

## march-april 2016

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## EDITORIAL

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### **This edition of HTB mainly features our first reports from the 23rd Conference on Retroviruses and Opportunistic Infections (CROI 2016), which took place in Boston.**

Research into new drugs included long-acting/extended release formulations with the potential for much longer dosing intervals than the current oral antiretrovirals, some of which might be useful as both treatment and PrEP.

Promising 32-week results were presented from the LATTE-2 study of dual long-acting injections of cabotegravir plus rilpivirine. And – one of the conference surprises – the first virological data from a new investigational NRTI, MK-8591 that has the potential for weekly oral dosing or even annual injections.

PrEP was a focus throughout the conference. We report the dramatic increase in use of oral TDF/FTC for PrEP in the US (with a few cautions), the first data on TAF, the possible roles for maraviroc and cabotegravir and only limited protection from the dapivirine vaginal ring. We also look to future formulations: “pills, films, gels, injections and depots”.

Dolutegravir remains an important potential option for all countries and we report promising 48-week results in children, early data in pregnancy, and that similar viral load reductions were seen at week 4 when dolutegravir was used with 2- or 3-drug initial ART.

We also report that global uptake of generic versions of this drug in low- and middle-income countries, together with TAF and reduced dose efavirenz could mean savings of up to US \$3 billion by 2025.

Other news includes a positive opinion on dual formulation of F/TAF adopted by the EU and new TAF-containing fixed dose combination (with FTC and rilpivirine) approved in the US.

Treatment access includes community opposition to dolutegravir and cabotegravir patents in India; transgender people are being left behind in the fight against HIV and South Africa's Mbeki still shows no remorse for his role in AIDS deaths.

Returning to PrEP, now established as a cornerstone to global programmes to reduce HIV incidence in the highest risk groups, we contrast approval in Canada with the decision by NHS England to not only block access to PrEP but to block even public discussion about PrEP.

This decision will help ensure at least 500 people continue to test HIV positive each month and that incidence rates next year will likely remain above 6000.

This is a sexual health crisis for those who are most vulnerable, especially those from the gay and trans communities.

## CONFERENCE REPORTS

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### **23rd Conference on Retroviruses and Opportunistic Infections (CROI 2016)**

**22 – 25 February 2016, Boston**

#### **Introduction**

**Every year, CROI brings more than 5000 researchers, doctors, community activists and other health workers to meet for one of the most scientifically important HIV conferences.**

This year the meeting was in Boston and with over 1000 studies presented, there is far more to report than the key studies that make headline news.

At CROI 2016, major studies presented research on basic and clinical science relating to prevention, new treatment and global access.

The programme and abstracts are posted to the conference website, with many posters also available as PDF files.

Webcasts from all oral presentations are also online.

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

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

<http://www.croiconference.org>

Reports in this issue of HTB are:

- Dual long-acting injections of cabotegravir plus rilpivirine: 32-week results from LATTE-2 study
- New NRTI MK-8591: weekly oral dosing and once-yearly slow-release dosing has potential for HIV treatment and PrEP
- Similar viral load reductions at week 4 when dolutegravir is used with 2- or 3-drug initial ART
- 48-week results for NNRTI doravirine compared to efavirenz
- Dramatic increase in use of oral TDF/FTC for PrEP in the US – plus a few cautions
- Future oral and long-acting PrEP: pills, films, gels, injections and depots
- First data on TAF as PrEP to prevent HIV infection
- Long-acting cabotegravir as PrEP protects macaques against IV exposure but will need two-monthly injections in human studies
- Role for maraviroc as HIV PrEP likely need dual combinations
- Dapivirine vaginal ring shows only limited PrEP protection against HIV for African women
- Early data from dolutegravir use during pregnancy
- Dolutegravir: 48 week results in children aged 6 to 12 years
- New antiretrovirals could mean savings up to US \$3 billion by 2025
- Countries with lower HIV prevalence have lower ART coverage
- Nigerian herbal medicines widely used by HIV positive people can contain antiretrovirals
- Cure research news from CROI 2016

CROI 2016: ANTIRETROVIRALS

## **Dual long-acting injections of cabotegravir plus rilpivirine: 32-week results from LATTE-2 study**

**Simon Collins, HIV i-Base**

**The idea of injections every few months as an alternative to daily oral drugs has always been popular. Although current ART is safe, effective and tolerable, some people hope for alternatives to pills.**

The preference appears to persist – at least based on results from a late-breaking phase 2b study presented at CROI – even when the injections involve relatively large volumes into gluteal muscle.

David Margolis from ViV Healthcare presented 32-week results from the LATTE-2 study, using a dual long-acting (LA) formulation of the integrase inhibitor cabotegravir (CAB) and the NNRTI rilpivirine (RPV). [1] Safety and efficacy of oral versions of these two drugs were previously established over 96 weeks in the LATTE-1 study.

LATTE-2 enrolled 309 treatment naive participants into a 20-week oral drug induction phase (CAB 30 mg + abacavir/3TC). Oral rilpivirine was added for the final four weeks and people with undetectable viral load from week 16 to 20 (91%, n=286) were randomised 2:2:1 to one of three open label arms: 4-weekly (4W) injections (n=115), 8-weekly (8W) injections (n=115) or a control arm continuing with oral CAB plus abacavir/3TC (n=56).

Baseline CD4 and viral load were 489 cells/mm<sup>3</sup> and 4.3 log copies/mL (with 18% >5 logs). Only 8% of participants were women and 15% were African American.

At week 32, viral suppression to <50 copies/mL was achieved in 94%, 95% and 91% of the 4W, 8W and oral arms respectively, which met prespecified criteria for showing each intramuscular injection (IM) arm was not worse than the oral treatment group. Virologic non-response rates were slightly lower in the 4W arm (<1% v 4% in the other arms) with lower non-virologic reasons for discontinuation in the 8W arm (vs 5% in each of the other two arms).

There were two protocol defined virologic failures (confirmed viral load >200 copies/mL), one in each of the 8W and oral arms, none with evidence of drug resistance.

Excluding injection site reactions (ISRs), tolerability was good, but with higher rates of fever (3%), fatigue (3%) and flu-like illness (2%) in the combined injection arm compared to a single report of fatigue in the oral arm. None of the grade 3/4 side effects were judged related to study drug, including the single death related to epilepsy.

ISRs were very commonly reported but reduced from 86% of participants at day 1 to 33% at week 32. Most were grade 1 (80%) or grade 2 (19%). Median duration of ISR was 3 days with 90% lasting less than 7 days. Most common reactions were pain (67%), swelling (7%) and nodules (6%). Only two participants stopped due to ISRs.

In a patient satisfaction survey >95% of participants reported injections were preferable to daily oral induction phase and that they would be willing to continue injection in the future.

In the PK analysis, cabotegravir stayed between the 10 to 30 mg target concentrations established in LATTE-1, with troughs well above the protein adjusted IC90. Although rilpivirine levels also remained well above the PA IC90, levels were lower over the first 16 weeks than achieved with 25 mg oral dose, and this was highlighted as an area that will need further study.

#### C O M M E N T

**The translation of long-acting injectables from research studies to the real world may bring additional concerns, for example, how to withdraw drug when adverse events and drug reactions occur?**

**With the move to annual CD4 and viral load monitoring, undetected viral rebounds risk accumulating resistance over months of replication in the face of ongoing drug pressure? A related question is the impact of not being able to remove drug pressure on resistant virus once it is detected? Both these issues might be especially important for rilpivirine, which as an NNRTI is more vulnerable to drug resistance.**

**It is unclear whether cabotegravir will have the same resilience to drug resistance as dolutegravir in naive patients, or have the same vulnerability in people with previous integrase experience.**

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## **New NRTI MK-8591 (EFdA): weekly oral dosing and once-yearly slow-release dosing has potential for HIV treatment and PrEP**

**Simon Collins, HIV i-Base**

**One of the surprises at CROI 2016 was the first virological data from a new highly potent NRTI that in a slow-release formulation has the potential for annual dosing and that is undergoing research as both treatment and PrEP.**

In an oral late-breaker, Jay Grobler from Merck presented results from a dose-ranging study in macaques to develop a model for phase 1 studies with MK-8591 (EFdA). [1]

Baseline SHIV viral load ranged from 6 to 8 log copies/mL and following single doses that ranged from 3.9 to 18.2 mg/kg viral load dropped by approximately 1.5 logs and was sustained for seven days.

PK data from a phase 1 multiple-dose study in HIV negative adults (using 10 mg, 30 mg and 100 mg) once-weekly for three weeks showed that with the 10 mg dose target intracellular target drug concentrations were exceeded for more than seven days.

A slightly cheeky slide was shown from the phase 1b study showing that EFdA produced more rapid viral suppressions compared to historical data for TDF and TAF.

Early data on a solid-state slow release parenteral injection formulation that has an option for removability, showed sustained release for more than 180 days in rat studies, with the potential for cover to be extended to a year.

The poster detailing the phase 1 study results in six HIV positive men reported a mean viral load reduction of 1.67 log (95%CI: 1.47 to 1.87) was seen at day 7, following a single 10 mg dose, after which ART was started. Baseline CD4 count was >400 cells/mm<sup>3</sup> and viral load ranged from 10,000 to > 430,000 copies/mL. Although there were no serious safety concerns, there were six cases of headache. There was no detection of drug resistance. [2]

EFdA is active against wild-type and MDR variants of HIV-1 and HIV-2 (including with K65R) and has an EC50 in PBMCs of 0.2 nM and half life for the intracellular triphosphate in PBMCs of approximately 100 hours. It is modestly sensitive to M184V (3-5 fold) suggesting a higher dose might be appropriate given high potency and good safety data, although dose for development has not yet been selected. Preclinical studies have not shown concern for mitochondrial toxicity.

Previous reports about this compound have highlighted a similar structure to a flavour enhancement for soy sauce. Yamasa originally developed the compound before Merck acquired development rights in 2012.

C O M M E N T

**The new NRTI from Merck has the potential to change everything dramatically for treatment and PrEP - with removable slow release once-yearly dosing.**

**This shows the real potential for pushing drug development over the next 5-10 years - and why advocacy for continued pipeline research is important.**

**This is very early days but animal safety data has so far been good.**

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## Similar viral load reductions at week 4 when dolutegravir is used with 2- or 3-drug initial ART

Simon Collins, HIV i-Base

**Given the number of independent groups reporting data from studies using dolutegravir monotherapy at the EACS conference in October 2015 [1], it was strange to see no further updates from these groups at CROI 2016.**

One related study that managed to slip into CROI as poster was an analysis from the PADDLE study that at EACS reported rapid viral suppression sustained to 24 weeks from using initial therapy with dolutegravir plus lamivudine (DTG+3TC) dual therapy. [2]

In order to look at early viral dynamics from this strategy Omar Sued from the Fundación Huésped, Buenos Aires and colleagues compared viral load results in PADDLE to historical data from the SPRING and SINGLE studies where dolutegravir was started with two NRTIs.

Although PADDLE included more intensive monitoring, data was only calculated in this analysis for time-points that were shared by all three studies, ie at weeks 2, 4, 8, 12 and 24.

Viral load changes were similar after a dual therapy regimen DTG/3TC compared to two DTG-based triple therapy regimens. Two-way ANOVA revealed significant effects for treatment ( $F_{2,1605}=30.3$   $p<0.001$ ) and time ( $F_{4,1605}=22.8$   $p<0.001$ ), without significant interactions. (See Table 1).

**Table 1: Viral load reductions with dolutegravir in 2 vs 3 drug combinations**

	PADDLE	SINGLE	SPRING-1
BL pVL (mean+SD)	4.43 (0.50)	4.30 (0.45)	4.31 (0.52)
Av. effects (mean ±SD)	-2.75 (±0.45)	-2.53 (±0.49)	-2.61 (±0.48)

C O M M E N T

**These results, albeit encouraging, should be interpreted with caution, as the analysis is based on a cross-study comparison of mean values and PADDLE is a small pilot study.**

**Comparative viral dynamics really require looking at very early time points over the first few hours and days. Of interest, the PADDLE study did collect this early data.**

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## 48-week results for NNRTI doravirine compared to efavirenz

Simon Collins, HIV i-Base

### Phase 2 results in treatment naive patients using doravirine (MK-1439) – an NNRTI in development with Merck – were presented in a poster from José Gatell from Barcelona Hospital and colleagues. [1]

This was a randomised, double-blind, placebo controlled phase 2 dose finding study in two parts. In part 2, new patients started using the selected 100 mg doravirine dose. All participants were treatment naive and used tenofovir DF/FTC as background NRTIs.

Combined 48 week data included 42 people randomised to the 100 mg once-daily dose in part one of the study plus 66 participants who were added in part two (n=108), compared with 109 control patients randomised to efavirenz.

Baseline demographics included ~90% men, 75% white, with mean age 35 (range 19-67) years and median CD4 count and viral load of approximately 425 cells/mm<sup>3</sup> (range 92 to 1121) and 2.6 log copies/mL (range 2.6 to 6.7).

At week 48, viral suppression to <40 copies/mL was reported for 77.8% vs 78.7% of the doravirine vs efavirenz groups respectively, (difference -1.1%; 95%CI -12.2 to +10.0). There were slightly fewer discontinuations in the doravirine group (12% vs 14.7%) which included fewer discontinuations related to side effects (2.8% vs 5.5%).

