific meeting had much to report - with 14 articles in this issue and more to follow next month (these will be posted earlier online).

The conference was particularly notable for the number of studies involving new drugs or formulations – and we start with bictegravir, doravirine and GS-9131) and dolutegravir formulations for younger children.

We also include four studies on ART use in pregnancy, disappointing news that dolutegravir monotherapy studies are now discontinued, a case of PrEP failure, plus more encouraging news that ART might protect against accelerated brain ageing.

This issue also reviews six journals articles, including a new focus on CMV coinfection.

And sexual health reports in England include a dramatic drop in HIV incidence in London clinics and a successfull ongoing pilot HPV vaccine programme in gay men and transgender people – at last.

Less impressive is the continued block to PrEP.

### SUPPLEMENTS with this issue of HTB

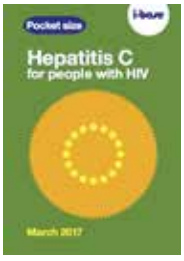
- Pocket guides - concertina leaflets (March 2017)

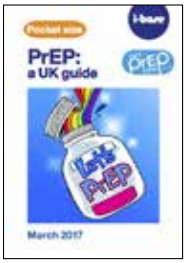
Pocket leaflets are shorter versions of the more detailed i-Base booklets - but small enough to fit in a pocket...

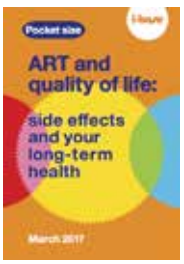
- Intro to ART
- Guide to PrEP
- HCV coinfection
- ART and quality of life

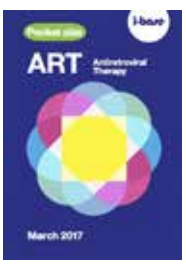
All free to UK clinics.

Please order online or using the form on the back cover of this issue of HTB.



# CONFERENCE REPORTS

## 24th Conference on Retroviruses and Opportunistic Infections (CROI 2017)

**13-16 February 2017, Seattle**

### Introduction

**The 24th Conference on Retroviruses and Opportunistic Infections (CROI 2017) was held in Seattle from 13-16 February 2017.**

More than 4000 researchers and health workers (and a good inclusion of community activists) worked through more than 1000 studies presented at the meeting.

Luckily, CROI supports broad open access to the conference materials online, including comprehensive webcasts of all oral presentations – available immediately after each session.

The programme for the meeting and abstract book – and nearly all posters – are now online as PDF files.

http://www.croiconference.org/electronic-materials

The searchable abstracts database links directly to PDF files for most posters.

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

CROI is one of the leading scientific HIV meetings. But despite the last minute reversal of the proposed US travel restrictions, many delegates were suggesting that if similar entry restrictions are reimposed, then international medical conferences should perhaps not be held in the US and that CROI could be moved to Mexico or Canada.

This detracts nothing from the leading work by IAS-USA and US scientists. It is a way to refuse to normalise racist policies that exclude global inclusion in medical conferences.

And the exciting news: there was much to report.

The following reports are in this issue.

- Pharmacokinetics and full phase 2 results for bictegravir, a new integrase inhibitor
- New NNRTI doravirine is non-inferior to darunavir/r in phase 3 treatment naive study
- NRTI GS-9131 resurfaces at CROI 2017: in vitro sensitivity to nuke-resistant HIV
- Dolutegravir exposure increases when fixed dose combination tablets are crushed
- Pharmacokinetics, safety and efficacy of dolutegravir in very young children
- Efavirenz, tenofovir and emtricitabine associated with fewest adverse birth outcomes in Botswana
- Adverse pregnancy outcomes and risk factors in the PROMISE trial
- Women on lopinavir/ritonavir-based regimens at conception at higher risk of preterm delivery in UK study
- No increase in adverse birth outcomes with maternal TDF/FTC in US study
- Dolutegravir monotherapy studies stopped due to integrase resistance: dual therapy studies continue
- No evidence of accelerated brain ageing in HIV positive people on effective ART
- Acute infection with wild-type HIV on PrEP with good drug levels
- Fit for purpose: antiretroviral treatment optimisation (Feb 2017)
- Seattle-lite: pre-conference workshops – watch online

CROI 2017: NEW DRUGS

## Pharmacokinetics and full phase 2 results for bictegravir, a new integrase inhibitor

**Simon Collins, HIV i-Base**

**Two oral presentations on a new integrase inhibitor bictegravir were included in the first session at CROI 2017 looking at new treatment and treatment strategies.**

Bictegravir (formerly GS-9883) is a once-daily integrase inhibitor (INI) that has in vitro activity against many INI-resistant viruses and a plasma half-life of 18 hours.

Bictegravir has high protein binding (99%) limiting likely penetration to sanctuary sites but does not require boosting or need to be taken with food.

Clinical results were presented by Paul Sax from Brigham and Women's Hospital in Boston from a phase 2 in treatment naive participants, with dolutegravir as the comparitor. [1]

This was a randomised double-blind, placebo controlled, 48-week study. The study randomised 98 treatment naive participants 2:1 to either bictegravir 75 mg (n=75) or dolutegravir 50 mg (n=33), both taken once daily with FTC/TAF as background NRTIs. This was a non-inferiority study with the primary endpoint of viral suppression at week 24 and secondary efficacy and safety endpoints at week 48.

Baseline characteristics were similar in each arm and included >90% male, 55% white, median age 30 to 36 years (range 19 to 68). In the bictegravir vs dolutegravir arms, median viral load was 4.41 vs 4.48 log, with 15 vs 21 people >100,000 copies/mL and median CD4 count was 441 vs 455 cells/mm$^3$, with 5 vs 9 participants with CD4 <200 cells/mm$^3$.

At week 24, viral suppression to <50 copies/mL by snapshot analysis was achieved by 97% vs 94% in the bictegravir vs dolutegravir groups respectively (difference +2.9; 95%CI: –8.5% to +14.2%, p=0.50). For the secondary endpoint at week 48, these rates were 97% vs 91% (difference: +6.4; 95%CI: –6.0% to 18.8%, p=0.17), with no statistical difference between groups. Two patients discontinued from each arm, one in each was lost to follow up, with one due to side effects in the bictegravir arm and one due to adherence in dolutegravir arm. No patients discontinued to lack of viral efficacy and only one person in each arm discontinuing for other reasons while viral load was above 50 copies/mL.

CD4 increases were similar in each arm: +258 vs +192 cells/mm$^3$, p=0.16.

Tolerability in both groups was also good with no discontinuations due to treatment-related side effects or deaths – and no significant other differences between groups – though the study number were small.

The most common side events were diarrhoea (12% in each group) and nausea (8% vs 12%). One participant in the bictegravir group discontinued due to urticaria (hives) after week 24. Grade 2 to 4 lab abnormalities including creatinine kinase, AST, hyperglycemia, ALT, LDL, amylase, haematuria, and gylcosuria occurred in 2% to 13% of participants by were generally similar in each group. Small reductions in eGFR (reported with integrase inhibitors) were also similar.

A second oral presentation on bictegravir, by Joseph Custodio from Gilead Sciences, provided pharmcokinetics on this new compound from single (5 mg to 600 mg) and multiple dose (5 mg to 300 mg over 14 days) evaluations for potential drug interactions in HIV negative volunteers. [2]

Potency of the compound is impressive, with mean plasma concentration more than 20 x above the IC95 at 24 hours and low intrapatient differences.

Bictegravir exposure was dose proportional for doses from 25 mg to 100 mg. Elimination was approximately 60% ± 5.5% from faeces and 35% ± 5.0% from urine with glucuronidation and oxidation contributing to the major clearance pathways.

The drug interaction study showed increased bictegravir AUC (61-74%) by CYP3A4 inhibitors (voriconazole and darunavir/c), with a greater increase (~4-fold) by potent dual inhibitors of UGT1A1 and CYP3A4 (atazanavir and atazanavir/c).

Bictegravir AUC was reduced by 75% by rifampin, a potent CYP3A4/UGT1A1/P-gp inducer and by 38% with rifabutin.

### COMMENT

**These early results show the potential for bictegravir to be an important new drug and phase 3 studies are already underway using a fixed dose combination coformulated with FTC/TAF.**

**This FDC uses an improved formulation of bictegravir that only requires a 50 mg dose. Although food increased bictegravir levels of the single formulation by >80%, in the FDC combination this is reduced to a 20% increase. Although both formulations could be taken with or without food, bictegravir will only be marketed as a component of an FDC.**

**The full results of the phase 2 study are also published online in the Lancet HIV. [3]**

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## New NNRTI doravirine is non-inferior to darunavir/r in phase 3 treatment naive study

**Simon Collins, HIV i-Base**

**A late-breaker oral presentation included results from a phase 3 study comparing the NNRTI doravirine to boosted darunavir, showing similar viral suppression and low rates of side effects at the 48-week primary endpoint. [1]**

Doravirine is a once-daily NNRTI from Merck that can be taken with or without food. It has few drug interactions and that retains activity against common first generation NNRTI mutations (K103N, Y181C, G190A and E138K). Last year at CROI, results from a phase 2b study reported non-inferiority compared to efavirenz. [2] A fixed dose combination of doravirine/TDF/3TC (using generic NRTIs) is already in phase 3 studies and a long-acting formulation is in development. [3, 4]

The current study, presented by Katherine Squires from Thomas Jefferson University, Philadelphia, randomised 769 treatment-naive adults to either doravirine (100 mg) or darunavir/r (800 mg/ 100 mg), both once-daily with investigator choice of TDF/FTC (87%) or ABC/3TC (13%) as background nukes.

Baseline characteristics include mean age 35 years (SD+/– 10.5), 84% male, 73% white/ 22% black with 10% having a clinical history of advanced stage HIV. Mean CD4 and viral load were approximately 420 cells/mm$^3$ (+/– 215) and 4.4 log copies/mL (+/– 0.7 log), with 20% >100,000 copies/mL and 4% >500,00 copies/mL.

At week 48, viral load was <50 copies/mL in 83.8% (321/383) vs 79.9% (306/383), in the doravirine vs darunavir/r arms respectively, (difference 3.9%, 95%CI: –1.6 to +9.4]), showing non-inferiority. Results of the stratified analysis of participants with baseline viral load >100,000 copies/mL, were 81.0% (64/79) vs 76.4% (55/72) respectively. Similar suppression was reported for the 17 participants in the doravirine arms with baseline viral load >500,000 copies/mL.

CD4 increases were similar at week 48: 193 vs +186 cells/mm$^3$ (difference +7 cells/mm$^3$; 95%CI: –21 to +35).

Discontinuations were similar in each arm although slightly less with doravirine than darunavir/r (n=56 (15%) vs n=71 (19%), respectively). Reasons included loss to follow up (4% vs 5%), lack of efficacy 3% vs 4%), withdrawn consent (3% each arm), side effects (1% vs 3%), non-compliance (2% vs 1%), doctor decision (1% in each), pregnancy (n=1 vs 0), protocol violation (<1% vs 2%) and death (n=1 vs 0).

Drug-related side effects were similar between arms. Drug-related side effects were reported in just over 30% of each arm, serious side effects in 5% vs 6% and discontinuations by 1.6% vs 3.1% (doravirine vs darunavir/r respectively)

The most common were diarrhoea (6% vs 13%), nausea (7% vs 8%), and headache (6% vs 3%) for doravirine vs darunavir/r respectively. Fasting LDL-C and non-HDL-C were reduced in the doravirine arm and increased in the darunavir/r arm (–4.5 and –5.3 vs +9.9 and +13.8 mg/dL, p<0.0001).

Drug resistance tests in 7/19 vs 8/24 people who were non-responders or rebounders, included one person with both NRTI and INI resistance at week 24. This person was non adherent and discontinued at week 24. No PI mutations were observed.

Two posters were also presented at CROI 2017: (i) on increased doravirine levels from a drug interaction with ritonavir [5] and (ii) on the ability to use doravirine in severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$) without dose adjustment [6].

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## NRTI GS-9131 resurfaces at CROI 2017: in vitro sensitivity to nuke-resistant HIV

**Simon Collins, HIV i-Base**

**A poster presented in vitro results of an NRTI compound from Gilead that appears has been in preclinical development for at least a decade. [1]**

GS-9131 is a prodrug of GS-9148 – and early animal and *in vitro* drug resistance studies on GS-9148 were presented at CROI in 2006. [2]

Other previously published studies have highlighted the potential for low risk of toxicity in animal studies. The compound retains *in vitro* phenotypic sensitivity to broad NRTI resistance including mutations at K65R, L74V and M184V and multiple TAMS.

The poster at CROI 2017, confirms results from previously published studies (from 2007) into the activity against common NRTI mutations. The compound has good potency (EC50: 25 to 200 nM) with activity against HIV-1 subtypes A, B, C, D, E, F, group O and N (EC50: 0.29 to 113 nM), and also against HIV-2. [3]

Serial passaging of HIV-1 in the presence of GS-9148 selected two resistance pathways: (i) a primary K70E mutation plus D123N and T165I; or (ii) Q151L with K70E, L74I, and L187F/M. These variants conferred reduced susceptibility to GS-9131 of <3-fold and 50-fold, respectively.

Of note, synergistic activity was reported for GS-9131 in combination with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TFV and TAF.

The poster concludes: "GS-9131 is an attractive candidate for further clinical development with a potential for once daily dosing and efficacy in patients with NRTI resistance" which seems slightly incongruous given how long this compound has been with the company.

**C O M M E N T**

**This early data is interesting. The potency and resistance profile of this compound would help a larger number of people now than ten years ago. Coformulation with other drugs that overcome drug resistance is important for both high- and low-income countries.**

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## Dolutegravir exposure increases when fixed dose combination tablets are crushed

**Polly Clayden, HIV i-Base**

**Dolutegravir exposure was higher after crushing the originator fixed dose combination (FDC) tablet and taking with enteral nutrition, compared to taking the whole tablet.**

These findings from a pharmacokinetic (PK) evaluation were presented at CROI 2017.

Marieke Roskam-Kwint and colleagues from the Radboud University, Nijmegen, Netherlands conducted a study to investigate whether the dolutegravir/abacavir/lamivudine FDC could be crushed and taken with enteral nutrition without altering PK.

