

## november-december 2016

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Programme

<http://www.hivglasgow.org/scientific-programme>

Webcasts

<http://www.hivglasgow.org/webcasts>

Abstract book

Published as a supplement to the Journal of the IAS. International Congress of Drug Therapy in HIV Infection 23-26 October 2016, Glasgow, UK. JIAS (19) supplement 7 (2016). Online in several formats including PDF and html.

<http://jiasociety.org/index.php/jias/issue/view/1485>

The following reports from this conference are included in this issue of HTB.

- 1000-fold mark-up for drug prices blocks access to HIV, HCV and cancer drugs in high-income countries
- Once-daily raltegravir formulation matches twice-daily results in age, gender, race and baseline viral load/CD4 subgroup analyses
- Attachment inhibitor BMS-068/GSK-934: 96-week results in treatment-experienced patients
- Once-weekly albuviridine infusion: early results of T-20-like compound in Chinese study
- Simplifying HIV treatment: dual therapy works but monotherapy with either boosted-PIs or dolutegravir does not
- Dolutegravir-based ART in combination with rifampicin-based TB treatment is safe in a small cohort of co-infected patients
- Further reports of CNS-related side effects with dolutegravir
- Generic PrEP bought online for UK use is validated by drug testing service
- Immunology and HIV persistence – implications for a cure
- Selected webcasts from Glasgow 2016

## **1000-fold mark-up for drug prices in high-income countries blocks access to HIV, HCV and cancer drugs**

**Simon Collins, HIV i-Base**

**An opening lecture at the 2016 Glasgow HIV Congress challenged the current model of drug pricing by showing mark-ups that are commonly more than 1000 times higher than production costs and that make many medicines now largely unaffordable in high income countries.**

The analysis was presented by Andrew Hill, an independent advisor to international health organisations but who also has worked for many of the largest pharmaceutical companies. [1]

Three examples of the current urgency for better pricing are PrEP, new drugs for viral hepatitis (both HBV and HCV) and the broad range of chemotherapies for cancer. Even discounting very low access to cancer treatment in low- and middle-income countries (LMIC), globally, more than five million people die annually from preventable infections due to hepatitis B and C, HIV, TB and malaria. [2]

This analysis argues for a more affordable model based on the bulk costs of the active pharmaceutical ingredients (per kilogram) and include 10-50% profits after allowing for manufacturing and other production costs. [3]

The presentation also showed the disparity of prices charged for the same drugs across similar high-income countries, with the US generally paying highest. For example, a 12-week course of daily sofosbuvir has target production costs of about €55 but currently costs €50,000 in the US and only €3,485 in Australia (based on volume discount to treat hepatitis C in Australia on a population level).

Differences between target costs for a range of HIV, hepatitis and cancer medicines compared to current prices are shown in Table 1 below. For example, the annual US vs target generic prices for commonly used ARVs are approximately \$18,000 vs \$161 for abacavir/3TC, \$21,000 vs \$67 for tenofovir-DL/FTC and \$34,400 vs \$110 for Atripla. The recently off-patent cancer drug imatinib (Glivec/Gleevec), used to treat chronic myeloid leukaemia, has a US price of \$106,000 but a potential generic target price of just \$180.

**Table 1: Examples of current and target prices (US\$) of commonly used drugs**

Drug	Current US price	Current lowest generic *	Minimum target cost	Comment / patent expiry
Hepatitis B (annual cost)				
entecavir (USD)	15,111	427.00	36.00	Expired
Hepatitis C direct acting antivirals (DAAs) (3 month course)				
sofosbuvir	49,680	324	62	
daclatasvir	50,653	153	14	
sofosbuvir + ledipasvir	56,700	507	96	
sofosbuvir + velpatasvir	74,760	–	181-216	
HIV antiretrovirals (annual cost)				
abacavir/3TC	18,600	161	161	Dec 2016
tenofovir/FTC	21,120	67	67	Jul 2017
efavirenz/TDF/FTC	34,428	110	110	Dec 2017
efavirenz	12,120	36	38	Expired
nevirapine	7,776	28	28	Expired
rilpivirine	12,900	–	40	2021
atazanavir	19,872	219	219	2018
darunavir	19,584	–	658	2018
Cancer drugs (treatment cost)				
imatinib	106,322	790	180	Chronic Myeloid Leukaemia
erlotinib	79,891	1932	240	Non-Small Cell Lung Cancer
sorafenib	139,138	1332	1450	Renal Cell Carcinoma
lapatinib	75,161	18,603	4020	Breast cancer
cabazitaxel	120,613	30,810	660	Metastatic prostate cancer
dasatinib	10,408	1183	15	Chronic Myeloid Leukaemia

\* From India, Thailand, Brazil or South Africa.

In some high-income countries, including the UK, it is legal to import generic medicine for personal use (defined as a three-month course). This has become increasingly used to enable the only access to PrEP and HCV medications, often supported by community websites and buyer's clubs.

Three other posters at Glasgow 2016 present new data on effectiveness of generic medicines. A pharmacokinetic analysis of generic PrEP used by gay men at the Dean Street clinic supported the used of several FDA-approved generic formulations that are easily available online. [4]

Two other posters reported high HCV cure rates reported by users of two international online buyer's clubs. [5, 6]

In addition to making large profits from this inflated approach to pricing medicines in high-income countries, many of the largest manufacturers avoid billions of dollars in US tax by registering profits in offshore accounts. In 2015, Pfizer, Merck, J&J, Amgen, Abbott and BMS avoided USD \$ 20, 16, 14, 9, 7 and 7 billion dollars respectively. [7]

#### C O M M E N T

**This study was based on a growing body of work that has been presented by Dr Hill and colleagues at other major conferences. At AIDS 2016 in Durban he connected pricing to other global health targets by showing that \$90, \$90, \$90 are achievable goals to treat HIV and HBV for a year and to cure HCV in LMICs. [8]**

**High-income countries should not be planning health care based on LMIC prices while medicines are in patent - wealthier economies can and should pay more for medicines. But the excessive greed shown by the current prices is destabilising drug pricing globally and more importantly blocking access to treatment that people need now. As such, the personal use of generic versions of in-patent drug is easy to support.**

**Two years ago at Glasgow, Dr Hill reported how the availability of new generic ARVs could save the UK more than £1.25 billion over five years. [9]**

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**Once-daily raltegravir formulation matches twice-daily results in age, gender, race and baseline viral load/CD4 subgroup analyses**

**Simon Collins, HIV i-Base**

**The once-daily formulation of raltegravir showed similar efficacy and safety results compared to the original twice daily formulation across all demographic and baseline subgroups, further supporting non-inferiority compared to the current twice-daily version. [1]**

The new formulation is dosed at 1200 mg once-daily (requiring 2 x 600 mg tablets) compared to the original formulation (dosed at 1 x 400 mg tablet twice-daily).

The new analysis was presented by Pedro Cahn from Fundacion Huesped, Buenos Aires, using pre-specified subgroups in the phase 3 ONCEMRK study.

The findings add to the primary efficacy and safety results that were presented at the IAS conference in Durban in July 2016 (that were also reported in HTB). In summary, 89% of participants suppressed viral load to <50 copies/mL at week 48 for both formulations with similar CD4 increases and safety results. [2, 3]

As with the primary analysis, the sub-group analysis found no differences between formulations by baseline viral load (above/below 100,000 and 500,000 copies/mL), CD4 count (above/below 200 cells/mm<sup>3</sup>), age (above/below median 34 years), gender, race/ethnicity or coinfection with HBV or HCV. No differences were seen by geographical location or for clade B vs C.

Side effects were also similar between the two formulations for all sub-groups.

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## Attachment inhibitor GSK-934/BMS-068: 96-week subgroup analysis in treatment-experienced patients

Simon Collins, HIV i-Base

### Safety results for the attachment inhibitor GSK-934 (previously called BMS-663068/fostemsavir) combining two late breaker abstracts were reported in an oral presentation by Cyril Llamas from Viiv Healthcare. [1, 2]

This was a subgroup analysis from a phase 2b randomised dose-ranging study in 251 treatment-experienced patients that used atazanavir/r in the control arm. However, rather than using 2 NRTIs as background drugs, all participants used raltegravir (400 mg twice-daily) plus tenofovir-DF (once-daily) as the background drugs. After 48 weeks, all participants in the GSK-934 arms were switched to the selected dose of 1200 mg once-daily.

Approximate baseline characteristics included median age 39 years (range 20 to 68), 60% of the participants were male, and ethnicity included 40% white, 30% black, 30% other. Mean pre-treatment viral load was 4.85 log copies/mL (SD +/- 0.9 log) and 44% had viral loads >100,000 copies/mL. Mean CD4 count was 230 cells/mm<sup>3</sup> (SD +/- 135 cells/mm<sup>3</sup>) and 39% had <200 CD4 cells/mm<sup>3</sup>.

Pooled data was presented for all BMS-068 for all participants at 96 weeks, however 30% of the GSK-934 participants and 40% of the control patients discontinued before week 96.

The 96-week efficacy and safety analysis from this study was also reported at CROI earlier in the year, with 61% vs 53% having viral load <50 copies/mL at week 96. [3]

The new analysis reported similar results for the active vs control arms when looking at subgroups for viral load above/below 100,000 copies/mL and for baseline CD4 above/below 200 cells/mm<sup>3</sup>, gender, age (above/below 50 years) and race/ethnicity. Similar response rates across the active arms were also seen across the range of baseline susceptibility (especially above/below 1.0 nM).

Although side effects were general mild and similar between group (grade 1 to 4: 91% vs 98%, grade 3/4: 12% vs 14%), a lower percentage of drug-related side effect occurred for the attachment inhibitor (grade 2 to 4: 8.5% vs 37%) and there were fewer drug-related discontinuations (2.5% vs 10.0%). The single death in the active arms was unrelated (gun shot wound).

GSK-934 is an attachment inhibitor that attaches to gp-120 near the CD4 binding site and prevent conformational changes needed for attachment. It is active against nearly all HIV-1 subtypes, though not sub-type AE or group O and has no in vitro cross resistance to drugs from other classes.

International phase 3 studies are ongoing in treatment-experienced patients with drug resistance that leaves them sensitive to two or fewer drug classes. [4]

The compound was acquired by Viiv Healthcare in December 2015 and the full new compound name is GSK3684934. [5]

### C O M M E N T

**As with other drugs in new classes, GSK-934 has the potential to become an essential life-saving option for people with multidrug resistance.**

**Although this study was not powered to see differences in sub-groups, the lack of any immediate signal is encouraging.**

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## Once-weekly albuvirtide infusion: early results of T-20-like compound in Chinese study

Simon Collins, HIV i-Base

**Partial interim results were reported for the entry inhibitor albuvirtide, a long-chain peptide active against gp-41, similar to enfuvirtide (T-20), by Dong Xie from Frontier Biotechnologies, the Chinese pharmaceutical company developing this compound. [1]**

Albuvirtide is being developed in China as an alternative second-line combination, where access to oral drugs is limited (no integrase inhibitors, or second-generation NNRTIs or PIs). Early studies reported mean viral load reductions of about 1.0 log copies/mL in treatment naive participants using the 320 mg dose following multiple doses over six weeks. [2]

Differences between albuvirtide compared to T-20 include a plasma half-life of 12-14 days allowing once-weekly intravenous infusion (rather than twice-daily sub-cutaneous injections) and a side effect profile that does not include injection site reactions (ISRs).

This is an open label phase 3 non-inferiority study that randomised 389 treatment experienced participants to a second-line combination of lopinavir/r plus either albuvirtide or WHO-recommended NRTIs. Entry criteria included having viral load >1000 copies/mL on first-line ART.

The study is being run at 12 sites in China with about half of participants coming from urban and half from rural sites. The primary endpoint is the percentage of participants with viral load <50 copies/mL at week 48. Participants in the albuvirtide arm required weekly clinic visits compared to 3-monthly visits for the control arm.

Baseline characteristics included mean age 40 years (SD +/- 11) and 25% were women. Mean CD4 count and viral load were approximately 240 cells/mm<sup>3</sup> (SD +/- 140) and 3.8 log (+/- 1.0 log) copies/mL (with 10% having >100,000 copies/mL). Overall, 80% had at least one major drug resistant mutation, with most having both NNRTI and NRTI mutations. Approximately 75% of participants were using tenofovir at baseline.

This interim analysis included 208/389 participants, with results available for 175/208 participants in the modified ITT analysis: 83 vs 92 at 24 weeks and 50 vs 48 at 48 weeks, in the albuvirtide vs NRTI groups respectively.

Although both groups showed 80% viral suppression at 24 weeks, by week 48 rates were 80% vs 66% in the albuvirtide vs control group respectively (difference 14.4%, 95%CI: -3.0 to 31.9). This showed non-inferiority at both time points.

Tolerability was good and most side effects seemed comparable between groups: about 75% reported side effects (mostly mild diarrhoea) with only 5 vs 3% classified as serious events (only one of which, GI-related in the NRTI group, was drug-related). No ISRs were reported.

Based on these results, albuvirtide has already been submitted for conditional approval in China and there are plans to run additional international studies in other countries next year, especially if paired with other long-acting drugs.

### C O M M E N T

**These promising early results are interesting as this compound has a unique profile to currently approved drugs and it would likely help people with current multi-drug resistance, including to integrase inhibitors, who are dependent on new drugs.**

**A sub-cutaneous formulation of albuvirtide is also in development that would allow self-injections at home, rather than weekly clinic visits.**

**T-20 is now extremely rarely used, largely due to difficulty with injections.**

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## **Simplifying HIV treatment: dual therapy works but monotherapy with either boosted-PIs or dolutegravir does not**

**Simon Collins, HIV i-Base**

### **Several oral presentations at Glasgow 2016 provided data on simplification strategies.**

In the first study, Roberta Gagliardini from the Institute of Clinical Infectious Diseases in Rome presented results from the multi-site open-label Italian ATLAS-M study that randomised 266 participants on stable ART with ritonavir-boosted atazanavir (ATV/r) plus 2 NRTIs to switch to either ATV/r plus 3TC or to stay on triple therapy. [1]

The primary endpoint was lack of viral failure at 48 weeks, with 96 week results now available.

Baseline characteristics included: approximately 78% male, median age 44 years (IQR 36 to 51), median CD4 count 600 cells/mm<sup>3</sup> (IQR 460 to 780) and median CD4 nadir 260 (IQR 132 to 360). The current regimen had been used for median 28 months (IQR 16 to 52 months) and tenofovir-DF was one of the NRTIs for 79% of participants.

At week 96, significantly more participants did not have virological failure in the dual vs triple groups: 77.8% vs 65.6% (difference 12.2%; 95%CI: 1.2 to 23.2). Viral failure occurred in two (1.6%) vs eight (6.3%) participants in the dual vs triple groups respectively, p 0.056.