In patients with baseline viral load <100,000 copies/mL approximately 87% in each group reached <40 copies/mL at week 48 but greater suppression was reported for the efavirenz group for those starting with viral load >100,000 copies/mL (74% vs 84%). Both groups reported 91% rates using a <200 copies/mL test.

There were few laboratory abnormalities greater than grade 2 but lipids, liver enzymes and lipase generally favoured the doravirine group and abnormal glucose fasted occurred slightly more in the doravirine group (3.2 % vs 1.1%).

Ongoing studies include as part of a single tablet, fixed dose combination with generic NRTIs: doravirine/tenofovirDF/3TC. [2]

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CROI 2016: PREVENTION

## Dramatic increase in use of oral TDF/FTC for PrEP in the US - plus a few cautions

Simon Collins, HIV i-Base

### Dozens of studies at CROI 2016 reported an overwhelmingly positive impact of TDF/FTC, which is currently the only FDA-approved HIV medicine with a PrEP indication.

The most optimistic of these studies covered scale up programmes that are transforming approaches to HIV prevention. When taken daily, oral TDF/FTC works, preventing infections with a close to 100% efficacy.

Event-driven or “as needed” dosing - although not approved - is also an increasingly widely used approach but requires doses both before and after sex (as in the IPERGAY study).

## Uptake and roll out

Many of the studies are from the US, where TDF/FTC has been approved as PrEP since 2012 - including uptake in high incidence urban settings including San Francisco, Boston, New York and Washington. [1, 2, 3, 4, 5]

Although US uptake was originally slow, the most rapid increase in use has been in the last two years to more than 40,000 people - but this is still early days in terms of potential use. Many of these US studies include problems of drug access even with assistance programmes that provide PrEP free.

Many presentations emphasised community initiatives, including an impressive overview by long-term prevention activist Jim Pickett using global examples including from programmes in Chicago. Many of these approaches normalise PrEP - similar to sun-lotion - some not even mentioning HIV. Essential viewing. [6]

Other studies highlighted cautions, generally minor compared to the achievement of prevention and the goal of cutting HIV incidence. Higher STI rates were sometimes reported - but these studies were often uncontrolled and ignored the increasing incidence that predated PrEP. Increased reporting of STIs is balanced, including by higher rates of detection and treatment, including in the UK, because of more frequent routine monitoring. [7]

Many US studies recommended more frequent STI monitoring - from every 6 months in current US CDC guidelines to every 3 months that has been standard in European studies. [8, 9]

Other studies looking at practical issues relating to deliver of PrEP included the use of rapid tests to confirm initial negative status, but also the increased chance of detecting recent infections using 4th generation HIV tests and perhaps viral load in cases of recent high risk. [10, 11, 12]

## Case report of HIV infection on PrEP due to drug resistance

It has always been known that PrEP only works when the drugs are sensitive to HIV. PrEP failure due to drug resistance, even in the context of good adherence, was always possible - and the first case was reported at CROI 2106.

In this example, a gay man was unfortunately infected with multidrug resistant HIV, including to TDF/FTC - and the case was widely reported as one of the leading news stories. Baseline resistance testing shown multiple NRTI, NNRTI and integrase associated mutations. [13]

This case is important for being reported on a community PrEP discussion group and for becoming the first well-documented example. Estimating the resulting impact this has on overall PrEP efficacy is difficult, but the denominator would be based both on number of overall PrEP exposures (rather than number of people using PrEP), together with the background incidence of drug resistance in that setting.

Taken together, these cases are likely to continue to be very rare, especially in the context of the overwhelmingly positive effect PrEP is having on reducing HIV infections and improving quality of life.

Luckily the prevalence of drug resistance to TDF/FTC is currently very low in countries with high rates of viral load suppression on ART and where viral load monitoring is routine.

In the UK for example, low-level resistance to either drug was <1% in newly diagnosed individuals. High-level resistance to tenofovir with K65R was only reported in 10 people from 2010-2013 (0.06%). [14]

## Safety issues with TDF/FTC

Safety results are holding up surprisingly well with TDF/FTC, with low incidence of serious side effects, but this is again dependent on routine monitoring.

When side effects occur, the plausible association with both adherence and dose/absorption was highlighted in several studies. For example, incidence of side effects is underestimated in many PrEP studies by low adherence and two poster reported greater reductions in renal function, with drug levels.

Monica Gandhi from UCSF reported that tenofovir levels in hair samples correlated with the risk of reduced eGFR in a subset of 200 men from the open label phase of the iPrEX study. Over 18 months, the mean percentage reduction in eGFR from baseline was 2.6 mL/min (SE 0.8) vs 5.6 (SE 0.7), for those with tenofovir levels in the first vs fourth quartiles [OR 4.4 (95%CI: 1.1 to 17.4), with  $p = 0.045$  for trend]. Reduced eGFR was also associated with lower CrCl <90 mL/min and older age (>40 years). [15]

A similar dose relationship was reported from the US Demo Project with greater decline in CrCl associated with drug levels linked to >4 doses a week (approximately 5% over the first 12 weeks and stable thereafter). [16]

In the heterosexual African Partners PrEP study, proximal tubulopathy was rare and occurred at similar rates in the active and placebo groups, although one case of Fanconi's syndrome related to TDF was reported in a person using other nephrotoxic drugs. [17]

Reductions in bone density in a sub-group of participants in the iPrEX study were also significantly greater in participants with tenofovir diphosphate levels associated with taking four or more doses a week (>16 fmol/mL), compared to people

in the placebo group. In the subset of participants with multiple DEXA results, these changes reversed during the interruption in PrEP between the end of the main study and access in the open label phase. [18]

While overall tolerability was good, the dose relationship of both kidney and bone toxicity with TDF/FTC levels suggests benefits of event-based dosing strategies such as the IPERGAY study. [19, 20]

It also suggests advantages for tenofovir alafenamide (TAF) if it is proven to have PrEP activity. This is not yet clear because while a macaque study was exciting for showing 100% protection against repeated rectal exposure, a single-dose PK study in HIV negative women reported either low or undetectable levels of tenofovir diphosphate in vaginal and rectal tissue. [21, 22]

These two results are difficult to reconcile unless levels in tissue are not directly related to the protective mechanism for PrEP, with the intracellular levels in lymph cells being crucial.

## C O M M E N T

**The regulatory decision for TDF/FTC for PrEP in Europe is still being reviewed.**

**A decision about NHS access in the UK is not expected until June 2016.**

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## **Future oral and long-acting formulations for PrEP : pills, films, gels, injections and depots**

**Simon Collins, HIV i-Base**

**Just as the term PrEP has started to gain awareness and recognition as a generic word for a pill to prevent HIV infection, CROI 2016 included potential PrEP alternatives to daily or event-driven oral tenofovir DF plus emtricitabine (TDF/FTC).**

Many of these studies are at an early stage of research but others could potentially become options within 2-3 years.

Other formulations include injectable compounds, long-acting implants, gels and a microbicide vaginal ring.

Two key issues with potential PrEP drugs were repeated concerns in these studies. Firstly, the difficulty of running efficacy studies without good models of efficacy - whether in animal or ex vivo studies; and secondly, the lack of surrogate markers for PrEP efficacy that would help select the best compounds for future studies. Interpreting PK drug levels is complex with many studies reporting differences between levels in similar sites - for example in vaginal or rectal fluid compared to in vaginal or rectal tissue.

The strategy for future studies is also discussed in a comment at the end of this article, driven by the need for a wider range of effective PrEP together with the increasing challenge to prove efficacy in high-risk populations now that oral TDF/FTC (with good adherence) is associated with such high rates of protection.

### **TAF, the new tenofovir: first PrEP data**

Two studies on the new TAF formulation of tenofovir presented results that at first seem contradictory.

In animals studies all six monkeys receiving TAF effectively were protected from rectal exposure compared to all six monkeys receiving placebo that became quickly infected. This is exciting. [1]

In contrast, measuring drug levels in a small group of eight HIV negative women following a single dose of TAF (two women received placebo), showed lower active drug levels in genital and rectal tissue - even though these were expected to be higher. [2]

Further studies need to determine whether these lower levels are going to affect PrEP efficacy.

### **LA injections: cabotegravir and rilpivirine**

The second PrEP compound with exciting results was the long-acting (LA) slow-release formulation of cabotegravir, which is given by intramuscular injection (into the buttocks). Again there were results from both animal and human studies.

The animal studies were exciting for showing that cabotegravir LA protected against HIV transmission directly into blood - rather than just against sexual exposure. This is remarkable because the risk of infection by blood exposure is so much higher. If similar protection is seen in human studies, this means that injections every two months might protect people vulnerable to HIV infection through shared injecting drug use. [3]

The human cabotegravir study mainly reported on tolerability of the injections. Although side effects were significantly higher with the active injections (compared to people who received saline) overall patient satisfaction still remained pretty high.

This study also found that injections are needed every two months, rather than every three months as initially hoped. Unfortunately, one person in each of the active and placebo groups became HIV positive during this study. [4]

Although rilpivirine LA was also an early candidate for PrEP it seems unlikely that research will continue for this indication. This decision is because the protection in rectal tissue does not seem likely in vaginal tissue, based both on drug level and test tube studies. [5, 6]

### **Maraviroc as PrEP: better to study in combination?**

Maraviroc was approved an HIV drug in 2007 but was never widely used in first-line ART because it was not quite as good as other options. Although it was well tolerated it needs a separate test before it can be used as treatment and has significant interactions with some other HIV meds. However, because it blocks HIV from entering CD4 cells, many researchers were interested in whether it might have a role as PrEP.

Results of a phase 2 study presented at CROI 2016 hinted that maraviroc might work as PrEP but test tube studies suggested this might be better in combination with either tenofovir or FTC. [7, 8]

### **Dapivirine: first efficacy results of a vaginal ring**

Another PrEP compound that was widely reported at CROI 2016 involved the use of a monthly vaginal ring that slowly released an NNRTI called dapivirine.

Two very large studies in African women reported reductions in HIV transmission that were statistically better than a placebo ring, and that protection was higher when the ring was used. As with several other large PrEP studies, low adherence complicated interpretation of the results. Most disappointing, was that the ring produced no protection for women under 21, in whom HIV risk is the highest. [9, 10]

The need for alternative formulations for different risk groups is clear, but even in the context of good adherence, dapivirine appears to be less effective than oral tenofovir/FTC.

A more difficult question to answer is whether efficacy would be improved to a more acceptable level if the ring coformulated dapivirine with a second slow release antiviral.

### **Tenofovir: implants, gels and rings**

Unlike long-acting injections that are permanent, some researchers are looking at slow release implants that would be able to be removed - similar to a contraceptive implant.

A small silicon tube containing tenofovir alafenamide (TAF) reported good pharmacokinetics in a dog study. Modelling TAF for human protection suggests that a 50 mg dose might only be needed to provide protection for a year. [5]

Another formulation, also using TAF, is being studied in a three-monthly biodegradable implant that would not need to be removed if it was used for the full period. [11]

Use of implants might also help overcome the issue of the extremely long half-life of long-acting injections, which with rilpivirine LA have included NNRTI drug resistance when infections occur.

An oral presentation reported from a six-month international phase 2 study on the acceptability of a 1% tenofovir rectal gel, administered with an applicator. This was an open label cross over study with three groups: (i) daily use of the gel; (ii) event-based use with a pre- and post-sex dose; and (iii) a control group using oral TDF/FTC. [12]

Adherence measures included daily SMS text messaging and real-time PK evaluations. Overall, average age was 30 (though lower in the South African sites), with 80% of participants having some level of college education. Of 195 participants, most identified as male (71%), transgender (10%), female (2%), not stated/declined (15%).

Tolerability was similar in all three groups with approximately 30% in each arm reporting side effects that were grade 2 or higher. All interventions were acceptable (>70% said they liked each option) even though overall there was a greater preference for oral PrEP compared to gel. PK sampling showed approximately 90% use with both daily oral and daily rectal doses. Event-based gel was preferable to daily gel.

Several posters presented early results on other tenofovir formulations, including a 2" x 2" quick dissolving film (for vaginal use) [13], a gel that could be used vaginally or rectally [14] and a vaginal ring that identified cervical tissue as the source of infection in a macaque study. [15]

### **PC-1005 gel**

PC-1005 is the development name for a gel formulation of the NNRTI MIV-150 and zinc acetate that is being studied as a way to provide dual protection against both HIV-1 and HSV-2. [16, 17]

Although MIV-150 has shown efficacy in macaque studies following rectal exposure, two studies at CROI 2016 on vaginal gels looked at acceptability and efficacy in test tube studies. Another slow release ring formulation has been developed that protects against HIV-1, HVS-2, HPV and pregnancy. [18]

### **MK-8591: an ARV with potential for annual dosing**

Although only in early stages of development, two studies reported data on EFdA (MK-8591), a new NRTI in development by Merck that, due to a very long half-life and potency that requires very low dosing, is being studied both for treatment and prevention. [19]

This compound has a PK profile that with an intracellular half-life of >24 hours might allow once-weekly oral dosing with a 10 mg dose and has the potential for very extended dose parenteral formulations. In a rat study, a single dose solid state slow release formulation provided drug coverage for longer than six months, with data suggesting that this might be extended in humans to longer than one year. [20]

While no specific data were presented on use as PrEP it is notable that the company are already highlighting a potential interest in prevention research. If this compound does show PrEP efficacy, it would allow radically different approaches to the design for PrEP studies, for example, allowing randomised cluster approaches (similar to the PopArt study).