The investigators explained that if people are unconscious or unable to swallow tablets for other reasons, antiretrovirals are sometimes crushed and dissolved before they are given. Crushing can influence PK, possibly leading to treatment failure and development of resistance with low exposure or toxicity if it is too high. They also note that a PK interaction between dolutegravir and enteral nutrition is possible, based on the known interaction between dolutegravir and cations in antacids and supplements.

This was an open-label, 3-period, randomised, cross-over, trial. Participants were randomly assigned to receive: a single dose of the FDC whole tablet fasted (reference); crushed and suspended FDC fasted (intervention 1); crushed and suspended FDC, followed by 250 mL enteral nutrition, taken orally (intervention 2). There was a 7-day washout period between different treatment periods.

A 48-h PK profile was measured for all compounds. Geometric mean ratios (GMR) with 90% confidence interval (CI) for AUC0-inf and Cmax were calculated for intervention 1 and 2 vs reference. The definition of bioequivalence was standard: when the 90% CI was within 80–125% for AUC and Cmax.

The study included 22 HIV negative participants (21 white and 1 mixed-race, 10 female). Participants were a median of 25 years (range 18–54) years and BMI 23 kg/m2 (range 20–27).

The investigators found for intervention 1 (crushed tablet fasting) vs reference (whole tablet), the GMR dolutegravir AUC0-inf was 129.5 (90%CI: 119 to 132) and Cmax was 129.5 (95%CI: 123 to 136). The GMRs and 90% CI for AUC0-inf and Cmax for abacavir and lamivudine were within the 80–125% bioequivalence range.

For intervention 2 (crushed tablet, ethereal nutrition) vs reference, the GMR dolutegravir AUC0-inf was 118.4 (90%CI: 112 to 125) and Cmax was 121.7 (95%CI: 115 to 128). Abacavir Cmax decreased by 17%.

As dolutegravir exposure increased by 26% and 30% for AUC0-inf and Cmax with crushed tablets and Cmax increased by 21% with crushed tablets plus ethereal nutrition compared to whole tablets fasted, bioequivalence could not be demonstrated.

The investigators recommended that the dolutegravir FDC can be crushed for people with difficulties swallowing or with an enteral feeding tube and can be combined with enteral nutrition. Although no dose-limiting toxicity of dolutegravir has been observed to date, they advise against crushing dolutegravir if someone needs twice daily dosing and to take it with food.

**C O M M E N T**

**These data are also useful to inform possible paediatric administration of dolutegravir as pill crushing is sometimes used in this population.**

Reference

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## Pharmacokinetics, safety and efficacy of dolutegravir in very young children

**Polly Clayden, HIV i-Base**

**Dolutegravir granules-in-suspension achieved satisfactory exposures in children aged between 2 and 6 years, according to data presented at CROI 2017.**

**Dolutegravir was potent and well tolerated through four weeks in this analysis.**

IMPAACT P1093 is an ongoing phase 1/2 open-label pharmacokinetic (PK) and dose finding study of dolutegravir in age-defined paediatric cohorts: 4 weeks to <18 years of age. Doses that provide dolutegravir exposure comparable to that from 50 mg once daily in adults with acceptable safety and tolerability are selected for each age group.

Dolutegravir is approved for children and adolescents aged 6 years and above, weighing at least 30 kg. Theodore Ruel and colleagues from P1093 presented 4 week results from an interim analysis of the 2 to <6 years cohort.

In this study children received dolutegravir granules-in-suspension at doses of ~0.8 mg/kg once daily. Children were ART-experienced but INSTI-naive at enrolment. They had been on a failing regimen for up to 12 weeks or off ART for at least 4 weeks. PK targets, based on adult data, were geometric means of: AUC24h range of 37 to 67 mg*hour/L (primary) and C24h range of 0.77 to 2.26 mg/L (secondary).

Intensive PK performed on 10 participants was used to determine the dose. The dolutegravir granules-in-suspension was evaluated at ~0.8 mg/kg once daily – based on data from the older P1093 cohorts.

PK was completed after oral administration of weight-based dose between days 5–10, after which the background regimen was optimised. Safety, tolerability, and viral load were assessed at 4 weeks, and the study is ongoing to 48 weeks.

At baseline the children (5 female and 5 male) were a median: age 4.3 years (IQR 3.6 to 4.6); weight 15.5 kg (13.8 to 15.9); CD4 count 1323 cells/mm$^3$ (IQR 763 to 2441); CD4 percent 28.0%(IQR 22.0 to 31.4) and viral load 4.8 log10 copies /mL (IQR 4.7to 5.3).

Mean dolutegravir dose was 0.87 mg/kg (range 0.58 to 1.06). The geometric mean (CV%) AUC24h was 44.7 (36%) mg*hour/L and C24h was 0.51 (68%) mg/L. C24h was below the target but above the pharmacodynamic threshold reported in adults. There was considerable variability among the participants.

Viral load was <400 copies/mL in 8/10 participants and <50 copies/mL in 6/10 after 4 weeks of treatment. There were no grade 3 or 4 side effects or drug related discontinuations.

**C O M M E N T**

**The granules-in-suspension formulation will not be commercially available but these data will form the basis for dolutegravir dosing as dispersible tablets to be studied in this and younger age cohorts, which are now enrolling.**

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Ruel T et al. Dolutegravir pharmacokinetics, safety and efficacy in HIV+ children 2 to <6 years old. CROI 2017. 13–17 February 2017. Seattle, Washington. Poster abstract 806.

http://www.croiconference.org/sessions/dolutegravir-pharmacokinetics-safety-and-efficacy-hiv-children-2 (abstract and poster)

CROI 2017: PREGNANCY

## Efavirenz, tenofovir and emtricitabine associated with fewest adverse birth outcomes in Botswana

**Polly Clayden, HIV i-Base**

**Maternal antiretroviral therapy (ART) of efavirenz, tenofovir and emtricitabine was associated with lower risk of adverse birth outcomes compared with other regimens, among infants exposed to ART from conception in Botswana.**

Rebecca Dash presented these findings at CROI 2017 on behalf of investigators from the Tsepamo study. The aim of the study was to compare birth outcomes with in-utero exposure from conception to the five most common ART regimens used in Botswana between August 2014 and August 2016.

She showed data from a planned two-year analysis of a four-year birth outcomes surveillance conducted at eight maternity wards in government hospitals across the country, representing about 45% of all births in Botswana. Data were extracted from all consecutive births at 24 weeks or more gestational age, using obstetric records.

Botswana provided an ideal setting to do this analysis. There is high HIV prevalence (about 22%), high uptake of ART in pregnancy (about 90%) and the majority of women (over 95%) deliver in a healthcare facility. Due to changes in national guidelines there was also a variety of regimens at conception to compare.

Since 2012, Botswana guidelines have recommended tenofovir, emtricitabine and efavirenz (TDF/FTC/EFV) for adults with CD4 <350 cells/mm$^3$ and all pregnant women (WHO Option B). Women who were stable on previously recommended regimens (WHO Option A) were not switched. By 2014 when the study started, TDF/FTC/EFV could be compared with the four other most common regimens: tenofovir/emtricitabine/nevirapine (TDF/FTC/NVP), zidovudine/lamivudine/nevirapine (AZT/3TC/NVP), tenofovir/emtricitabine/lopinavir/ritonavir (TDF/FTC/LPV/r), and zidovudine/lamivudine/lopinavir/ritonavir (AZT/3TC/LPV/r).

Of note in May 2016, Botswana switched to Treat all with a dolutegravir-based regimen for all adults including pregnant women but these births were not captured in this two-year interim analysis.

Outcomes included stillbirth, neonatal death (<28 days), preterm birth (<37 weeks), very preterm birth (<32 weeks), small for gestational age (<10th%), very small for gestational age (<3rd%) and two combined endpoints of any adverse outcome and any severe adverse outcome.

Between August 2014 to August 2016, there were 47,124 births of which 47,027 (98.8%) were included in the analysis; 11,932 (25%) were to HIV positive women. Almost half, 5780 (48%) started ART before conception, while receiving the following regimens:

- TDF/FTC/EFV: 2,503 (43%)
- TDF/FTC/NVP: 775 (13%)
- AZT/3TC/NVP: 1,403 (24%)
- TDF/FTC/LPV/r: 237 (4%)
- AZT/3TC/LPV/r: 169 (3%)

The remaining women received other 3-drug, non-standard or unspecified ART, or changed/stopped ART.

Women on TDF/FTC/EFV tended to be younger than those on all other regimens. They had fewer weeks from HIV diagnosis to conception as well as weeks on ART before conception. Those receiving AZT/3TC/NVP had less education. They were also more likely to have had five or more previous pregnancies as were women on LPV/r regimens. Among approximately 25% women with documented CD4 count, median values were quite high, ranging from 478 cells/mm$^3$ for women on TDF/FTC/EFV to above 600 cells/mm$^3$ for women receiving LPV/r-based regimens. Very few women had low CD4 counts <200 cells/mm$^3$.

Overall rates for adverse birth outcomes and severe adverse outcomes were extremely high (as much as 48% and 23% respectively with LPV/r-based regimens) in the group of ART-exposed infants from conception. TDF/FTC/EFV was associated with the lowest risk for combined adverse birth outcomes, p<0.001. See Table1.

Preterm birth was very common in this group of women and ranged from 19–30%. Women receiving TDF/FTC/EFV had a lower risk for preterm birth than those receiving a LPV/r-based regimen or AZT/3TC/NVP. Women receiving TDF/FTC/EFV had the lowest risk for very preterm birth. The risk was more than double among those receiving AZT/3TC/LPV/r (which had the highest rate): 4.1% vs 9%, aRR 2.2 (95%CI: 1.3 to 3.8).

The investigators found similar results for small for gestational age and very small for gestational age outcomes: range 17–29% and 7.3–14%, respectively. TDF/FTC/EFV had the lowest risk for both

**Table 1: Adverse birth outcomes and severe adverse outcomes by ART regimen**

| Regimen | TDF/FTC/EFV | TDF/FTC/NVP | AZT/3TC/NVP | TDF/FTC/LPV/r | AZT/3TC/LPV/r |
|---|---|---|---|---|---|
| Adverse outcome | 36% | 42% | 47% | 48% | 45% |
| Severe adverse outcome | 12% | 18% | 21% | 20% | 23% |
| Adverse outcome aRR (95%CI) | ref | 1.2 (1.0–1.3) | 1.3 (1.2–1.4) | 1.3 (1.1–1.5) | 1.2 (1.0–1.5) |
| Severe adverse outcome aRR (95%CI) | ref | 1.4 (1.2–1.7) | 1.7 (1.4–2.0) | 1.6 (1.2–2.1) | 1.2 (1.4–2.6) |

Adjusted for maternal age, educational attainment and gravida.

outcomes except for small for gestational age among AZT/3TC/LPV/r exposures.

There were fewer stillbirths among women exposed to TDF/FTC/EFV. AZT/3TC/NVP was associated with more than twice the risk of still birth: 2.4% vs 6.1%, aRR 2.3 (95%CI: 1.6 to 3.3).

Results were again similar for neonatal death. The lowest rate was seen with TDF/FTC/EFV exposure. The risk was almost double with AZT/3TC/NVP: 1.2% vs 2.2%, aRR 1.9 (95%CI: 1.1 to 3.3). And it rose to four times greater with AZT/3TC/LPV/r: 4.4%, aRR 4.0 (95%CI: 1.8 to 9.2).

The investigators performed several sensitivity analyses. CD4 count in pregnancy, time on ART or time with HIV before pregnancy did not substantially change the associations between ART regimens and either total or severe birth outcomes.

### COMMENT

**The investigators rightly emphasised the importance of expanded monitoring of pregnancy outcomes in different settings particularly as new antiretrovirals become available. More research is badly needed to better understand the mechanisms of adverse birth outcomes, which in this study occurred frequently in women with fairly high CD4 counts and well-controlled HIV.**

**As dolutegravir-based ART became the recommended adult first-line in Botswana since May of last year (including for pregnant women starting ART), there is heightened interest in data from this programme. To date information about the drug in pregnancy is scarce, and trial results will not be available for two years or more.**

**The first dolutegravir data from Botswana (notably for women starting in pregnancy not before conception) should be analysed in June–July of this year, when the investigators get to approximately 800 exposures. This should provide outcomes from enough women for a reasonably tight 95%CI around rates of adverse pregnancy outcomes (and also avoid biased reporting of women who deliver earlier ie who have preterm delivery).**

**At present, women on legacy regimens in Botswana are not switched from these until after delivery, but this might change in 2017–2018. If the government of Botswana does change its policy and switches women to dolutegravir, the investigators will try to capture this in their surveillance data and see if the adverse outcomes can be mitigated by such a switch. Such data would really help isolate the potential drug effect, if outcomes improve (assuming dolutegravir is similar to efavirenz, and not like nevirapine or lopinavir/r, which currently is unknown).**

Reference

Zash R et al. Adverse birth outcomes differ by ART regimen from conception in Botswana. CROI 2017. 13–17 February 2017. Seattle, Washington. Oral abstract 25.

http://www.croiconference.org/sessions/adverse-birth-outcomes-differ-art-regimen-conception-botswana (abstract)

http://www.croiwebcasts.org/console/player/33345 (webcast)

## Adverse pregnancy outcomes and risk factors in the PROMISE trial

**Polly Clayden, HIV i-Base**

**The multisite, multifactorial PROMISE trial found that antiretroviral therapy (ART) in pregnancy reduced vertical transmission, but also increased the frequency of several adverse birth outcomes compared with antenatal zidovudine (AZT) alone. [1]**

PROMISE was conducted at 14 sites in seven countries: India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe.

The trial randomised HIV positive women with CD4 counts 350 cells/mm$^3$ or more (not eligible for ART based on local guidelines), who were at least 14 weeks pregnant, but not in labour, to receive one of three antenatal regimens: AZT only (Arm A), AZT plus lamivudine (3TC) plus lopinavir/ritonavir (LPV/r) (Arm B), or tenofovir DF (TDF) plus emtricitabine (FTC) plus LPV/r (Arm C). Women receiving ART in PROMISE were randomised again to continue or stop their regimen after their first pregnancy.

