

## september-october 2015

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## EDITORIAL

### **This issue of HTB includes the last conference reports from IAS 2015 and the 16th PK workshop together with conference news from the 55th ICAAC.**

We also report on newly released treatment guidelines from both BHIVA and WHO, most significantly recommending universal ART irrespective of CD4 count based on results from the START study. BHIVA also notably drop efavirenz as a preferred drug for first-line ART and WHO recommends broader use of PrEP. Both these evidence-based guidelines will advance the standard of care but challenge financially constrained health systems.

Issues of treatment access are covered in other articles include concerns over the Transatlantic Trade and Investment Partnership (TTIP) proposals. This protracted trade proposal (currently in the 11th round of negotiations) is designed to extend the power of large multinational companies. TTIP is being discussed/negotiated/imposed in secret but potentially threatens to extend patent restrictions on medicines. We include an example of the excesses of monopoly drug licensing with the example of price increases for pyrimethamine in the US and a new report on the TTIP threat for global access to treatment.

Related to access to drugs in the UK, we include several articles about buying generic medications online for personal use. Awareness that this is both legal and cost effective makes this an option that many people in the UK might have to consider for prompt access to new hepatitis C drugs and for generic tenofovir/FTC for PrEP.

The support by an Australian medical association for people to access generic versions of new hepatitis C drugs is based on both their high efficacy and safety data but extremely limited access due to out-of-reach prices of the originator versions. We include the guidance in full because this is just a important for people in the UK.

Other PrEP news includes the launch of the first NHS clinic to offer monitoring services needed by people who are already independently sourcing PrEP online. Also, that two new community websites include excellent information on how to do this.

The team at 56 Dean Street should be commended for this service, which developed from a private PrEP clinic launched in August 2015. A revision to the initial pricing means that routine monitoring and advice is now available as a free NHS service.

The NHS now needs to rapidly decide for criteria on how and when PrEP will be prescribed: currently the Dean Street clinic can only provide private prescriptions for medication and drug level testing to confirm that generic PrEP includes active tenofovir DF.

## Supplements to this issue of HTB

Two supplements are included with this issue of HTB. Both resources are updated to include the recommendations from the 2015 BHIVA guidelines.

### **Introduction to ART (16th edition)**

The 2015 update to the i-Base guide to combination therapy – now in its 16th edition – has been retitled *Introduction to ART*.

This 48-page A5 booklet includes essential information for anyone starting treatment (or already on treatment), especially if they are recently diagnosed.

### **New pocket guide to ART**

The second supplement – *Pocket ART* – is a new small concertina folding A7 leaflet that is designed to be an even simpler and more direct introduction to ART.

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

All with all i-Base material, both resources are free in the UK. Please order online or use the fax-back form on the back cover of HTB.



## CONFERENCE REPORTS

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### **55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)**

**17 – 21 September 2015, San Diego**

#### **Introduction**

**This large annual meeting usually includes some interesting studies, even though HIV now has a smaller role in the programme than in previous years.**

The programme and abstracts from the conference are available online in a searchable database.

<http://www.abstractsonline.com/plan/start.aspx?mkey=%7B7A574A80%2DEAB1%2D4B50%2DB343%2D4695DF14907E%7D>

<http://www.abstractsonline.com/plan/AdvancedSearch.aspx>

Reports in this issue are thanks to NATAP.org.

- No transmission of integrase-resistant HIV seen in California cohort
- Doubled hypogonadism rate in middle-aged men with HIV: fat is a factor
- Protection against flu but not HBV in vaccinated perinatally HIV-infected children

### **No transmission of integrase-resistant HIV seen in California cohort**

**Mark Mascolini, for NATAP.org**

**Genotypic analysis of transmitted drug resistance (TDR) in a large California cohort disclosed not a single case of TDR to integrase inhibitors. TDR rates involving NRTIs, NNRTIs and PIs were in line with previously reported findings.**

Integrase inhibitors have been on the market since 2007, noted Monogram Biosciences researchers who conducted this study. But rates of TDR to this increasingly used antiretroviral class remain poorly characterised. The Monogram team found only three cases of integrase inhibitor TDR reported in the literature. In contrast, volumes of work have addressed TDR to the first three antiretroviral classes.

To learn more about recent TDR to integrase inhibitors and the first three classes, Monogram investigators analyzed genotype resistance test results in their commercial database from March 2013 through June 2015. They looked specifically at samples from 13 California sites of the AIDS Healthcare Foundation Network, and they characterised a sample as resistant according to the surveillance drug resistance mutations list in the Stanford University HIV Drug Resistance Database ([http://cpr.stanford.edu/input/sdrm/SDRM\\_2009.txt](http://cpr.stanford.edu/input/sdrm/SDRM_2009.txt)).