### **VRC01: using monoclonal antibodies for PrEP**

Finally, in a plenary talk at the start of the conference, John Mascola from the US National Institute of Health provided an overview of using broadly neutralising monoclonal antibodies (mAbs) both for prevention and treatment. [21]

Animal studies using the monoclonal antibody (mAb) VRC01 have shown proof-of-concept for PrEP use and have been used to determine optimal dose, with the hope that dosing might only need to be every two months.

Two large phase 2 studies using 2-month dosing schedule are planned by HPTN to start by mid-2016. One of these aims to enrol 2400 gay men and transgender women in North and South America and the other is enrolling 1500 women in sub-Saharan Africa.

Not addressed in the talk, but a concern for all new PrEP studies, is the ethical issue that both these studies plan to use an inactive placebo-control.

Also, as VRC01 misses 13% of viruses, and more potent antibodies are expected shortly, this raises questions about whether it would be better to wait until two or more mAbs are combined in order to provide full coverage.

## **C O M M E N T**

**With so many new compounds and formulations with potential role for PrEP, the research and approval pathway for rapidly evaluating the most promising drugs is unclear.**

**Oral TDF/FTC works so well that in the context of good adherence, it is difficult for another compound to show better than near 100% efficacy. However, other drugs could easily show better tolerability, convenience and easier adherence that might show differences, especially long-lived slow release formulations.**

**New compounds also ideally need to be able to demonstrate efficacy in smaller studies before enrolling much larger and longer studies. Some PrEP compounds do not have non-human primate efficacy models - which with TDF/FTC supported dramatic and perhaps 100% early efficacy.**

**Traditional phase 3 studies enrolling thousands of participants for many years are costly, for a final intervention that needs by definition to be low cost and affordable. New approvals for PrEP are likely to depend on independent and publicly funded research that perhaps tests multiple new candidates in a single study.**

**Progress is only likely to be practical if efficacy studies can enrol populations with both very high incidence and a commitment to adherence. But even the designs for the recent PROUD and IPERGAY studies might not be acceptable today. PROUD included a control arm that deferred access to PrEP and IPERGAY used a placebo design that limited recruitment when participants already knew that TDF/FTC worked.**

**As for long-acting injectable treatment, long-acting PrEP will need to overcome issues relating to the extremely long half life that currently - in research studies - are suggesting oral dosing for a year is a requirement for people that want to stop long-acting PrEP.**

**CROI 2016 provided exciting tentative results but the next stages will be critical to whether and how quickly these can become real world options.**

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## First data on TAF as PrEP to prevent HIV infection

Simon Collins, HIV i-Base

**Of the studies at CROI 2016 of new compounds with potential for development as PrEP, data on the new version of tenofovir - called TAF - were amongst the most awaited and the most difficult to interpret.**

One of the reasons that many activists and doctors challenged Gilead's initial decision to only develop TAF as a component of fixed dose combinations, was that in addition to the need for TAF for treatment, there was also the potential use for PrEP.

Somewhat reluctantly, the company conceded by developing TAF/FTC as a separate dual formulation. Although this was a later priority in the development programme, the dual formulation is now filed with the FDA and EMA. Based on early results at CROI 2016, including two orals representation on Wednesday morning, this insight for the potential for TAF as PrEP might prove important.

In the first presentation, Gerado Garcia-Lerma from the US CDC in Atlanta reported results on the effectiveness of oral TAF and FTC following rectal exposure to simian HIV.

The animal dose of 1.5 mg/kg was selected to approximate to human drug levels using 25 mg TAF, based on a previous macaque study show similar levels of tenofovir diphosphate (TFV-DP) in cells (PBMCs) to previous animal studies with tenofovir DF but lower than expected exposure in rectal tissue.

TAF/FTC was dosed 24 hours before and two hours after weekly rectal exposure for 19 weeks, with six animals in the active arm and six receiving placebo.

All the control animals became infected within 1 to 10 exposures and seroconverted with high viral loads compared to none of the animals receiving TAF/FTC.

These results are very exciting, but came with a caution for a need for human efficacy studies before TAF is used for PrEP.

The second study, presented by Katy Garrett from the University of North Carolina, reported on levels of tenofovir and TFV-DP following a single oral 25 mg dose of TAF.

This study included eight HIV negative women, median age 27 years, who had drug levels measured in plasma, cervical fluid and vaginal and rectal tissue for 14 days after the single oral dose, with results compared to historical results in a similar TDF study.

In plasma and genital fluid, TFV concentrations peaked at 1 hour and were undetectable by day 7.

Levels of TFV-DP in PBMCs peaked at 12 hours in plasma, were still detectable at 10 days and were undetectable by day 14; however, TFV-DP levels in the genital tract were variable and largely undetectable.

In rectal tissue, TFV levels peaked at 3 days and were detectable throughout, but TFV-DP also peaked at 3 days but was undetectable by day 7.

When comparing these results to previous data with TDF, TAF resulted in the expected lower plasma and higher PBMC exposure. TAF levels in cervical fluid were 11-fold lower, with 58% undetectable (vs 23% with TDF). TFV exposure was 2-fold lower in genital tissue and TFV-DP was 1-fold lower (with 75% undetectable vs 25% with TDF).

In rectal tissue, instead of the expected increase compared to TDF, TFV levels were 10-fold lower, and TFV-DP were 13-fold lower (with 63% undetectable vs 0% with TDF).

The results from both studies need to be interpreted together before efficacy studies in humans. The high level of protection in the macaque study suggests that previous use of tissue concentrations as a surrogate marker for PrEP efficacy with TDF might not be appropriate for the mechanism of action with TAF.

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## Long-acting cabotegravir as PrEP protects macaques against IV exposure but will need two-monthly injections

Simon Collins, HIV i-Base

**Slow release, long-acting formulations have the potential to overcome difficulties with adherence to oral PrEP, even with reduced event-driven dosing.**

A long-acting (LA) injection of cabotegravir (an analogue of dolutegravir) is being developed as HIV treatment and also being studied for PrEP.

Cabotegravir LA has a very long half life (approximately 50 days), with therapeutic drug levels sustained for at least three months and detectable drug from a single dose recoverable a year later. Animal studies have already reported high protection in models that mimic sexual transmission.

Two oral presentations on the use of cabotegravir LA (CAB) for PrEP were included at CROI 2016.

In the first, Chastity Andrew from Aaron Diamond Centre reported remarkable results in several macaque studies that cabotegravir protected against intravenous (IV) SHIV challenge - a much higher risk than sexual transmission and closer to human risk from blood transfusion or shared injecting drug use. The first of these reported results from 13 animals (5 were placebo controls) who were given a single dose of cabotegravir (50 mg/kg, equivalent to human 800 mg dose) at baseline and week 4, followed by a single IV challenge with an SHIV dose high enough to expect infection. While all placebo animals became infected within one week of exposure, only one of the animals receiving CAB became infected - with 7/8 being protected out to 24 weeks. Plasma concentrations in the single infection were above the 4 x protein adjusted (PA) IC90 target.

When this study was repeated using only a single 50 mg/kg CAB injection, all 5 control animals became infected, but this time all 8/8 animals receiving CAB were protected ( $p=0.0008$ ), showing that the second dose was not required for

protection. However, drug levels fell below the 4 x PA IC90 earlier at 5 weeks compared to 9 weeks in the single vs two injection dose.

A third study used a lower (25 mg/kg) dose injection with IV challenge at week 2, and a second standard dose (50 mg/kg) injection at week 4. This schedule resulted in all 5/5 controls being infected compared to only 2/8 animals receiving active drug, both of which had the lowest PK drug levels.

This showed that a second injection is not needed for protection against single challenge, but is likely to be needed to sustain drug levels and protection over two rather than one month. Two of the three infected animals were with wild-type virus and one had novel mutation, previously not associated with cabotegravir resistance.

The second study was a phase 2a safety and pharmacokinetic (PK) study of a three 800 mg doses (each with two intramuscular injections) using both cabotegravir long-acting injection in HIV negative men. [2]

The study randomised HIV negative men aged 18 to 65 years (median age 30 years; range 20-61) who were at high risk of HIV to either active (n=105) or placebo control (n=21). Recent PrEP use and chronic liver disease were exclusion criteria.

The study had a four-week oral induction phase followed by 12-weekly 800 mg IM injections at weeks 5, 17 and 29. Results presented at CROI were for 12 weeks after the last injection, and continued follow-up will continue out to 52 weeks. Participants in the control arm used oral placebo and saline injections.

Data was presented for 87/94 (82%) and 20/21 (95%) who completed the oral and all injections, with four people discontinuing due to intolerance to injections.

There were two seroconversions, one in each of the placebo groups that occurred before the third injection and at 24 weeks after the last injection in the placebo vs active groups respectively.

In the PK analysis, plasma concentrations of cabotegravir were lower than observed in the previous HIV positive LATTE study where cabotegravir was used as treatment. Of concern, mean drug levels dropped below the target 4 x PA IC90 levels before 12 weeks and dropped below the PA IC90 for some participants. This meant 15-31% of trough concentrations were below the PA IC90 and only 30-37% were above the 4 x PA IC90 therapeutic target.

Although few people discontinued, side effects occurred significantly more often in the active vs placebo arms, in both the oral and IM phases. Most related to injection site reactions and were grade 2 or lower, but 10% of events (27/272 events) were grade 3, all in the active arm. Overall patient satisfaction was reported as high for both formulations, although four people discontinued the study (after the third injection) due to injection reactions. These surveys scored higher for the injection over the oral phase.

The PK results have resulted in changing the future dosing to use injections every 8 rather than 12 weeks.

Two posters from this study reported injections to be broadly acceptable to most participants but that tolerability concerns are real and might not be acceptable for all people. As with PrEP itself, the options of oral pills and injections will be individualised based on personal preference. [3, 4]

Clinical data from the long-acting dual formulation of cabotegravir plus rilpivirine as treatment in HIV positive people in the LATTE-2 study were presented as a late-breaker abstract. [5]

Next stage studies include a large randomised non-inferiority study (HPTN-083) compared to oral TDF/FTC, that is still being planned. [6]

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## Role for maraviroc as HIV PrEP likely to need dual combinations

Simon Collins, HIV i-Base

**Although the CCR5 inhibitor maraviroc (MVC) is largely underused as an antiretroviral drug it has many properties that support research as a compound for PrEP.**

These include high drug levels in vaginal and rectal tissue and a side effect profile that has potential advantages compared to TDF/FTC.

First results from the phase 2 HPTN 069/ACTG 5305 study using maraviroc for oral PrEP were presented at CROI 2016 by Trip Gulick from Weill Cornell Medical College. [1]

This was a very well designed double-blind placebo controlled study that randomised 407 HIV negative adults to one of four active PrEP groups: (i) MVC 300 mg; (ii) MVC + FTC; (iii) MVC + TDF; or (iv) a control group taking TDF/FTC. It is important that all groups included active in addition to placebo treatment, even though this involved all participants taking three pills once daily.

This study enrolled 399 gay men and 7 transgender women at risk of HIV infection, defined by having at least one high level risk during the previous 90 days. Median age was 30 years (range 18 to 70); 62% were white, 28% black and 22% were Latino. Some level of college education (67%) or higher (13%) was reported by 80% of participants.

The primary endpoint was safety and tolerability over 48 weeks, not efficacy. Secondary endpoints included lower grade side effects and acceptability and to characterise the PK and other circumstance if infections occurred.

Most people (84%; 340/406) remained in the study. By week 48, 7% had stopped early and 9% were lost to follow-up, with no differences between groups.

For the primary endpoint of tolerability, there were 67 reports of grade 3/4 side effects, with no significant differences in pairwise comparisons between study groups (all  $p > 0.05$ ). None of the low-level grade 2 events were reported by more than 8% in any group, but these were generally higher in groups using two active drugs.

STIs associated with HIV risk were diagnosed in 90 participants (22%) during follow-up and at baseline in 31 participants (8%). These results are important for confirming that this was an appropriately high risk group.

Although this study was not powered for efficacy, there were five new HIV infections all with R5 tropic virus: 4/5 in the MVC alone group and one in the MVC+TDF group. However, all had drug levels that suggested low adherence.

Only one of these cases had significant MVC drug levels but these had been highly variable during the study and might not have been detectable at the time of infection. Two people had no detectable drug levels at any study visit (including person in the MVC+TDF group), and two had MVC levels at the time of diagnosis that were well below that associated with daily dosing.

By comparison, 80% of participants overall had detectable drug concentrations at weeks 24 and 48, showing sufficiently broad use and tolerability to not rule out some level of protective benefit in each group.

However, several other presentations highlighted the complexity of PrEP research given that exact mechanism is not understood, even for TDF/FTC, and that surrogate markers for one compound might not be appropriate for others.

In an oral presentation of a substudy from the HPTN 069/ACTG 5305 study, Ian McGowan from University of Pittsburgh reported that MVC did not increase T cell activation - a potential concern that could increase the risk of HIV infection. In explant studies where biopsy tissue was exposed to HIV, there were significant levels of suppression in samples from all dual therapy groups at week 24 that was sustained out to week 48, but this was not seen in the MVC monotherapy samples.