Three posters at CROI 2017 reported findings from further investigations from the PROMISE trial into risk factors for adverse birth outcomes including in second pregnancies among women remaining on ART. [2, 3, 4]

### Higher risk of adverse birth outcomes with lopinavir/ritonavir-based ART

The first poster showed results from an investigation into the association between antiretroviral regimen and adverse birth outcomes. LPV/r-containing ART was associated with a significantly increased risk of such outcomes after controlling for baseline factors and obstetrical complications. For severe birth outcomes, the risk was higher among women receiving TDF/FTC compared with AZT/3TC.

The investigators looked at: preterm delivery (<37 weeks); low birthweight <2500 g; composite outcome (preterm delivery, low birthweight, stillbirth, and spontaneous abortion); very preterm delivery (<34 weeks); very low birthweight (<1500 g); and severe composite outcome (very preterm delivery, very low birthweight, stillbirth, and spontaneous abortion).

They estimated gestational age at delivery by Ballard score. Multivariable models were adjusted for baseline factors: maternal age, BMI, viral load, CD4, alcohol use, country, gestational age at entry and number of previous preterm births and several obstetrical complications.

A total of 3423 women with a median age of 26 years, who enrolled and delivered in PROMISE were included in the analysis: 1507, Arm A; 1497, Arm B; and 419 Arm C.

For outcomes with preterm delivery and/or low birth rate, women receiving AZT+3TC+LPV/r (Arm B) and TDF+FTC+LPV/r (Arm C) each had higher risk for adverse birth outcomes compared with AZT alone (Arm A). When the analysis was restricted to severe outcomes, the risk associated with Arm C remained higher.

When the investigators compared the two ART regimens head-to-head, Arm C had a higher risk of severe adverse birth outcomes: very preterm delivery, AOR 2.56 (95%CI: 1.47 to 4.46) and very low birthweight, AOR 3.37 (95%CI: 1.33 to 8.53).

## Several obstetrical and clinical risk factors for low birth weight and preterm delivery

An associated poster further described obstetrical and clinical risk factors for low birthweight and preterm delivery among women in PROMISE. In low-income countries, these conditions are linked to significant mortality and morbidity in newborns. Besides receipt of antenatal LPV/r-based ART, a number of obstetrical risk factors contributed to the adverse birth outcomes.

In the final multivariate models, adjusted for country and gestational age at entry, obstetrical risk factors for low birth weight and/or preterm delivery included several common complications of pregnancy: pregnancy induced hypertension; chronic hypertension; interuterine growth restriction; abruptio placenta; oligohydramnios; premature labour; premature rupture of membranes; and vaginal bleeding (low birthweight only).

Other clinical risk factors were: maternal BMI; multiple gestation; number of previous premature births; maternal age (preterm delivery only) and baseline viral load (preterm delivery only).

Although confidence intervals were very wide, the risk was extremely elevated for several risk factors including: abruptio placenta AOR 20.33 (95%CI: 3.60 to 114.81) and premature rupture AOR 10.8 (95%CI: 4.9 to 23.8) for preterm delivery; and multiple gestation AOR 21.96 (95%CI: 11.05 to 43.64), interuterine growth restriction AOR 49.09 (95%CI: 5.66 to 425.66), oligohydramnios AOR 11.04 (95%CI: 3.49 to 34.90), and premature rupture of membranes AOR 12.79 (95%CI: 5.69 to 28.77), for low birthweight.

## Spontaneous abortion and stillbirth more common among women conceiving on ART

A third poster from the PROMISE substudies showed results suggesting that women randomised to continue ART after their first pregnancy who subsequently conceived were more likely to have spontaneous abortion or stillbirth compared to women randomised to stop ART.

Rates of adverse pregnancy outcomes for women who conceive on ART might be increased, but data are conflicting.

Subsequent pregnancies occurred in 277/1652 (17%) women: 144/827 continued ART and 133/825 stopped ART).

A pregnancy outcome was available for 266 women with median age 26 years (IQR 22–30) and median CD4 638 cells/mm$^3$ (IQR 492–833) at estimated conception. At the time of conception 65% of women were virologically suppressed.

Spontaneous abortions were more common in the continue ART arm. There was a significantly higher rate in this arm when spontaneous abortions and stillbirths were combined. See Table 1.

Twelve weeks before pregnancy diagnosis, 86% in the continue ART arm were on a boosted/non-boosted PI regimen vs 6% NNRTI. In the stop ART arm (15%) restarted ART before pregnancy diagnosis. Of these 74% were on a PI regimen vs 26% NNRTI. Among those in the stop ART arm restarting in pregnancy, 53 were on PI vs 27% NNRTI. Use of integrase inhibitors was very rare (<1%) as were regimens with NRTIs only.

Of 113 women in the continue ART arm on a regimen that included a boosted or non-boosted PI, 16% had a spontaneous abortion and 5% a stillbirth. Only 8 women in this arm were on an NNRTI without PI and half of these had a spontaneous abortion and none a stillbirth.

**Table 1: Pregnancy outcomes for initial subsequent pregnancy in PROMISE**

| | Continue ART (n=140) | Stop ART (n=126) | p-value |
|---|---|---|---|
| Live birth | 100 (71%) | 100 (79%) | |
| Spontaneous abortion | 27 (19%) | 13 (10%) | 0.06 |
| Stillbirth | 6 (4%) | 2 (2%) | 0.29 |
| Spontaneous abortion or stillbirth | 33 (24%) | 15 (12%) | 0.02 |

Of 113 women in the continue ART arm on a regimen that included a boosted or non-boosted PI, 16% had a spontaneous abortion and 5% a stillbirth. Only 8 women in this arm were on an NNRTI without PI and half of these had a spontaneous abortion and none a stillbirth.

In the continue ART arm 15 women with a subsequent pregnancy were not receiving ART at the time of conception. In this group 27% had a spontaneous abortion.

In the stop ART arm, the majority of women were not receiving ART when they conceived (79%). Of these 12% had a spontaneous abortion and 1% stillbirth.

The investigators noted that pregnancy testing was frequent in PROMISE allowing for early detection of pregnancy and the opportunity to capture early losses that might be missed in clinical practice.

### COMMENT

**Large randomised trials such as PROMISE provide multiple opportunities to compare outcomes with various strategies and circumstances.**

**More research is needed to understand the potential mechanisms behind these findings. For the elevated risks with TDF/FTC/LPV/r, these might include an independent effect of TDF/FTC, drug-drug interactions with LPV/r or other biological factors.**

**Along with optimisation of ART regimens, public health interventions are urgently needed to address obstetrical risk factors. The potential for such factors must be thoroughly evaluated as part of comprehensive antenatal care for HIV positive women. The investigators rightly suggest that this includes educating women about early warning signs of adverse pregnancy so they can seek immediate medical care.**

**More data are needed to look at pregnancy outcomes on women who conceive on ART and this is particularly important as new regimens are introduced to ART programmes in the era of Treat all.**

**Observational data from Botswana, presented at CROI 2017, also show notable differences between regimens (among women conceiving on ART) but very high risk of adverse outcomes among HIV positive women receiving ART. [5]**

References

Unless stated otherwise, all references are to the presentations and abstracts from the Conference on Retroviruses and Opportunistic Infections 2017 (CROI 2017), 13–17 February 2017. Seattle, Washington.

1. Fowler MG et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. N Engl J Med 2016; 375:1726-1737. http://www.nejm.org/doi/full/10.1056/NEJMoa1511691
2. Chi BH et al. Antenatal antiretroviral therapy and adverse birth outcomes: the PROMISE trial. Poster abstract 776. http://www.croiconference.org/sessions/antenatal-antiretroviral-therapy-and-adverse-birth-outcomes-promise-trial (abstract and poster)
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## Women on lopinavir/ritonavir-based regimens at conception at higher risk of preterm delivery in UK study

**Polly Clayden, HIV i-Base**

**HIV positive pregnant women receiving lopinavir/ritonavir (LPV/r)-based regimens were at higher risk of preterm delivery compared with those on NNRTI-based ones in UK and Ireland.**

This was according to findings from the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) presented at CROI 2017 – but this association was only among women who were receiving ART at conception.

Pregnant women on other ritonavir boosted PI-based regimens were also at higher risk compared to women on NNRTI-based regimens but the association was only apparent in women with CD4 counts of 350 cells/mm$^3$ or more.

Some studies suggest that HIV positive women on boosted PI-based ART in pregnancy might be at higher risk of preterm delivery (<37 weeks of gestation) but evidence is not consistent. There is also conflicting evidence as to the contribution of timing of ART start, immune status and interaction with other antiretrovirals on preterm delivery risk.

NSHPC is a large national study that collects population-based surveillance data on all HIV positive pregnant women and children in care in the UK and Ireland. The study previously reported an increased preterm delivery risk with in women receiving 3-drug or more ART vs mono/dual therapy delivering from 1990 to 2005: 14 vs 10%, respectively.

In order to better characterise this finding, NSHPC investigators conducted a study to assess whether antenatal boosted PI-based regimens – particularly LPV/r ones – increase the risk of preterm delivery compared with NNRTI-based regimens in women delivering from 2007 to 2015. And to look at whether of ART at conception and first antenatal CD4 count affect these associations.

The evaluation included singleton live births to diagnosed women. The most recent pregnancy was included if women had repeated pregnancies during the study period. Women received NNRTI + 2NRTI or PI + 2NRTI; those who changed a drug or regimen during pregnancy were excluded. Women with a history of IDU were also excluded.

The investigators used logistic regression analyses adjusted for: calendar year, maternal age, region of origin, parity, ART at conception, and CD4 count (stratified by below and above 350 cells/mL).

There were 1889 (31.1%) pregnant women on NNRTI + 2NRTI, 2368 (39%) on LPV/r + 2NRTI, and 1816 (29.9%) on another boosted PI + 2NRTI, included in the analysis. There were 169 (9%), 284 (12%) and 176 (9.7%) preterm deliveries respectively across the three groups; 1577 (83.5%), 565 (23.9%) and 948 (52.2%) women conceived on ART, respectively.

The investigators found that women on LPV/r-based regimens were at higher risk of preterm delivery irrespective of CD4 count compared to women receiving NNRTI-based ones: aOR 2.01 (95%CI 1.03 to 3.91) and aOR 1.64 (95% CI 1.08 to 2.47), for ≤350 and >350 cells/mm$^3$ respectively.

Women receiving another boosted PI at conception only had an elevated risk of preterm delivery with ≤350 cells/mm$^3$: aOR 2.05 (95% CI 1.07 to 3.89).

Increased preterm delivery risk was also associated with: first antenatal CD4 ≤350 cells/mm$^3$, aOR 1.28 (95% CI 1.04 to 1.58); older age (>36 vs <28 years), aOR 1.41 (95%CI: 1.05 to 1.89), and ART at conception, aOR 1.27 (95%CI: 1.01 to 1.61).

Reference

Favarato G et al. Do HIV+ women on protease inhibitors deliver preterm? Findings from a UK study. Poster abstract 778.

http://www.croiconference.org/sessions/do-hiv-women-protease-inhibitors-deliver-preterm-findings-uk-study (abstract and poster)

## No increase in adverse birth outcomes with maternal TDF/FTC in US study

**Polly Clayden, HIV i-Base**

**Among pregnant women with HIV in the US, use of tenofovir, emtricitabine, lopinavir/ritonavir (TDF/FTC/LPV/r) was not associated with increased risk of adverse infant birth outcomes when compared to zidovudine, lamivudine, LPV/r (AZT/3TC/LPV/r) or TDF, FTC, atazanavir/ritonavir (TDF/FTC/ATV/r).**

In the PROMISE trial, infants of women randomised to TDF/FTC/LPV/r had elevated risk of very preterm birth, very low birth weight, and death compared to those randomised to AZT/3TC/LPV/r.

Data from two large prospective US cohort studies (IMPAACT P1025 and PHACS ) were used to compare risk of adverse birth outcomes for infants with in utero exposure to AZT/3TC/LPV/r, TDF/FTC/LPV/r, and TDF/FTC/ATV/r. The results from this comparison were shown at CROI 2017.

Exposure was classified by first regimen used during pregnancy. The investigators evaluated the risk of the following outcomes: preterm (<37 weeks) and very preterm (<34 weeks) birth, low (<2,500 g) and very low (<1,500 g) birth weight, composite adverse and severe adverse outcomes (outcomes above plus foetal loss, infant mortality).

Of 4,646 enrolled infants, 128 (2.8%), 539 (11.6%) and 954 (20.5%) had mothers who received TDF/FTC/LPV/r, TDF/FTC/ATV/r and AZT/3TC/LPV/r respectively. Table 1 shows risk of outcomes by initial ART regimen.

**Table 1. Risk of outcomes by initial ART regimen in pregnancy**

| 1st regimen | TDF/FTC/LPV/r | TDF/FTC/ATV/r | AZT/3TC/LPV/r |
|---|---|---|---|
| Preterm birth | 27 (21.4%) | 86 (16.1%) | 184 (19.5%) |
| Very preterm birth | 5 (4.0%) | 26 (4.9%) | 44 (4.7%) |
| Low birth weight | 30 (23.8%) | 86 (16.2%) | 175 (18.8%) |
| Very low birth weight | 1 (0.8%) | 10 (1.9%) | 18 (1.9%) |
| Adverse outcome | 36 (28.1%) | 127 (23.7%) | 256 (27.2%) |
| Severe adverse outcome | 7 (5.5%) | 28 (5.2%) | 51 (5.4%) |

In crude and adjusted analyses, the investigators found TDF/FTC/LPV/r was not associated with adverse birth outcomes compared to AZT/3TC/LPV/r or TDF/FTC/ATV/r. The study was underpowered to evaluate severe outcomes. TDF/FTC/LPV/r use in pregnancy was uncommon in the two large US cohorts.

Reference

Rough K et al. TDF/FTC in pregnancy shows no increase in adverse infant birth outcomes in US cohorts. CROI 2017, Seattle. Poster abstract 779.

http://www.croiconference.org/sessions/tdfftc-pregnancy-shows-no-increase-adverse-infant-birth-outcomes-us-cohorts (abstract and poster)

CROI 2017: TREATMENT STRATEGIES AND COMPLICATIONS

## Dolutegravir monotherapy studies halted due to integrase resistance: dual therapy studies continue

**Simon Collins, HIV i-Base**

**Several studies at CROI 2017 reported a similar conclusion: reducing ART to dolutegravir monotherapy should be stopped. However, can still be studied, especially with lamivudine.**

Initial hopes that dolutegravir was sufficiently robust against developing drug resistance that might enable it to be used as monotherapy have not been upheld. Although the majority of people continue to maintain undetectable viral load, the risk of viral rebound is unpredictable and associated with drug resistance to integrase inhibitors. These risks are now recognised as being too serious for monotherapy to be used - either in research or clinical practice.