The analysis involved 339 genotypic results of HIV-positive people who had not begun antiretroviral therapy. Overall 2013-2015 TDR prevalence stood at 24.9% but varied substantially from year to year – 24.2% in 2013, 30.2% in 2014, and 15.9% in 2015. For the whole 3-year period, TDR prevalence was highest for NNRTIs (16.9%), followed by NRTIs (6.5%), and PIs (4.2%). No samples harboured integrase inhibitor TDRs.

NNRTI TDR prevalence jumped from 13.2% in 2013 to 22.6% in 2014 then dropped to 10.2% in 2015. NRTI TDR prevalence fell through the three study years, from 9.9% to 5.7% to 4.5%. PI TDR rates stayed nearly flat: 4.4% to 4.4% to 3.4%. The most frequently transmitted mutations were K103N/S (13.0%), L90M (2.7%), and Y181C/I/V, M41L, and M184V/I (2.1% each).

Prevalence of TDR involving the first three antiretroviral classes proved lowest in 149 samples from people 19 to 29 years old (about 20%), rose to about 30% in 163 samples from people 30 to 49 years old, and came close to 60% in 26 samples from people 50 or older.

Monogram data indicate that prevalence of integrase inhibitor mutations acquired during therapy has stayed low across the 3 years of study – below 4% in 2013 and 2014, and below 3% in 2015.

“Despite predictions to the contrary,” the Monogram team concluded, “the study demonstrates that TDR involving

integrase inhibitors has been and remains surprisingly rare.” But substantial prevalence of TDR to the other classes, they suggested, supports continued use of pretreatment HIV resistance testing.

Reference

Volpe JM, Yang O, Petropoulos CJ, Walworth CM. Absence of integrase inhibitor resistant HIV-1 transmission in the California AIDS Healthcare Foundation Network. ICAAC 2015, September 17-21, 2015, San Diego.

## **Doubled hypogonadism rate in middle-aged men with HIV: fat is a factor**

**Mark Mascolini, for NATAP.org**

**Hypogonadism (low testosterone) affected 12% of middle-aged HIV-positive men, a rate twice that seen in the general population, according to results of a preliminary study in France. More than 5.5 years of antiretroviral therapy (ART) and total fat above 19% independently predicted hypogonadism in these men.**

French researchers from Turcoing Hospital and other centres noted that hypogonadism has been linked to an array of conditions in men, including osteoporosis, decreased lean body mass, erectile dysfunction, depression, and metabolic syndrome. The research team observed that hypogonadism prevalence has dropped in men with HIV since the arrival of combination ART and is no longer correlated with low CD4 counts. But because hypogonadism remains poorly defined in men with HIV, they undertook this preliminary single-centre study to define the prevalence of hypogonadism and to identify risk factors.

This cross-sectional study involved 113 young and middle-aged men with virologic suppression on ART. The researchers defined hypogonadism as serum free testosterone (measured twice in the morning, when testosterone is highest) below 70 pg/mL. They used logistic regression to identify factors associated with hypogonadism. They also measured an array of other variables including sociodemographic factors and anthropometric measures and bone density by DXA scan.

The study group had a median age of 41 (interquartile range 36 to 46), 94% were Caucasian, median body mass index measured 23 kg/m<sup>2</sup>, 42.5% smoked, 11.5% drank more than 20 g of alcohol daily, and 57.5% were physically active. Fourteen men (12.4%) had hypogonadism, all due to hypothalamic-pituitary axis dysfunction. This rate is twice that of men in the general population, the researchers noted. Men with hypogonadism were older than those with normal testosterone (median 45.3 versus 41 years) and had a higher smoking prevalence (50% versus 41%). They did not differ from eugonadic men in body mass index (23.5 versus 23 kg/m<sup>2</sup>), trunk fat (18% and 18%) or total fat (20% and 19%).

Men with hypogonadism had a longer duration of HIV infection and antiretroviral therapy, and a higher proportion had taken an integrase inhibitor (21% versus 11%). Osteoporosis was more prevalent among men with hypogonadism (15.4% versus 9.6%,  $p = 0.03$ ), and they had higher median sex hormone-binding globulin (61.65 versus 40.4 nmol/L,  $p = 0.001$ ), lower estradiol (18 versus 13.5 pg/mL,  $p = 0.001$ ), and lower prolactin (6 versus 18 pg/mL,  $p = 0.01$ ). Logistic regression identified three variables independently associated with higher odds of hypogonadism, at the following adjusted odds ratios (aOR) and 95% confidence intervals:

- Total fat mass above 19%: aOR 6.41, 1.3 to 32.6,  $p = 0.03$
- More than 5.5 years of ART: aOR 8.54, 1.7 to 42.86,  $p = 0.01$
- More than 2 years of integrase inhibitor therapy: aOR 17.03, 2.2 to 129.6,  $p < 0.01$ .

The researchers noted that the association with longer integrase inhibitor therapy must be interpreted cautiously because of the wide confidence interval. They concluded that hypogonadism is common in young and middle-aged men with HIV and should be tracked. They suggested that antiretroviral duration longer than five years and total fat above 19% could be used to identify men at risk. The investigators are recruiting a larger sample to confirm these findings.