A poster from Julie Fox from Guys and St Thomas' Hospital in London reported good PK data in genital fluid and genital/rectal tissue, in both men and women, following a single oral dose of MVC, with higher levels compared to plasma, absorption within a few hours. Concentrations stayed above the MEC target level of 25 ng/mL for 24 hours and remained above the unadjusted IC90 for 72 hours. [3]

This poster also suggested that interpretation of high drug levels in rectal sample and the urethral might partial reflect excretion of unchanged drug which would limit their use as a surrogate marker for tissue concentrations.

Taken together these limited data suggest that continued research with MVC should likely be in two-drug combinations.

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### C O M M E N T

**This study was important for several reasons, not least for the choice of study design that included active treatment for all participants.**

**Although having active control groups makes it more difficult to show efficacy, there are increasing ethical concerns for PrEP studies to now include oral TDF/FTC as the standard of care control.**

**Although MVC alone may have had fewer side effects, the concerns from the ex vivo study suggested that there might be important advantage for dual PrEP combinations.**

**As monotherapy with either TDF or FTC is less effective than TDF/FTC combined, future studies using dual therapy seem appropriate. These will not be decided until results from an ongoing cohort in 188 women using MVC are available.**

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## **Dapivirine PrEP vaginal ring shows only limited PrEP protection against HIV in African women**

**Simon Collins, HIV i-Base**

**A slow-release monthly vaginal ring containing dapivirine was reported to reduce rates of HIV infection compared to placebo in two large randomised studies. Overall protection however appears limited.**

These results were presented at a press conference two days before studies were due to be presented in detail. This considerably limited the ability to report detailed results as other dapivirine studies were embargoed until later in the week.

Although both presenters concluded that their results were positive, the ring showed little or no protection for the youngest women who were at highest risk and are in greatest need. Although the ring was designed with the hope that it would minimise the risk of low adherence, many women did not use the ring consistently during the studies.

Both studies – MTN-020/ASPIRE and IPM 027 – were double-blind placebo controlled phase 3 studies, and even in the context of good adherence, efficacy fell well below 100%. The results showed that dapivirine might only have limited potential for reducing HIV incidence on a population level and might be much less effective for someone wanting optimal protection.

One of the studies, MTN-020, was simultaneously published in the New England Journal of Medicine, and this paper is the main focus of the report below. [1]

### **MTN-020/ASPIRE**

Results from MTN-020/ASPIRE were presented by Jared Baeten from the University of Washington, Seattle. This study screened 5516 women and enrolled 2629 women aged 18-45 years at 15 sites in Malawi, South Africa, Uganda, and Zimbabwe. [1, 2]

Baseline characteristics included median age 26 years (IQR 22 to 31 years), with 95% having at least secondary school education (level not specified). Nearly all women had one main partner (99.5%) had a primary partner and 41% were married, almost half (45%) had an independent income. Women were sexually active (mean 26 times in previous 3 months, +/-24). Only 17% had more than one partner in the previous 3 months, almost 60% reported using a condom the last time they had sex, 6% reported transactional sex and only 2% reported anal sex (for which a vaginal ring would offer no protection).

Retention in the study was reported as good with women attending 91% of expected monthly visits.

Adherence in the study was more difficult to report. The main assessment by 3-monthly drug level testing reported adherence at 80%. However, the effective design of the ring ensured that target levels are reached within 8 hours of the ring being inserted. Although the ring was designed as an intervention to insert once a month, the ring seems to have often been taken out between clinic visits.

Interpreting these results is difficult. Actual adherence would be overestimated - and true efficacy therefore underestimated - if the ring was only inserted the day before a clinic visit.

Secondary adherence measures included remaining drug levels in returned rings, but this is the subject for future analyses.



For the primary endpoint of new infections, during 4280 patient years of follow-up (PYFU), with median follow-up of 1.6 years (IQR 1.1 to 2.3 years), 168 women became HIV positive: 71 in the active group vs 97 in the placebo group. This resulted in incidence rates of 3.3 vs 45 per 100 years of follow up, respectively. The relative reduction overall in HIV incidence from dapivirine compared placebo was 27% (95%CI: 1 to 46,  $p=0.046$ ), reaching statistical significance.

Two further post hoc sub-group analyses were also reported showing higher efficacy.

1. A 37% reduced risk (95%CI: 12 to 56,  $p=0.007$ ) was reported after excluding two sites with the lowest rates of retention and adherence. In these two sites, infections occurred more frequently in women in the active ( $n=17$ ) vs placebo group ( $n=12$ ).
2. A 56% reduced risk (95%CI: 31 to 71,  $p=0.0003$ ) when restricting results to women older than 21 years of age (as adherence was lower in women aged 18-21).

Safety results looked similar between the two groups with 14% of people in each group reporting a primary safety endpoint. Serious events were reported by 4% of women in each group, with 2% in each group having grade 4, 12% reported grade 3, and <1% deaths ( $n=4$  and 3). None of these events were attributed to the ring or active drug.

It is notable that NNRTI drug resistance in women who became HIV positive during the study was not higher in the active group: 8/68 (12%) in the active vs 10/96 (10%) in the placebo group,  $p=0.80$ .

### **IPM 027 study**

Results from the IPM 020 study were presented by Annalene Nel from the International Partnership for Microbicides (IPM). [3]

IPM 027 enrolled 1959 women (1762 in South Africa and 197 in Uganda) aged 18 to 45 who were randomised 2:1 to dapivirine:placebo ring. The two-year study was stopped early following a recommendation from the Data and Safety Monitoring Board (DSMB) due to higher than expected HIV incidence.

Limited data on baseline demographics include mean age at enrolment of 26 years, 59% completed secondary school and 91% were mothers. Nearly all women (>98%) had a primary partner, 96% reported having sex weekly over the previous three months.

During 2805 patient years of follow up (761 women completed two years), 133 women became HIV positive: 77 vs 56 in the active vs placebo groups. This produced incidence rates of 4.08 vs 6.10 per 100 person-years.

Overall, dapivirine reduced the risk of infection by 31% (95% CI: 0.90 to 51.5%;  $p=0.040$ ) compared to placebo. When analysed by age there was no significant benefit for women <21 years: 15% (95%CI: -60% to +59%). In women aged >25 years, the reduction was 37.5% (95% CI: 3.5 to 59.5%).

Although a trend to higher protection correlated with higher adherence (measured by lower levels of drug in the returned rings), this was one of several subsequent post hoc analyses.

Similar product-related side effects (approximately 87%, with <5% grade 3-4), were reported for active and placebo groups, including serious side effects. This included similar reports in both groups of unusual bleeding between periods, discomfort and pain.

Four additional studies on the 25 mg dapivirine ring were presented at CROI 2016.

Two posters reported PK, safety and generally high acceptability from a US 12-week, phase 2a study (MTN-024/IPM 031) in 96 post-menopausal women randomised 3:1 to active vs placebo ring. [4, 5]

Mean age was 57 years (range 46-65); 66% were white, 31% were black, and 3% were of other race. Side effects (grade 2 or higher) were reported in 8% vs 13% in the active vs 13% groups respectively ( $p=0.68$ ). One grade 3 vaginal pain was related to the device.

Adherence reported by drug levels in the returned rings was consistent with use through the month (median 21.1 mg, with 4 mg associated with sustained use during one month). Adherence by self report included 73% of women using the ring throughout the study and 91% reported never removing the ring for more than 12 hours.

Six women reported that at some point the ring fell out and 26 reported partial slippage, mainly due to bowel movements; 18 women removed the ring at some point due to discomfort, worries, or to clean the ring. High rates of acceptability were reported by the majority of women.

Two posters included cost effectiveness and population effect modelling that generally relied on higher adherence and efficacy levels than were seen in the above studies. At the highest modelled efficacy (75%) it was predicted that the ring might reduce 4-7% of infections in South Africa. [6, 7]

Dapivirine was originally identified by Tibotec in the late 1990s (with a development name TMC-120). In 2004, when an alternative NNRTI was selected for development as treatment, dapivirine was made available for public research as a microbicide for use in low income countries in a royalty free licensing agreement. Development was led by the International Partnership for Microbicide who plan to apply for regulatory approval based on these studies. [8]

C O M M E N T

**While demand for effective new prevention options are clearly needed, the most disappointing outcome from both studies is an inability to know with any confidence the likely level of protection in the context of perfect adherence - especially as comparative oral PrEP using tenofovir/FTC sets the bar high at close to 100%.**

**Although the results with dapivirine cannot rule out a population benefit (linked to high background incidence and available options), low levels of efficacy are not helpful for individual protection.**

**Both studies are now planning to ask all women to continue using the dapivirine ring in an extended open label follow-up phase.**

**Using an NNRTI as the active compound was complicated by the lack of an animal model that could prove efficacy, relying on in vitro and other animal data mainly focused on tissue penetration.**

**While 100% high efficacy was demonstrated for tenofovir/FTC in macaque studies long before human studies were planned, the lack of a SHIV model means that phase 3 studies were used to provide first proof of principal results in women.**

**The ring itself is an impressive product with rapid drug deliver to steady state in tissue and steady drugs levels for 4 to 12 weeks, although there is significant intra- and inter-patient variability.**

**It is unclear why the ring was either difficult or not acceptable to use in practice in the African studies.**

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CROI 2016: PREGNANCY AND PMTCT

## Early data from dolutegravir use during pregnancy

Polly Clayden, HIV i-Base

**Dolutegravir (DTG) exposures in pregnancy are similar to that in non-pregnant adults but lower compared with postpartum. [1] More data are needed before DTG can be widely recommended during pregnancy, according to findings shown at CROI 2016.**

IMPAACT P1026s is an ongoing, non-randomised, open-label, parallel-group, multi-centre phase 4 prospective study of antiretroviral pharmacokinetics (PK) and safety in HIV positive pregnant women, which includes an arm for DTG. [2]

In this evaluation the investigators collected samples at 20 to 28, and 30 to 38 weeks gestation, and between 3 to 12 weeks after delivery: pre-dose, and 1, 2, 4, 6, 8, 12 and 24 hours post DTG 50 mg dose. They also collected infant washout samples if the child weighed >1000 grams at birth and had no severe malformations or medical conditions.

DTG was measured using a validated LC-MS/MS with a quantification limit of 0.005 mcg/mL. Two-tailed Wilcoxon signed rank tests compared within-participant PK parameters with a two-sided p-value <0.10.

Data were available for second trimester (n=9), third trimester (n=15) and infant washout (n=10). Women were: black (66%), white (14%), Latina (10%), Asian/Pacific Islander (5%) and Native American/Alaskan (5%). They were a median age of 31.8 years (range 21.6–42.3) at delivery.

The investigators found DTG AUC to be 25–30% lower in the second and third trimester compared with paired postpartum. The differences were not significant (n=4 for second and n=7 for third trimester comparisons with postpartum).

DTG Cmax was significantly lower in the third trimester compared with postpartum. C24 was 41% lower in the second and third trimester but differences were not significant. See Table 1 for maternal DTG PK parameters.

The investigators noted that 6/9 (67%) participants in the second trimester, 12/15 (80%) in the third trimester and 8/9 (89%) postpartum had an AUC above the 10th percentile (37.5 mcg\*hr/mL) of non-pregnant adults (historical controls).

All 15 women had viral load <50 copies/mL at delivery.

**Table 1: Maternal DTG PK parameters**

Parameter, median (IQR)	2nd trimester n=9	3rd trimester n=15	Postpartum n=9	Historical control* Geometric mean (%CV)
AUC0-24 (mcg*hr/mL)	58.4 (47.6–64.5)	48.7 (40.3–57.6)	71.1 (58.0–83.1)	53.6 (27)
C0 (mcg/mL)	0.88 (0.64–1.98)	1.01 (0.75–1.42)	1.76 (0.99–2.29)	–
Cmax (mcg/mL)	4.59 (3.89–5.22)	3.92 (3.36–4.44)	5.10 (3.75–7.23)	3.67 (20)
Tmax (hr)	2 (2–4)	4 (2–4)	2 (2–4)	2–3
C24 (mcg/mL)	0.86 (0.64–1.37)	0.91 (0.74–1.21)	1.70 (0.76–2.00)	–
Cmin (mcg/mL)	0.86 (0.69–1.37)	0.86 (0.55–1.13)	1.70 (0.70–2.00)	1.11 (46)
CL/F (L/hr)	0.86 (0.78–1.05)	1.03 (0.87–1.24)	0.70 (0.60–0.86)	1
T1/2 (hr)	10.5 (8.7–12.6)	11.2 (10.3–13.00)	12.3 (10.5–15.6)	14

\* From DTG package insert

Washout PK data were available for 10 infants. The elimination half-life was approximately 35 hours. See Table 2.

**Table 2: DTG infant washout (n=10)**

Parameter	Median (IQR)
Cmax (mcg/mL)	1.96 (1.42–2.48)
Tmax (hr)	6.9 (3.3–8.6)
T1/2 (hr)	34.5 (28.6–39.9)

At the time of analysis nine infants were not infected and nine results were pending.

The investigators reported one maternal adverse event that was possibly treatment related: moderately increased ALT. They also observed two SAEs: pre-eclampsia and atypical pre-eclampsia.

They reported four infant congenital anomalies: total anomalous pulmonary venous return; polycystic right kidney and cystic fibrosis; congenital chin tremor; filum terminale and sacral dimple. Four infants had hypoglycaemia.