### Dolutegravir monotherapy - no longer recommended

José Blanco from Hospital Clinic Barcelona reported on a combined analysis on 122 patients from three separate clinical cohorts – in Munich (n=52), Barcelona (n=44) and Montreal (n=26) – in an oral presentation at the start of CROI 2017. [1]

All participants were treatment-experienced patients with no history of integrase inhibitor resistance who switched to dolutegravir monotherapy. The analysis used a comparison cohort of 1082 patients from Barcelona (n=680) and Montreal (n=402) clinics of patients using dolutegravir as part of dual or triple drug ART.

Overall, virological failure in the monotherapy group was reported in 11/122 (9%; 95%CI: 6 to 18%), with incident genotypic integrase resistance detected in 7/11 patients. In comparison, virological faliure was reported in 64/1082 patients in the control group (6%; 95%CI: 5 to 7%). This resulted in an odds ratio (OR) for virological failure in the monotherapy group of 1.58 (95%CI: 0.73 to 3.13). However, none of the patients in the control group developed genotypic integrase mutations.

Details for the 11 patients (8 men, 3 women) in the monotherapy group with virological failure included median age 50 years (42 to 70), many had been HIV positive for more than 20 years (range 10 to 29) and median of 7 previous ART combinations (range 1 to 11) with history of mean 3 (range 0 to 8) previous virological failures. However, comparable data were not presented for either the whole monotherapy cohort or the control group.

In 5/11 (45%) dolutegravir was the first integrase inhibitor, 8/11 had been virologically suppressed for > 3 years, adherence was <95% in 4/11 cases and time from failure to resistance testing was a median of 5 weeks (IQR: 3 to 14).

Mutations detected for the 9/11 patients included different resistance pathways: 92Q/155H (n=1), 97A/155H (n=1), 155H/148R (n=1), 118R (n=2), 148K (n=1), 148H (n=2) and 148 R (n=1).

A late breaker poster from a Belgium study of dolutegravir reported a similar concern about drug resistance and has already switched all participants to triple therapy.

Ingeborg Wijting from the Erasmus University Medical Centre reported results from the DOMONO study that randomised 104

patients with viral suppression <50 copies/mL for >6 months to either switch to dolutegravir monotherapy or to stay on their three-drug ART for 24 weeks. If the monotherapy strategy performed well then all participants moved to dolutegravir monotherapy at 24 weeks. To overcome the lack of a 48-week control, a concurrent group of 152 patients on ART was also used for a post hoc analysis (non-randomised).

Entry criteria included no history of treatment failure, CD4 nadir >200 cells/mm$^3$ and viral load zenith <100,000 copies/mL.

At baseline, median time on ART was 40 months and median CD4 nadir was 340 cells/mm$^3$.

At week 24, dolutegravir monotherapy was non inferior to triple ART for the primary endpoint of viral load VL<200 copies/mL. Viral suppression was maintained in 49/50 monotherapy vs 53/53 in triple ART group (difference 2%, 95%CI: +12% to -5%), with no integrase resistance in the single case of viral failure.

Also at week 24, 46/53 participants initially randomised to triple ART, switched to monotherapy. Overall, of the 96 participants on dolutegravir monotherapy, 94/96 reached week 24. 92/94 had a VL<200 copies/mL, with no resistance in the two viral failures.

However, when 77/96 participants reached week 48, viral failure had developed in 8 (2 before week 24 and 6 after). Genotypic resistance testing was successful in 6/8 cases and 3/6 samples showed integrase mutation: 155H (n=1), 263K (n=1) and a new mutation not previously described for dolutegravir 230R (n=1).

This met the prespecified criteria for stopping the study and all participants added dual NRTIs to return to triple therapy ART. Virological failure occurred significantly less compared in the 48 week control group (3/152 vs 8/96, p=0.03) and the study concluded: "The genetic barrier of dolutegravir monotherapy is insufficient to allow for maintenance monotherapy".

## Dolutegravir plus lamivudine dual therapy

While monotherapy is clearly not now recommended, even in research, several ongoing studies are looking at whether dual therapy with lamivudine maintain viral load and limit the risk of viral rebound.

Data on this approach was reported from the ANRS LAMIDOL study – an ongoing open-label, single-arm, multicentre trial that switched 110 patients on PI-, NNRTI- or INI-based first-line triple ART to dual therapy of dolutegravir 50 mg and lamivudine 300 mg, both taken together once daily.

Entry criteria included having an undetectable viral load for more than two years, a nadir CD4 count >200 cells/mm$^3$, and no previous drug resistance.

For the first eight weeks (phase 1), the PI (22%), NNRTI (58%) or INI (20%) was switched to dolutegravir, leaving dual NRTIs unchanged. Then from weeks 8 to 56 (phase 2), participants switched the dual NRTIs to lamivudine, remaining on dolutegravir plus lamivudine dual therapy.

Phase 1 enrolled from October 2015 to February 2016 in 19 HIV clinics in France. At week 8, six participants did not roll-over in phase 2; three due to intolerance to dolutegravir and three due to viral load > 50 copies/mL.

Baseline demographics included 86% male, 72% MSM, median age 45 years (range 24 to 70), median time since diagnosis 6.3 years (range 2.3 to 24.5), median time on ART 4.0 years (range 0.5 to 11.3). Median CD4 count was 743 cells/mm$^3$ (range 373 to 1115) and CD4 nadir was 339 cells/mm$^3$ (range 203 to 1155).

All participants have reached week 48, including 40 weeks on dual therapy. One patient had viral rebound after 4 weeks on dual therapy confirmed at 77 copies/mL at week 8, despite adequate plasma C12h of dolutegravir (2401 ng/mL) and lamivudine (299 ng/mL). One patient was lost to follow-up after 32 weeks on dual therapy and one participant had their treatment changed after 40 weeks, based on their doctor's decision.

The only drug-related serious side effect was hospitalisation due to suicidal ideation during phase 1 in a patient with previous psychiatric disorders. Seven other serious events were judged unrelated to study drugs.

These researchers noted that all participant will reach 48 weeks of dual therapy by March 2017, but that longer follow up and additional studies are need to investigate this approach.

### COMMENT

**Patients currently stable on dolutegravir monotherapy should be advised to at least add lamivudine to their current ART or to return to triple ART. This is essential as reported cases of viral rebound are both unpredictable and linked to loss of significant future treatment options.**

**The Barcelona DOLAM study reported at EACS (Martinez et al) has discontinued the monotherapy arm based on a DSBM recommendation after meeting planned stopping rules of >5% virological failure in any arm (in n=2 patients). Although the DOLAM study has stopped the monotherapy arm it will continue patients in the dual (dolutegravir plus lamivudine) and triple ART groups. Choice of treatment for participants in the monotherapy group is based on the doctor's choice. [4]**

**While some studies (including DOLAM) were very carefully designed, others led to later questions about the level of informed consent to this experimental approach.**

**Although no cases of drug resistance had previously been reported in dolutegravir studies in treatment naive patients, the implications of integrase inhibitor resistance - with the loss of the option to use the current most effective ARV class – show that the move to monotherapy was optimistically premature.**

**At least two other large dual therapy studies with lamivudine are still ongoing.**

**The ACTG is currently running a single arm phase 2 study of dolutegravir plus lamivudine dual therapy in 300 treatment naive patients with viral load <500,000 copies/mL. [5]**

**ViiV are currently enrolling a phase 3 study randomising participants to either dolutegravir plus lamivudine or dolutegravir plus TDF/FTC in treatment naive participants with viral load <100,000 copies/mL. [6]**

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## No evidence of accelerated brain ageing in HIV positive people on effective ART

**Simon Collins, HIV i-Base**

**A European study reported no evidence of accelerating brain ageing in HIV positive people on ART, based on highly sensitive brain imaging scans and cognitive testing over two years.**

Although some differences were reported at baseline for the HIV positive group, the use of ART was significantly associated with preventing further differences in every domain.

The study was run in Amsterdam and London and is notable for including closely matched HIV negative control groups. Results were presented at CROI 2017 in a late-breaker poster by James Cole from Imperial College London on behalf of the COBRA collaboration. [1]

The results are also important because people were followed over time and the rates of change related to normal ageing were compared between HIV positive and HIV negative people with similar background risks. Neurocognitive changes are one of the leading concerns held by HIV positive people, especially in relation to ageing.

In this study, 134 HIV positive people on ART with undetectable viral load for at least 12 months and a control group of 79 HIV negative people were enrolled at the Amsterdam Medical Centre and Imperial College London. Retainment in the study was good with follow-up results available for 120/134 HIV positive and 76/79 HIV negative participants (at a median of just under two years (1.9 years).

Mean age at baseline was 57 years (SD+/– 7). In the HIV positive group, the mean CD4 count was strong 646 cells/mm$^3$ (+/– 213) and nadir CD4 showed historical HIV damage 185 (+/– 144) cells/mm$^3$, reflecting a common history shared by many older HIV positive people. Although this was a largely male study, with only nine HIV positive women and six HIV negative women, this reflected the gender balance of the ageing HIV positive population in each country.

Neuroimaging was conducted using magnetic resonance imaging (MRI) for multiple regions at baseline and after two years, with changes adjusted for age, time between scans, intracranial volume and the type of scanner. Similar adjusted analysis were produced for neuropsychological assessments.

The main results showed that there were some differences between the two groups at baseline, with the HIV positive group having slightly smaller grey matter volume (0.65 vs 0.68 L, p=0.02), abnormal white matter microstructure (p<0.01) and poorer cognitive function (in 4/7 functions: attention, processing speed, motor function and global cognitive performance, all p <0.01), compared to the HIV negative group.

Mean changes between baseline and follow-up found no significant differences between the positive vs negative groups in any of the 14 scanning regions, including rate of grey mattter loss, or in the 7 neuropsychological functions, and no consistent pattern of change. Changes that occurred were therefore related to ageing (rather than HIV). Cognitive performance also didn't reduce over time and global cognition score increased in both groups (+0.79 vs +0.45 in HIV positive vs HIV negative, respectively) – suggesting that there may have been a learning effective from the repeated tests.

The researchers concluded that their analysis found no evidence of accelerated brain aging in HIV positive people on ART compared to matched HIV negative controls.

An ongoing analysis is looking for risk factors that can explain the slightly lower baseline results, perhaps related to duration of infection, time before starting ART, nadir CD4 count and lifestyle factors. The results will be just as important as the current study.

*Simon Collins is a member of the scientific advisory board for the COBRA collaboration.*

### C O M M E N T

**These results are reassuring and support another benefit to universal ART that is now recommended in treatment guidelines.**

**Although the potential factors that might explain the differences between the two groups at baseline were not discussed in the study, the lack of a long-term impact on the rate of further change, even in people who have had low CD4 nadir counts is also encouraging.**

**It is clearly important for similar research to look at whether results are similar for women, as the low numbers in this study mean it is not powered to show any differences.**

Reference

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CROI 2017: PREVENTION

# Acute infection with wild-type HIV on PrEP with good drug levels

**Simon Collins, HIV i-Base**

**A poster at CROI 2017 reported a case of HIV infection on PrEP with good adherence that cannot be explained by exposure to drug-resistant HIV. [1]**

However, the case is complex with some aspects that are difficult to explain.

Previous reports of infection on PrEP have almost exclusively been related to either starting PrEP in early undiagnosed infection or to low drug levels linked to adherence. However, amongst the tens of thousands of people successfully using PrEP, two infections have so far been reported with drug-resistant HIV. [2, 3]

This new report is different for being an infection with wild-type HIV in the context of good adherence. It was actually highlighted several months ago in a press release, but with such limited details that there was little benefit from early reporting. [5] The poster at CROI, presented by Elske Hoornenborg from the Public Health Service in Amsterdam, now provides considerably more details.

It involves a 50-year-old man who enrolled in the Amsterdam Preexposure Prophylaxis Project (AMPrEP). He tested HIV negative at entry using both 4th generation Ag/Ab and viral load tests.

At the 8-month visit, after reporting fever for a few days, the routine Ag/Ab test was indeterminate, with atypical western blot and viral load that was undetectable. Based on a concern for resistance, PrEP was stopped and he abstained from any further sex. He was monitored with weekly viral load tests which were negative at one week, detectable at around 10,000 at two weeks – at which point he was recalled to start treatment – and viral load increased to >100,000 at the baseline sample when treatment was started.

Four-drug ART was started while waiting for drug resistance results (tenofovir/FTC, darunavir/r, dolutegravir) – and after wild-type virus was confirmed, darunavir/r was stopped. Viral load become undetectable within four weeks.

Self-reported daily adherence to PrEP was excellent, and this was supported both by pill count and high drug levels in dry blood spot (TDF-DP levels of 2234 and 2258 fmol/punch at 6 and 8 months, respectively. In the opinion of the investigator, the meticulous diary records and personal characteristics meant that less than daily adherence was not a concern.

Other factors relating to HIV risk though were very high – and these can actually be used to show the strong protection from PrEP over the previous eight months. These factors included high numbers of partners (38 to 75 per month for seven months, with a median of 3 to 5 partners on days that he had sex), frequent condomless sex, Chemsex (meth, meph, GHB, plus ketamine and coccaine – though this involved injecting on two earlier periods, this was with sterile single needles), high likelihood of mucosal trauma (duration of activity with Chemsex is generally longer with less sensitivity to trauma) and new STIs (rectal gonorrhoea twice and chlamydia).

A further detail that is difficult to explain – but actually a very important one – is the positive Ag/Ab test with not only undetectable viral load in plasma, but undetectable DNA in PBMCs and rectal samples (taken at the time of diagnosis). Generating a systemic antibody response is dependent on systemic exposure to viral load and yet these negative test show this wasn't the case. Other examples of positive antibody responses with undetectable viral load have not been reported, especially when HIV DNA is not detected. One interpretation of this detail is that perhaps HIV infection occurred after stopping PrEP.

The authors conclude that this case highlights the importance of routine monitoring in order to detect rare cases of infection very early. The lack of resistance developing to PrEP drugs is at least one positive outcome.