There were few differences in clinical events between the two groups. However, the impact of discontinuing tenofovir-DF in the dual therapy group improved eGFR (+5 vs. -3 mL/min/1.73 m<sup>2</sup>, p<0.001) but worsened lipids (total cholesterol +15 vs. 0 mg/dL, p=0.005; new onset grade 3/4 hypertriglyceridaemia (7.6% vs 1.6%, p=0.027) although HDL was better in the dual arm (+5 vs 0 mg/dL, p=0.002). Hyperbilirubinemia occurred more frequently in the dual therapy arm (59.6% vs 35.8%, p=0.001).

In a second study, Laura Ciaffi from IRD INSERM presented results from the French ANRS MOBIDIP study conducted in Cameroon, Senegal and Burkino Faso. [2]

This study randomised 265 participants (between March 2014 to January 2015) who were on stable second-line boosted-PI treatment (either darunavir/r or lopinavir/r) to switch to either boosted PI monotherapy or dual therapy with additional 3TC.

Baseline characteristics in this study included being a largely female cohort (73%), with a median age of 42 years (IQR: 36 to 50), CD4 count 475 cells/mm<sup>3</sup> (IQR: 379 to 652) and median time on second-line ART was 37 months (IQR: 30 to 47). Nearly all participants (94%) had developed drug resistance on their first treatment that included the M18V mutation associated with high-level resistance to 3TC.

In March 2016, after an early analysis, the independent Data and Safety Monitoring board (DSMB) recommended stopping the monotherapy arm due to higher rate of virological failure compared to the dual therapy arm. Viral failure was reported by <3.0% (95%CI: 0.8 to 7.6) and 22.6% (95%CI: 15.8 to 30.6) of patients in the dual and mono arm respectively (p<0.001).

Median time to failure was 24 weeks and all patients resuppressed viral load when the NRTI background was reintroduced.

José Arribas from University Hospital La Paz in Madrid presented results from a 48 week open-label study that randomised 249 patients with viral suppression on boosted darunavir + two NRTIs to either switch to dual therapy with DRV/r plus lamivudine (3TC) or remain on triple therapy. [3]

This was a non-inferiority study (lower margin -12%) based on a primary endpoint of viral suppression at week 48.

Baseline characteristics were balanced between groups although duration of viral suppression was significantly shorter in the dual-ART group (21 vs 28 months). Approximately 75% of participants were using tenofovir-DF/FTC as background NRTIs and 25% were using abacavir/3TC.

Viral suppression (<50 copies/mL) at week 48 by ITT analysis was 89% (112/126) vs 93% (114/123) in the dual vs triple combination groups (difference -3.8 [95% CI: -11.0 to +3.4]). This difference was tighter in the observed analysis when censoring discontinuations for non-virologic reasons: 97% vs 98% (difference -1.7 [95% CI: -5.8 to +1.4]).

Severe side effects were similar at 5% in each group with non-significant differences in discontinuations (1% vs 2%).

However, somewhat surprisingly, switching to dual therapy was not associated with significant changes in e-GFR and TC/HDL ratio relative to continuing triple therapy.

CD4 responses were also similar and no emergent drug resistance was detected.

Finally, perhaps the most controversial approaches to reduced maintenance therapy has come from several European studies using dolutegravir monotherapy, one of which presented longer follow-up data at Glasgow 2016.

Bart Rijnders from Erasmus University Medical Centre in Rotterdam presented results from the 48-week DOLUMONO study that randomised 104 people who were on stable ART to switch to dolutegravir monotherapy either immediately or after 24 weeks.

This was a non-inferiority study (using lower limit -12%) based on primary endpoint of viral suppression (<200 copies/mL) at week 24. Entry criteria included never having had a CD4 count <200 cells/mm<sup>3</sup> or a viral load >100,000 copies/mL. Dolutegravir could be taken with or without food, but if viral load became detectable above 20 copies/mL participants were told to take dolutegravir with a meal (as this boosted drug levels).

Approximate baseline characteristics included 89% male, 82% Caucasian, median age 45 (IQR: 37 to 56), median viral load zenith 22,000 copies/mL (IQR: 7,000 to 60,000) and CD4 nadir 345 cells/mm<sup>3</sup> (IQR: 270 to 500) and had been on ART for a median 40 months (IQR: 25 to 68).

At week 24, nearly all participants (all except one) remained undetectable, with viral suppression in mono vs triple groups of 98% (49/50) vs 100% (53/53), finding non-inferiority for monotherapy (difference 2%; 95%CI: +12 to -5%).

However, the single patient with virologic failure on dolutegravir monotherapy in the immediate switch group had a viral load rebound to 50,000 copies/mL after four weeks, despite 100% adherence (by pill-count and plasma levels). Genotypic sequencings on stored pre-cART plasma and at dolutegravir failure did not show integrase inhibitor-associated mutations. At baseline they had been suppressed on ART for four years and was currently on rilpivirine/FTC/tenofovir-DF. CD4 nadir was 290 cells/mm<sup>3</sup> and viral load zenith was only 18,500 copies/mL. Viral load was resuppressed to <50 copies/mL using rilpivirine/FTC/tenofovir-DF.

Also, low level viraemia (50 to 200 copies/mL) is a concern and occurred in more patients in the monotherapy arm (3/49 vs. 0/53, p=0.12), although this difference was not statistically significant.

Longer follow-up results, including for the deferred switching arm were also reported.

At 24 weeks, 7/53 people in the deferred switching arm did not switch due to doctor decision (n=3), moving location (n=1), withdrew consent (n=1) other (n=2). One participant in the deferred switch group stopped dolutegravir at 12 weeks due to disturbed sleep (with viral load <50 copies/mL).

This left 95/104 people that used monotherapy, with 24-week monotherapy results available for 85/95. Of these, viral load was <200 copies/mL in 83/85 (95%; 95%CI: 91 to 99) and <50 copies/mL in 79/85 (93%; 95%CI: 85-97).

A second case of virologic failure also occurred in the deferred switch group with viral load rebounding to 387 copies/mL at week 12. This person reported only 90% adherence but had therapeutic plasma drug levels at week 12. They had been suppressed on ART for nine years and at baseline was taking efavirenz/FTC/tenofovir-DF. CD4 nadir was 220 cells/mL and viral load zenith was only 7400 copies/mL. Genotype testing was unsuccessful due to low viral load. Restarting efavirenz/FTC/tenofovir-DF reduced viral load to 99 copies/mL at four weeks.

Two other participants from the early switch group also had viral rebound after 30 weeks of monotherapy: one to 3,500 copies/mL and the other to 13,500 copies/mL. Both reported 100% adherence, confirmed by plasma drug level. Both resuppressed to <50 copies/mL on rilpivirine/FTC/tenofovir-DF. Resistance testing showed an integrase-associated mutation at 230R in one patient, conferring low-level resistance to raltegravir and elvitegravir.

From the dozens of posters at Glasgow 2016 looking at reduced drug combinations, generally using dual therapy, four provided additional data relevant to the oral presentations discussed above. All four studies used lamivudine (3TC) as the second drug: two with PIs and two with dolutegravir.

Maria Fontecha-Ortega from Hospital de Getafe and colleagues presented results from a 48-week, single-arm, open-label, prospective study that switched 99 treatment experienced patients from a current combination associated with side effects or a need to simplify treatment to 3TC plus a boosted PI (darunavir: 71, lopinavir: 21 and atazanavir: 7).

At baseline, mean age was 50 years (range: 35 to 74), 66% were male, 65% became positive through injecting drug use and 55% had HCV coinfection. The median duration of HIV infection was 20 years (IQR: 16 to 24), nadir CD4 count was 193 cells/mm<sup>3</sup> (IQR 90 to 306) and 42% had a previous AIDS diagnosis.

Overall, participants had been pre-treated with a median of six regimens (IQR: 1 to 10) for 40 months (IQR: 12 to 65). At the time of switch, viral load was <50 copies/mL in 92% and median CD4 count was 555 cells/mm<sup>3</sup> (IQR 394 799).

At week 48, viral load was undetectable in 97%, including patients with viral load that was previously detectable. Median CD4 count increased by +35 cells/mm<sup>3</sup> at 6 months and +80 cells/mm<sup>3</sup> at 12 months.

During 218 patient years of longer follow-up, there were only four virological failures, 1/4 due to a drug interaction and 3/4 due to adherence. An additional 16 people changed treatment due to side effects: diarrhoea (2), other GI (1), drug interactions (13, mainly HCV-related).

As 64% of the group has switched away from using tenofovir-DF, there were significant increases in cholesterol and triglycerides over 6 months that partially reversed by week 24. This was balanced by significant improvements in renal monitoring including eGFR and urinary markers.

In a second Spanish poster, Juan Pasquau from Hospitalario de Granada and colleagues presented preliminary retrospective results from 46 patients who switched to dual therapy with 3TC and unboosted atazanavir (400 mg/day). [10]

This group had previously used ART for an average of 12 years using median 4 (IQR 3 to 6) previous treatment combinations. Median age was 49 years (IQR 41 to 53), 65% were male, 43% had a previous AIDS diagnosis and 18% were co-infected with HCV. The mean CD4 nadir was 229 cells/mm<sup>3</sup> (IQR 107 to 375).

Although viral suppression was generally good (one case of virological failure during 44 patient-years of follow-up) and 95% of viral load results were <50 copies/mL (and 67% were <20 copies/mL), only 34/46 participants had reached 24-week primary endpoint. Of these, 1/34 had viral load >50 copies/mL.

Jacques Reynes from Montpellier University Hospital and colleagues presented results from a prospective cohort of 27 patients who switched from virally suppressive triple therapy to once-daily 3TC plus dolutegravir (50 mg) due to problems with side effects. [11]

This group (20 men, 7 women) had a median age of 59 years (range 41 to 77), median nadir CD4 167 cells/mm<sup>3</sup> (range: 8 to 450); and median baseline CD4 of 601 cells/mm<sup>3</sup> (range 198 to 1153). Before switching to dual therapy, participants had been taking ART for a median of 215 months (range: 22 to 329) and the last ART for about four years (median of 51 months, range 13 to 108 months). ART at the time of switch included tenofovir-DF in 48%, boosted PI in 81% and raltegravir in 26%.

Of note, 10/27 (37%) had previous documented M184V mutation associated with high-level drug resistance to 3TC.

At week 48 there were no cases of virologic failure but three participants discontinued: 2/3 due to side effects (fatigue, GI, weight gain) and 1/3 intensified treatment following a viral load result of 52 copies/mL at week 18.

No impact of the switch was seen in any changes in low level viral load (detectable or not below 20 copies/mL).

Quality of life was reported to improve following the switch to two small once-daily pills and it is notable that many of these participants had long treatment histories, including low nadir CD4 count and M184V mutations.

Finally, Franco Maggiolo from ASST Papa Giovanni XXIII in Bergamo and colleagues presented a poster from a prospective cohort of 94 Italian patients with intolerance to current suppressive ART (<50 copies/mL for > 6 months) who switched to 3TC plus dolutegravir. [12]

This group was 76% male with mean age of 53 years (+/- SD 11) who had been on ART for a mean 11.3 years (+/- SD 6.8). This group had used a mean 4 previous combinations (range: 1 to 10) and been on their current ART for about four years.

During six months of follow-up there were no discontinuations or virological failures.

The CD4 count increased by mean 61 cells/mm<sup>3</sup> (p 0.018) but without significant changes of CD8 cells or CD4/CD8 ratio. Tolerability was good with small decreases in cholesterol and triglycerides (despite switch from tenofovir-DF) and small increases in plasma creatinine (from 0.92 to 1.00 mg/dL, p<0.0001).

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#### C O M M E N T

**Although a significant proportion of people retain viral suppression in the monotherapy arms of these studies, the unpredictability of viral rebound, sometimes after many years of viral suppression and in the context of good adherence, suggests that the promising early data with dolutegravir [5] should be rethought to include lamivudine as dual therapy.**

**The failure of boosted atazanavir monotherapy in the ANRS study should not have been a surprise given early data showing this to be suboptimal, all of which was published before this study enrolled the first patient. This included a BMS study that was stopped early due to safety concerns from the Data and Safety Monitoring Board (DSMB) due to high failure rates. [6, 7, 8]**

**It is worrying that this ANRS study was conducted after this date (enrolment started in 2014) and in a population with fewer treatment options, although it is reassuring that all participants resuppressed when NRTIs were added again.**

**A retrospective review of 285 people who switched to unboosted atazanavir with abacavir/3TC was recently published by the EuroSIDA cohort. The percentage of people with virological success at 48/96/144 weeks was 90%/87%/88% (using TLOVR analysis) and 74%/67%/59% (using snapshot analysis), respectively.**

**Multivariate analysis showed associations between viral failure and nadir CD4 count (HR: 0.63 [95%CI: 0.42–0.93] per 100 cells higher); time with viral load ≤50 copies/mL (HR 0.87 [95% CI: 0.79–0.96] per 6 months longer), and previous failure with a protease inhibitor (HR 2.78 [95% CI: 1.28–6.04]). [13]**

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## **Dolutegravir-based ART in combination with rifampicin-based TB treatment is safe in a small cohort of co-infected patients**

**Polly Clayden, HIV i-Base**

**Twice daily dolutegravir in combination with rifampicin was well tolerated and produced good outcomes in a small retrospective study presented at HIV Drug Therapy Glasgow 2016. [1]**

A rifampicin-based regimen is first-line TB treatment worldwide and co-administration of HIV and TB treatment is now standard of care. But there are significant drug interactions with ART as rifampicin is a potent inducer of cytochrome p450 and UGT.

Dolutegravir is a substrate of UGT1A1 and CYP3A4 so co-administration with rifampicin decreases dolutegravir plasma concentrations.

A previous phase 1 study showed 50 mg dolutegravir twice daily taken with rifampicin gave dolutegravir concentrations similar to those with 50 mg once daily. [2]

Muge Cevik and colleagues from Leeds Teaching Hospitals presented data from a retrospective case note review of TB/HIV co-infected patients who received rifampicin-based TB treatment with dolutegravir based ART. In this cohort, dolutegravir is used in co-infected patients who experience side effects with efavirenz or where efavirenz is contraindicated.

The investigators identified seven people (six women) who received a dolutegravir-based regimen in combination with rifampicin. Their median age was 41 years (range 27 to 48) and all were of black African origin. Five were ART naive. Three received dolutegravir with abacavir and 3TC and four FTC/TDF.

Median baseline CD4 count was 90 copies/mL (range: 3 to 365). Five people had very low CD4 count at baseline (<100 cells/mm<sup>3</sup>), four had viral load >100,000 copies/mL and only one was undetectable. At six months from starting ART, median CD4 count was 230 cells/mm<sup>3</sup> (range: 104 to 625) and all but one had undetectable viral load.