The investigators noted DTG AUC and trough appear to be lower in pregnancy compared with postpartum but are still similar to those seen in non-pregnant adults.

DTG infant elimination half-life was more than twice that of the mothers in the study and historical non-pregnant adult controls.

## C O M M E N T S

**The DTG arm of IMPAACT 1026s now has 30 mother-infant pairs enrolled and is closed to new enrolments. The protocol takes up to eight months to complete for each mother-infant pair and in turn more data from the study to be presented.**

**The investigators are looking carefully at the four infants with possible congenital anomalies, to assess first trimester exposure to DTG and other drugs. At the time of analysis data were not available showing how long the mothers in the study were on treatment.**

**The investigators will also look into the family history of the infant with polycystic right kidney and cystic fibrosis. The congenital chin tremor resolved and the study sites did not consider the other anomalies to be related to DTG.**

**More data about the four infants will be released as more information is provided by the sites.**

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CROI 2016: PAEDIATRIC CARE

## **Dolutegravir: 48 week results in children aged 6 to 12 years**

**Polly Clayden, HIV i-Base**

**Dolutegravir (DTG) is safe and effective in children age 6–12 years, according to results presented at CROI 2016. [1]**

IMPAACT P1093 is an ongoing phase 1/2, multicentre, open-label, pharmacokinetic (PK), dose finding and safety study of DTG plus optimised background regimen (OBR) in infants, children and adolescents. [2] The evaluation takes a staggered approach and participants are studied in de-escalated, age-defined cohorts.

In adolescents (12–18 years), paediatric weight band dosing of approximately 1 mg/kg once daily gave comparable PK exposures to those seen in adults receiving 50 mg once daily. Data for this age group were included in the adult regulatory filings and DTG is approved for children age 12 and above in over 50 countries. [3]

Twenty-four week PK, safety and efficacy data from the 6–12 years age group has recently been submitted to the FDA. [4] The IMPAACT investigators reported 48-week results at CROI 2016.

Participants were ART-experienced but integrase inhibitor (INI)-naive, with viral load >1000 copies/mL. They were either on a failing ART regimen for at least 12 weeks or off ART for four weeks. Participants were only eligible if they had at least one other fully active drug for the OBR.

In stage 1 of the study, DTG was added to the failing ART regimen and the OBR optimised after intensive PK (day 5–10). In stage 2, participants received DTG and OBR when they joined the study. The primary endpoint was virologic suppression to <400 copies/mL at 48 weeks (FDA snapshot algorithm); <50 copies/mL was a secondary endpoint.

A total of 23 children were enrolled (11 stage 1 and 12 stage 2) and 21 (93.3%) completed 48 weeks. Baseline demographics were: 70% male, 52% black, 17% white, 13% Asian, and 26% Latino. Median age was 10 years and weight was 30 kg (range 18–54). Median viral load was 5 log<sub>10</sub> copies/mL (IQR 4.5–5.5), median CD4 count 645 cells/mm<sup>3</sup> (IQR 466–732) and CD4 per cent was 24% (IQR 14.3–28.7). Participants had received ART for a median of 9.3 years (IQR 6.4–10.4) before study entry. Sites were in the United States, South Africa and Thailand.

Of 23 participants: 6 weighed >40 kg, 6 weighed 30–40 kg, 8 weighed 20–30 kg and 3 weighed 15–20 kg. They received DTG doses of: 50 mg, 35 mg, 25 mg and 20 mg respectively, with the exception of one participant in the >40 kg weight band who received 70 mg (greater than the adult 50 mg dose). The study used tablets of 10 mg, 25 mg and 50 mg (already approved adult and adolescent formulation).

Previously reported DTG geometric mean (CV%) for PK parameters were: AUC<sub>24</sub> 50.46 ug\*h/mL (63%) and C<sub>24</sub> 0.92 ug/mL (89%). [3]

At 48 weeks, 78.3% of participants had viral load <400 copies/mL and 74% <50 copies/mL. The median change in CD4 per cent from baseline was +9% (IQR 7–14%).

The investigators found DTG to be generally well tolerated with no discontinuations due to adverse events. They reported no DTG-related adverse events. IMPAACT P1093 is continuing to evaluate infants and young children 4 weeks of age and above.

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#### C O M M E N T S

**ViiV Healthcare (the originator manufacturer of DTG) filed two reduced strength tablets (10 mg and 25 mg) for the 6–12 years age group with the FDA at the end of last year.**

**The two cohorts in the youngest age groups (6 months–2 years and 4 weeks–6 months) started with a granules in suspension formulation but use of this will stop once the 5 mg dispersible tablet formulation is available on site. [5, 6] Only the dispersible tablets will be available commercially. These will be strawberry cream flavoured. The primary completion date for the whole study is May 2018. [2]**

**Every paediatric expert consultation has identified DTG as a priority for children in low- and middle-income countries. Generic versions of DTG are already on the way for adults. [7] The development of appropriate generic formulations of DTG for children should follow as swiftly as the originator manufacturer, generic manufacturers, and regulators can do so.**

**Several issues have been raised concerning DTG specifically and paediatric drug development in general and some were discussed at a Themed Discussion at CROI 2016 aptly titled: “New drugs for kids: what’s taking so long?” [8, 9]**

**The discussion included the problems with the age-staggered approach that results in delays in approval and availability of new drugs, particularly in the youngest age group where options are lacking. WHO uses a weight band dosing approach and it would make sense to investigate weight band dosing in paediatric antiretroviral development from the beginning, optimising the use of PK data and modelling. In P1093, with the dispersible tablet in the younger cohorts, the investigators are trying to capture enough data to inform weight band dosing.**

**Moving away from the age-staggered approach to weight bands it could also be possible to open multiple cohorts simultaneously, if formulations are available, which would speed up availability of new drugs for infants and children considerably.**

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CROI 2016: TREATMENT ACCESS

## **New antiretrovirals could mean savings up to US \$3 billion by 2025**

**Polly Clayden, HIV i-Base**

**The introduction of three new antiretrovirals into ART programmes in low- and middle-income countries (LMIC) – tenofovir alafenamide fumarate (TAF), low dose efavirenz (EFV400) and dolutegravir (DTG) – could represent over US \$3 billion in savings by the end of 2025.**

The Clinton Health Access Initiative (CHAI) presented these potential cost savings at CROI 2016.

CHAI used their forecast for currently available products as baseline and modelled differences in prices of new and current products. They assumed that TAF would displace tenofovir disoproxil fumarate (TDF) and AZT and EFV400 and DTG would displace EFV600 and nevirapine (NVP) in first-line; and DTG would replace TDF and AZT-based backbones in second-line.

They estimated price discounts of new products over time using: costs of raw material (either directly from manufacturers or from the India Import/Export database); API process costs (from patents or literature; and formulation costs (assumed API accounts for 70-90% of the cost formulation and packaging); volumes needed for economies of scale (chemistry inputs based on patents/scientific literature); and manufacturer profit margins (assumed approximately 25%).

CHAI's estimated per patient per year (pppy) price savings at launch and scaled up with new products are shown in Table 1. Market share of new products and cumulative savings to 2025 are shown in Table 2.

**Table 1: Estimated pppy savings with new products**

ARV	vs	At launch	At scale
TAF	TDF	\$0-2	\$20-24
EFV400	EFV600	\$10-11	\$10-14
	NVP	<\$1	\$0-2
DTG	EFV600	Parity-slight premium	\$17-21
	NVP	Parity-slight premium	\$1-2

**Table 2: Market share and cumulative savings 2025**

ARV	Market share	Saving
TAF	95% of first-line	\$1.8 billion
DTG	80-90% of first-line and second line	\$1.1 billion
EFV400	10-15% of first-line	\$0.3 billion

The authors note that they expect EFV400 to peak at approximately 25% market share in 2021 before DTG takes over.

TAF, EFV400, and DTG will enable programmes in LMICs to put more people on ART. CHAI add that these findings support advocacy for accelerated availability of these new products, and they strongly encourage the swift uptake of new antiretrovirals to realise their savings potential. CHAI stress that clear commitments for rapid adoption of the new products by national programmes would encourage more generic manufacturers to produce larger volumes at competitive prices, and help increase the number of people on ART.

#### C O M M E N T

**DTG and EFV400 based generic products will become available over the next couple of years. TAF, which represents the biggest saving of US\$ 1.8 billion by the end of 2025, needs a few more steps.**

**The potential for savings in generic-accessible LMIC is vast and, as CHAI rightly point out, will enable more people to take ART.**

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## Countries with lower HIV prevalence have lower ART coverage

**Polly Clayden, HIV i-Base**

**Low- and middle-income countries with adult HIV prevalence less than 5% had significantly lower rates of ART coverage in adults, pregnant women and children than those with higher prevalence. Lower prevalence countries also had a smaller percentage of women attending antenatal (ANC) visits and early infant diagnosis (EID) for infants.**

Andrew Hill and colleagues from Liverpool University; Chelsea and Westminster Hospital; Imperial College; University of Oxford; World Health Organisation and UNITAID presented this analysis at CROI 2016.

They used data from the UNAIDS 2014 database that includes country-level information on epidemic size, HIV prevalence, ART coverage, ANC visits and EID. They noted that higher prevalence countries (at least 5%) are prioritised in PEPFAR and Global Fund ART programmes but 50% of HIV positive people live in lower prevalence countries.

Fifty-two low- and middle-income countries with at least 50,000 HIV positive people were included in the analysis: 40 with less than 5% HIV prevalence (total 16 million HIV positive) and 12 at least 5% HIV prevalence (total 16.1 million HIV positive).

The investigators used least squares linear regression to correlate adult HIV prevalence with estimated rates of ART coverage (adults, pregnant women and children), ANC, and EID. They weighted the analysis by epidemic size and controlled for GDP/capita and region (African vs non-African countries).

They found lower prevalence countries to have significantly lower rates of treatment coverage in adults, pregnant women and children,  $p < 0.01$  for each comparison. Lower prevalence countries also had a smaller percentage of women attending ANC visits and EID for infants than higher prevalence ones,  $p < 0.01$ . See Table 1.

**Table 1: ART coverage in lower vs higher prevalence countries**

Countries	Lower prevalence (<5% HIV+ adults)	Higher prevalence (>5% HIV+ adults)
Number	40	12
HIV epidemic size	16 million	16.1 million
Adult HIV prevalence	1.6%	14.6%
Adults on ART	31.7%	48.3%
Children on ART	22.4%	42.6%
Pregnant women on ART	46.7%	89.1%
Pregnant women with $\geq$ ANC	55.3%	68.1%
Infants received EID	20.1%	72.3%
Annual HIV death rate	4.5%	2.5%
Annual HIV transmission rate	6.2%	5.4%

The annual death rate for HIV positive people was 4.5% in the lower prevalence countries compared with 2.5% in the higher prevalence countries. The respective HIV transmission rates were 6.2% and 5.4%.

The investigators acknowledged a subset of lower prevalence countries with high rates of HIV testing and ART coverage eg Thailand, Rwanda, Vietnam and Dominican Republic. But many other lower prevalence countries need to prioritise HIV testing and ART for adults, pregnant women and children eg Russia, China, Nigeria, India and Pakistan, they wrote.

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## **Nigerian herbal medicines widely used by HIV positive people can contain antiretrovirals**

**Polly Clayden, HIV i-Base**

**Herbal medicine use among HIV positive people in Nigeria is widespread, poorly recorded and often precedes ART initiation. Contamination with antiretrovirals is possible and concerning, particularly in untreated people, say the authors of a study of herbal medicine presented at CROI 2016.**

Joshua Gini and colleagues from the University of Liverpool conducted the evaluation in collaboration with Dalhatu Araf Specialist Hospital Lafia, State Specialist Hospital Gombe, Federal Medical Centre and Faith Alive Foundation Hospital and PMTCT Centre, in Nigeria.

Nigeria has an estimated HIV positive population of 3.3 million, making up almost 10% of the global HIV burden. The use of herbal (or traditional) medicine is high in the general population and it is also high among HIV positive people.

The study included an analysis of herbal medicine for possible contamination with antiretrovirals and a country-wide survey of its use in the HIV positive population.

The investigators collected herbal medicine samples from urban and rural sites in eight states across Nigeria for drug analysis, following a standard protocol. They approached street vendors requesting traditional remedies for non-specific symptoms against a background of HIV and only purchased herbals sold as powders or liquids. They recorded instructions for use, date and site.

The University of Liverpool analysed the samples for efavirenz, nevirapine, lopinavir, darunavir, ritonavir, atazanavir, tenofovir, FTC, and 3TC using validated LC-MS/MS methods.

The analysis revealed, out of 138 herbal samples, three (2%) from two cities (Jos and Ibadan) contained measurable antiretrovirals. Tenofovir (0.2 ng/mg powder) and FTC (0.0065 ng/mg powder) were detected in one sample from Jos.

Two samples from Ibandan also contained tenofovir (0.2 and 1.6 ng/mg powder) and FTC (0.123 and 0.00049 ng/mg powder), and one of these also contained 3TC (0.25ng/mg powder).

The questionnaire-based survey was conducted in 742 HIV positive patients attending one rural (Rural Hospital Idong) and three urban (Specialist Hospital Gombe, Faith Alive Foundation Clinic Jos and Dalhatu Araf Specialist Hospital Lafia) ART facilities. Mothers were interviewed for information on paediatric patients. Data were collated and analysed using SPSS.