## COMMENT

**As with the cases of infection on PrEP with drug-resistant HIV, this case is disappointing, but it does put PrEP now on a more realistic grounding.**

**Firstly, in the context of widespread PrEP use this is clearly a rare event.**

**Secondly, HIV infection is determined by at least a dozen various risks that each are likely to increase or decrease the risk of infection. This case is likely to be explained by an overlap of factors that are not readily measurable. These factors include volume and viral load in partners sexual fluid, type of sex, genetic factors and potentially shared injecting drug use.**

**It is more realistic to think of PrEP as a highly effective way to protect against HIV, supported by highest quality of evidence, even in the context of less than daily adherence.**

**Acceptance of some level of risk – however small – is probably a more realistic view of PrEP – as indeed it is for the high level of protection provided by Treatment as Prevention (TasP).**

**In the context of the very large numbers of exposures every year that are protected by PrEP, any risk is clearly extremely low, whether the denominator is tens of thousands of people or millions of individual events.**

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CROI 2017: OTHER NEWS

## Fit for purpose: antiretroviral treatment optimisation (Feb 2017)

**Polly Clayden, HIV i-Base**

**Some ARVs have shown superior or non-inferior efficacy at reduced doses compared to existing recommended ones.**

These drugs offer improved durability and tolerability, higher bioavailability, lower pill burden, and the potential for fewer side effects.

The ARVs are: dolutegravir (DTG), tenofovir alafenamide (TAF), efavirenz (EFV) 400 mg, and darunavir/ritonavir (DRV/r).

Launched at CROI 2017, this new edition of an annual i-Base publication reviews and updates current and planned research for treatment optimsation studies looking to get increased outcomes from reduced doses in low- and middle-income countries.

Fit for Purpose i-Base – Feb2017

http://i-base.info/wp-content/uploads/2017/02/Fit-for-Purpose-ii-Base-Feb2017.pdf (PDF)

## Seattle-lite: pre-conference workshops – watch online

**Simon Collins, HIV i-Base**

**The commitment to providing all presentations online as open access educational resources is one of the most impressive aspect of the annual CROI meetings.**

Options include to watch the presentations with slides, download audio only or as podcasts, pause, repeat, enlarge slides to catch the details – and that this now becomes live on the same day.

And every year, before the main conference, state-or-the-art lectures provide sharp overviews of key subjects. Each lecture reviews current knowledge on the subject and sets the background for the new research that will be presented during the main conference.

So these lectures are already online – and are an excellent way to spend an hour or two to sharpen your knowledge.

This year's programme is listed below. Pick your favourite and click a link…

http://www.croiwebcasts.org

**Workshop 1: Science and cure**

Molecular virology: Understanding HIV – Paul Bieniasz

Advances in antibodies – Richard Koup

Advances in prevention – James McIntyre

HIV complications – Judith Currier

HIV reservoirs: obstacles to a cure – Nicolas Chomont

**Martin Delaney Lecture: Good practice in research and involving the community**

History and principles of good practice – Stacey Hannah

Good practice in prevention trials – Deborah Baron

Good practice in cure trials – David Evans

**Workshop 2 Clinical trial design**

Prevention trials in the PrEP era – Deborah Donnell

Implementation of trials – James R. Hargreaves

Recruiting hard to reach populations – Carl A. Latkin

**Workshop 3: Frontiers in lab science**

High throughput genome engineering – Judd Hultquist

Identifying and profiling virus-specific T cells – Evan William Newell

Quantifying HIV-1 MRNA structure – Silvi Rouskin

**Workshop 4: Hepatitis C – interactive case studies**

Staging and treatment of early stage HCV – John Scott

Resistance to DAAs and retreatment of chronic HCV – Alessandra Mangia

Common drug interactions with DAAs – Debika Bhattacharya

Issues with cirrhosis – Sanjay Bhagani

# ANTIRETROVIRALS

## US Stribild label updated: new indication to include patients age 12 and older

**FDA Update**

**On 31 January 2017, the US label for the fixed dose combination Stribild was expanded to include paediatric patients aged 12 years and older who weigh at least 35 kg. [1]**

Recommendations were based on 48-week results from Study GS-US-236-0112 showing that exposures (AUC) of elvitegravir and tenofovir in 14 paediatric subjects aged 12 to less than 18 years were increased by 30% and 37%, respectively, compared with exposures achieved in adults.

These differences were deemed acceptable based on the overall safety profile of these drugs and exposure-safety assessments. The other components of Stribild had similar exposures in adolescents compared with adults.

Other changes in the product label included:

- The section on new onset or worsening renal impairment was updated to include serum creatinine and serum phosphorus as part of renal function testing prior to and during administration of Stribild.
- The section on bone loss and mineralisation defects was updated with information about the effects of tenofovir DF on bone mineral density in paediatric and adolescent patients.
- The warnings and precautions section was also revised to emphasise severe acute exacerbations of Hepatitis B in patients with HIV/HBV coinfection.

For full details please see the full US prescribing information.

Stribild is a fixed dose combination that contains elvitegravir, cobicistat, emtrictiabine and tenofovir disoproxil fumarate, manufactured by Gilead Sciences.

Reference

Gilead Sciences. Drug label information of Stribild. (January 2017)

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=74ae2a93-b267-444c-8f0f-a2a6522260ee

## Option to take crushed Stribild tablets with food or enteral nutrition

**Gareth Hardy, HIV i-Base**

**The boosted integrase inhibitor-based fixed dose combination (FDC) Stribild (STB) can be safely crushed without affecting pharmacokinetics. [1]**

Mieke Jongbloed-de Hoon et al from Radboud University Medical Center, Nijmegen carried out this open-label, three-period, single dose, randomised, cross-over, trial in 24 HIV negative volunteers to asses the safety and absorbance of the four constituent drugs in the FDC, when taken with a standard breakfast meal or with enteral nutrition.

Stribild is an FDC of elvitegravir (EVG), cobicistat (COBI) booster, emtricitabine (FTC) and tenofovir-DF (TDF).

For people who are severely ill or have difficulty swallowing, taking whole tablets can be difficult. While crushing tablets helps with administration in such cases, it can also adversely affect the pharmokinetics (PK) of the drug, leading to decreased or increased drug levels, and in turn drug resistance or toxicity. In addition, the integrase inhibitor elvitegravir can form complexes with cations contained in enteral nutrition, reducing its absorbance. As no information is currently available about crushing STB, this study aimed to determine the bio-equivalence of crushed STB taken with a standardised breakfast or with enteral nutrition, in comparison to administration of the whole tablet.

The study consisted of three treatment regimens:

A. Reference treatment: a single dose of a whole tablet of STB combined with breakfast.

B. Intervention 1: a single dose of a crushed and suspended tablet of STB combined with breakfast.

C. Intervention 2: a single dose of a crushed and suspended tablet of STB combined with enteral nutrition.

Volunteers were randomised to one of the six possible sequences: ABC, ACB, BCA, BAC, CAB, or CBA, with each treatment period followed by a seven-day wash out. The standardised 350 kcal breakfast contained two slices of buttered wheat bread (one slice with 40+ cheese and one with luncheon meat or cervelat) and one cup of tea; 350 mL of enteral nutrition, Nutrison (Nutricia), contained also 350 kcal and was orally ingested.

Three standard PK curves were produced for each participant with frequent blood samples taken over a 32-hour period following observed intake. Liquid chromatography was used to measure plasma concentrations of EVG, COBI, TFV and FTC.

Half the participants were women, median age was 37 and all were Caucasian except one who was mixed race. Intervention 1 (crushed STB with standardised breakfast) versus reference treatment (whole tablet) for time 0 to 32 hours AUC was bio-equivalent. All the 90% confidence intervals for EVG, COBI, TFV and FTC fell between 80-125%. In contrast, bio-equivalence for Cmax of EVG, COBI and TFV could not be shown between intervention 1 and the reference treatment (whole tablet). For EVG the 90% CI was above the required limit of 80-125% at 105-127%. For COBI and TFV the 90% CI was under the required limits, at 76-91% and 71-92% respectively. For intervention 2 (crushed STB with enteral nutrition) versus reference treatment, all 90% CIs were within the required limits, meaning that the AUC and Cmax of crushed STB with enteral nutrition was bio-equivalent with reference treatment.

While crushed STB with breakfast had no influence on the total AUC, (compared with a whole tablet with breakfast), it did have a small influence on the Cmax. The Cmax of EVG was increased by 16% and the Cmax of TFV was decreased by 19%. The authors state that these differences between Cmax of crushed STB and a whole STB are small and considered to be less relevant in clinical practice, as inter-patient variation is much larger.

Reference

Jongbloed-de Hoon M et al. Pharmacokinetics of crushed elvitegravir combination tablet given with or without enteral nutrition. JAIDS. 2017. Epub ahead of print DOI: 10.1097/Q AI.0000000000001296

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## ART adherence in first four months predicts long-term viral suppression in 12-year study

**Gareth Hardy, HIV i-Base**

**Good adherence during the first four months of ART makes long-term undetectable viral load more than three times more likely according to results from a French cohort study published in the Journal of AIDS.**

Camelia Protopopescu al from INSERM, Marseille and colleagues recruited people in the APROCO-COPILOTE cohort, a French multicentre prospective, observational study of HIV positive people who initiated ART between 1997 and 1999 with 12 years follow up.

Standardised self-administered questionnaires were used to collect data on adherence to ART at month 1, 4 and then every 8/12 months until month 144. Adherence was scored based on adherence over the previous four days and was graded as: high (100%); medium (80–99.9%); and low (less than 80%). Given that previously published analysis of this cohort had revealed that 80% of participants achieved viral suppression by month 4, this time point was therefore used for assessment of "early adherence". "Maintenance adherence" was subsequently evaluated at each visit from 1 year to 12 years (months 12 to 144).

"Prolonged viral suppression" (PVS) was defined as maintaining an undetectable viral load for all three of the most recent visits, including the current one. As PVS required three consecutive visits at four-month intervals, the study period for maintenance adherence started 8 months after month 12, i.e. from months 20 to 144.

The study followed 891 participants who had at least one assessment of both maintenance adherence and PVS and who were followed for a median of 11 (IQR 5.3 to 12) years. At baseline, median CD4 count was 286 (IQR 141-429) and 20% has a diagnosis of AIDS.

The percentage of participants with PVS increased over the course of follow up visits, from 48% of 687 participants with available data at month 20, to 74% of 429 participants at month 132 (median follow up duration) to 73% of 229 participants at month 144.

Early adherence at month 4 was high for 57% of participants, medium for 33% of participants and low for 10% of participants. Maintenance adherence for the follow up period from month 20-144 was high at all visits for 66% of participants, fluctuating between medium and high, but never low, for 25% of participants and at least one episode of being low for 9% of participants.

Long term PVS was significantly associated with early adherence patterns that were high (adj. OD 3.72; 95%CI: 1.98 to 6.98) or medium (adj. OD 1.98; 95%CI: 1.02 to 3.83) versus low. In multivariate analysis, this association remained high even after adjusting for the month 20 to 144 time-varying maintenance adherence patterns "always high adherence" (adj. OD 3.28; 95%CI: 2.64 to 4.08) and "adherence fluctuating between medium and high" (adj. OD 2.26; 95%CI: 1.81 to 2.83) versus low. Other factors independently associated with PVS included older age, birth within the EU and a viral load <500 copies/mL at month one.

This reports suggests that adherence in the first 4 months of ART is a significant predictor of long-term prolonged viral suppression. The authors also draw attention to the finding that migrants born outside the EU are less likely to achieve PVS and suggest that this group is more likely to present with advanced HIV infection and lower CD4 counts at HIV diagnosis. This stresses the need for special attention to adherence support in migrant populations.

Reference

Protopopescu C et al. Prolonged viral suppression over a 12-year follow-up of HIV-infected patients: the persistent impact of adherence at 4 months after initiation of combined antiretroviral therapy in the ANRS CO8 APROCO-COPILOTE cohort. JAIDS (2017) EPub Ahead of Print DOI: 10.1097/QAI.0000000000001249.

https://www.ncbi.nlm.nih.gov/pubmed/27861235

## TREATMENT ACCESS

### Sutezolid added to MPP as potential TB drug

**Simon Collins, HIV i-Base**

**On 24 January 2017, a joint press statement announced agreement to add first TB drug to the Medicines Patent Pool (MPP).**

The agreement will "enable open non-exclusive licenses with multiple drug developers to conduct research and develop drug combinations that include sutezolid". These can include product development organisations, companies and governments.

Sutezolid showed promise in phase 2a studies but there have been no further studies since 2013. The primary patent owned by Pfizer expired in 2014, but Sequella and JHU still hold secondary patents and clinical data on the drug. [2]

That this has occurred for a drug whose primary patent has since expired highlight the low priority for developing new TB treatment. Almost 700 community-based organisations including Universities Allied for Essential Medicines (UAEM), MSF's Access Campaign, TAG, TB CAB, Public Citizen and JHU students and alumni have, for years, called on JHU to license sutezolid as broadly as possible and with a public health approach, and to also release access to early trial data. [3]

The statement noted a caution that the agreement has no impact on the final pricing for drugs that are successful.

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## PREGNANCY

### Pregnancy common in ART trials in sub-Saharan Africa despite exclusion criteria

**Polly Clayden, HIV i-Base**

**A new analysis from two ANRS studies reports that HIV positive women in clinical trials in sub-Saharan Africa are likely to get pregnant as often as those receiving care outside of research settings and questions why pregnancy is still commonly an exclusion criterion.**

Instead, the investigators say it is essential to take a pragmatic approach and revisit the relevance of the criteria for exclusion of pregnant women in such trials.

An increasing number of ART clinical trials are now conducted in sub-Saharan Africa, a region with the highest fertility rate in the world and a very high social value associated with child bearing.

Pregnancy and breast feeding are exclusion criteria in the majority of antiretroviral therapy (ART) clinical trials. Women of child bearing age agree to defer pregnancy for the duration of the study and are counselled before enrolment on using dual protection (condoms and a non-barrier contraceptive method), which are usually provided free.

A previous study conducted in Botswana reported a pregnancy rate of 7.9 per 100 person years (PY), despite women's verbal agreement to defer childbearing until after the study was closed.