One ART-experienced patient had viral load of 240,000 copies/mL at baseline. This was someone with transmitted antiretroviral resistance mutations to NRTIs (T69 deletion) and NNRTIs (Y181C and G190A). She had well documented poor adherence and had stopped her HIV treatment completely before re-starting ART with FTC/TDF plus dolutegravir (twice-daily) two weeks after starting TB treatment. At six months her viral load was 3,100 copies/mL. A month later she was undetectable but resistance testing showed a new M184 mutation and her regimen was changed.

All participants completed TB treatment and none experienced grade 3/4 side effects or TB-IRIS.

#### C O M M E N T

**Alongside that in pregnant women, lack of data in people receiving concomitant TB treatment was one of the main reasons for WHO to recommend dolutegravir-based first-line ART as an alternative rather than preferred regimen. [3]**

**So far the evidence for using dolutegravir 50 mg twice daily in the presence of rifampicin comes from the PK study in HIV negative volunteers (fasted) mentioned above. Robust clinical data are urgently needed to demonstrate the efficacy, safety and tolerability of twice daily dolutegravir in combination with rifampicin.**

**The originator company ViiV Healthcare is sponsoring an open-label phase 3 study of dolutegravir (DTG) vs efavirenz with rifampicin co-treatment with an estimated primary completion date of December 2017.**

**In the meantime, there are probably a few small “real life” studies or reports of such co-treatment emerging – like this example from Glasgow. These smaller studies will need careful evaluation, to see how rigorous the methodology is. But in the absence of better data – but expected increased use of dolutegravir, including in low-income settings [5] – it might be possible to add these to the interim data from the main clinical trial when the time comes to look at the evidence for the next iteration of the guidelines in 2017.**

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## Further reports of CNS-related side effects with dolutegravir

Simon Collins, HIV i-Base

**Several studies at Glasgow 2016 provided additional information about real world experience with the integrase inhibitor dolutegravir.**

Although registrational studies showed that dolutegravir has higher efficacy and fewer side effects compared to many other drugs, post marketing experience has included higher reports of CNS-related side effects in a minority of patients.

These CNS symptoms include dizziness, nervousness, depression, headache, reduced concentration, insomnia and other sleep problems and other unexplained pain.

Four studies reported on retrospective analyses from clinical cohorts - two in Germany, one in Spain and one in the UK. Two other UK studies reported on generally good results from switching from efavirenz to dolutegravir. And an analysis from the manufacturer ViiV included evidence supporting this being an issue, but tried to minimise the results by suggesting this was only seen in an “outlier” study.

The largest cohort report was presented by Michael Sabranski from the Infectious Diseases Centre in Hamburg and colleagues. This was a retrospective analysis from all treatment naive patients who started on an integrase inhibitor based combination at two large German out-patient clinics from 2007 to 2016 (but which excluded patients in clinical studies). [1]

The analysis included 1704 patients who used 1950 integrase-based combinations.

Rates of discontinuations linked to any side effect vs neuropsychiatric side effects were 7.6% vs 5.6% for dolutegravir (n=985), 7.6% vs 0.7% for elvitegravir (n=287) and 3.3% vs 1.9% for raltegravir (n=678), see Table 1. The difference

between dolutegravir and other two integrase inhibitors for neuropsychiatric side effects was significant ( $p < 0.0001$ ).

In multivariate analysis, neuropsychiatric side effects that led to dolutegravir discontinuation were observed significantly more frequently in women (hazard ratio [HR] 2.64; 95%CI: 1.23 to 5.65,  $p = 0.012$ ), patients older than 60 years (HR 2.86; 95%CI: 1.42 to 5.77,  $p = 0.003$ ) and HLA-B\*57:01-negative patients who started abacavir at the same time (HR 2.42; 95%CI: 1.38 to 4.24,  $p = 0.002$ ).

These findings did not change when excluding patients who started in 2016 (following greater awareness of these side effects), although starting in 2016 (compared to 2014/2015) had a HR 11.36 95%CI 4.31 to 29.41,  $p < 0.0001$ .

Symptoms generally resolved quickly after discontinuation (although they returned in six people who were later re-challenged with dolutegravir). Also importantly, no association was found in people with previous intolerance to efavirenz.

**Table 1: Neuropsychiatric side effects leading to discontinuation**

	dolutegravir	elvitegravir	raltegravir
N	985	287	678
Insomnia/sleep problems	36	2	4
Poor concentration	8	0	0
Dizziness	13	1	3
Headache/paraesthesia	16	1	6
Depression	7	0	1

A second German study reported on 411 patients who were enrolled between March and May 2016 into the prospective non-interventional DOL-ART cohort to look at responses to dolutegravir outside a clinical study. This was a largely treatment experienced group with only one quarter being treatment-naïve. During the first year 10.7% of patients experienced side effects with 4.4% discontinuing dolutegravir for this (including 1.2% for depression).

The Spanish study was a retrospective analysis of dolutegravir-related discontinuations from Hospital Ramon y Cajal in Madrid, presented by Maria Vivancos-Gallego and colleagues. [3]

From September 2014 to May 2016, 827/2470 patients (33.5%) using dolutegravir (naïve and experienced, with 70% using single tablet combination with abacavir/3TC), 104/827 (12.6%) later discontinued dolutegravir for any reason. Side effects were the primary reason in 36/104 cases (34% of discontinuations and 4.3% of people using dolutegravir overall).

Most frequent toxicities leading to drug interruption included headache ( $n=9$ ), high cholesterol ( $n=8$ ), insomnia ( $n=7$ ) and dizziness ( $n=6$ ). One case was reported of serious mood disorders which recovered soon after discontinuation.

A similar retrospective analysis compiled from 178 patients using dolutegravir at the Royal Liverpool Hospital in Liverpool from June 2013 to June 2016 was presented as a poster. [4]

Approximately 29% were treatment-naïve (52/178) and 71% were treatment experienced (126/178). Baseline demographics included: 72% men and 28% women; 78% Caucasian, 20% African/Caribbean and 2% Asian/other; and with median age 40 years (range 18 to 76).

Overall, side effects were recorded for 59/178 (33%) of this group with 20% of people (35/178) reporting CNS side effects. Other side effects included gastrointestinal (10%), neurological (7%), musculoskeletal (3%), lethargy (3%), skin related (2%) and urological (1%).

Two UK studies, presented results from people switching to dolutegravir because of neuropsychiatric side effects on efavirenz-based combinations.

An open label study randomised 40 patients with CNS side effects on efavirenz-based combinations to either immediately switch to dolutegravir or to switch following a four-week delay. The primary endpoint was rate of CNS toxicity measured by patient questionnaire at 4 weeks with numerous tolerability-related secondary endpoints. [5]

This group was largely male (38/40) with mean age 48 years (range 28 to 67).

CNS scores were significantly improved at 4 weeks post-switch and maintained at 12 weeks ( $p < 0.001$  at both time points). Statistically significant reductions were also reported for abnormal dreams ( $p < 0.001$ ), dizziness and depression ( $p = 0.008$ ) and improved for anxiety and depression scores, quality of life and quality of sleep.

In a related study, Michael Keegan from the Chelsea and Westminster Hospital in London reported on markers that might be related to the (currently unknown) pathogenesis of CNS complications associated to efavirenz. [6] Both indoleamine 2,3-dioxygenase-1 activity (IDO-1) and kynurenine/tryptophan ratios (KYN/TRP) improved following a switch from efavirenz to dolutegravir and these results also correlated with self-reported improvement of symptoms. Severe CNS side effects that included suicidal ideation was only reported in one case. Discontinuation rates were low however, with only 10/178 people stopping treatment (6%) with 8/10 (4%) being due to side effects.

Finally, Viiv Healthcare, the manufacturer of dolutegravir, presented an analysis in a poster on psychiatric side effects in four randomised, blinded, placebo-controlled treatment-naïve phase 3 studies. [7]

This included 2634 participants, half of whom received dolutegravir. Of the four studies presented (SPRING-2, SINGLE, FLAMINGO and ARIA), only one reported psychiatric side effects at higher than 5%. When Romina Quercia from Viiv presented a summary of this poster in an oral discussion, the results were controversially down-played as this study being an outlier due to lack of investigator assignment of the side effects being linked to the investigational drugs.

In practice, however, the outlier (SINGLE) was the only study where researchers would have been actively looking for CNS-related side effects. It was the only study with efavirenz in the comparator arm and it also included a questionnaire on CNS events. In SINGLE, anxiety was reported by 7% vs 7%, depression by 8% vs 10%, insomnia by 17% vs 11% and sleep problems by 10% vs 21%, all in the dolutegravir vs efavirenz groups respectively.

Most of these were low grade reports and the number of people discontinuing treatment were low, in SINGLE these occurred less often for the dolutegravir vs efavirenz group respectively (anxiety 0 vs 4, depression 1 vs 7, insomnia 1 vs 3 and sleep problems by 2 vs 7).

While Viiv tried to explain the results from SINGLE as at least partially due to a design bias that involved more careful receding of CNS-related side effects because efavirenz was the comparator, the double-blind study design actually makes this the study that would have been most likely to report unbiased results.

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#### C O M M E N T

**These real-world reports of CNS-related side effects with dolutegravir are similar to those from other research groups that we reported in the previous issue of HTB. [8, 9, 10]**

**The results do not detract from the importance of dolutegravir as an essential new HIV drug. Instead they highlight an area where greater care is needed when using dolutegravir.**

**It is also reassuring that previous CNS problems with efavirenz are not predictive of similar risk with dolutegravir - indicating a likely different mechanism. However, the increased associations reported by Sabranski et al, with sex, age and abacavir use deserve further attention.**

**In discussions at the conference, few doctors were surprised by the results, with most reporting similar experiences when they have switched small but noticeable numbers of patients to alternative drugs because of CNS-related side effects.**

**The revised version of the EACS guidelines (October 2016) now includes a stronger reference to CNS side effects with dolutegravir. [11]**

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## Generic PrEP bought online for UK use is validated by drug testing service

Simon Collins, HIV i-Base

**A useful study for people using generic PrEP that they have bought online was presented by Nneka Nwokolo from the NHS sexual health clinic at 56 Dean Street in London. [1]**

This study included testing plasma samples for active levels of both tenofovir and emtricitabine from HIV negative people attending the Dean Street clinic. It was based on a clinic that was set up in February 2016 in response to increasing numbers of patients who were buying generic PrEP online.

Although the NHS was not able to prescribe PrEP, some clinics have launched free services to enable people to receive appropriate monitoring if they are buying PrEP online. This included the option to provide a blood sample to test for drug levels.

Overall, 234 gay men were registered at the PrEP clinic and 212 people provided samples for this analysis. Median age was 37 (IQR 31-45), 85% were Caucasian and 35% used chemsex drugs (meth, meph or G). Daily PrEP was used by most people (85%) with only 15% using event-based dosing. The majority of men (92%) had bought PrEP because of information and links provided on a community website ([iwantprepnw.co.uk](http://iwantprepnw.co.uk)), with most using one of two recommended suppliers (predominantly Cipla's Tenvir-EM).

Drug levels were measured in plasma using HPLC with UV detection, with a sensitivity range of 25 to 10,000 ng/mL.

The median (range) levels of plasma TFV and FTC were 103 ng/mL (range: 21 to 597 ng/mL) and 142 ng/mL (17 to 1876 ng/mL), respectively. Median time post-dose for sampling was 15.5 hours (range 0.5 to 27). At 24-hours post-dose, all levels were above median minimum 24-hour targets of 19 ng/mL and 22 ng/mL, for TFV and FTC respectively, based on historical data.

Other safety monitoring results included that baseline eGFR was normal in all participants with paired samples. STIs were diagnosed at baseline or within three months in a quarter of the group (n=39, 26%). An additional 13 people had an STI at a follow-up visit. No new cases of HIV were detected from 58 person-years of follow-up (median 91 days per person).

### C O M M E N T

**The study was set up to check whether some internet suppliers (currently recommended by community websites like HIV i-Base and [iwantprepnw.co.uk](http://iwantprepnw.co.uk)) are reliable sources for genuine generic medicines. [2, 3]**

**The results were overwhelmingly positive.**

**The study was not set up to check generic formulations per se as the quality of FDA pre-qualified and WHO-approved generics is already well established.**

**Until the NHS provide PrEP, and this might not be widely until generic TDF/FTC is available, the study provides important validation that the websites used by the participant were selling genuine generics and not fake.**

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## Immunology and HIV persistence – implications for a cure

Gareth Hardy, HIV i-Base

**Steve Deeks from University California San Francisco and the amfAR Institute for HIV Cure Research presented a review of current strategies aimed at curing HIV. [1]**

While numerous approaches are being investigated, a cure for HIV is likely to need multiple approaches. However, large combined studies might begin within five years.

Deeks framed his talk with the proposition that for an HIV cure to have a global impact it must meet five conditions, as described in a modelling study conducted by Andrew Phillips using data from Zimbabwe [2].

1. Durable efficacy. A cure may allow wiggle room for viral failure in the short term (which would be picked up by monitoring), but not if it fails after longer periods which could mimic seroconversion and dramatically increase risk of transmission.
2. The product. This must be oral/parental and administered over a limited period of up to 6 months and not requiring specialised care.
3. Target population. Likely when ART has been started in early infection.
4. Safety. This should be comparable to current ART and maintain negligible transmission risk.
5. Cost. Upper cost of cost estimated at \$1400 per intervention.

The four most promising approaches to develop such a viable cure are not all conducive to global impact.

1. Gene and cell based therapies would build an HIV resistant immune system or excise integrated HIV, but are expensive and likely to have higher risk of difficult side effects.
2. Starting ART very early in infection reduces the size of the latent reservoir, but would have limited global impact for most people who are already HIV positive.
3. “Shock and kill” strategies aimed at inducing latent HIV with agents such as HDAC inhibitors, to reduce the size of the reservoir.
4. Immunotherapies aimed at establishing durable host-mediated control of HIV in the absence of ART.

A major concern with the “shock and kill” approach is that persistence of a small number of cells containing replication competent HIV could reseed systemic infection, which occurred in the so called “Boston patients” who remained aviraemic for months before viral breakthrough occurred. [3]

These patients’ viral loads rebounded to 10 million copies/mL with serious consequences, because they had no life-long protective immunity against HIV. Deeks says that this illustrates the need to combine reservoir reduction approaches with immunotherapy, which he suggests presents the best strategy for a viable cure with global impact. The most promising leads in development of immune based therapies come from the field of oncology where similar approaches have had remarkable success in reducing tumor sizes.