The investigators found, of 742 patients aged 2 to 91 years, the prevalence of herbal medicine use was 41.8% (310).

Of those who took herbals: 54.9% did so before they were diagnosed with HIV; 54.1% did so to cure HIV; only 5.5% believed themselves cured and 46.1% found herbal medicines to be of no help; 54.1% obtained them from the village herbalist and 35.1% from city vendors.

The investigators observed wide use of herbal medicines across all ages and in both genders regardless of educational or employment status. In over half the patients using herbal medicines, this preceded starting ART and continued during ART use: 82.2% who used herbal medicines were also receiving ART.

The investigators wrote that the lack of regulation and standardisation of herbal medicines argues strongly for further work to confirm their findings in other settings and to understand if antiretroviral contamination has a negative impact on ART programmes through the generation of drug resistance.

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CROI 2016: CURE RESEARCH

## Cure research news from CROI 2016

Richard Jefferys, TAG

**Results from several significant cure-related clinical trials were debuted during CROI 2016 and the meeting deserves kudos for pioneering comprehensive webcasting, and all sessions are now available online.**

Ole Søgaaard from Aarhus University in Denmark presented findings from a trial that combined the HDAC inhibitor romidepsin, a latency-reversing agent, with the therapeutic vaccine Vacc-4x. [1]

The rationale for this combined “kick & kill” approach is that romidepsin can cause latently infected cells to produce HIV proteins, potentially allowing these cells to be recognised and killed by HIV-specific T cell responses that have been induced or boosted by the vaccine. A series of immunisations with Vacc-4x and GM-CSF adjuvant were given first, followed by three infusions of romidepsin. Søgaaard reported that romidepsin administration led to significant increases in HIV RNA, consistent with a latency-reversing effect, after which there was a significant decline in levels of total HIV DNA averaging 39.7%, but only a slight and non-significant drop in levels of integrated HIV DNA (these are two surrogate measures of the size of the HIV reservoir). Virus outgrowth was quantified in six of 17 participants who showed detectable levels at baseline, and all six showed a significant decline of around 38%. However, despite this evidence of some diminution in the size of the HIV reservoir, no significant delay in HIV viral rebound was observed when ART was temporarily interrupted in the final phase of the trial. Søgaaard concluded that the data support the idea of combining latency-reversing agents with therapeutic vaccines, but improvements are needed to enhance the magnitude of the effect.

Joe Eron from the University of North Carolina discussed the ever first clinical trial of an antibody targeting the PD-1 pathway in people with HIV. [2]

PD-1 is a molecule that can become persistently upregulated on T cells that have become exhausted and dysfunctional, and antibodies that block the interaction between PD-1 and the ligands it binds to (PD-L1 and PD-L2) have been shown to restore T cell function. Two antibodies against PD-1 have been FDA-approved for the treatment of cancers due to their ability to enhance cancer-specific immunity and promote clinically significant tumor shrinkage. Additionally, CD4 cells latently infected with HIV commonly express PD-1, and antibodies against PD-1 have been shown to reverse viral latency in laboratory experiments.

The trial described by Eron was conducted by the ACTG and involved an antibody owned by Bristol-Myers Squibb that



targets PD-L1. The original intent was to study single infusions of various doses in people on suppressive ART, however only the lowest dose (0.3mg per kg) was administered due to an unexpected concern about the potential for retinal toxicity that emerged from animal experiments. No evidence of similar toxicity was observed in the six individuals who received the anti-PD-L1 antibody. However, one person developed autoimmune pituitary insufficiency nine months after the infusion, a serious concern because autoimmunity is a known risk associated with targeting the PD1 pathway.

Of the six anti-PD-L1 antibody recipients, two showed distinct evidence of increased Gag-specific CD8 T cell responses (measured both by interferon gamma production and expression of CD107a, a marker of cytotoxicity) but the overall average change compared to a control group of two placebo recipients did not reach statistical significance.

There was also no significant change in HIV RNA levels measured by a single-copy assay, however one individual did show a 10-fold drop in cell-associated HIV RNA and Eron noted that this was the person who experienced the greatest increase in Gag-specific CD8 T cell responses. In the question & answer period after the presentation, Eron also mentioned that this individual had the lowest CD4 T cell count and highest level of PD-1 expression on T cells at baseline (consistent with prior reports that PD-1 expression progressively increases during disease progression). [3]

The anti-PD-L1 antibody is not going to be studied further, but the anti-PD-1 antibody pembrolizumab (which is FDA-approved as a cancer therapy) is being evaluated in people with HIV and refractory cancers in a new clinical trial. [4]

The safety concern relating to autoimmunity makes it unclear if it will ever be possible to target the PD-1 pathway in people with HIV who do not have concomitant cancers - one possibility might be to try and restrict the activity of the anti-PD1 antibody to just HIV-specific T cells, if there is any biologically feasible way of doing so.

Katherine Bar from the University of Pennsylvania described results from a trial involving three infusions of the broadly neutralizing antibody (bNAb) VRC01, given before and after an interruption of ART in order to assess if viral load rebound would be delayed. [5]

The antibody was safe and well tolerated but did not prevent viral load rebound. There was evidence of a slight delay compared to historical controls, with more VRC01 recipients maintaining viral load suppression four weeks after interrupting ART, but the difference had disappeared after eight weeks. HIV samples from some participants displayed resistance to VRC01. Bar highlighted the need to better understand the relationship between HIV neutralization measured in vitro and antibody potency in vivo, and noted that combinations of different bNAbs will likely be required to improve results. Another somewhat similar trial conducted by Tae-Wook Chun at the National Institute of Allergy and Infectious Diseases was presented at CROI as a poster, and reported broadly consistent findings. [6]

After Bar's talk, Michel Nussenzweig from Rockefeller University commented that antibodies more potent than VRC01 may perform better, citing unpublished data from a trial of the bNAb 3BNC117 that is being led by his colleague Marina Caskey. In that trial, Nussenzweig said, viral load rebound was delayed by an average of 6.5 weeks after an ART interruption, with 30% of participants maintaining suppression for over nine weeks. 3BNC117 is one of several more potent bNAbs discovered after VRC01, so this offers some hope that superior results are achievable, particularly with combinations. For cure research, the ultimate aim is to test whether these bNAbs can help promote clearance of HIV-infected cells via mechanisms such as antibody-mediated cellular cytotoxicity (ADCC).

In the pre-clinical realm, Gilead caused a splash with data from a new study of their TLR7 agonist GS9620 in macaques, with results presented by James Whitney. [7] Last year at CROI, Whitney reported that a TLR7 agonist appeared to induce virus production by latently infected cells in SIV-infected macaques on ART.

The new study tested lower doses of two TLR7 agonists, GS-986 and GS9620 (the latter compound is already in clinical development for hepatitis B); the aim of using lower doses was to minimise induction of alpha interferon and associated toxicities. Evidence of latency reversal was observed in the form of SIV RNA increases after dosing, and two of nine macaques have maintained undetectable viral loads for 3-4 months after an ART interruption (no delay in viral load rebound was seen in the study presented last year).

Follow up of these animals is ongoing. Whitney stated that GS9620 is now entering a phase Ib trial in HIV-positive people on ART, but Gilead have not registered the trial in clinicaltrials.gov so information on enrollment criteria and locations is not available.

Morgane Gossez from the University of Oxford reported on an analysis of the SPARTAC trial comparing the frequency of post-treatment control of viral load in 22 participants in Africa and 44 in the UK. [8]

Five of the African individuals have maintained viral load below 400 copies for over 3.5 years of follow-up, whereas all of those from the UK experienced viral load rebounds. Further review of records indicated that two of the five post-treatment controllers had undetectable viral loads at the time of ART initiation, suggesting they may have been elite controllers, but that was not the case for the remaining three. Additional studies are being conducted to look for factors associated with this outcome. Gossez noted that the biomarkers previously reported to be associated with delayed viral load rebound in SPARTAC did not show significance in the subset of African participants, however, in responses to a question, Gossez acknowledged that this may have been due to the small sample size. The SPARTAC trial design is reviewed in a recent blog. [9]

The potential role of gene therapy in HIV cure research was addressed at CROI in a plenary talk by Paula Cannon from the University of Southern California. [10]

Cannon reviewed the various technologies that are now available to manipulate both host and HIV genes, and cited evidence from ongoing trials of Sangamo's gene therapy that positive effects may be achievable in people. Noting that gene therapy is sometimes viewed as too impractical to be pursued, Cannon made a strong case that it should be viewed as an important element of the cure research effort.

Lastly, in a poster presentation with echoes of the first report on Timothy Brown at CROI in 2008, a group of German researchers described the case of an HIV-positive individual who received a stem cell transplant from a CCR5delta32 homozygote donor as part of a series of treatments for cancer (acute myeloid leukemia). [11]

The individual experienced two relapses but ultimately the cancer went into remission in 2013. All tests for HIV DNA have since been negative in peripheral blood, rectal tissue and bone marrow, and HIV-specific antibody responses measured by Western blot are waning. Importantly, the individual remains on ART and researchers plan to search additional tissues for evidence of HIV before considering interrupting treatment.

This is only the second report of a successful stem cell transplant from a CCR5delta32 homozygote donor in a person with HIV (the first being Timothy Brown) - although it has been tried in other cases [12], these individuals died either due to the underlying cancer or complications from the procedure. The researchers are hoping that, like Brown, this individual may be cured of HIV, but it remains to be seen whether this hope will be borne out.

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## ANTIRETROVIRALS

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### EU adopts positive opinion on dual formulation of F/TAF

Simon Collins, HIV i-Base

**On 26 February 2016, Gilead Sciences issued a press release reporting that the scientific committee of the European Medicines Agency (EMA) had adopted a positive opinion for the new dual NRTI combination of emtricitabine (FTC) plus tenofovir alafenamide (TAF).**

A positive opinion is usually sufficient for a drug to be approved by the European Commission, with the final decision expect by the third quarter of 2016.

The formulation uses 200 mg of FTC with two doses available for TAF: 25 mg and 10 mg.

Despite the Gilead press release, this is not a fixed dose combination because F/TAF needs to be taken in combination with other additional drugs.

F/TAF is manufactured by Gilead and will have the tradename Descovy.

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### New TAF-containing fixed dose combination approved in the US

Simon Collins, HIV i-Base

**On 1st March 2016, the U.S Food and Drug Administration (FDA) approved a new fixed-dose combination (FDC) for adults and adolescents (older than 12 years) that contains a new formulation of tenofovir DF.**

The FDC contains rilpivirine (25 mg), emtricitabine (200 mg) and tenofovir alafenamide (TAF) (25 mg). The indication is for initial treatment in people with viral load <100,000 copies/mL.

It is also indicated as a switch treatment for people on stable treatment with undetectable viral load (<50 copies/mL) for more than six months, who do not have a history of previous treatment failure.

Both indications are dependent on not having drug resistance associated with any of the three drugs.

As with other rilpivirine-containing combinations, this FDC also needs to be taken with a meal (>400 kcal).

It is not recommended in patients with CrCl <30 mL/min.

This FDC is manufactured by Gilead and has the brand name Odefsey. The original manufacturers of rilpivirine, Janssen, will have marketing rights in 17 countries.

Please see prescribing information for further details. [2, 3]

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#### C O M M E N T

**A decision on approval in the EU is expected by 3Q2016.**

**Last week, the European Medicines Agency (EMA) announced a positive opinion on the two-drug combination of emtricitabine plus TAF, with expected full approval within a few months. [4]**

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## TREATMENT ACCESS

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### **Community oppose dolutegravir and cabotegravir patents in India**

#### **MSF news**

**On 8 February 2016, community organisations in India reported that they have filed patent oppositions against dolutegravir and cabotegravir in the Indian courts.**

Médecins Sans Frontières/Doctors Without Borders (MSF) supports these patent oppositions, which challenge an attempt by ViiV Healthcare to obtain monopoly rights in India.

The company has so far failed to make dolutegravir available in India for people who have run out of other treatment options. Cabotegravir is still in the clinical trial phase of development.

“Many of us have now developed resistance to existing medicines and are in dire need of new drugs to stay alive,” said Anand Singh\*, living with HIV who filed the patent opposition. “Affordable generic medicines from India have been one of the cornerstones for being able to put nearly 16 million people on HIV treatment in developing countries.”

Dolutegravir has been available for use in the US and Europe for more than two years, and is now part of first-line HIV treatment in the US as it reduces virus levels faster, is very well tolerated and has a high barrier to resistance. In developing countries, it is urgently needed for some patients who have developed resistance to available first- and second-line medicines. However, the drug is not available from ViiV in India as the company has neither applied for registration in the country, nor makes the drug available under ‘compassionate use’ programmes for dying patients in India.

ViiV licensed dolutegravir to several Indian generic companies in 2014 under a voluntary license signed between ViiV and the Medicines Patent Pool, as well as at least one bilateral license outside of the Medicines Patent Pool. Yet, ViiV has effectively blocked access to the drug through license conditions that limit its supply to public sector entities and NGOs in India with prior permission from the company – and not through private sales. If ViiV now gets a patent for dolutegravir in India, open generic competition among Indian producers would be blocked, keeping the drug out of reach of patients who desperately need immediate access.