Investigators from ANRS12169-2LADY and ANRS12286-MOBIDIP trials – comparing three boosted PI regimens, and the efficacy of a mono or dual-therapy of PI with or without 3TC respectively, conducted in Cameroon, Senegal and Burkina Faso – described their experience of pregnancies among women participants. These findings were published online in HIV Clinical Trials, 1 November 2017.

The goal of the study was to describe the reproductive behaviour and pregnancy outcomes among women on second-line ART enrolled in the trials and compare them with those of HIV positive women in non-research settings.

The investigators reported 66 women had 84 pregnancies between January 2010 and July 2015 (1046.3 PY of follow up). The majority (51) of women had one pregnancy during follow up, 12 had two and three had three.

Compared with the other women participants in 2LADY, women who became pregnant were: younger (31 vs 36 years, $p<0.001$), less likely to be single (24.2% vs 40.1%, $p=0.005$), were more likely to have disclosed their HIV status to their partner (95.5 vs 31.7, $p<0.001$), and had been receiving ART for a shorter time before enrollment (3.5 vs 4.2 years, $p<0.001$). There were no differences in CD4 or viral load at enrollment.

Sixty pregnancies (71.4%) were in women receiving lopinavir and 27 (32.1%) in those receiving darunavir.

The investigators noted that 13 of 66 women who became pregnant had received medroxyprogesterone before pregnancy. But these women received a median of only one dose. Seven women received medroxyprogesterone or a levonorgestrel-releasing implant after pregnancy.

The overall pregnancy rate (per 100 PY) was 8.03 (95%CI: 6.5 to 9.9). Twenty women (7.1%), including two pregnant women lost to follow up at time of analysis. The pregnancy rate was highest in Senegal, 10.0 (95%CI: 6.4 to 15.7) vs Cameroon, 7.5 (95%CI: 5.6 to 9.9) and Burkina Faso, 7.9 (95%CI: 4.9 to 12.7).

The median time from enrollment to first pregnancy was 1.7 months. The investigators found that the incidence of pregnancy was stable during the first two years, then declined, and peaked again after four years of follow up – partially because of recurrent pregnancies.

The 84 pregnancies resulted in: 60 (73.2%) live births, 13 (15.8%) miscarriages, three (3.6%) stillbirths, two (2.4%) extra-uterine pregnancies and four (4.8%) voluntary abortions. Two women were lost to follow up. The overall fertility rate was 5.73 live births per 100 PY (95%CI: 4.45 to 7.39).

The median gestation was 38 weeks (IQR 37 to 40) and median birth weight 2.9 kg (IQR 2.6 to 3.2). Nine (15%) infants had low birth weight, four of them were also premature. The investigators only recorded one birth defect (ankyloglossia). Four infants needed resuscitation at birth; one died from respiratory disease. One woman died of bleeding at delivery.

In multivariate analysis, miscarriages/stillbirths were not associated either with age, CD4 nadir, duration of ART, CD4 count, or viral load at the start of pregnancy. The investigators noted a trend in an increased proportion of miscarriages/stillbirths with darunavir vs lopinavir exposure: OR 3.1 (95%CI: 0.9 to 10.1).

The investigators looked at the scarce published data on the reproductive behavior of HIV positive women in West and Central Africa, and found the few studies available to be very heterogeneous in terms of population sample, types of data collected, study period, and ART availability, making comparisons hard. But the reproductive behaviour of HIV positive women enrolled in clinical trials in sub-Saharan Africa appeared to be similar to that of women in non-research settings.

They concluded that this finding needs to be taken into account when planning trials in such regions with high fertility rates. The option to get pregnant in a trial should be discussed in ethics committees in the context of the level of risk associated with investigational antiretrovirals during pregnancy. Family planning counselling and contraception options need to improve.

The investigators also noted that the reported rate of miscarriage/stillbirth in this study is not different from those reported in HIV negative women, which is reassuring for HIV positive women considering pregnancy and receiving ART.

## COMMENT

**This study was conducted in African countries with some of the highest fertility rates in the world: in Burkina Faso and Senegal women have an average of almost 6 and almost 5 children respectively. So, the finding that women of child-bearing age get pregnant in clinical trials with long follow up is unsurprising.**

**The more salient point to take from this article is that pregnancy is frequently an exclusion criterion for ART trials and women who conceive during this period are often switched from an investigational drug or regimen, sometimes not until later in pregnancy, when it is detected.**

**In some cases it might be more appropriate to continue on the study drug (in the context of level of risk/benefit) with careful monitoring, and this needs to be taken into account when designing trials that include women of child-bearing age.**

**If women do continue on study drug in pregnancy, it is important that the data on maternal and infant outcomes is captured. New antiretrovirals always have scant information to guide recommendations in pregnancy after approval for high-income countries and this can delay their inclusion in global guidelines.**

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# TREATMENT GUIDELINES

## Drug-drug interactions and hormone therapy for gender transitioning

**hiv-drugiteractions.org**

Liverpool University have produced a new printable drug interaction chart for hormone therapy for gender transitioning.

http://hiv-drugiteractions.org

The resource was launched at the SSSTDI conference in Ireland during a presentation on Sexual Health - a Transgender Perspective.

## New NICE/PHE testing guidelines

**On 1 December 2016, NICE together with Public Health England, published new guidelines about introducing routine HIV testing in 20 areas of high incidence. [1, 2]**

The guidelines also recommend routine HIV testing for up to 3.7 million people for anyone joining a new GP practice and/or having other blood tests.

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2. HICE guidelines. HIV testing: increasing uptake among people who may have undiagnosed HIV. NICE guideline [NG60] December 2016 https://www.nice.org.uk/guidance/NG60

## WHO guidelines on HIV self-testing and partner notification

**WHO press statement**

**On 29 November 2016, WHO has released new guidelines on HIV self-testing to improve access to and uptake of HIV diagnosis.**

According to a new WHO progress report, lack of an HIV diagnosis is a major obstacle to implementing the recommendation that everyone with HIV should be offered antiretroviral therapy (ART).

The report reveals that more than 18 million people with HIV are currently taking ART, and a similar number is still unable to access treatment, the majority of which are unaware of their HIV positive status.

Links to the guidelines and related resources are below.

**Progress report 2016: Prevent HIV, test and treat all - WHO support for country impact**

http://www.who.int/hiv/pub/progressreports/2016-progress-report/en

**Guidelines on HIV self-testing and partner notification**

http://www.who.int/hiv/pub/vct/hiv-self-testing-guidelines/en

**Policy brief HIV self testing**

http://apps.who.int/iris/bitstream/10665/251549/1/WHO-HIV-2016.21-eng.pdf (PDF)

**Policy Brief partner notification**

http://apps.who.int/iris/bitstream/10665/251548/1/WHO-HIV-2016.22-eng.pdf (PDF)

**WHO Video: HIV self-testing - Questions and Answers**:

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# HIV COMPLICATIONS

## Effects of ART initiation on human papillomavirus antibody response

**Gareth Hardy, HIV i-Base**

**Starting ART may improve antibody responses that in turn reveal exposure to serotypes of human papillomavirus (HPV) that are a high risk for anal cancer.**

Jean-Damien Combes from the International Agency for Research on Cancer, Lyon, and colleagues investigated the effects that ART-mediated immune reconstitution has on the appearance of HPV antibodies and their prognostic value for predicting risk of cancer. [1]

High risk HPV serotypes, in particular HPV-16, can cause persistent anal infection and lead to higher rates of anal cancer in HIV positive men. Combes and colleagues assessed antibodies to HPV antigens L1 and E6 that are useful clinical indicators. L1 antibodies do not always develop after HPV infection, but they are an indication of cumulative exposure to HPV. E6 antibodies are highly specific markers of HPV-related cancer and may occur years before cancer diagnosis, though they are more associated with oropharyngeal than anal and cervical cancers.

The researchers conducted this sero-epidemiological study of 281 HIV positive gay men who started ART between 1995 and 2004 in the Swiss HIV Cohort Study to evaluate HPV L1 and E6 antibodies before and after ART. Men who had available serum samples taken within one month before ART and 21 to 27 months after ART initiation were identified for the study. A multiplex HPV serology assay was used to determine the presence of antibodies to the L1 antigen of HPV serotypes 6, 11, 16, 18, 31, 33, 35, 45, 52 and 58, as well as to the E6 antigen of HPV-16. Individuals diagnosed with HPV-related cancer after ART initiation were identified from the cohort database or through linked registries.

Before starting ART, 32.4% of participants had detectable antibodies against HPV-16 L1 antigen. Seropositivity for other high-risk HPV types was as high as 17.8% for HPV-31. Seropositivity for at least one high-risk HPV type was 45.2%. One person was positive for HPV-16 E6 antigen.

After starting ART, seropositivity increased for all HPV antibodies including to 60.5% for at least one high risk type. Prevalence of antibodies to HPV-16 L1 rose to 48%, which corresponds to a prevalence ratio of 1.48 (95%CI: 1.20 to 1.83) compared with before ART. Seropositivity for HPV-31 increased to 34.5%. Two additional individuals seroconverted for HPV-16 E6 antibodies. Seroconversion to HPV-16 L1 after initiation of ART was associated with low CD4 count and low CD4 ratio when starting ART. This result was consistent with L1 seroconversion for any high risk HPV type.

Five cases of anal cancer were diagnosed during 3771 person-years of follow up. Anal cancer only occurred in participants who were positive for antibodies against HPV-16 L1 antigen after initiation of ART. The participant who was HPV-16 E6 antibody positive before ART did not go on to develop any cancer. Of the two participants who seroconverted for HPV-16 E6 antibody after ART, one died seven months later from lymphoma and the other developed anal cancer nine years later. Anal cancer incidence among the three HPV16-E6-positives post-HAART was significantly increased compared with HPV16-E6-negatives (IRR: 63.1, 95%CI: 1.1 to 1211).

In this study, half the participants were seropositive for at least one high risk HPV type before starting ART and a further one-fifth seroconverted to the L1 antigen of high risk HPV types over the following two years. Those with the lowest CD4 counts and lowest CD4:CD8 ratio before starting ART were most likely to seroconvert after ART. The researchers suggest that this indicates that anal exposure to HPV is not sufficient to reveal a detectable antibody response and that ART-mediated immune reconstitution makes an important contribution to the appearance of HPV antibodies. Although cancer cases were small, ART-related seroconversion appeared to improve the ability of HPV-16 L1 and E6 antibody to predict cancer risk.

Reference

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## Rosuvastatin for chronic obstructive pulmonary disease (COPD) in people with HIV

**Gareth Hardy, HIV i-Base**

**Daily rosuvastatin stabilised clinical markers of chronic COPD progression and might reverse an important marker of pulmonary dysfunction commonly seen in HIV positive people, according to a pilot study reported by Alison Morris and colleagues from the University of Pittsburgh. [1]**

COPD is found in approximately 15–20% of HIV positive individuals, and is usually related to smoking but it is not a complication that is improved by ART. [2] Impairments in diffusing capacity for carbon monoxide (DLCO) have also been reported in up to 64% of HIV positive people in some studies, and occurs both in smokers and non-smokers. [3]

Both conditions are associated with localised and systemic inflammation. Use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) as opposed to inhaled corticosteroids is an attractive option for treatment of COPD because corticosteroids may have serious side effects in HIV positive people. Trials of statins for COPD in HIV positive people have so far produced conflicting results. Morris and colleagues conducted this prospective, randomised, double blind, placebo controlled, pilot-study of rosuvastatin (10 mg daily for 24 weeks) in HIV positive people with COPD, to determine feasibility for a larger multicentre study, and to assess impact on pulmonary function.

Inclusion criteria included a forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) below 0.70 and/or DLCO below 80%-predicted. Participants were not using lipid-lowering medication, were on or off ART and had a stable smoking status. The primary endpoint was difference between treatment and placebo in the 24-week change of post-bronchodilator FEV1%-predicted. Secondary endpoints included decline in other pulmonary function measures. The researchers used simulations to compare the observed values in each treatment group with the simulated null distribution.

Baseline spirometry for the 22 patients recruited, revealed median postbronchodilator FEV1 of 83%-predicted, and a median DLco value of 64%-predicted. For the placebo group, median FEV1%-predicted significantly declined by 4.5% (p = 0.027) at week 24 compared with baseline. In contrast, the median FEV1%-predicted remained stable in the rosuvastatin group at week 24 compared with baseline. The difference between groups was not significant. While there was no significant change in DLCO%-predicted between baseline and week 24 in the placebo group, DLCO%-predicted significantly increased by 6.7% between baseline and week 24 in the rosuvastatin group (p = 0.027). Again, this change was not significant between treatment groups.

The study demonstrated that rosuvastatin prevented any significant decline in FEV1%-predicted over 24 weeks in contrast to the placebo group, but was not powered to measure a difference between the groups. Rosuvastatin also led to improvements in DLCO, which was not seen in the placebo group. This is important because an impaired DLCO is the most common pulmonary function abnormality in HIV positive people and no therapies currently exist to treat it.

Nevertheless the authors concede that this study was limited by its small sample size and lacked statistical power. In addition, HIV positive people were recruited with pulmonary function deficits, who were current or former smokers. It is not clear what effect rosuvastatin may have had on COPD development in people with normal pulmonary function.

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# HIV PATHOGENESIS

## Soluble CD163 as a marker of CMV mediated immune activation

**Gareth Hardy, HIV i-Base**

**Cytomegalovirus (CMV) may be a driver of harmful immune activation in HIV positive people, even after more than one year of successful ART, according to a study by Serena Vita and colleagues who investigated the relationship between plasma markers of immune activation and CMV serostatus in HIV positive people. [1]**

Residual immune activation that persists after ART is a major concern because it is likely to play a role in age-related degenerative conditions such as dementia and cardiovascular disease. [2]

Vita and colleagues enrolled matched CMV+/HIV+ and CMV–/HIV+ people at a 2:1 ratio from the ICONA (Italian COhort Naïve of Antiretrovirals) Foundation Study cohort, which is a multicentre prospective HIV observational study. Participants underwent CMV serology at enrolment and plasma samples were taken for immunological testing at least one year after successful ART-induced suppression of viral load to below detection and increases in CD4 cell count to above 200 cell/mm$^3$ blood. There was also an HIV negative control group who were almost all CMV+.