Deeks discussed advances in vaccine development and immune based therapies for HIV, which are now tackling the previously significant barriers. These were placed in the context of lessons learned from cancer immunotherapy, which suggest that for durable immune control of HIV to be established, three conditions must be met: (i) low disease/viral burden; (ii) low inflammation; and (iii) sustained tissue resident T cell responses that target immune escape variants.

New promising vaccine approaches that have demonstrated induction of durable T cell responses include the CMV-based vaccine developed by Louis Picker at the Oregon Health and Science University that induces a broad range of aggressive and unconventional CD8 T cell responses. [4]

Furthermore, promising advances have been achieved by using adjuvants that signal through the immune system’s Toll-like receptors (TLRs). These include Gilead’s TLR-7 agonist, GS-9680, that even administered without a vaccine reduced reservoir size and led to immune control in SIV-infected rhesus macaques [unpublished data].

Another critical lesson learned from advances in oncology immunotherapy is that inflammatory environments often activate immune regulatory signalling pathways and can be a substantial hindrance to development of T cell responses. Such pathways include PD-1, CTLA-4, IDO, interleukin-10 (IL-10) and type-I interferon (IFN-I). Inhibitors of these molecules are being developed, some of which are showing promising results in cancer therapy [5].

Deeks finished the talk by explaining that while treat-early, treat-hard strategies may be beneficial for new HIV infections, as demonstrated by the VISCONTI cohort [6], this approach will not help the tens of millions of people who are currently living with HIV. Here he suggests that the most promising approach will be to first reduce the reservoir with latency reversing agents, such as HDAC inhibitors (perhaps by up to 2 logs) – which might be sufficient to allow long-lived, broad HIV-specific T cell responses to maintain control HIV if these responses can be induced by new vaccines, adjuvants and anti-inflammatory agents.

Promisingly, Deeks is optimistic that many of these individual therapies now being tested may be ready for combination use in large clinical trials within the next five years.

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## Selected webcasts from Glasgow 2016

### Simon Collins, HIV i-Base

#### **The Glasgow conference provides free access to presentations at the meeting with webcasts of all oral presentations.**

A selection of these are included below.

#### **Immunology of HIV persistence: implications for the development of a cure**

Steve Deeks, University of California, San Francisco

<https://vimeo.com/188976430>

A comprehensive and positive overview of strategies for cure research, concluding that although combination approaches are likely to be needed, that larger strategy studies should be running in patients within the next five years.

#### **Where next for ARVs?**

Roy Gulick, Weill Cornell Medicine, New York

<https://vimeo.com/188976431>

A useful and comprehensive review tracking the continued improvements with latest ARVs and an overview of pipeline HIV compounds likely to overcome drug resistance to current drugs (including doravirine, bictegravir and GSK934/BMS-068, EFdA).

The talk also covers strategies using reduced drugs and dosing, new ways to deliver drugs, cost and access.

#### **HIV treatment as prevention: from a research hypothesis to a new global target and beyond**

Julio Montaner, British Columbia Centre for Excellence in HIV/AIDS, Vancouver

<https://vimeo.com/188645056>

A historical perspective on the effectiveness and cost effectiveness of treatment as Prevention (TasP) as an essential cornerstone for overcoming the global HIV epidemic, well past the 90:90:90 targets, by one of the earliest proponents.

#### **Initiation of ART early in HIV infection: START to finish**

Jens D Lundgren, University of Copenhagen

<https://vimeo.com/188645058>

An overview of the results of the START study - from first planning stages ten years ago to the numerous sub-studies and additional research since the main results were presented last year. Not only were the advantages of earlier treatment seen consistently across demographic and HIV subgroups.

More than a dozen recent analysis:

- Converting relative risk into absolute risks, showing numbers needed to treat by different subgroups,
- The greater prognostic use of CD4:CD8 ratio over CD4 count at higher CD4 counts, and
- Improved quality of life with earlier treatment.
- Plus unexpected finding that despite reduced inflammation from earlier ART this did not directly improve cardiovascular risk, cognitive function or pulmonary function.

#### **Transition to adult care**

Pablo Rojo, Complutense University, Madrid

<https://vimeo.com/188645060>

An overview of the complexities of issues relating to both paediatric and adolescent care in relation to calendar year of infection and the implications this has for transitioning to adult care services.

### **Treatment for cancer, HIV and viral hepatitis in Europe using low cost generic drugs: what could be done?**

Andrew Hill, Chelsea and Westminster Hospital, London

<https://vimeo.com/188625117>

One of the keynote lectures that was a conference highlight in showing the potential for medicines to be both cheaper and affordable in all settings. Also reported above in HTB.

### **Ending the HIV/AIDS pandemic: follow the science**

Anthony Fauci, US NIAID/NIH, Bethesda

<https://vimeo.com/188625118>

Keynote lecture in memory of Joep Lange and Jacqueline van Tongeren on the importance of building on scientific research to end global AIDS.

## CONFERENCE REPORTS

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### **2nd HIV Research for Prevention Conference (HIVR4P) 2016**

**17-20 October 2016, Chicago**

#### **Introduction**

**This second biennial HIV Research for Prevention (HIVR4P) conference was held this year in Chicago from 17 to 21 October.**

Although the conference programme is online, this does not link to the study abstracts, but the abstract are available as a PDF file. These are also available using an App that is free to download.

The programme was very varied and included a strong focus this year on the pipeline for new formulations and compounds for pre-exposure prophylaxis (PrEP).

Importantly, all oral sessions are webcast 24 hours after the presentations.

Abstracts are published as an open-access supplement to AIDS Research and Human Retroviruses. ([www.liebertpub.com/aid](http://www.liebertpub.com/aid)). Many conference posters are available to view and download online.

Programme:

<http://www.professionalabstracts.com/hivr4p2016/iPlanner/#/grid>

Webcasts:

<http://webcasts.hivr4p.org>

Abstract book:

[http://hivr4p.org/images/HIVR4P\\_2016\\_Abstract\\_Book.pdf](http://hivr4p.org/images/HIVR4P_2016_Abstract_Book.pdf)

App:

Search Apple Store or PlayStore for "HIVR4P2016"

Posters

<http://www.abstractstosubmit.com/hivr4p2016/eposter>

The following reports from this conference are included in this issue of HTB.

- Burgeoning PrEP pipeline: new drugs, formulations and delivery options
- Second case of drug resistant HIV infection in person adherent on PrEP
- TDF/FTC can be used as PrEP by breastfeeding mothers without risk to the baby

- Potential for EFdA as PrEP to prevent HIV transmission in women and their infants
- Antibody therapy leads to sustained post-treatment SIV control in macaques

## **A burgeoning PrEP pipeline: dozens of new drugs, formulations and delivery options**

**Simon Collins, HIV i-Base**

### **A clear highlight for HIV R4P 2016 was the unexpected volume of research into new molecules and formulations for PrEP.**

This large specialised event has worked effectively to focus on prevention research in a meeting that is large enough to include diversity but that is still small enough to meet and talk with researchers and to get a comprehensive overview of both preclinical and clinical studies.

The diversity of the studies is shown by the number of new compounds being studied for PrEP. See also Table 1.

- Currently approved antiretrovirals (lamivudine, emtricitabine, tenfovir-DF, TAF, raltegravir, elvitegravir, darunavir, rilpivirine, etravirine and maraviroc).
- New compounds from existing classes: NNRTIs (dapivirine, MIV-170, IQP-0528); integrase inhibitors (cabotegravir, MK-2048); entry inhibitors (viviviroc, 5P12-RANTES, DS003/BMS-599793, PIE-12 trimer D-peptide, Nifviroc); and NRTIs (EFdA).
- New compounds from new classes: neutralising antibodies (VRC01, griffithsin).

It was similarly impressive to see the range of new delivery systems and formulations that are in development. See also Table 2.

- Single and multi-compound vaginal rings.
- Other vaginal/rectal inserts or suppositories often designed to rapidly dissolve within a minute or two.
- Vaginal and rectal gels - sometimes developed for both or only one compartment.
- Small, thin fast-dissolving vaginal films of nanoformulations that instantly dissolve on contact with moisture. Including MK-2048, viviviroc, TDF, VRC01 and others. These films deliver similar drug levels as gels but are much less messy.
- Long-acting soft implants - incorporating long-acting slow release formulations into something similar to a 1 mm in diameter, 2 cm long strip of cotton-like material that can be inserted under the skin, for example at the back of the neck.
- Long acting injections (cabotegravir).
- Fast absorbing small-volume rectal formulations that are designed to be rapidly absorbed into rectal tissue, similar to an enema.

Many of the new studies incorporated two, three or four compounds into new formulations, adding experimental compounds to already-approved drugs.

Together, this collective body of research suggests a huge potential for PrEP to become better and easier to use.

Other than cabotegravir LA injections and TAF which are in late phase studies by the drug manufacturers, this majority of this research at the meeting was almost entirely driven and presented by independent academic research groups, supported by either public or charitable funding. Although some pharmaceutical companies provided support in kind with drugs, many of the researchers said that this was often not the case, with some research groups having to manufacture their own versions of the active compounds or unlicensed compounds.

This pipeline also sets a challenge to regulators, funders and researchers to develop approval pathways that might compare multiple investigational compounds and formulations in the same study - both for faster proof of principle and to reduce research costs.

Many of the selected references included below could have been categorised under several sub-headings - (ie as new compounds and gels and multi-function combinations) but are only listed once, just to give an idea of the diversity of the PrEP pipeline.

**Table 1: PrEP investigational compounds**

Currently approved antiretrovirals	New compounds from existing classes	New compounds from new classes
NRTIs: lamivudine, emtricitabine, tenfovir-DF, TAF. NNRTIs: rilpivirine, etravirine. PIs: darunavir Integrase inhibitors: raltegravir, elvitegravir. Entry inhibitors: maraviroc	NRTIs: EFdA. NNRTIs: dapivirine, MIV-170, IQP-0528. integrase inhibitors: cabotegravir, MK-2048. Entry inhibitors: vivriviroc, 5P12-RANTES, DS003/BMS-599793, PIE-12 trimer D-peptide, nifviroc	Neutralising antibodies: VRC01, griffithsin.

**Table 2: PrEP pipeline for delivery systems and formulations**

Formulation	Comment
Vaginal rings	Single and multiple compound. Combinations include coformulations of PrEP with contraception and STI treatment (HPV, HSV)
Vaginal and rectal inserts or suppositories	Designed to rapidly dissolve within a minute or two
Vaginal and rectal gels	Sometimes developed for both or only one compartment. Improved formulations - closer to lubricants.
Fast-dissolving films	Nanoformulations that instantly dissolve on contact with moisture. Including MK-2048, vivriviroc, TDF, VRC01 and others. Less messy than gels.
Long-acting soft implants	Long-acting slow release formulations that can be inserted under the skin similar to contraceptive implants.
Long acting injections	Cabotegravir
Rectal "douche" formulations	Hypo-osmotic for rapid absorption into tissue from small volumes.

**C O M M E N T**

**This is an exciting period for prevention research. Even if only a few of these products in preclinical studies continue through clinical studies to approval, within 5-10 years TDF/FTC will look as archaic for PrEP as AZT monotherapy looks compared to modern ART.**

**Health advocates and PrEP users should be following (and driving) research into pipeline research just as treatment activists drove the development for ART.**

**One challenge - and it is a significant one, will be to develop better models and requirements for regulatory approval. PrEP studies are larger, more expensive and generally longer than ARV treatment studies with few surrogate markers of efficacy other than the impact on HIV transmission.**

**As PrEP becomes more effective the challenge to match results in control arms will become increasingly difficult, given that all participants in research studies need to receive the current standard of care as minimum.**

**This is likely to require public investment, perhaps using multiple new compound with early promise in the same studies.**

Selected references

All references are to the programme and abstracts of the 2nd HIV Research for Prevention Conference (HIVR4P), 17-21 October 2016. Abstracts are published as an open-access supplement to AIDS Research and Human Retroviruses. ([www.liebertpub.com/aid](http://www.liebertpub.com/aid)). Many conference posters will be available to view and download online ([www.abstractstosubmit.com/hivr4p2016/eposter/](http://www.abstractstosubmit.com/hivr4p2016/eposter/)).

**New compounds**

Herrera C et al. Increased activity of the entry inhibitor DS003, a BMS-378806 analogue, through binding to the CD4-induced epitope in HIV-1 gp120. Poster P08.04.

Kay M et al. Preclinical characterization of a potent D-peptide inhibitor of HIV entry: cholesterol-conjugated PIE12-trimer. Poster PD08.04LB.

Madani N et al. Prevention of vaginal transmission of simian-human immunodeficiency virus (SHIV) in rhesus monkeys by small-molecule CD4-mimetic compounds. Poster PD08.03LB.

Mason R et al. Next generation SIV broadly neutralizing antibodies mediate complete neutralization of SIVmac239. Poster PD08.05LB.

McBride J et al. Osmotically activated release of 5P12-RANTES from silicone elastomer matrices. Poster P07.23.

Moss J et al. Intravaginal drug delivery system with dual microbicide delivery. Poster P07.24.

### **Multi-function formulations: combining PrEP with other treatments (for HPV, HSV-2, STIs) or contraceptives**

- Calenda G et al. Pharmacodynamics of griffithsin after vaginal application of a gel or intravaginal ring in macaques. Poster P07.15.
- Calenda G et al. GRFT/carrageenan gel Inhibits HIV and HSV-2 in human cervical mucosa. Poster P07.19.
- Holt J et al. Pharmacokinetics of dapivirine and levonorgestrel in sheep when administered vaginally in a silicone matrix ring. Poster abstract PD04.01.
- Kleinbeck K et al. Preclinical safety and stability assessment of a dual compartment microbicide gel targeting multiple viral sexually transmitted infections. Poster P07.34.
- Levendosky K et al. Preclinical evaluation of a griffithsin/carrageenan formulation to prevent HIV infection. Poster P08.17LB.
- Murphy D et al. Manufacture, release testing and content assay of dapivirine and dapivirine + levonorgestrel vaginal rings for testing of pharmacokinetics in sheep. Poster P07.11.
- Shankar G et al. Development and evaluation of release profile of innovative two-polymer (SR-2P) bioadhesive vaginal microbicide gels to prevent HIV. Poster P07.47LB.
- Srinivasan P et al. Pharmacokinetics of a multipurpose prevention technology pod-intravaginal ring for HIV-1, HSV, and contraception. Poster PD03.04.
- Tyo KM et al. Electrospun Polymer Nanofibers for Long- term Protection against HIV and HSV-2. Poster P07.32.