“People with HIV in India have had to deal with long delays and it has taken years for new HIV drugs and monitoring tools to be introduced in the treatment programme by the National AIDS Control Organisation (NACO),” said Loon Gangte, of the Delhi Network of Positive People (DNP+). “Without access to dolutegravir in the private sector, people living with HIV who have developed resistance to existing HIV medicines will not be able to get effective treatment they need to stay alive. The irony is that the drug will be produced in India and exported to Africa, but won’t be available to Indian patients who need it.”

The second drug, cabotegravir, with a similar structure as dolutegravir, is still under development by ViiV. Clinical trials are on-going to evaluate this compound, which is being developed as an oral tablet but also as a long-acting injectable formulation, which could make new treatment options available for people living with HIV.

“Patents for these drugs would mean complete monopoly status for a company which has already restricted the availability of an important HIV drug in India,” said Leena Menghaney, Head of MSF’s Access Campaign in South Asia. “The only way people living with HIV in India and across the developing world will be able to access these new life saving HIV medicines is if unrestricted competition among generic producers can take place.”

Source:

MSF news. Pharma company ViiV’s attempt to secure patents for key HIV drugs dolutegravir and cabotegravir opposed in India: ‘Patent opposition’ seeks to ensure availability of affordable generics. (08 February, 2016)

<https://msfaccess.org/about-us/media-room/press-releases/pharma-company-viivs-attempt-secure-patents-key-hiv-drugs-dolute>

### **MSF call for cap for MDR-TB drug costs: only 180 people use delamanid over two years**

#### **MSF press release**

**On 24 February 2016, Médecins Sans Frontières (MSF) reported in a press release that more than two years after the approval of the new TB drug delamanid, only 180 people globally have used it, due to the high cost. [1]**

Delamanid is one of only two new TB drug to be approved in the last 50 years, and is effective against multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB.

Delamanid needs to be taken with other drugs to treat drug-resistant TB. These regimens, without delamanid, cost between \$1,000 – \$4,500 per course at the lowest prices available to developing countries. Otsuka, the manufacturer of delamanid, said that it would charge some developing countries US \$1,700 per treatment course. [2]

To date, Otsuka has registered delamanid in only four countries (Germany, Japan, South Korea, and the United Kingdom), none of which has a high burden of DR-TB.

MSF demand that the company register delamanid in high DR-TB burden countries and in countries where clinical trials for the drug took place.

To help with widespread scale up of DR-TB treatment, MSF is advocating for a target price of \$500 per treatment course for drug-resistant TB.

Dr. Grania Brigden, TB Advisor for MSF's Access Campaign said: "delamanid is neither affordable nor available in most countries today. The price [...] needs to come down to an affordable level [...] If people can't access delamanid, this promising new drug will be effectively worthless."

#### References

1. MSF press release. Developing countries hit with high price for important new tuberculosis drug: More than two years after drug approved, only 180 people globally have received it  
<http://www.msfaaccess.org/about-us/media-room/press-releases/developing-countries-hit-high-price-important-new-tuberculosis-dr>
2. DR-TB drug regimen prices are from the forthcoming MSF publication, DR-TB Drugs Under the Microscope, 4th Edition, March 2016.

## Global Fund provides Uganda with a year of drugs to meet shortages

Ann Ithibu, Global Fund Observer

**In January, in response to a shortage of antiretrovirals in Uganda, The Global Fund Secretariat arranged to procure a supply of the drugs.**

In addition, as a precautionary measure, the Secretariat is providing Uganda with a full year's supply of drugs, the first batch of which is expected to arrive in March.

This comes as a relief to the 241,000 Ugandans who are receiving ARVs purchased with money from The Global Fund.

With donor support, Uganda has scaled up antiretroviral treatment: The number of antiretroviral treatment facilities has risen from 475 in 2011 to 1,603 in June 2014. ART coverage increased from 43% in 2013 to 48% in June 2014.

These successes were under threat by the shortage that hit Uganda in the last few months of 2015. According to the Ministry of Health's pharmacy division stock status report of 1 October 2015, some of the key adult first- and second-line ARVs and some paediatric ARVs were out of stock out at the National Medical Stores. The NMS distributes essential medicines and medical supplies to all public health facilities in Uganda.

The report revealed that some ARVs were also out of stock at the facility level. However, the number of HIV-infected people affected by the shortage is not clear.

The shortage is believed to be caused by the depreciation of the Ugandan shilling and an increase in the number of HIV-infected individuals being placed on ART. The Ugandan shilling depreciated by approximately 27% against the dollar in the 2014-2015 fiscal year. As a result, the principal recipient, the Ministry of Finance, Planning and Economic Development (MoFPED), was unable to purchase all of the ARVs it had budgeted for.

Uganda has been scaling up ART services through its test and treat strategy. Under this strategy, treatment is initiated immediately upon diagnosis, regardless of the CD4 count, for pregnant women, key populations, HIV/TB co-infected persons, infected persons with an uninfected partner, and children aged less than 15 years. According to the Fund, Uganda has been adding about 20,500 people to its ARV rolls every year since 2014.

In October 2015, the PR informed the Secretariat about the shortage and requested that planned drug deliveries be speeded up. The decision to send a year's supply was reached after the Global Fund conducted a risk-benefit analysis. The Global Fund will likely end up using more money than was budgeted in the grant for ARVs. This, in turn, could result in the grant running out of funds before it is scheduled to end in 2017. However, the Fund believes that this is a risk worth taking.

#### Source

Global fund Observer (GFO). Fund addresses shortages of ARVs in Uganda: front-loading a year supply. GFO 281 (24 February 2016)  
<http://www.aidspace.org/ru/node/3624>

## Transgender people left behind in the fight against HIV: Only 17 out of 130 countries have transgender representatives

Stéphanie Braquehais, Global Fund Observer

**Transgender people are the most affected by HIV but remain largely excluded from policy, program, and funding decisions at national, regional, and global levels, according to a report released in February. [1]**

The report, entitled *Most impacted, least served*, was produced by IRGT (International Reference Group on Transgender women and HIV/AIDS) a global network of transgender women with the support of MSMGF (Global Forum on MSM and HIV).

The author of the report reviewed and analyzed studies assessing HIV infection burdens in transgender people published between 2000 and 2011 and interviewed a dozen key informants, activists and civil society organization representatives, and Global Fund officials and donors.

The report said that transgender people are at elevated risk of facing stigma, discrimination, and repressive laws and policies in many countries, which reduces their access to care and treatment.

According to the respondents, some initiatives have been successful in engaging transgender people in Global Fund processes, such as the Pehchan initiative in India, the Asia Pacific Transgender Network, REDLACTRANS in Latin American and Caribbean, and the IRGT.

But, globally, little data is available on the transgender population. The report aims to close the gap.

The report showed that according to studies, the HIV prevalence among transgender women is 19.1%, which is 49 times higher than the general population. It should be noted, however, that no data was collected in countries with generalized epidemics, including all of sub-Saharan Africa.

According to the report, only 39% of the countries reported to UNAIDS that their national AIDS strategies addressed transgender people.

Since 2009, The Global Fund has adopted several strategies and policies to increase the engagement of KAPs (key affected populations, which include transgender people) in funding and policy processes.

However, their participation remains low. In 2015, of the 140 countries receiving Global Fund support, only 21 individuals on 17 country coordinating mechanisms (CCMs) self-identified as transgender. The report identified several reasons for this, including the following:

- Civil society organisations avoid speaking about problems for fear of undermining their relationships with principal recipients and CCM members;
- The selection of representatives is rarely transparent; and
- KAP representatives wear too many hats (LGBTI, sex workers, drug users, etc.).

The report said that in middle income countries transitioning from The Global Fund, transgender people are the hardest hit, particularly in countries with repressive laws.

Some progress has been observed in Latin America and Asia. However, the report said that these achievements are fragile, and at risk of being reversed. The recommendations in the report include (1) support trans-specific data collection; (2) build the capacity of transgender activists; and (3) reinforce the involvement of transgender activists in The Global Fund decision-making processes.

### Source

Global fund Observer (GFO). Report shows that transgender people are left behind in the fight against HIV: Out of more than 130 CCMs, only 17 have transgender. GFO 281 (24 February 2016).  
<http://www.aidspace.org/ru/node/3630>

### Reference

IRGT (International Reference Group on Transgender women and HIV/AIDS). *Most impacted, least served*. (04 February 2016).  
<http://msmgf.org/14394>

## Mbeki shows no remorse for role in AIDS deaths

### TAC press statement

#### In the following press statement, TAC responds to open letter published by AIDS denialist and former President Mbeki. [1]

On March 7, 2016 former president of South Africa Thabo Mbeki published a letter titled "A brief commentary on the question of HIV and AIDS". The letter comes seven and a half years after Mbeki was forced to step down as President of South Africa and forms part of a series of letters attempting to reframe the Mbeki Presidency. [2]

The Treatment Action Campaign (TAC) has a long history of struggling against the state-sponsored AIDS denialism of Thabo Mbeki and his Minister of Health Manto Tshabalala-Msimang. In 2002 we won a landmark case in the Constitutional Court compelling the state to make antiretroviral treatment available to HIV-positive pregnant women. Following this ruling we monitored the provision of treatment to pregnant women and advocated for a wider rollout of treatment to HIV-positive people. Even with a judgement from the highest court in the land and continued public pressure, the HIV treatment programme only gained significant momentum once Mbeki and Msimang were removed from office in 2008.

The impact of Mbeki's AIDS denialism was catastrophic. Two independent studies have estimated that delays in making antiretroviral treatment available in the public sector in South Africa resulted in more than 300,000 avoidable deaths. It also resulted in an estimated 35,000 babies being born with HIV who would not otherwise have been HIV positive.

Under Mbeki's watch life-expectancy in South Africa dropped to 54 in 2005. Life-expectancy has recovered dramatically in the post-Mbeki era to 63 in 2015. This increase is widely attributed to the ambitious rollout of antiretroviral therapy in the public healthcare system under the leadership of Health Minister Aaron Motsoaledi.

Many of our family members, friends and comrades died while Mbeki's government dragged its feet and indulged pseudo-scientific nonsense. Yet, neither in his letter, nor in any other forum that we are aware of, has Mbeki apologised or showed any remorse or acknowledgement of his role in the over 300,000 avoidable AIDS deaths in South Africa.

Instead, he has chosen to repeat many of the flawed arguments he used in the early 2000s. We provide brief notes below in response to some of his arguments, but we will not engage with those arguments in more detail, nor will we engage with any of the other red herrings in his letter.

The important point, and the point Mbeki still refuses to face, is that he intentionally delayed the introduction of life-saving treatment to the people he was trusted to serve. His actions led to at least 300,000 avoidable deaths. He has refused to take responsibility or to apologise to any of those who suffered directly or indirectly because of his actions. For this history will judge him harshly. He deserves it.

#### References

1. TAC press statement. Mbeki shows no remorse for role in AIDS deaths (08 March 2016). <http://www.tac.org.za/news/mbeki-shows-no-remorse-role-aids-deaths>
2. Mbeki T. A Brief Commentary on the Question of HIV and AIDS. (7 March 2016). <http://www.thabombekifoundation.org.za/Pages/a-brief-commentary-on-the-question-of-HIV-and-AIDS.aspx>

#### Notes:

1. In his letter Mbeki quotes Stats SA figures from 2006 ranking HIV as the ninth highest cause of mortality in South Africa. As done previously, Mbeki fails to place the Stats SA data in proper context. The data he quotes is based on the cause of death written on death certificates. There are a number of reasons why this underestimates the role of HIV. Firstly, for stigma-related reasons HIV was often not written on death certificates. Secondly, in many cases where the cause was indicated as TB or pneumonia, HIV would in fact have been the underlying cause. Thirdly, many people would have died of AIDS-related diseases without ever having known their HIV status – especially so given the much lower testing rates in Mbeki's time. Mbeki's misuse of Stats SA data is nothing new. TAC e.g. published a briefing note on it in 2008. Maybe more disturbingly, a 2001 Medical Research Council report on the matter seems to have been ignored by the former President.
2. The latest estimates from the Medical Research Council's Rapid Mortality Surveillance Report show that the average life expectancy in South Africa has reached nearly 63 years, an increase of nearly 9 years since the low in 2005. We also recommend this 2013 article by Nathan Geffen published in the journal HTB South: South Africans are living longer: antiretroviral treatment vindicated.
3. In his letter Mbeki writes "[I must also mention that I never said "HIV does not cause AIDS". This false accusation was made by people who benefitted from trumpeting the slogan 'HIV causes AIDS' as though this was a religious edict. What I said is that 'a virus cannot cause a syndrome'. As you know, AIDS is an acronym for 'Acquired Immune Deficiency Syndrome' – therefore AIDS is a syndrome, i.e. a collection of well-known diseases, with well-known causes. They are not, together, caused and cannot be caused by one virus! I said that HIV might be a contributory cause of immune deficiency – the ID in AIDS!]” Mbeki is simply wrong. A virus can cause a syndrome and it has long ago been proven that HIV causes AIDS. His word games in this regard are a cowardly form of confiscation.
4. We will not engage with Mbeki's quotations from the document "Castro Hlongwane, Caravans, Cats, Geese, Foot & Mouth and Statistics", nor with his quotations from an AIDS denialist film. We see no point in responding to patently absurd conspiracy theories. For those interested in revisiting stale old AIDS denialist arguments and our responses to them we recommend the website AIDS Truth.