The researchers compared the levels of systemic inflammatory mediators that promote chronic inflammation such as TNF-alpha, IL-6, soluble (s) CD163 and sCD14, which have been shown to be independent predictors of morbidity and mortality in HIV infected people. While TNF-alpha and IL-6 are inflammatory cytokines produced by blood monocytes and their tissue-residing matured descendants macrophages, surface-bound CD163 and CD14 can be shed from monocytes and macrophages as a soluble protein following activation by pro-inflammatory stimuli.

A total of 69 HIV+ participants were recruited, 46 of whom were CMV+ and 23 CMV–, along with 16 HIV negative controls, of whom 12 were CMV+. Plasma levels of sCD163 were significantly higher in the CMV+/HIV+ group compared with the CMV–/HIV+ group ($p<0.0001$) or the HIV negative control group ($p<0.0001$). In contrast, levels of sCD14, IL-6 and TNF-alpha were not significantly different between CMV+/HIV+ people and CMV–/HIV+ people.

Plasma levels of sCD163 also correlated with levels of plasma CMV-specific IgG antibodies ($r=0.49$, $p=0.0006$). In addition, plasma CMV IgG antibodies correlated with IL-6 ($r=0.42$, $p=0.0041$) and TNF-alpha ($r=0.34$, $p=0.021$) but not sCD14.

Furthermore, differences were observed in traditional markers of HIV disease progression between those with HIV/CMV co-infection and those who were HIV+ without CMV infection. CD8 cell counts were significantly increased in CMV+/HIV+ people in contrast to CMV–/HIV+ people ($p <0.0001$).

CD4:CD8 ratios were lower for those with CMV/HIV co-infection ($p <0.0001$) compared to the CMV–/HIV+ group. Plasma CMV IgG antibody levels inversely correlated with CD4:CD8 ratios ($r=0.40$, $p=0.0063$) as well as with CD4 cell count ($r=–0.39$, $p=0.0006$) in CMV positive/HIV positive people. sCD163 levels inversely correlated with CD4:CD8 ratios ($r=-0.38$, $p=0.0075$). Interestingly, the researchers

also found that the duration of HIV infection correlated with sCD163 levels for those with HIV and CMV coinfection (r=0.29, p=0.04), but not for who were CMV–/HIV+, suggesting that the two viral infections interact over time to cause monocyte/macrophage activation.

Elevated sCD163 levels have been described both as a marker of HIV activity before and after ART [3], as well as with ART-associated co-morbidities such as neurocognitive disorder. [4]

While the sample sizes in this report are small, the association of sCD163 with CMV/HIV coinfection described here suggests that CMV may be an important driver of macrophage activation which in turn critically contributes to inflammatory degenerative co-morbidities in HIV positive people, despite viral suppression with ART.

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## Levels of CMV antibody are linked to HIV progression and immune activation in Ugandan women

**Gareth Hardy, HIV i-Base**

**Levels of anti-CMV IgG antibodies in the blood were associated with HIV disease progression and increased markers of immune activation in a Ugandan cohort of untreated women with HIV.**

The results were reported from a prospective cohort study in participants of an acyclovir trial, by Eshan Patel and colleagues in the journal AIDS. [1]

CMV co-infection has been reported in numerous studies to increase HIV disease progression, which is likely to result from bidirectional antagonism between the two infections: HIV mediated immunosuppression leads to increased CMV activity which contributes to greater immune activation and HIV replication. [2, 3]

Patel and colleagues used plasma anti-CMV IgG antibody titres as an indirect measure of CMV activity and assessed its relationship with CD4 cell counts, HIV viral load, plasma C-reactive protein (CRP), plasma soluble CD14 (sCD14) as well as the study primary endpoints. Primary endpoints were time to starting ART, reaching a CD4 cell count <250 cells/mm$^3$ or non-traumatic death. CRP is a measure of generalised immune activation while sCD14 is a measure of monocyte activation.

CMV IgG was measured at baseline in all women, and then annually among a subset of women who initiated ART during the study. CD4 count, viral load, plasma CRP and sCD14 were measured bi-annually for 24 months.

Overall, 300 women with HIV/CMV coinfection contributed 426 person years of follow-up (with a median of 1.8 years) There was a positive association between increasing CMV IgG titres and viral load, sCD14 and CRP at enrolment (p = 0.05).

Of the 300 study participants, 150 reached a primary end point. CMV antibody titres across the cohort were divided into tertiles. Compared to women in the lowest CMV IgG tertile at baseline, women in the highest tertile had a significantly increased probability of reaching a primary endpoint (p <0.001), as well as an increased relative hazard of disease progression (HR 2.21; 95%CI: 1.49 to 3.27, p <0.001). The relationship was independent of acyclovir study arm, age, baseline CD4 count or viral load.

In an analysis of 1,200 person visits that excluded post ART-initiation data, women in the baseline high CMV IgG tertile experienced annual increases in sCD14 (p = 0.022) and CRP (p = 0.001). In contrast, women in the lowest tertile experienced annual decreases in sCD14 (p = 0.022) and no change in CRP. These changes were independent of time-updated CD4 cell counts, viral load, acyclovir study arm or time interaction.

Changes in anti-CMV IgG antibody titre between pre-ART and post-ART were assessed in 70 women. Across the whole group CMV IgG titre increased (p = 0.006). While median time on ART was only 140 days, visit specific analysis was performed for 95 person visits and found that CMV IgG titre above the post-ART median were associated with increased sCD14 (p = 0.019) and CRP (p = 0.028) independently of acyclovir study arm, age, time updated CD4 cell count, or pre-ART CD4 cell count nadir.

The authors conclude that their data supports the hypothesis that CMV may contribute to systemic immune activation during untreated HIV infection. However the associations reported in this concise communication do not imply causality or directionality. In addition, the authors discuss the possibility that increases in CMV IgG titres are not necessarily reflective of increased CMV activity. Secondary to this, while increases in CMV IgG titres after ART may reflect immune reconstitution, they may also be due to subclinical immune reconstitution inflammatory effects.

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# HIV PREVENTION

## Brighton heads towards zero HIV: first UK city with UN Fast Track status

**Martin Fisher Foundation press release**

**As part of the Martin Fisher Foundation "Towards Zero" campaign, Brighton & Hove is set to become the first UK city to have United Nations Fast Track City status. [1]**

The Martin Fisher Foundation worked closely with Brighton & Hove City Council to achieve this.

The initiative is led by Mayors and city governments from more than 65 high HIV burden cities around the world. [2]

This means working across the city to achieve:

- 90% of people living with HIV (PLHIV) knowing their HIV status
- 90% of PLHIV who know their HIV-positive status on antiretroviral therapy (ART)
- 90% of PLHIV on ART achieving viral suppression
- Zero discrimination and stigma

The Martin Fisher Foundation vision is to move TOWARDS ZERO HIV stigma, ZERO new HIV infections and ZERO deaths from HIV in Brighton & Hove by 2025.

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## Four London clinics report dramatic drops in HIV incidence in gay men: PrEP, early testing and early ART likely to be key

**Simon Collins, HIV i-Base**

**At the end of December, several leading London sexual health clinics used social media to report significant drops in number of gay men who were diagnosed HIV positive during 2016.**

These preliminary data are based on early reviews. A similar number of tests were run each year and a similar number of STIs were reported for each period. This suggests that increased use of PrEP together with early diagnosis and early ART are likely to explain much of the drop.

On 22 December, the 56 Dean Street clinic reported a 40% drop from 626 HIV diagnoses in gay men during 2015 to 373 in 2016 on their FaceBook page. Figures are for January to November for each year. [1]

The following day, using Twitter, the Mortimer Market Centre reported a 50% drop in HIV diagnoses from January to September 2016 compared to figures from the previous year and Homerton Sexual Health services reported a 40% reduction. [2, 3]

A few days later, on 28 December, Barts Sexual Health tweeted that HIV diagnoses in gay men at this clinic had dropped by 36% in 2016 compared to 2015. [4]

If confirmed, these results would be unprecedented: for the last 15 years, annual UK HIV incidence in gay men has either been stable or steadily increased. The lack of change in STI rates during 2016, indicates that decline in HIV is not from changing sexual behaviour linked to HIV risk but more likely to be related to increased protection against HIV specifically - notably from PrEP and earlier use of HIV treatment.

- Several hundred men at London clinics would have been using PrEP as part of the PROUD study, after early results in October 2014 offered PrEP to all participants. [5]
- Community activists, motivated by the slow pace of NHS bureaucracy, publicised the option to buy generic PrEP easily and cheaply online (6, 7, 8]
- Several NHS sexual health clinics (including 56 Dean Street, Mortimer Market and Barts) developed new PrEP services to offer the free monitoring tests for people using generic PrEP.
- HIV treatment became more routinely available for anyone diagnosed HIV positive. The risk of sexual transmission is effectively zero once someone is stable on effective treatment. [9]

The Dean Street clinic, accounts for approximately half of HIV diagnoses in gay men in London, reported that 50% of their cases were in men who were recently infected (within four months). This is when someone is most infectious and early treatment (now routinely offered at the clinic) dramatically reduces transmission risk to close to zero.

PrEP is more than 99% effective when taken as either a daily or on-demand dosing. Greater access to PrEP during 2016 makes the reports of reduced HIV incidence seem more than just a coincidence. Early diagnosis and early treatment are likely to have had just as much impact.

Over the same period NHS England blocked all attempts to provide PrEP and, by wanting further research, now proposes to further delay when doctors might be able to prescribe PrEP by at least another three years. [10]

NHS England still stubbornly sticks to a commissioning guidelines that HIV treatment should be delayed for years until significant immune damage has occurred. Luckily, HIV treatment can be prescribed if a someone wants to reduce the risk to their partners.

**C O M M E N T**

**These results are more significant than those produced by any prospective UK HIV reduction programme this century.**

**That this was largely accomplished without formal support from NHS England - these clinics developed their own programmes - should force a national change in approaches to sexual health.**

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## NHS England fudges PrEP access and delays on-demand access to PrEP by years; blocks doctors from prescribing PrEP now

**Simon Collins, HIV i-Base**

**After almost a year of turmoil, requiring NHS England to face court challenges for what has now been proven to be an illegal decision to block access to PrEP, a new press statement still fails to allow a single doctor to protect the health of their patients by prescribing PrEP based on clinical need. [1]**

Instead, a press release issued at one minute past midnight on Sunday 4th December, detailed plans for further delays. Foremost of these was a promise of funding for a study that is dependent on drug manufacturers meeting unspecified prices for their products, and speculation that this may or may not be possible.

It is difficult to be impressed with this compromise. Rather than meet the real need of people currently at highest risk, it will further delay access to an option to prevent HIV transmission that has clearly passed the criteria for safety, efficacy and effectiveness laid out for other NHS treatments. PrEP has not only been available in the US since July 2012, but has been part of a strategy to overcome the HIV pandemic recommended in guidelines from the World Health Organization since 2015. [2]

By deferring to a need for further research, but without being able to identify key scientific questions that remain unanswered, the plans are intellectually dishonest.

Instead, in addition to any research, the proposals should have included the ability for doctors who are already experts in managing sexual health to assess individual risk, and prescribe PrEP, even if access to PrEP remained capped or restricted. For example, after many delays, the NHS eventually approved access to the latest effective treatments for hepatitis C, though later capping access.

Two examples that have previously been used to explain the urgency of access to PrEP are worth repeating. [3]

1. A woman who explains to her doctor that her husband refuses to use condoms and that this has led to her needing treatment for STIs will hear her doctor say "come back when you are HIV positive and then I can prescribe HIV drugs for the rest of your life, two of which would have kept you negative if I could have prescribed them today".

2. A 17-year-old man with low self-esteem related to a history of childhood abuse and who has transactional sex with clients who take off condoms will be told that he can't be prescribed the same drugs that he has already accessed five times this year as PEP to help him stay HIV negative.

In the two examples above, based on the new NHS plans, a doctor can say: "you might be able to join a study in six months, but only if you access care at one of a limited number of research centres and if you feel sufficiently engaged and supported to attend additional clinic visits and fill in questionnaires about your sex life and risk".

If someone has a life that is more chaotic, for example if they have issues relating to substance use, or if they have limited free time due to restrictions at work, they will likely be excluded from the research anyway. This is despite these very issues increasing the need to have alternative options to protect against HIV.

The clinical research that is essential for proving safety and efficacy has already been sufficiently rigorous for both the US and European regulatory agencies to approve PrEP.

The UK PROUD study also contributed to a large body of growing research showing that PrEP often also leads to behavioural changes that lower a person's risk of HIV. PrEP therefore achieves a double effect: it directly protects against HIV when at risk and also helps people be more confident in negotiation risk.

Proposing further research raises a major limitation that studies generally recruit participants who are not reflective of either the general population or the population at highest need.

For example, the circumstances needed to take part in a research study rarely ensures that trial participants reflect the diversity of gender, class, race, education, geographical proximity to a large city and economic status. By definition, research studies therefore usually underrepresent communities for whom equity of health care should instead be paramount. And risks of HIV transmission often directly correlate with issues of social exclusion listed above.

So the hush-hush "important new plans" released in the early hours of Sunday morning are not an optimistic advance. These proposals fudge the clear community demand for immediate access to effective treatment.

Instead, they create additional hurdles to access based on spurious claims for a need for further evidence, that in turn effectively blocks access for many of the people most in need. It is also extremely strange that NHS England tactfully chose to release this news in the early hours of Sunday morning when many people are likely to be at highest risk.

Notes: PrEP stand for Pre-Exposure Prophylaxis. In the context of HIV this currently involves using a co-formulation of two widely used HIV drugs to protect against HIV transmission. If taken when needed – either daily, or in

some circumstances only when at risk – PrEP reduces the risk of transmission by more than 99%. More information about PrEP is included in a multi-organisation UK guide to PrEP, available online. [4]

**C O M M E N T**

**The proposed study is unlikely to enroll before August 2017.**

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## Update on PrEP in Scotland

**HIV Scotland newsletter**

**On 5th December 2016, Gilead submitted an application to the Scottish Medicines Consortium (SMC) for PrEP to be made available on the NHS in Scotland. [1]**

The SMC have subsequently invited groups to make Patient Group Submissions by 6 February 2017, and will announce whether they approve of providing PrEP on the NHS in Scotland on 10 April 2017.