### **Vaginal and rectal gels**

- Calenda G et al. Pharmacodynamics of griffithsin after vaginal application of a gel or intravaginal ring in macaques. P07.17.
- Carballo-Diéguez A et al. High levels of adherence to a rectal microbicide gel and to oral PrEP achieved in MTN-017. Oral abstract OA20.01.
- Shetler C et al. Tenofovir/IQP-0528 combination gel effectively inhibits HIV and is not affected by semen. Poster P08.06.
- Ham A et al. IQP-0528: the pharmacokinetics of an anti-HIV NNRTI in non-human primates from various dosage forms. Poster PD03.05.
- McBride J et al. Sheep pharmacokinetics of a topical aqueous gel containing the anti-HIV CCR5 receptor inhibitor 5P12-RANTES. Poster P07.22.
- Russo J et al. Preclinical evaluation of prototype rectal griffithsin gels for HIV prevention. Poster P08.08.

### **Fast-dissolving vaginal and rectal tablets, implants and suppositories**

- Clark MR et al. Long-acting intrauterine system delivers integrase inhibitor throughout the reproductive tract of rabbits and macaques. Poster P07.40.
- Dobard C et al. Pharmacokinetic evaluation of rectal tenofovir suppositories in macaques. Poster P07.07.
- Lal M et al. A convenient, self-administered microbicide fast-dissolving insert as pre-exposure prophylaxis for HIV prevention. Late breaker poster P07.46LB.
- Littlefield S et al. Clinical performance, acceptability, and optimization of fast-dissolve vaginal inserts designed for HIV-prevention: results from two clinical studies. Oral abstract OA06.05.
- Swarnar S et al. A biodegradable, subcutaneous implant for delivery of antiretroviral (ARV) drugs. Poster P07.44.
- Zhang W et al. Development and proof-of-concept clinical evaluation of a freeze-dried topical microbicide insert for on-demand HIV prevention. Oral abstract OA12.02.

### **Fast-dissolving films (vaginal)**

- das Neves J et al. Pharmacokinetics and safety of vaginal tenofovir/efavirenz-loaded nanoparticles-in-film in Mice. Abstract P07.25.
- Grab S et al. Extended release of a combination dapivirine/MK-2048 film for HIV prevention. Poster P07.43.
- Ham A et al. IQP-0528: the pharmacokinetics of an anti-HIV NNRTI in non-human primates from various dosage forms. Poster PD03.05.
- Jiang Y et al. Vaginal safety evaluation of a triple antiretroviral drug-loaded electrospun fiber microbicide in nonhuman primates. Poster abstract PD03.03.
- Regev G et al. Novel application of hot melt extrusion for the manufacture of vaginal microbicide films. Poster P07.16.
- Vaca GB et al. Safety and efficacy assessment of VR01-N and MB66 microbicide film in an in vitro vaginal environment. Poster P07.15.

### **Intravaginal rings (IVR)**

- Calenda G et al. Pharmacodynamics of griffithsin after vaginal application of a gel or intravaginal ring in macaques. P07.17.
- Dezzutt C et al. Evaluation of MK-2048 and vicriviroc MK-2048A formulated as single or combination intravaginal rings for development as a vaginal microbicide. OA12.05. - data for CROI 2017)
- Evanoff A et al. A single-reservoir microbicide intravaginal ring for dual delivery of tenofovir and elvitegravir. Oral abstract OA12.04.
- Marshall LJ et al. Impact of vaginal ring geometry and drug loading on pharmacokinetics of dapivirine and darunavir in macaques. Poster abstract P07.13.
- Marshall LJ et al. Utility of the sheep model for testing the 28-day MK-2048A intravaginal ring and determining the correlates of exposure for vicriviroc and MK-2048. Poster P06.07.
- Murphy D et al. Visualising maraviroc release from silicone elastomers using magnetic resonance imaging. Poster abstract P07.10.
- Wilson M et al. Formulation development of DS003 ethylene vinyl acetate vaginal rings. Poster P07.39.

### **Douche applications**

- Date A et al. Optimizing enema vehicle osmolality for improved colorectal microbicide delivery. Poster abstract PD03.02.

## Second case of drug resistant HIV infection in person adherent on PrEP

Simon Collins, HIV i-Base

**Unfortunately, one of the studies that was widely reported from the R4P 2016 conference was a second case of HIV infection in a person who was very adherent to PrEP. [1]**

This new report was presented as a late breaking oral abstract by Howard Grossman from the Cleveland Clinic, a doctor who is an advocate for PrEP and who has written about benefits from a personal perspective.

It involved an HIV negative man whose partner was on effective ART with undetectable viral load and who started daily PrEP in January 2016. Self-reported adherence was 100%, confirmed by high drug concentrations in plasma and hair samples.

This man tested HIV positive at his routine HIV screening in May using a 4th generation AgAb HIV test and only reported having condomless sex with two people other than his main partner (11 and 5.5 weeks earlier). His risk was as the active (insertive) partner. Phylogenetic analysis showed that the infection was not related to his main partner.

His viral load was undetectable (<20 copies/mL) and dolutegravir was added to tenofovir-DF/FTC as treatment. However, resistance testing of proviral HIV DNA detected RT mutations K65R, M184V, K103S, E138Q and Y188L associated with high level drug resistance to NRTIs including tenofovir, FTC and NNRTIs. Darunavir/cobicistat was added to ART and viral load continued to be undetectable.

One surprise from the questions after the session was almost an obsessive focus on adherence, even though this would have no impact on the extensive mutations actually seen in the genotypic test.

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### C O M M E N T

**Although this case is disappointing, it is not unexpected, and unfortunately other cases are likely to be reported in the future. PrEP can only be active against HIV that is sensitive to the drugs used in PrEP. A similar case was reported earlier this year at CROI. [2]**

**Luckily, the prevalence of K65R/M184V mutations are low, detected in approximately 1% of new HIV diagnosis in the UK (and the US) although this will vary by geographic region. This person was just unlucky to become infected from limited exposure to other partners.**

**It might help explain the impact on overall PrEP efficacy to consider two distinct situations.**

**Firstly, that PrEP still remains close to 100% effective in the context of protection against HIV that is not resistant to PrEP drugs.**

**Secondly however, efficacy is likely to fall significantly, even in the context of perfect adherence, if exposure is to HIV with resistance to either TDF or FTC and that this drop to zero with exposure to HIV that is resistant to both TDF and FTC (ie with K65R and M184V).**

**The risk in this second scenario will be dependent on viral load of the source partner, and if this person was in acute infection they might not have been diagnosed or on ART.**

**Earlier in the session it was reported that up to 100,000 people have used PrEP in the US, so with only two cases of failure due to the risk of MDR infection overall efficacy is still incredibly high.**

**Dr Grossman remains committed to continuing to use PrEP himself.**

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1. Grossman H et al. Newly acquired HIV-1 infection with multi-drug resistant (MDR) HIV-1 in a patient on TDF/FTC-based PrEP. Research for Prevention 2016, 17-21 October 2016, Chicago. Oral abstract OA03.06LB.
2. Knox C et al. HIV-1 infection with multiclass resistance despite preexposure prophylaxis (PrEP). 23rd CROI 2016, Boston. Late-breaker poster abstract 479aLB.  
<http://www.croiconference.org/sessions/hiv-1-infection-multiclass-resistance-despite-preexposure-prophylaxis-prep>

## TDF/FTC can be used as PrEP by breastfeeding mothers without risk to the baby

Simon Collins, HIV i-Base

**A study reporting that low TDF/FTC concentrations in breastmilk do not put a baby at risk will be important in enabling women to routinely use PrEP irrespective of whether or not they are breastfeeding.**

Kenneth Mugwanya from University of Washington presented results from a pharmacokinetic study in 50 mother and infant pairs. The mothers were given daily PrEP for ten days with drugs levels measured in both breast milk samples and infant plasma samples. [1]

Median age of the infants was 13 weeks.

Only very small quantities of tenofovir (median med 0.2 ng/mL) transferred to milk - approximately at 3% of blood levels in the mothers. Tenofovir was not quantifiable in 94% of infant plasma samples. Based on the milk concentration, the infants had TFV exposures at less than 0.01% of the proposed infant therapeutic dose (6 mg/kg).

Emtricitabine (FTC) concentrations in breast milk were also low, although somewhat higher (median 212.5 ng/mL). These concentrations were consistent with those seen with 3TC, abacavir and AZT. Overall, 47/49 samples had detectable FTC in infant plasma, but at small concentrations (13.2 ng/mL), equivalent to approximately 0.5% of the proposed therapeutic infant dose.

Even though this was a small study, it provides the first data to suggest that PrEP can be safely used by women who are breastfeeding.

Full results from the study were published as an open access paper in PLoS Medicine in September 2016. [2]

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## Potential for EFdA as PrEP to prevent HIV transmission in women and their infants

Simon Collins, HIV i-Base

**One of the most promising candidates for future PrEP is a small molecule, highly potent NRTI EFdA, for which limited data have been presented, mostly in animals.**

It is notable then that a late breaker poster of several mouse studies was presented by Martina Kovarova, on behalf of an independent research group from University of North Carolina, rather than Merck who own the compound. [1]

As background, the poster notes that most HIV infections globally occur in women, that the majority of women are of child-bearing age, that without treatment 45% of women will transmit HIV to their baby mainly through breastfeeding and that only 31% of HIV positive children currently have access to ART.

This study used bone/liver/thymus (BLT) humanised mice as a preclinical model to study the efficacy of EFdA to prevent vaginal and oral transmission - with potential use to protect against sexual and breastfeeding transmission. The compound should generate excitement as it has the potential to be formulated in a slow-release small removable implant that would provide therapeutic doses for up to a year. EFdA has an IC50 of 14 nM, low cytotoxicity, sensitivity to drug resistant isolates and a low risk of drug resistance.

BLT and non-humanised mice were dosed with 10 mg/kg EFdA (approximately 5-fold higher than the equivalent human therapeutic dose) or left untreated. The ability to protect against in vitro challenge was tested in serum, cervicovaginal secretions and saliva. In all three samples, in vitro HIV inhibition was significantly higher from treated vs untreated animals ( $p < 0.01$  for serum and genital and  $p < 0.05$  for saliva).

The mice (6 untreated and 11 treated) were then exposed to three high dose vaginal challenges (approximately 100-fold higher than experienced for human sexual transmission) at 48 hour intervals while receiving daily EFdA for eight days. The degree of protection was highly significant with none of the treated mice becoming infected compared to all the control animals ( $p < 0.0002$ ).

Similar results were seen following oral exposure to high dose HIV with only 1/8 treated animals becoming infected compared to 5/5 untreated controls ( $p = 0.0031$ ).

These results will support clinical development of EFdA as a potential PrEP compound to prevent HIV transmission in women and their infants.

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#### C O M M E N T

**These results show good proof of concept. Even though the EFdA dose was higher than the comparative human therapeutic dose, the dose of HIV challenge was significantly higher again.**

**It is frustrating that so little data on this compound have been published by Merck, and that this exciting research into PrEP was conducted independently.**

**A similar poster on this research was also presented at IAS 2016 in Durban. [2]**

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<http://programme.aids2016.org/Abstract/Abstract/9652> (Abstract)

## **Antibody therapy leads to sustained post-treatment SIV control in macaques**

**Richard Jefferys, TAG**

**In an opening lecture for the R4P 2106 conference, Anthony Fauci from US NIAID, reported that sustained post-treatment control of SIV has been achieved in macaques using an antibody therapy developed for the treatment of inflammatory gastrointestinal (GI) disorders. [1]**

The study had hit headlines the previous week when the results were published in the journal Science. [2]

The antibody targets  $\alpha 4\beta 7$ , a receptor expressed on CD4 T cells (and other immune system cells) that is involved in promoting trafficking to the GI tract. Some, but not all [3], studies have suggested that  $\alpha 4\beta 7$  also plays a role in mediating HIV infection of target CD4 T cells.

The rationale for the study came from previous experiments which found that infusions of the antibody prior to an SIVmac239 challenge [4] reduced post-infection viral loads in macaques and, in low-dose challenge studies, [5] lessened the risk of SIV acquisition. The mechanism remains unknown but the researchers hypothesise that it relates to inhibition of trafficking of CD4 T cells, natural killer cells and plasmacytoid dendritic cells to the gut, limiting the availability of target cells for SIV and also dampening the inflammatory immune response that promotes and disseminates virus replication.

In the latest work, 18 macaques were challenged with the same dose of SIVmac239 used in previous experiments (200 TCID<sub>50</sub>) and all became infected. Five weeks post-challenge, combination antiretroviral therapy (ART) was initiated in all animals and maintained for 90 days. Around three weeks prior to ART cessation, 11 macaques were administered the anti- $\alpha 4\beta 7$  antibody by infusion while the remaining seven received a control antibody. The antibody administrations were then continued every three weeks (after ART withdrawal) until a total of eight infusions had been given, at which point all treatments were stopped. Three macaques developed antibodies against the anti- $\alpha 4\beta 7$  antibody and were excluded from further study, so analyses were limited to eight animals in the anti- $\alpha 4\beta 7$  group and seven controls.

After ART cessation, control macaques all experienced a rebound of SIV viral load within two weeks; levels averaged around a million copies/ml and persisted throughout follow up. Outcomes in recipients of the anti- $\alpha 4\beta 7$  antibody were very different: two animals never rebounded, and the remaining six were able to exert control of SIV viral load within four weeks, for the most part to undetectable levels but with some intermittent blips. This suppression of SIV was maintained out to 81 weeks of follow up (the last anti- $\alpha 4\beta 7$  antibody infusion occurred at week 32). Levels of proviral SIV DNA in GI tissues followed a similar pattern, persisting at detectable levels in the control animals but declining to undetectable levels in the anti- $\alpha 4\beta 7$  antibody group from week 30 onwards.

Measurements of CD4 T cell numbers in blood and gut showed an ongoing repopulation in the anti- $\alpha 4\beta 7$  antibody group compared to declines in controls. Notably, this recovery included Th17 and Th22 CD4 T cell subsets, which are known to contribute to the maintenance of GI barrier integrity. In terms of possible mechanisms of viral load containment, increases in cytokine-producing natural killer cells and innate lymphoid cells were seen in the gut post-ART in the anti- $\alpha 4\beta 7$  antibody recipients but not controls. Some evidence of preferential induction of antibodies against the V2 region of the SIV envelope was also reported. SIV-specific CD4 and CD8 T cell responses were assessed based on expression of CD107a, IFN- $\gamma$ , MIP-1- $\beta$  or TNF- $\alpha$  but did not show significant differences between groups.

At the end of the presentation, Fauci updated the Science paper by noting that suppression in the animals had now continued out to two years.