## SIDE EFFECTS AND COMPLICATIONS

### **Alcohol risks are higher in HIV positive people and linked to increased mortality**

**Gareth Hardy, HIV i-Base**

**Alcohol may affect HIV positive people differently and be an independent factor related to all cause mortality, according to a paper from one of the largest US cohort studies. [1]**

The paper, published in January 2016 in *Drug and Alcohol Dependence*, looked the relationship between alcohol use and physiological harm or mortality in the most comprehensive HIV study to date.

Amy Justice from the Yale School of Medicine worked with colleagues looking at medical records from the Veterans Aging Cohort Study (VACS), a large cohort of HIV positive and negative patients receiving care at the Veterans Health Administration (VHA) from 1997 to 2014. The study used medical records of mortality as well as two index-based assessments of alcohol consumption and clinical events.

The VACS Risk Index predicts hospitalisation, frailty and mortality among HIV positive and negative patients and includes measures of HIV-specific and general organ injury. [2] The index is a composite of weighted point values assigned to age, CD4 cell count, HIV RNA, haemoglobin, kidney function, HCV infection, and liver cirrhosis. A higher index for an individual indicates worse clinical markers.

The researchers also used the Alcohol Use Disorders Identification Test - Consumption (AUDIT-C), which is a tool to screen for alcohol use in large clinical populations.

AUDIT-C consists of 3 questions:

- How often do you have a drink containing alcohol?
- How many standard drinks containing alcohol do you have on a typical day?
- How often do you have six or more drinks on one occasion?

Answers to these questions were scored 0-4 based on severity and summed for a total score ranging from 0-12. Heavy episodic drinking (HED) was assessed using a cut-off based on any positive response to AUDIT-C item 3, and its frequency was considered separately.

The primary aim of the study was to determine whether alcohol use was associated with all-cause mortality and physiologic injury as measured by the VACS Index from the date of the first AUDIT-C to death or July 31, 2014. The second aim was to determine whether physiologic injury was associated with different AUDIT-C scores according to HIV status. Women were excluded from the analysis because they made up only 3% of the cohort and have a markedly different sensitivity to alcohol.

The analysis included 18,145 HIV positive patients and 42,228 HIV negative individuals for whom the mean age was 52.5 years and 54.0 years respectively. HCV infection was more common in HIV positive (31%) than HIV negative individuals (16%,  $p<.001$ ). Of the HIV positive people, 76% were on ART with undetectable viral load.

The median follow-up was 4.8 years (IQR: 3.6 to 5.3) with a mortality rate of 2.7 per 100 person-years among HIV positive and 1.8 among HIV negative individuals ( $p<.001$ ). Mortality rates increased together with AUDIT-C scores for both HIV positive and negative individuals and this difference became wider with higher AUDIT-C scores (interaction term from Cox PH model:  $p=0.02$ ). A similar pattern was found between mortality and alcohol exposure when measured as the estimated total number of drinks per month or HED.

In a combined multivariate model of hazard ratios (HR), HIV was significantly associated with mortality (HR 1.35; 95%CI: 1.26-1.45), with a significant interaction for HIV and AUDIT-C ( $p=0.02$ ). Age, smoking, and HCV infection were also significant predictors of mortality in this model.

Of note, the number of drinks per month and HED were important predictors of mortality, with a greater effect in HIV positive people. Mortality HRs were significant for HIV positive people who consumed an estimated 30 or more drinks per month compared to HIV negative people where this level was more than 70 drinks per month. Furthermore, in HIV negative individuals there was a slight decline in mortality risk for those who consumed 3-7 drinks per month compared to 1-2 drinks per month, suggesting a protective effect from light alcohol consumption. This effect was not seen in HIV positive people. In combined models both drinks per month and HED, over the previous 12 months, were independently associated with mortality, with a significant interaction term for HIV and drinks per month ( $p<.001$ ).

Physiologic injury, as measured by the VACS Index, increased together with AUDIT-C scores for HIV positive people, where AUDIT-C scores of 5 to 7 and 8 to 12 were significantly associated with injury compared to those with AUDIT-C scores of 1 to 3 (beta 0.47; 95%CI: 0.22 to 0.73; and beta 1.05; 95%CI 0.77 to 1.34, respectively). In contrast, only a



score of 8 to 12 was associated with injury in HIV negative people (beta 0.29; 95% CI 0.16, 0.42). Similar relationships were observed between VACS Index and the estimated total drinks per month and HED for HIV positive people, with a protective effect seen for those consuming between 3 to 29 drinks per month in HIV negative individuals, which was not seen in HIV positive people.

These results show that mortality and physiologic injury are associated with moderate to low levels of alcohol consumption in HIV positive patients. Harm caused by alcohol occurred at lower levels of consumption in HIV positive compared with HIV negative people. The authors suggest that HIV positive patients consuming more than 30 alcoholic drinks per month (or one per day) are at increased risk of all-cause mortality and physiologic frailty. National recommended limits for alcohol consumption in the US are 14 drinks per week (two per day).

The association between harm and lower levels of alcohol use in HIV positive patients may be explained by two factors. Firstly, previous studies have reported that HIV positive people have higher blood alcohol levels given a unit exposure. [3] A second factor is that even modest alcohol use has been associated with poor adherence to antiretroviral therapy. [4]

#### References

1. Justice AC et al. Risk of mortality and physiologic injury evident with lower alcohol exposure among HIV infected compared with uninfected men. *Drug and Alcohol Dependence*. Jan 2016. (16) 00045-4.  
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2. Akgun KM et al. Risk factors for hospitalization and medical intensive care unit (MICU) admission among HIV-infected Veterans. *J. Acquir. Immune. Defic. Syndr.* 2013. (62) 52-59  
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<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3860503/pdf/arh-33-3-280.pdf> (PDF)

## TRANSMISSION & PREVENTION

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### Canada approves TDF/FTC as PrEP

#### CATIE news

**On 23 February 2016, Health Canada approved TDF/FTC for use as pre-exposure prophylaxis (PrEP).**

Even with approval, access is unclear and might vary depending on health insurance coverage.

The coformulated TDF/FTC (Truvada) costs about \$1,000 per month in Canada. According to the Canadian NGO CATIE: "To facilitate access, private insurance companies need to move swiftly to add Truvada (when used as PrEP) to their list of reimbursed medicines. However, not everyone at high risk for HIV has private insurance. Canada's provinces and territories now need to consider adding PrEP to their lists of subsidised medicines (these lists are called formularies). Unless they provide subsidies, it is unlikely that Truvada will reach its full potential to significantly stem the spread of HIV."

Similar to the UK, many Canadians are buying generic PrEP online.

#### Source

CATIE news. Truvada approved for HIV prevention in Canada. (29 February 2016).

<http://www.catie.ca/en/catieneews/2016-02-29/truvada-approved-hiv-prevention-canada>

### NHS England pulls proposed timeline for PrEP: perpetuates HIV and sexual health crisis in gay men and trans youth

#### Simon Collins, HIV i-Base

**On 21 March 2016, NHS England blocked access to the most effective new option for protecting people at highest risk from catching HIV. [1]**

This decision is despite evidence that in high risk populations, as enrolled in the UK PROUD study, PrEP is one of the most effective treatments: needing to treat only 13 people to prevent an infection. [2]

Community activists who were concerned about the continued delays - data from PROUD were released in October 2014 - had launched a campaign to for the planned public consultation to continue as planned. This would have enabled a decision on access to be made in June. [3]

Although the commissioning report looking at the evidence supporting PrEP has been written and circulated for confidential comments, NHS England has refused to take the essential next step to ask for public comments.

This is another example of the NHS using bureaucracy to delay access to effective treatment, similar to the way that for access to sofosbuvir to treat hepatitis C was drawn out.

The rationale for this is inexcusable. With more than 500 people diagnosed in the UK every month, these are infections that could be prevented. Instead, more than 6000 people each year will become dependent on lifelong treatment due to the lack of political will that prioritising the sexual health of people who are often already marginalised.

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#### C O M M E N T

**It is also notable that HIV rates have been constant for at least the last ten years, despite the vast majority of HIV positive people being uninfected because they are on effective treatment. The lack of any reduction in infection rates highlights the limitations and failure of prevention programmes based only on using condoms.**

**Over the last two years an increasing number of community activists – including HIV i-Base – have helped publicise the effectiveness of PrEP. This has led to increasing use of generic PrEP bought online for personal use. While this is legal in the UK and affordable for some, it is not an option for many of those who are most vulnerable.**

**The lack of positive information to support young people during school years irrespective of sexuality already disproportionately affects young people who are gay or transgender and who are at highest risk of becoming HIV positive.**

**At a time when there is a global move to expand access to PrEP, including in WHO guidelines, it is extremely regressive for the UK to block further access.**

**This is an especially shoddy way to treat UK participants in research. These participants proved the effectiveness of an intervention that helped ensure they remained HIV negative and that is now blocked for wider access.**

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[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(15\)00056-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00056-2/fulltext)
3. NAT Campaign. Write to the CEO of NHS England about PrEP. <http://act.lifewithhiv.org.uk/lobby/whereisprep>

## **UK community campaign calls for NHS England to be accountable for PrEP timeline**

**Simon Collins, HIV i-Base**

**The increasing frustration over lack of NHS access to PrEP, has led to a community campaign calling for the NHS to stick to its already delayed timeline for access. [1]**

These concerns are especially important given that the UK PROUD study reported such dramatically protective results almost 18 months ago in October 2014. [2]

The campaign calls for NHS England to open an immediate public consultation, in order for the decision over PrEP to be taken at a meeting in June 2016. There is urgent concern about how further delays might impact on whether PrEP is made available in England.

The campaign is calling for people to email a letter via the campaign website to Simon Stevens, Chief Executive of NHS England to ask him to make the consultation available immediately.

#### References

1. NAT Campaign. Write to the CEO of NHS England about PrEP. <http://act.lifewithhiv.org.uk/lobby/whereisprep>
2. UK PROUD study to provide PrEP to all participants earlier than expected: planned follow-up to continue to two years. (14 October 2014). HTB December 2014. <http://i-base.info/htb/27593>

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## OTHER NEWS

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### **HIV positive transplant donors approved in the US**

**Simon Collins, HIV i-Base**

**After many years of campaigning, the US is set to enable HIV positive people to be able to donate organ for transplant operations.**

This was previously illegal, even between when this was a life-saving operation who was also HIV positive, and both partners gave full consent.

In a press release on 8 February 2016, Johns Hopkins University in Baltimore announced that it will be the first - and apparently only - hospital to launch this programme. It is based on a programme that was first established in South Africa.

In the US this required legislation from the 2013 HOPE Act. It is hoped that it might include 500 to 600 HIV positive donors each year for up to 1000 HIV positive recipients.

Approximately 120,000 people in the US are on a transplant waiting list, with only 1 in 4 likely to receive an organ.

Source

Johns Hopkins press release. Johns Hopkins is first and only center in the United States approved for HIV-positive to HIV-positive organ transplants. (08 February 2016).

[http://www.hopkinsmedicine.org/news/media/releases/johns\\_hopkins\\_is\\_first\\_and\\_only\\_center\\_in\\_the\\_united\\_states\\_approved\\_for\\_hiv\\_positive\\_to\\_hiv\\_positive\\_organ\\_transplants](http://www.hopkinsmedicine.org/news/media/releases/johns_hopkins_is_first_and_only_center_in_the_united_states_approved_for_hiv_positive_to_hiv_positive_organ_transplants)

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## FUTURE MEETINGS

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### **Conference listing 2016**

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.

#### **22nd Annual Conference of the British HIV Association (BHIVA)**

19–22 April 2016

<http://www.bhiva.org>

#### **10th Annual Conference of the Children's HIV Association**

27 May 2016, Bristol

<http://www.bhiva.org>

#### **17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy**

8-10 June 2016, Washington DC

<http://www.virology-education.com>

#### **18th Annual Conference of the National HIV Nurses Association**

29 June–1 July 2016, Manchester

<http://www.nhivna.org>

#### **3rd International HIV/Viral Hepatitis Co-Infection Meeting**

17 July 2016, Durban

<http://www.iasociety.org/co-infections/hepatitis>

**21st International AIDS Conference (IAS 2016)**

17-22 July 2016, Durban

<http://www.aids2016.org>

**18th International Workshop on Comorbidities**

12 – 13 September, New York

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

**20th Annual UK Resistance and Antiviral Therapy Meeting**

15 September 2016, London

<http://www.mediscript.ltd.uk>

**7th International Workshop on HIV & Aging**

26 - 27 September 2016, Washington DC, USA

<http://www.virology-education.com>

**BHIVA Autumn Conference 2016**

6–7 October, London

<http://www.bhiva.org>

**HIV Research for Prevention Conference (HIVR4P) 2016**

17-20 October 2016, Chicago

<http://www.hivr4p.org>

**Congress on HIV Therapy (Glasgow 2016)**

23-26 October 2016

<http://hivglasgow.org>

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## PUBLICATIONS & SERVICES FROM i-BASE

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

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

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

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



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- HIV testing and risks of sexual transmission (February 2013)
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## **htb(e)**

### **HIV TREATMENT BULLETIN (e)**

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:

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