HIV Scotland are working together with Terrence Higgins Trust Scotland, SX and Waverley Care as part of the #PrEP4Scotland campaign to write a submission. To help us understand people's experience of PrEP in Scotland and to gather questions people may have, we conducted an online survey that received more than 300 responses.

HIV Scotland is also working on a project to better understand the needs of heterosexual people in relation to PrEP. [2]

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## New York reports fewer HIV diagnoses in 2015: target to reduce new infections by 75% by 2020

**Simon Collins, HIV i-Base**

**New data released for New York, show that this major city with high HIV prevalence - approximately 120,000 HIV positive people currently live in the city - is steadily reducing the number of new infections. [1]**

New York is also significant for setting targets for reducing new infections, as part of an ambitious new programme that includes reducing late diagnosis and easy access to both PrEP and PEP. This strategy includes a target to reduce new infections by 75% by 2020. [2]

In 2015, there were 2,493 new HIV diagnoses and 1,307 new AIDS diagnoses in the city. At the end of 2015, a total of 121,616 people had been diagnosed with HIV/AIDS and were presumed to be living. In 2015, there were 1,678 deaths among people with HIV.

From 2001 to 2015, the number of new HIV diagnoses significantly decreased overall and by gender, race/ethnicity, age at diagnosis, borough of residence, and transmission risk ($p < 0.01$ for all subgroups except transgender people, Asian/Pacific Islanders, MSM, and transgender people with sexual contact. Although approximately 60% of new diagnoses are in MSM (1450/2493), the absolute numbers have significantly and steadily fallen over the last eight years (2007-2015).

Area-based poverty level appear to strongly correlate with new diagnosis: with 188, 698, 594 and 735 diagnoses in areas with low, medium, high and very high poverty levels, respectively. However, some of the highest HIV incidence levels were reported for high-income areas

This report includes graphic trends in HIV diagnoses over time for key populations, maps displaying the distribution of HIV, and measures of specific key outcomes such as linkage to care, viral suppression, and mortality among people with HIV (PWH).

New features include data by gender instead of sex at birth, a section focused on HIV among African/American and Latino/Hispanic people, data on Hepatitis C infection, and a comparison of select characteristics among newly diagnosed men who have sex with men and transgender women.

The executive summary highlights:

- For the first time in the history of the NYC epidemic, the annual number of new HIV diagnoses dropped below 2,500, to 2,493 in 2015 (8.3% decline from 2014).
- New HIV diagnoses among men who have sex with men and among women both declined substantially in 2015 (a 10.5% decline and an 8% decline from 2014, respectively). Also in 2015, the number of new HIV diagnoses among people aged 20-29 reached a significant new low since 2001.
- There were no HIV infections diagnosed among infants born in NYC in 2015, a major achievement within the overall elimination of mother-to-child-transmission of HIV.
- The all-cause mortality rate and rate of HIV-related deaths among people living with HIV have continued to fall dramatically since 2001.
- The proportion of people in HIV care who achieved viral suppression increased in 2015 (83% compared to 81% in 2014).

Overall in 2015, 71% of new diagnoses led to timely linkage to care, and 83% of people on ART had viral suppression (<200 copies/mL).

However, disparities by gender, race/ethnicity, HIV transmission risk, geography, and area-based poverty level persist. African/Americans continue to be disproportionately affected by HIV. In 2015, 42% of all newly diagnosed HIV infections in NYC were among African/Americans who comprise only 22% of the city's population.

Outcomes including HIV diagnosis rates, short-term survival after HIV diagnosis, and viral suppression among PWH in care were also worse for Black and Latino/Hispanic people with HIV.

Differences in linkage to care and viral suppression were reported by some demographics including race, sex, gender and transmission risk.

Co-infection with Hepatitis C virus (HCV) is significant. Among PWH in care, only just over half (58%) had recently been screened for HCV, but 12% of those tested had a recent positive result.

COMMENT

**This report is important as an example of a healthcare approach to HIV that sets hard targets to reducing new infections. Even though these data are optimistic, the impact of the new End the Epidemic (EtE) programme will not be seen until next year. However, rates of decline are not yet steep enough to reach 2020 targets.**

**Unfortunately, the UK has consistently failed to set targets and over the same 15-year period HIV incidence in the UK has remained unchanged - despite high levels of access to treatment and high rates of viral suppression in people on ART. [3]**

**Although there are significant differences between New York and the UK, some of the similarities are important. The city actually has more people living with HIV as the whole of the UK; both countries are high-income settings with a public health infrastructure; and both have excellent surveillance data that makes it possible to evaluate the impact of health interventions.**

**The widespread availability of PrEP in NYC as an option for all populations at high risk is one significant difference. This is in contrast to the recent decision by NHS England to delay PrEP access for years. [4]**

**In NYC, PrEP is widely advertised in the city as a public health issue, including on public transport.**

**Data on transgender people and HIV has been collected in NYC since 2005. [5]**

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# OTHER NEWS

## AT LAST: Gay men and transgender people in England get vaccine to prevent genital warts and anal cancer – impressive pilot results

**Simon Collins, HIV i-Base**

**Gay men and transgender people in England now have limited access to the quadrivalent HPV vaccine. Early results from an ongoing pilot study are extremely encouraging.**

After years of community campaigning for the NHS to provide equity of care to gay men, the first data show that the vaccine is easy to deliver with a high level of interest in uptake. Limited data on the pilot programme were presented in a small informal briefing by Public Health England (PHE) who manage the programme. [1]

### Background

Although there are over 100 types of HPV viruses (40 of which infect the genital tract) a few key strains are linked to the majority of health complications. The vaccine being used has extremely high efficacy against strains 6, 11, 16 and 18. HPV strains 6 and 11 cause more than 90% of genital warts. HPV 16 and 18 are linked to more than 70% of cancers in the in the vagina, vulva and cervix and 90% of HPV-related cancers in men (overall, covering anus (80-85%), penis (50%) and mouth and throat (36%) – not all these cancers are HPV-related.

The UK public health approach was to only vaccinate girls aged 12-13 in a school vaccination programme launched in 2012 (with a later "catch-up programme" extending for girls aged 13-17). If the uptake is high – and it has been – heterosexual adolescents become protected from the concept of herd immunity.

But even at the time, this decision was criticised for being particularly flawed. It provided no protection for gay men who are at significantly higher risk for many HPV-related cancers, especially if they are HIV positive.

After years of campaigning for equity of access, in November 2015, the Joint Committee on Vaccination and Immunisation (JCVI) – an independent UK committee of experts – recommended the vaccine for gay men and other men who have sex with men, up to and including the age of 45 (with no lower age limit). This was based on estimates of cost effectiveness if delivery costs were low. The recommendation noted that there are likely to be considerable benefits outside these boundaries in specific individuals. This includes gay men at higher ages, sex workers, and HIV positive women and men. [2]

A review of UK public health databases suggested that 110,000 gay men would be eligible based on the upper age limit of 45 years. The network of sexual health clinics strongly support expanding access to gay men – by agreeing to nominal reimbursement of £10 per vaccine shot. Both BHIVA and BASHH strongly support the pilot programme. [4, 5]

## Summary update on pilot programme

The high level of efficacy – highly protective against four key strains – is already well-established. [3] The PHE programme is to look at operation questions above demand and access.

- The programme includes 43 sexual health clinics across England. [6] Clinics were chosen to provide best geographical coverage. All clinics that were asked to join accepted. These clinics are in 15 towns and cities (Brighton, Bournemouth, Weymouth, London, Milton Keynes, Great Yarmouth, Norwich, Bristol, Salisbury, Swindon, Chippenham, Manchester, Birmingham, Solihull and Newcastle).
- Enrolment started from June 2016 and by November 2016 all clinics were providing vaccinations. This took slightly longer than expected.
- Approximately 15,000 injections have been ordered (no data on number of people vaccinated).
- More than 3,700 participant questionnaires (on acceptability and service) have been returned to PHE.

## Aims of the programme

The aims of the HPV-MSM immunisation pilot are to evaluate two main areas. [7]

1. The cost-effectiveness of providing the vaccine through GUM and HIV clinics. Evaluate vaccine uptake, the impact on clinic attendance, and to identify and find any unforeseen issues that may arise during the pilot.
2. The response to the offer of a full course of the HPV vaccine "opportunistically" to all MSM up to and including the age of 45 years attending participating GUM and HIV clinics. This means asking people at a routine clinic visit - i.e. without publicity or a public information campaign. A leaflet on the programme was produced for use in participant clinics. [8]

The programme is designed for people to be offered vaccinations at routine clinic appointments - so that service costs are kept to a minimum. However, men who register at a participating clinic primarily for the vaccine are still able to receive it – but these cases need to be noted so that cost effectiveness can be calculated more accurately.

So far, there are minimal reports of people accessing the vaccine this way.

## Other questions

The meeting allowed the chance to ask questions on the programme. Together with discussion this clarified the following points.

- The programme for gay men is considerably smaller than the programme for girls that currently vaccinates 350,000 young women each year.
- In practice, clinics seem to find it easy to integrate the vaccine into routine clinic appointments. Uptake is high. The HPV vaccine can be given at the same time as other vaccinations, for example, hepatitis B.
- Although planned as a programme for men who have sex with men, transgender people are able to join the programme. The team were uncertain about how this data would be collected, based on the current enrolment forms.
- Although the pilot is only available in a limited number of clinics, there is not likely to be a later catch up programme for people who are currently 44 or 45 but who are not attending participating clinics.
- Although registering at a clinic just to access the vaccine is not recommended, people who are doing this are not being refused the vaccine; this use is just coded for later analysis.
- There are no plans to expand the current list of 43 participating clinics during any part of the pilot programme.
- The pilot MSM programme is running separately to the upcoming JCVI report on vaccinating adolescent boys.
- Programmes in Wales, Scotland and Northern Ireland are separate, and currently only thought to be at a planning stage.
- PHE cannot directly publicise the pilot programme but community organisations can do this. The NHS patient leaflet has been printed and is widely available at participating clinics.
- A likely timeline for full access was suggested as 2018/2019 (see Table 1).
- The cost of the programme has not been made public.

## Data on vaccine effectiveness and response

Although this programme is impressive, it was also clear that funding has not been provided for clinical research.

By not linking the programme to a clinical research group, missed opportunities include losing data on:

- Current UK prevalence and distribution of HPV strains and prevalence in different populations.
- Vaccine responses in people who have already been infected.
- The impact of age on responses to the vaccine.
- The impact of HIV (with or without ART) on responses to the vaccine.

While none of these questions should prevent access, not at least storing baseline samples even in a subset of participants seems a missed opportunity.

Of note, the vaccine is still likely to have a protective effect even if someone has already been exposed and/or remains infected with these viral strains. The vaccine boosts natural immune responses by significantly higher levels. This is especially important for HIV positive people whose risk of HPV-related cancers are much higher than the general population.

**Table 1: Selected timeline for access to HPV vaccine in England**

| | |
|---|---|
| 2006 | Gardisil-4 approved in the US – against the four strains 6, 11, 16 and 18 (quadrivalent). |
| 2008 | JCVI recommend UK programme to vaccinate girls. |
| 2012 | UK programme to vaccinate girls aged 12-13, later expanded to ages 13-17. |
| 2015 | JCVI recommend vaccination for gay men and other men who have sex with men, aged 45 or younger. |
| 2016 | 43 clinics enrolled in programme (from May to November). |
| 2017 | First data analysis in March with preliminary report expected in May. This will likely only include information about the first one or two infections. The full course of three injections is planned to be given over 12 months (but up to 24 months is allowed). Extended roll out continues in same 43 clinics. |
| 2017 | JCVI to evaluate programme for vaccination for all boys (similar to the programme for girls). |
| 2018/19 | Full roll out expected, based on commissioning provisions. |

## COMMENT

**Although this programme is branded as for gay men it is important that doctors know there is flexibility to include transgender people - and the programme is essential for redressing the current inequity of access to protection against HPV.**

**Efficacy data from the Australian programme of vaccinating girls in schools led to a 77% reduction in HPV types responsible for almost 75% of cervical cancers, almost 50% reduction in the incidence of high-grade cervical abnormalities in girls under 18 years old and a 90% reduction in genital warts in heterosexual men and women under 21 years of age. [9]**

**Similar levels of protection should be available to all citizens, irrespective of gender or sexuality.**

**A small study (n=50) presented at the BHIVA conference last year reported that almost half of gay men aged 18 to 25 had high risk HPV genotypes in anal swabs and HPV DNA was detected in 68% of participants. [10]**

**HPV is spread by skin to skin contact. It is likely both under-diagnosed and undertreated given HPV testing is never routinely available.**

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# FUTURE MEETINGS

## Conference listing 2017

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.

**Australasian Chapter of Sexual Health Medicine (AChSHM) Annual Scientific Meeting**

18 March 2017, Sydney

http://sexualhealthmedicineasm.com.au

**23rd Annual Conference of the British HIV Association (BHIVA)**

4-7 April 2017, Liverpool

http://www.bhiva.org

**International Workshop on Clinical PK of Antiviral Therapy**

14-16 June 2017, Chicago

http://www.virology-education.com

**HIV & Hepatitis Co-infection 2017**

21-23 Jun 2017, Lisbon, Portugal

http://www.virology-education.com

**HIV Paediatrics 2017**

21-22 July 2017, Paris, France

http://www.virology-education.com

**12th International Workshop on HIV Transmissions**

21-22 July 2017, Paris, France

http://www.virology-education.com

**IAS HIV Cure & Cancer Forum**

22-23 July 2017, Paris, France

https://www.iasociety.org

**9th IAS Conference on HIV Science**

23-26 July 2017, Paris, France

http://www.ias2017.org

**16th European AIDS Conference**

25-27 October 2017, Milan

http://www.eacsociety.org

**International Workshop on HIV Drug Resistance and Treatment Strategies (IWHDR)**

6-8 November 2017, Johannesburg

http://www.HIVresistance2017.co.za

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- Introduction to ART (September 2016)
- HIV & quality of life: side effects & better 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)

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- **Guide To HIV testing and risks of sexual transmission** *(July 2016): 52-page A5 booklet*

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- **Guide to HIV, pregnancy and women's health** *(November 2015): 52-page A5 booklet*

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- **Guide to changing treatment: what to do if viral load rebounds** *(February 2015): 24-page A5 booklet*

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