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

**The results of the study appear very encouraging, and the researchers are hoping to rapidly evaluate whether they have any relevance to humans. A small clinical trial of the anti- $\alpha 4\beta 7$  antibody vedolizumab, which is FDA-approved for the treatment of ulcerative colitis and Crohn's disease, is now recruiting at the National Institutes of Health Clinical Center. [6]**

**The target population is HIV-positive people who have been on suppressive ART for at least two years and the primary goal is assess safety (the antibody has been reported to have a favourable side effect profile for approved indications). [7]**

**An ART interruption is planned to evaluate any effects on viral load rebound.**

**Media coverage of the paper has generally been accurate, but has had to wrestle with the uncertainty that exists among scientists regarding how ART-free control of viral load should be described. The press release issued by the researchers uses the term “sustained SIV remission” in the headline but adds: “also known as a “functional cure”” in the body text. [8]**

**The problem, as TAG has highlighted in the past, is that it cannot be assumed that ART-free control of viral load automatically equates to a state of health that can be considered as remission or a functional cure i.e. a state of health equivalent to an HIV positive person on suppressive ART or a comparable HIV negative person. [9]**

**It is known from studies of elite controllers and individuals with HIV-2 infection that low or even undetectable viral loads do not necessarily completely eliminate the risk of disease progression. Thus, if an intervention leads to a state of ART-free control of viral load, it will be necessary to carefully evaluate immunological and health outcomes over a long period before concluding that HIV remission or a functional cure has been achieved.**

**One possible technical issue that has been noted about the study is that after the SIVmac239 challenge, peak viral loads averaged around three million copies/ml, which, as Louis Picker points out in an accompanying *Science* news article by Jon Cohen, [10] is unusually low for SIVmac239 – in one of the prior studies [4] by the same researchers, peak viral loads in controls averaged >32 million copies/mL.**

**The study authors do not address this apparent discrepancy. Although it would not explain the differences between the anti- $\alpha 4\beta 7$  antibody recipients and controls, the generalisability of the findings could be limited if the SIVmac239 challenge stock was unusually attenuated.**

Source: TAG basic science blog. (17 October 2016).

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## ANTIRETROVIRALS

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### **FDA approves maraviroc for children aged two and older**

**Polly Clayden, HIV i-Base**

**On 4 November 2016, ViiV Healthcare received approval from the US Food and Drug Administration (FDA) for maraviroc to treat CCR5-tropic HIV in combination with other antiretrovirals in paediatric patients two years old and above weighing at least 10 kg. [1]**

Maraviroc is not recommended in patients with dual/mixed- or CXCR4-tropic HIV.

New 25 mg and 75 mg tablets and a 20 mg/mL oral solution will be available in the US January 2017. The paediatric dose is based on body weight and the potential for drug-drug interactions with other medicines.

The FDA approval is based on results of an open-label trial in which 103 treatment-experienced paediatric patients with only CCR5-tropic HIV, aged 2 to 18 years and weighing at least 10 kg, received maraviroc twice daily in combination with optimised background therapy. [2]

At 48 weeks, 48% of patients achieved viral load less than 48 copies/mL and 65% viral load less than 400 copies/mL. The mean CD4 count increase from baseline to week 48 was 247 cells/mm<sup>3</sup>.

In the study, the dose was based on body surface area and whether or not the patient was receiving potent cytochrome P450 3A inhibitors and/or inducers.

The safety profile of maraviroc through 96 weeks was similar to that for adults.

US prescribing information for maraviroc has been updated accordingly. [3]

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#### C O M M E N T

**In contrast to most current paediatric antiretrovirals that take an age-staggered approach to approvals – this one included children and adolescents aged 2–18 years.**

**As with adults, widespread use of maraviroc is not expected.**

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### **Ibalizumab infusion reduces viral load in HIV positive people with multi-drug resistance**

**Simon Collins, HIV i-Base**

**After almost a decade with limited or no development, during which this compound was shuffled between companies, preliminary results from a phase 3 study show antiviral efficacy of the monoclonal antibody ibalizumab in people with multi-drug resistant HIV.**

The results were presented at the US conference IDWeek by Jay Lalezari from Quest Clinical Research, San Francisco. Unfortunately, this conference provides only the programme and abstracts online, from which this report is written, but not slides or webcasts.

The current study (TMB-301) is an ongoing single-arm study in 40 participants with MDR HIV with detectable viral load on their current combination. [2]

Ibalizumab works by attaching to CD4 receptors and blocking conformational changes that are needed to enter the cell. It is given using an intravenous (IV) infusion every two weeks.

The study design included:

1. Monitoring control phase from day 0 to 6 on the current failing combination.
2. Adding a single loading dose 2000 mg dose of ibalizumab on day 7.
3. Optimising background HIV drugs on day 14 to include at least one sensitive new drug (for 43% of participants this was an investigational compound).
4. From day 21 onwards, 800 mg ibalizumab was given every two weeks.

The primary endpoint results are the percentage of participants with >0.5 drop in viral load at day 14.

Limited baseline demographics included mean age 51 years, 15% women and 45% non-Caucasian. Mean duration of HIV infection was 21 years, with participants having used a mean of 10 previous antiretrovirals. Mean CD4 count was 161 cells/mm<sup>3</sup> with 50% <100 cells/mm<sup>3</sup> and one-third <10 cells/mm<sup>3</sup>. Mean viral load was 100,000 copies/mL with 18% of participants having viral load above this.

At baseline, 50% of participants had resistance to at least three classes, with major mutations to NRTIs, NNRTIs, PIs and INIs on 93%, 85%, 83% and 61%, respectively.

On day 14, mean and median viral load reductions were 1.1 log copies/mL. Viral load reductions of at least 1.0 log copies/mL were reported for 17/38 participants (60%) and 33/38 (83%) had reductions >0.5 log copies/mL (both p <0.0001, compared to control period).

No treatment related serious side effects or discontinuations were reported during days 0-14. The study is ongoing and will continue until week 24. A further phase 3 study is also ongoing. [3]

#### C O M M E N T

**This compound has such a slow development pathway, that the chance to see results is important. Phase 1b efficacy results were first reported in 2008. [4]**

**Ibalizumab is being developed by the Taiwanese company TaiMed but marketing and distribution rights for the US and Canada have been sold to Theratechnologies, whose only other product is tesamorelin (Egtifra) to treat visceral hypertrophy.**

**Top level results from this study were announced in a press release in May 2016. [5]**

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## GSK discontinues development of maturation inhibitor BMS-955176

### Simon Collins, HIV i-Base

**On 26 October 2016, a pharmaceutical news list announced that GSK will stop development of the lead maturation inhibitor BMS-955176. [1]**

This compound was acquired from Bristol-Myers Squibb last year and was already in phase 2b studies.

The announcement was made by GSK CEO Andrew Witty on a routine quarterly earnings call but has not yet been announced more formally.

The decision to end the development programme early was based on 24-week results from study AI468-038, a Phase 2b dose finding study in treatment naive patients, because of gastrointestinal intolerance and treatment-emergent drug resistance. [2]

The ongoing studies with BMS-955176 (AI468-038 and AI468-048) will end early.

Other earlier stage molecules were also acquired when GSK bought the BMS preclinical HIV pipeline in December 2015. This included a second maturation inhibitor in earlier development (BMS-986173) which will continue to be developed.

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#### C O M M E N T

**This is disappointing news as maturation inhibitors would expect to be active about HIV that is multi-drug resistant to HIV medicines from other classes.**

**The announcement referred to continuing development of two other maturation inhibitor compounds. As these are at earlier stages of development, this will set back the timeline for access.**

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## TREATMENT ACCESS

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### **CHAI's ARV market report shows more people than ever on ART in 2015 – and on better ART: but still some way to go**

**Polly Clayden, HIV i-Base**

**Two million more people started ART in 2015, marking one of the largest annual increases. But we still have a long way to go as less than half of the 37 million people living with HIV worldwide are now receiving treatment, according to the 7th CHAI ARV Market Report.**

The Clinton Health Access Initiative (CHAI) ensures rapid access to the best antiretroviral and diagnostic products at affordable prices for low- and middle-income countries (LMIC). And the organisation publishes an annual antiretroviral (ARV) market report for the public domain based on its work in over 30 countries. [1]

The latest issue reports that of the nearly 37 million people needing ART, 46% received it in 2015. This proportion included a growth of two million people receiving ART that year – one of the biggest annual increases ever.

In keeping with this increase, the overall LMIC market expanded to almost \$US 2 billion in 2015. And cost of ART for adults per person year (PPPY) decreased by 6–10% in 2015 from 2014 for adults and second-line for children in generic accessible countries. It now costs about \$US110 to treat an adult with a preferred ART regimen.

Over 70% of both adults and children received WHO preferred regimens (or optimal paediatric formulations as defined by the Interagency Task Team [IATT]). So, cost of treatment generally fell with higher volumes, while quality of treatment rose in generic accessible countries.

Three Indian generic manufacturers – Mylan, Cipla and Hetero – continued to supply approximately 70% of the generic accessible LMIC market.

More countries have adopted Treat All policies – including Botswana, Cambodia, Lesotho, Kenya and South Africa. And guidelines for oral PrEP are being considered for roll-out in many countries.

CHAI note that access to new generic drugs and formulations will provide benefits to people with HIV as well as cost savings.

The first generic dolutegravir (DTG) has now been tentatively approved by the FDA. Botswana became one of the first countries to include DTG in its national guidelines and several others will follow. Low dose efavirenz (EFV400) should be available in 2017 and tenofovir alafenamide (TAF) is also likely to come on to the ARV market over the next two or three years.

For children, the lopinavir/ritonavir (LPV/r) pellets have been launched in a number of countries and several are planning to use the abacavir/lamivudine (ABC/3TC) reduced strength, dispersible tablets.

CHAI are working with trial investigators, regulatory agencies and manufacturers to accelerate the development and availability of these new drugs and formulations.

C O M M E N T

**In the report, the authors from the usually measured organisation state that CHAI is “excited and optimistic about future opportunities in the ARV market”. This is with good reason as recent years have shown both improved regimens and more people receiving ART. Newer drugs and formulations should enhance the market further.**

**CHAI’s annual ARV reference price list for 2016 was also recently published and includes DTG for the first time at US\$4.00 for a bottle of 30 tablets. [2] CHAI notes that The Global Fund’s pricing served as an indicative reference before any generic manufacturer received approval and more refinement to this price is likely since Aurobindo’s tentative US FDA approval.**

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## **New online database for patent expiry dates in low- and middle-income countries**

**Simon Collins, HIV i-Base**

**The Medicines Patent Pool (MPP) have launched a new online database about patent and license information for HIV, HCV and TB drugs.**

The information in MedsPaL has been compiled from a large number of patent offices and other public sources of information. It enables a general understanding of the intellectual property status of over 100 formulations in low- and middle-income countries.

MPP are keen to get feedback on the new resource and the site also allows this.

MedsPaL is available at:

<http://www.medspal.org>

Reference

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## **Global Fund is \$2.6 billion short for 2017-2019: only \$10.3 rather than 12.9 billion is available**

**GFO Newsletter**

**An article in the 17 November issue of GFO newsletter, reports on how the available funding has significantly dropped in the last few months.**

The amount of money available for country allocations for 2017-2019 is \$10.3 billion. This amount includes \$1.1 billion in unused funds from the 2014-2016 allocation period. See Table 1 for details on how the final amount was calculated.

When the Global Fund announced that the Fifth Replenishment had generated US\$12.9 billion, it used a five-year simple moving average (SMA) to convert pledges made in local currencies into US dollars. However, for the purposes of determining how much money is available for the allocations, which are made at the end of 2016, foreign exchange spot rates were used. This explains the downwards adjustment of \$0.89 billion.

When the Global Fund announced that the Fifth Replenishment had generated US\$12.9 billion, it used a five-year simple moving average (SMA) to convert pledges made in local currencies into US dollars. However, for the purposes of determining how much money is available for the allocations, which are made at the end of 2016, foreign exchange spot rates were used. This explains the downwards adjustment of \$0.89 billion.

**Table 1: Calculation of amount available for allocations to countries in 2017-2019 (\$US billion)**

Item	Balance
5th replenishment results as announced 2016-09-17 (\$12.9 billion)	\$12.9 b
<i>Minus</i> adjustment of \$0.89 billion to reflect spot rates as at 2016-09-22	\$12.02 b
<i>Minus</i> adjustment of \$1.12 billion for technical assistance and other donor conditions	\$10.9 b
<i>Minus</i> Global Fund operating costs of \$0.9 billion	\$10.0 b
<i>Plus</i> \$1.1 billion in forecasted unused funds from 2014-2016 allocation	\$11.1 b
<i>Minus</i> \$0.8 billion set aside for Catalytic Investments	\$10.3 b
Total amount available for allocations to countries	\$10.3 b

The downwards adjustment of \$1.12 billion for technical assistance and other donor conditions is broken down as follows:

- \$0.35 billion to account for certain donors withholding portions of their announced pledge amounts to finance technical assistance in countries where Global Fund grant program are implemented;
- \$0.16 billion to account for Debt-to-Health pledges or other permitted earmarked pledges that cannot be considered for allocation purposes given the restricted, targeted nature of such pledges; and
- \$0.61 billion to account for other donor-specified conditions, including any matching pledge amounts from certain donors, up to any predetermined amounts or according to any pre-announced ratios or performance conditions, as well as risk provisions based on historical and anticipated pledge performance across donors.

### Bottom line

Only \$9.2 billion of the \$12.9 billion raised for the 5th Replenishment will go towards allocations to countries. This figure is arrived by deducting the \$1.1 billion in forecasted unused funds from 2014-2016 allocation from the \$10.3 billion total in the above table. This may surprise and even disappoint many people, but the Global Fund was simply following the same process used for the 2014-2016 allocations.

The inclusion of unused funds from the 2014-2016 means that the allocations for 2017-2019 will once again consist of a mix of new funding (from the 5th Replenishment) and existing funding (from the 2014-2016 allocations).

The Global Fund decided that no money from the \$1.1 billion in unused funds from the 2014-2016 allocations would be used to finance initiatives on the Unfunded Quality Demand (UQD) register. The rationale for this decision is as follows: Many initiatives initially registered as UQD have now been financed through grant-making efficiencies and optimisation efforts have partially or fully addressed other 2017 funding priorities. Initially, the Secretariat recommended using funds from the 2017-2019 allocation to finance \$36 million of the remaining registered UQD. However, of the \$700 million validated by the Finance and Operating Performance Committee in March 2016 as available for portfolio optimisation, nearly \$40 million remains available after covering all 2017 priorities with respect to shortened grants and early applicants. So that \$40 million more than covers the \$36 million required for the UQD initiatives.

### Comprehensive Funding Policy

The Board made some changes to the Comprehensive Funding Policy, most of them of the housekeeping variety. Some changes were required to reflect the allocation methodology adopted by the Board in April 2016.

The revised policy includes a description of the methodology for portfolio optimization, including clarification that during an allocation period, new funding may become available due to additional pledges and contributions; unused funds from a grant from a previous allocation period; and forecasted unused funds from grants in the current allocation period.

Other changes included clarifying how the announced replenishment results are derived, and updating the methodology for determining how much money is available for allocations to countries.

The revised policy clarifies that the proposed methodology for a given allocation period is decided by Secretariat but approved by the Audit and Finance Committee prior to its application.

### Civil society concerns

The Developed Country NGO Delegation issued a statement on 13 November which raised some concerns and advanced some recommendations to the Board.

The delegation said that the decision to use the spot rate for currency conversions rather than the SMA rate meant that the US pledge was effectively \$3.86 billion rather than the maximum \$4.33 billion. (According to US law, the country can only contribute 33% of total contributions.) “Access to the full \$4.33 billion will rely on the Global Fund raising additional funds to reach the target of \$13 billion by September 2017,” the delegation said.

The delegation said that the \$13 billion replenishment target was estimated as the minimum amount needed to keep the fight against the diseases “at the right side of the tipping point.” However, the delegation added, UNAIDS, the Stop TB Partnership, and Roll Back Malaria estimate that even with a \$13 billion Global Fund contribution, and even after accounting for contributions from other external funders and domestic investments, “there is a gap of \$20 billion between available resources and global need.”

The delegation said that using the amount of money available for allocations to country, it has done some calculations concerning the funding countries and regions can expect to receive. Its calculations reveal three trends that it labels “problematic”:

Most countries face a level of support that is flat-lined compared to previous allocations.

The region of sub-Saharan Africa is also expected to receive a flat-lined allocation.

Dramatic funding reductions are expected in three regions: Eastern Europe and Central Asia; Latin America and the Caribbean; and the Middle East and North Africa.

However, there is one important caveat: The delegation’s calculations could not take into account the qualitative and other adjustments that the Global Fund will perform after it runs the income level/disease burden model to determine initial allocations to countries. These adjustments can have a considerable impact on what some countries receive.

The delegation recommended that the Secretariat develop an ambitious strategy to mobilize additional resources for the 2017-2019 replenishment cycle. The delegation said that a concrete action plan should be presented to the 27<sup>th</sup> Board meeting, and that a mid-term replenishment meeting should be organized for 2018 and should include a pledging session.

Regarding the Comprehensive Funding Policy, the delegation criticized the requirement in the current policy that all grants approved in a given replenishment period be funded by money available in that period. It said that the Fund should “explore flexibilities” to ensure that funds raised in one replenishment period are spent in that period. “A substantial part (if not all) of the funding of grants that are mainly implemented in a subsequent replenishment term” – i.e. period – “could be funded from resources mobilized in that new replenishment term,” the delegation said.

*The information for this article came from two Board papers – Document GF-B36-02 Comprehensive Funding Policy; and Document GF-B36-03 2017-2019 Allocation: Sources and Use of Funding. Both documents should be available shortly at [www.theglobalfund.org/en/board/meetings/36](http://www.theglobalfund.org/en/board/meetings/36). Additional information came from a statement released by the Developed Country NGO Delegation, a copy of which should be available on the delegation’s website: <http://globalfund-developedngo.org>*

Source:

David Garmaise D, GFO Newsletter. \$10.3 billion is available for the 2017-2019 allocations to countries: Includes \$1.1 billion in unutilized funds from the 2014-2016 allocations. (17 November 2016).

<http://www.aidspace.org/node/3992>

## PREGNANCY & PMTCT

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### **Dolutegravir use in a London cohort – including nine pregnant women**

**Polly Clayden, HIV i-Base**

**Dolutegravir appeared to be safe and effective in pregnancy in a London cohort. Continued data collection is critical.**

Antiretroviral registrational trials are not representative of real life HIV cohorts with fewer women and rare pregnancies. Rebecca Simons and colleagues from Guy’s and St Thomas’ NHS Foundation Trust, London, presented data from an assessment of dolutegravir (DTG) in a clinic cohort – since its approval for use in England in January 2015 – at the 22<sup>nd</sup> BHIVA conference. [1]

The investigators used electronic pharmacy dispensing records to identify patients receiving DTG (plus backbone) or the fixed dose combination (DTG/abacavir/3TC) between 14 January and 30 November 2015.

They identified 181 cohort participants: 127 (70%) men and 54 (30%) women; 9/54 were pregnant. Median age was 42 (range: 22 to 77); 54% white and 25% black-African. Overall 2% were coinfecting with HBV and 6% with HCV.

Eight participants started on DTG and 43 the FDC, 38 were switched to DTG and 92 to the FDC.

The reasons for starting with a DTG-based regimen among treatment naive participants were: preference for an FDC (43%) and concern about CNS side-effects (20%). Reasons for switching included: simplification (31%), CNS or gastrointestinal side effects (26%) and virological failure (12%).

In the treatment-naive group, median baseline CD4 was 392 cells/mm<sup>3</sup> (range 16–833) and viral load 61,983 copies/mL (range 271–2,018,536). At 12 weeks, 79% had undetectable viral load and 93% were undetectable by 24 weeks. Median time to suppression was 42 days.

In the switching group, median CD4 at switch was 508 cells/mm<sup>3</sup> (range 21–1719) and viral load 61,983 copies/mL (range 271–2,018,536; 72% had a viral load <20 copies/mL at switch; of those 100% remained undetectable. Thirty-eight participants (28%) had a detectable viral load at switch (median 372 copies/mL [range 51–869,544]); 91% suppressed by 12 weeks.

There were 9/181 (5%) discontinuations due to toxicity in the cohort of which symptoms improved in 7/9 after stopping DTG. The reasons for these were: dizziness (22%), insomnia (33%), malaise/myalgia (33%). One participant developed acute kidney injury (reduced eGFR by 52%), which improved after stopping DTG.

The pregnant cohort included nine women: median age 27 years (range 22–41); 6/9 black African, 3/9 black British and 1/9 white. They started/switched to DTG or FDC median gestation of 21/40 weeks (range: 8 to 32) with baseline viral load 4959 copies/mL (range: 19 to 40,025).

Reasons given for use were: rapid viral suppression needed (n=4), previous poor adherence (n=4), previous GI side effects with PI (n=1), avoiding future drug-drug interactions with contraceptive implant (n=1), food requirements (n=1), and tolerance and pill-burden (n=1).

DTG FDC was well tolerated with no discontinuations. All seven women who delivered achieved undetectable viral load <20 copies/mL at delivery, one woman had not yet delivered at the time of analysis and the outcome for the remaining woman was unknown. Four women delivered by elective caesarean section and three vaginally. There was one preterm delivery at 28 + 2 weeks in a woman with pre-existing hypertension. The investigators observed no birth defects and all infants to date are HIV DNA PCR negative.

The investigators wrote: “In this diverse but representative cohort, including a significant proportion of women, virological efficacy and discontinuation rates were similar to phase 3 studies. DTG appeared to be a safe and effective treatment in pregnancy although continued data collection will be required.”

#### C O M M E N T

**Like the small cohort receiving DTG/rifampicin shown at Glasgow and described above, [2] small real life studies will contribute to the body of evidence in populations not typically represented in registrational trials, but badly needed to inform global guidance.**

#### References

1. Simons R et al. Dolutegravir use in 181 patients, 54 women and 9 pregnancies – a real life experience. HIV Medicine, Volume 17, Supplement 1, April 2016. Abstracts of the 22nd Annual Conference of the British HIV Association (BHIVA) Manchester. 19–22 April 2016. Poster abstract 9. <http://www.bhiva.org/documents/Conferences/2016Manchester/AbstractBook2016.pdf> (PDF)
2. Clayden P. Dolutegravir-based ART in combination with rifampicin-based TB treatment is safe in a small cohort of co-infected patients. HTB, 3 November 2016. <http://i-base.info/htb/30894>

## **HIV positive and HIV negative pregnancies in the UK and Ireland have similar outcomes including for older women: impressive 15-year review**

**Polly Clayden, HIV i-Base**

**There has been an increase in pregnancies in HIV positive women in recent years in the UK. The proportion among older women has also grown. There has not been an increased risk of preterm delivery, low birth weight or vertical HIV transmission among older mothers. But, similar to the HIV negative population, older HIV positive mothers have a heightened risk of multiple birth, stillbirth or an infant with chromosomal abnormality compared to younger ones.**

In the UK and Ireland, the National Study of HIV in Pregnancy and Childhood (NSHPC) collects comprehensive population-based surveillance data on all HIV positive pregnant women and their children.

Claire Townsend and colleagues conducted an analysis using NSHPC data to compare maternal characteristics and pregnancy outcomes in younger (<40 years) and older (≥40 years) HIV positive women delivering in the UK and Ireland between 2000 and 2014. They reported their findings in the 16 November 2016 edition of HIV Medicine.

The analysis included all singleton and multiple pregnancies reported by the end of June 2015 resulting in live birth or stillbirth to women diagnosed with HIV before delivery and delivering in 2000–2014. It found that among 15, 501 pregnancies, the proportion in older women rose from 2.1% (73/3419) in 2000–2004 to 8.9% (510/5748) in 2010–2014,  $p < 0.001$ .

Older women were more likely to receive ART in pregnancy, and at conception. ART was also started slightly earlier in this age group: median 22.8% vs 23.5% weeks in younger women,  $p = 0.02$ .

There was no evidence of an increased rate of emergency caesarean section or operative vaginal delivery among pregnancies in older vs younger women: 25.7% vs 23.9%,  $p = 0.2$ , and 3.1% vs 4.6%,  $p = 0.1$ , respectively. There was also no increased risk of preterm delivery or low birth weight among deliveries to older women. Infants of older women were slightly more likely to have very low ( $< 1.5$  kg) or high ( $\geq 4$  kg) birth weight but neither association reached statistical significance.

There was no difference in the rate of vertical transmission by maternal age: (older vs younger) 0.6% vs 0.8%,  $p = 0.05$ . There were 13 maternal deaths but none were in older mothers.

The risk of multiple births increased in older vs younger women: 3.0% vs 1.9%,  $p = 0.03$ . And the risk of an infant with a chromosomal abnormality was higher in older women: 1.6% vs 0.2%,  $p < 0.001$  (overall risk of congenital abnormality increased: 4.2% vs 2.8%,  $p = 0.02$ ; the rate of structural abnormalities was similar)

Older mothers had more stillbirths: 1.6 vs 1.0% in younger mothers. This was not statistically significant in univariate analysis: OR 1.70 (95% CI 0.99–3.01),  $p = 0.05$ . After adjustment for time period, parity (no previous births vs one or more previous birth) and type of ART, the association increased and reached statistical significance: AOR 2.39 (95% CI 1.32, 4.32),  $p = 0.004$ . The authors noted that, in this model, the only other variable significantly associated with the outcome was time period.

The authors explain that these findings are consistent with studies in the HIV negative population showing associations between older mothers and outcomes such as multiple pregnancies, chromosomal abnormalities, and stillbirth.

When they compared their data on multiple maternity rates to general population rates in 2014 they found the results to be consistent with their own: 2.9% for women aged 40–44 years (compared with 3.0% in the NSHPC study) and ranging from 0.96% for 20–24 year old women to 2.3% for 35–39 year olds (compared with 1.9% for  $< 40$  year olds).

They also note that the doubled risk of stillbirth associated with older mothers is similar to that found in a meta-analysis of five studies in the general population in high-income countries. The stillbirth rates in HIV positive women were higher than in the general population: 0.47% overall, 0.76% for 40–44 year olds and 0.95% for  $\geq 45$  year olds, with the greatest difference seen for younger women.

Unlike other studies in HIV positive mothers, they did not observe an increased risk of preterm delivery, although the rate was higher overall than in the general population (13.2 vs. 6.2%, respectively).

Limitations to this analysis are that few data are collected on background characteristics and clinical characteristics in pregnancy, and there was no information on factors such as smoking, or history of delivery complications or hypertension.

The authors concluded: “These findings have implications for pregnancy management of older HIV-positive women, given the increased risk of multiple births in this group, as well as pre-existing comorbidities and adverse outcomes such as stillbirth and chromosomal anomalies, as has been reported in the HIV negative population”.

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#### C O M M E N T

**These data are very reassuring.**

**The study shows that since 2000, the overwhelming majority of more than 15,000 HIV positive women have had pregnancies without complications. This includes women above and below 40. And similar to the general population women are choosing to have children older than in the past.**

**Although older age (ie above 40) was linked to higher rates of some complications, very similar age effects occur in HIV negative woman (ie general population data). Most older women understand these slightly higher risks, but it is important that neither HIV itself, nor ART, seems to be as important as maternal age.**

**For those reading the Townsend et al article in a hurry, the abstract does not emphasise the similarities between outcomes in older HIV positive and negative women. But the discussion section is excellent – so it is worth taking the time to read to the end.**

#### Reference

Townsend CL et al. Pregnancies in older women living with HIV in the UK and Ireland. HIV Medicine. 16 November 2016.  
<http://onlinelibrary.wiley.com/doi/10.1111/hiv.12469/full>.

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## TREATMENT GUIDELINES

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### **Factsheets for switching to Rezolsta (darunavir/c) or Evotaz (atazanavir/c)**

#### **Two new factsheets for doctors who are switching patients to coformulated cobicistat-boosted PIs.**

Rezolsta (darunavir/cobicistat) and Evotaz (atazanavir/cobicistat) are new fixed dose combinations (FDC) combining the HIV protease inhibitors darunavir and atazanavir with the pharmacokinetic enhancer cobicistat. When switching from ritonavir-boosted darunavir or atazanavir to the respective FDCs there are multiple clinical differences that need to be considered for each patient.

This resource has been jointly produced by the Royal Free London and Chelsea & Westminster HIV teams and the University of Liverpool HIV pharmacology group.

<http://www.bhiva.org/patient-specific.aspx>

<http://www.bhiva.org/documents/Publications/patient-specific/Resource-guide-to-switching-to-Rezolsta-or-Evotaz-UK.pdf> (PDF)

### **EACS Guidelines updated (October 2016)**

#### **The 2016 version of the EACS Guidelines (version 8.1) was released on 22nd October 2016.**

The guidelines aim to provide easily accessible recommendations for doctors involved in the care of HIV positive people.

The guidelines are available online on the EACS website and as a free App downloadable on IOS and Android, and will be available in eight languages.

#### Reference

EACS. European Guidelines for treatment of HIV-positive adults in Europe, version 8.1 (October 2016).

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

### **Swedish guidelines updated (November 2016)**

#### **The Swedish Medical Products Agency and the Swedish Reference Group for Antiviral Therapy (RAV) have jointly published recommendations for the treatment of HIV.**

Updates in this edition include use of tenofovir alafenamide (TAF) and recommendation that support use of PrEP.

From the first country to reach UNAIDS 90:90:90 target.

#### Reference

Eriksen J et al. Antiretroviral treatment for HIV infection: Swedish recommendations 2016. *Infectious Diseases* (November 2016), DOI: 10.1080/23744235.2016.1247495

<http://dx.doi.org/10.1080/23744235.2016.1247495>

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## HIV PREVENTION

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### **UK 2015 HIV statistics: high engagement with ART but new infections in gay men and late diagnosis overall still high**

**Simon Collins, HIV i-Base**

#### **On 20 October 2016, an early summary of latest annual HIV statistics (for the year 2015) were released from Public Health England. [1]**

The report shows that HIV continues to be an epidemic that disproportionately affects gay men (54% of all diagnoses) and that current prevention options are failing to reduce these rates.

In terms of the 90-90-90 global targets, the percentage of people who are undiagnosed will not be published until November, but this is likely to fall short of 90%. However, 96% of people who are diagnosed overall in the UK are receiving antiretroviral treatment (ART) and 94% of those on ART have undetectable viral load.

## New diagnoses

In 2015, 6095 people (4551 men and 1537 women) were diagnosed with HIV in the UK. This included 65 children, 5012 adults aged 15-49 years and 1018 adults aged 50 years or over.

After adjusting for missing exposure information, 3320 diagnoses (54%) were reported among gay, bisexual and other men who have sex with men. Although a slight decline on 2014 (3,360), new HIV diagnoses among MSM remained high. This reflects an increase in levels of HIV testing as well as ongoing transmission in this group.

A total of 2360 new diagnoses were reported in heterosexual men (1010) and women (1350).

Late diagnosis also remains a significant concern with 39% (2350/6028) of adults diagnosed late stage (defined as CD4 counts < 350 cells/mm<sup>3</sup>). This proportion was higher among heterosexuals, with 55% (490/890) of men and 49% (536/1,094) of women diagnosed late. Rates were lower in MSM (30%; 877/2923). A total of 305 people were diagnosed with AIDS at their HIV diagnosis (CD4 <200) cells/mm<sup>3</sup>).

For geographic differences, late diagnosis was 50% in the Midlands and East of England, 47% in the North of England, 41% in the South of England and 32% in London. MSM in London had a lower rate of late HIV diagnosis (23%; 296/1287) compared to those living outside London (36%; 554/1539). This geographical difference was also observed among heterosexual men outside London (men 57%; 315/552 and women 51%; 361/708) compared to London (men: 52%; 158/303 and women: 47%; 163/346)."

## Effectiveness and use of ART

In 2015, 88,769 people were living with diagnosed HIV and accessed HIV care (61,097 men and 27,672 women). The average age of people accessing care is now 45 and one in three (29,960; 34%) people are now aged 50 years or over.

Of these, 96% are on ART – a rise from 90% in 2014. Estimated rates of viral suppression are also good at 94% of those on ART. The report notes that this will dramatically reduce the likelihood for further HIV transmission even without condoms.

## Mortality rates

Mortality rates were similar to previous years: 613 people with HIV died in 2015, but less than half of these were likely to be AIDS related.

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## C O M M E N T

**Two years ago, an estimated 103,700 people (95% credible interval (CrI) 97,500-112,700) were HIV positive in the UK. A conservative increase of 4% would make this number close to 108,000 for 2015.**

**The UK therefore only diagnoses around 80% of people with HIV, falling short of the 90% global target for this critical first step to ending AIDS. In contrast, Sweden recently reported that at the end of 2015, 90% of HIV positive people were diagnosed, 99.8% of these people were linked to care and 95% of people on ART had undetectable viral load. [2]**

**Health prevention in the UK needs to define targets to reduce HIV incidence. As with many other countries and included in WHO guidelines, we need PrEP to play a key role.**

**The NHS needs to recognise this urgency and provide PrEP as part of an ambitious target to dramatically reduce HIV incidence.**

### Reference

1. Public Health England. HIV diagnoses, late diagnoses and numbers accessing treatment and care. HIV official statistics overview: 2016. PHE publications gateway number: 2016349.  
<https://www.gov.uk/government/statistics/hiv-annual-data-tables>
2. Gisslén M et al. Sweden, the first country to achieve the Joint United Nations Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO) 90-90-90 continuum of HIV care targets. HIV Medicine, online edition. DOI: 10.1111/hiv.12431 (2016).  
<https://www.ncbi.nlm.nih.gov/pubmed/27535540>

## NHS England had no legal basis to delay PrEP: Court of Appeal upholds judgement

Simon Collins, HIV i-Base

**On 10th November 2016, a decision in the UK Court of Appeal showed that earlier attempts by NHS England to avoid the process of evaluating PrEP had no legal basis. [1]**

The legal challenge had been brought by the National AIDS Trust (NAT) after NHS England attempted to derail its own evaluation process in February which delayed access the PrEP by almost a year. [2]

The opportunity to defer providing PrEP was likely to be a delaying strategy as the patent for the individual drugs used for PrEP run out in 2017. In this way, NHS England has squeezed the likely period that it pays for full price PrEP to a minimum. Over this time more than 5000 people are likely to have been diagnosed HIV positive [3], perpetuating a health crisis that is especially high in gay men and transgender people. [4]

Also over this time, community responses to the lack of access to one of the most effective proven protections against HIV included a growing information network that has enabled people to access high quality but low-cost generic versions of the same medicines. [5]

Even though an evidence review from NICE published a month earlier report high efficacy of PrEP in the UK [6], the press statement from NHS England continues to stress that the court decision supporting the ability of the NHS to provide PrEP does not guarantee it will do so. [6]

Even in this latest short statement, one of the four paragraphs makes little sense:

[The judgement]... “overturns the High Court in helpfully clarifying that Parliament did not intend that the NHS was expected to fund local authorities’ public health responsibilities just because they have not done so.”

## C O M M E N T

**This court decision, together with the NICE review, makes it increasingly likely that NHS England will have to provide some level of PrEP for people at high risk. Even if PrEP is approved, then as with new hepatitis C treatment, access is likely to be limited and capped.**

**Since PrEP was approved in the US in 2012, more than 30,000 people are likely to have been diagnosed with HIV in the UK.**

### References

1. NAT press release. Final PrEP HIV drug case win for National AIDS Trust at Court of Appeal. (11 November 2016). <http://www.nat.org.uk/press-release/final-prep-hiv-drug-case-win-national-aids-trust-court-appeal>
2. NHS England. Update on commissioning and provision of Pre Exposure Prophylaxis (PrEP) for HIV prevention. (21 March 2016). <https://www.england.nhs.uk/2016/03/prep>
3. Public Health England. HIV diagnoses, late diagnoses and numbers accessing treatment and care. HIV official statistics overview: 2016. PHE publications gateway number: 2016349. <https://www.gov.uk/government/statistics/hiv-annual-data-tables>
4. NHS England pulls proposed timeline for PrEP: perpetuates HIV health crisis in gay men and trans people. HIV Treatment Bulletin, March 2016. <http://i-base.info/htb/29819>
5. Wang X et al. InterPrEP: internet-based pre-exposure prophylaxis (PrEP) with generic tenofovir DF/emtricitabine (TDF/FTC) in London – analysis of pharmacokinetics, safety and outcomes. Oral abstract O315.
6. NICE. Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil). Evidence summary: new medicine (ESNM78), October 2016. <https://www.nice.org.uk/advice/esnm78/chapter/Key-points-from-the-evidence>
7. NHS England. Update on PrEP. (11 November 2016). <https://www.england.nhs.uk/2016/11/update-on-prep>

## NICE evidence review supports efficacy of Truvada as PrEP in the UK

**Simon Collins, HIV i-Base**

**On 7th October, the National Institute for Health and Care Excellence (NICE) published its evidence review on PrEP concluding: “There is little doubt that Truvada is effective in reducing HIV acquisition in high-risk people who are HIV-negative”.**

The online report has six sections: a summary, introduction and current guidance, product overview, evidence review, context and estimated impact for the NHS.

The NICE review includes results from both the UK PROUD study and the French/Canadian IPERGAY study that both reported efficacy rates of 86% for daily and event-based dosing respectively, although daily dosing is the only currently approved indication.

Importantly, the NICE review also references the Partners PrEP study in heterosexual couples where one partner was HIV positive where uses of daily PrEP reduced incidence of HIV by 75%. This is important for PrEP to be option to be available for heterosexuals in the UK at high risk of HIV.

A separate aspect of these studies that the research does not directly highlight, is that a comprehensive package of HIV prevention is provided for all participants in PrEP studies. This is likely higher level of support than the standard of care and yet participants not using PrEP in the studies, still became HIV positive.

The context notes that 2015 guidelines from both European (EACS) and World Health Organisation (WHO) already recommend PrEP. The professional medical associations BHIVA and BASHH also recommended PrEP in May 2016.

Although efficacy is clear the NICE report also notes that “issues relating to uptake, adherence, sexual behaviour, drug resistance, safety, prioritisation for prophylaxis and cost-effectiveness are also important to consider, especially at a population level”.

#### C O M M E N T

**This positive review was expected, given the previous evidence report produced by NHS England to decide on whether PrEP would be commissioned.**

**Both reviews were also expected to find in favour of PrEP, given that both the US and European drug approval agencies have already approved PrEP based on results from clinical studies.**

**The public consultation on PrEP is now concluded but NHS England have still to announce whether PrEP will be available.**

#### Reference

NICE. Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil). Evidence summary: new medicine (ESNM78), October 2016.

<https://www.nice.org.uk/advice/esnm78/chapter/Key-points-from-the-evidence>

## HEPATITIS

### Tenofovir alafenamide (TAF) approved in US to treat hepatitis B with EU set to follow

Simon Collins, HIV i-Base

**On 10 November 2016, tenofovir alafenamide (TAF) was approved by the US FDA for the treatment of chronic hepatitis B (HBV) infection in adults and adolescents ( $\geq 12$  years and  $\geq 35$  kgs body weight). [1]**

Approval was based on similar efficacy to tenofovir-DF (245 mg) but with improved safety based on kidney and bone markers.

However, for HIV positive patients, TAF needs to be used in combination with other HBV drugs.

The recommended dosage is 25 mg (one tablet) taken orally once daily with food

No dosage adjustment of TAF is required in patients with mild, moderate, or severe renal impairment. TAF is not recommended in patients with end stage renal disease (estimated creatinine clearance below 15 mL per minute)

For full details please refer to the full prescribing information.

Also, on 11th November the scientific committee for the European Medicines Agency gave a positive opinion recommending approval in the European Union. [2] The EU press statement notes that “ TAF as a single-agent for HBV is an investigational product and its safety and efficacy have not yet been established.” [2]

TAF is manufactured by Gilead Sciences and has the brand name Vemlidy for the HBV indication.

#### References

1. Gilead press statement. U.S. Food and Drug Administration approves Gilead's Vemlidy for the treatment of chronic hepatitis B virus infection. <http://www.gilead.com/news/press-releases/2016/11/us-food-and-drug-administration-approves-gileads-vemlidy-tenofovir-alafenamide-for-the-treatment-of-chronic-hepatitis-b-virus-infection>
2. Gilead press statement. European CHMP adopts positive opinion for Gilead's Vemlidy for the treatment of chronic hepatitis B virus infection. (11 November 2016). <http://www.gilead.com/news/press-releases/2016/11/european-chmp-adopts-positive-opinion-for-gileads-vemlidy-tenofovir-alafenamide-taf-for-the-treatment-of-chronic-hepatitis-b-virus-infection>

## ON THE WEB

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### *Conference materials online*

#### **NIAID Strategies for an HIV Cure Workshop**

**The third US National Institute of Allergy and Infectious Diseases (NIAID) scientific workshop on HIV cure research was held from 14-16 November 2016.**

For the first time, the proceedings are available by webcast at the meeting website.

Meeting:

<https://respond.niaid.nih.gov/conferences/hivcuremeeting2016/Pages/Agenda.aspx>

Webcasts:

<https://respond.niaid.nih.gov/conferences/HIVCureMeeting2016/Pages/default.aspx>

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

**26 - 27 September 2016, Washington DC**

**This annual workshop very helpfully makes the abstract book and some presentations available online after the meeting.**

Website:

<http://www.infectiousdiseasesonline.com/event/workshop/7th-international-workshop-hiv-aging>

Abstract book:

<http://regist2.virology-education.com/2016/7HivAging/Abstractbook.pdf> (PDF)

Some presentations are also available:

<http://www.infectiousdiseasesonline.com/7th-international-workshop-hiv-aging-2/>

#### **European HIV Clinical Forum: Integrase Inhibitors**

**22 October 2016, Glasgow**

**Abstracts, presentations and some webcasts are available from this workshop on integrase inhibitors, held in Glasgow just before the 2016 Glasgow HIV Congresss.**

<http://www.infectiousdiseasesonline.com/event/workshop/2nd-european-hiv-clinical-forum-integrase-inhibitors/>

Abstract book:

<http://regist2.virology-education.com/2016/hivGlasgow/Abstractbook.pdf> (PDF)

## FUTURE MEETINGS

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### Conference listing 2017

The following listing covers some of the most important upcoming HIV-related meetings and workshops. Registration details, including for community and community press are included on the relevant websites.

#### **7th International Workshop on HIV & Women**

11 – 12 February 2017, Seattle, WA, USA  
<http://www.virology-education.com>

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

13 – 16 February 2017, Seattle  
<http://www.croiconference.org>

#### **BHIVA 'Best of CROI' Feedback Meetings (2017)**

27 February – 9 March 2017, various UK cities  
February: London 27th, Edinburgh 28th,  
March: Wakefield 1st, Cardiff 2nd, Birmingham 7th, Haydock 8th, Newcastle 9th.  
<http://www.bhiva.org>

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

18 March 2017, Sydney  
<http://sexualhealthmedicineasm.com.au>

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

4 – 7 April 2017, Liverpool  
<http://www.bhiva.org>

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

14 – 16 June 2017, Chicago, (tbc)  
<http://www.virology-education.com>

#### **9th IAS Conference on HIV Science**

23 – 26 July 2017, Paris, France  
<http://www.ias2017.org>

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

6 – 8 November 2017, Johannesburg  
<http://www.HIVresistance2017.co.za>

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## PUBLICATIONS & SERVICES FROM i-BASE

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### **i-Base website**

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

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

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

Publications and regular subscriptions can be ordered online.

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

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

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

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- NEW: Introduction to ART (September 2016)
- NEW: HIV & quality of life: a guide to side effects & better long-term health (Sept 2016)
- NEW: Guide to PrEP in the UK (November 2016)
- HIV testing and risks of sexual transmission (June 2016)
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- ART

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

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