Reference

Pasquet A, Lachatre M, Soudan B, et al. Preliminary results of the study hypogonadism and persons living with HIV. ICAAC 2015, September 17-21, 2015, San Diego. Abstract H-1207.

## **Protection against flu but not HBV in vaccinated perinatally HIV-infected children**

**Mark Mascolini, for natap.org**

**Children perinatally infected with HIV usually had protective levels of antibodies against influenza after three or more vaccinations. But completing a hepatitis B virus (HBV) vaccination schedule usually did not yield protective levels of antibodies against HBV.**

B-cell compartment defects in perinatally infected children can thwart responses to standard vaccines, noted University of Texas investigators who conducted this study.

Poor responses to these vaccines and less durable immunity have led to proposals for booster immunisations, modified regimens, modified immunogens, and other revamped vaccination strategies. But now, the Texas team observed, many perinatally infected children have responded well to antiretroviral therapy for several years and have a good immunologic status. Some argue that these children are essentially normal immunologically and that they should follow standard paediatric immunisation schedules.

The University of Texas researchers conducted this study to see if immune responses to influenza and HBV vaccination in perinatally infected children with well-controlled HIV were equivalent to responses in HIV negative adults. They picked influenza and HBV vaccinations because the two have distinct immunisation schedules. All children had received three or more influenza shots and a complete series of HBV immunisations. All had taken antiretroviral therapy for at least 6 months. The researchers selected significantly older HIV negative adults as a rigorous set of controls for immunologic memory. They measured plasma antibodies to influenza (H1N1 and H3N2) and HBV by haemagglutination inhibition and ELISA.

The 21 youngsters with HIV had a median age of 15.2 years, compared with 42.0 in the 11 adult controls. Eleven children with HIV (52%) were girls, 14 (67%) had a viral load below 400 copies, and 7 had a viral load above 400 copies. CD4 percent in the HIV group averaged 29.8%. Only 3 children had started ART within the first year after HIV diagnosis. For the youngsters with HIV, median time elapsed between the last two HBV vaccinations was 10.1 years, and between the last two influenza vaccinations 0.6 year. Vaccine-specific antibody titers to H1N1 and H3N2 did not differ substantially between the youngsters with HIV and HIV negative controls, regardless of HIV load in the children. Antibody titers to HBV were significantly lower in children with HIV than in HIV negative controls, and the titers did not differ between children with a viral load above versus below 400 copies.

Defining protective titers against H1N1 and H3N2 as  $\geq 1.4$ , the investigators found no significant difference in proportions protected between either HIV group (above or below 400 HIV RNA copies) and the HIV negative controls. Defining protective titers against HBV as above 2.1, they recorded protective titers in 14.3% of the sub-400-copy HIV group and 28.6% of the 400-plus-copy HIV group, compared with 66.7% of HIV negative controls ( $p < 0.009$  for both comparisons).

The University of Texas team proposed that “the persistence of protective levels of neutralising antibodies to influenza but not HBV in this population may be the consequence of repeated influenza vaccinations.” If that explains the difference between protection against influenza and HBV, they suggested, it could stress “the potential efficacy of providing structurally different [antigen] motifs in an intermittent way to assure a long-lasting immune response in infected children.”

#### Reference

Contreras GA, Zahkour R, Murphy JR, Heresi GP. Revaccination in perinatally HIV-infected children: the case of influenza and HBV. ICAAC 2015, September 17-21, 2015, San Diego. Abstract H-1223.

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=8c3ac1f5-1f12-45ec-9c83-e5769a794609&cKey=ac03b8f5-5e83-496b-978b-bce0fd37a602&mKey=7a574a80-eab1-4b50-b343-4695df14907e>

## CONFERENCE REPORTS

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### **8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015)**

**19 – 22 July 2015, Vancouver, Canada**

#### **Introduction**

**This issue of HTB includes our final reports from the 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015) that was held from 19 – 22 July 2015.**

This large biennial meeting has a greater focus on clinical and scientific research than the broader social-based programme of the International AIDS Conference with which it alternates every two years.

The programme for the conference is now posted to the IAS 2015 website as PDF files and the Programme-at-a-Glance (PAG) is also online.

<http://www.ias2015.org>

<http://www.pag.ias2015.org>

As with previous IAS conferences, nearly all oral presentations are available as webcasts, including most plenary lectures, special symposia, oral abstract sessions and the opening and closing ceremonies. Many of the PowerPoint slides from talks and PDF files of posters are also online.

A short guide to using the programme-at-a-glance is online.

<http://i-base.info/htb/28686>

Unfortunately, URL hyperlinks to individual abstract and webcasts are not longer available with the current PAG, which is likely to limit access to this otherwise important aspect of the conference.

Reports in the issue are:

- The PrEP experience: IAS 2015 and beyond
- Raltegravir for neonates will require a complicated dosing regimen
- News and notes on HIV cure research from IAS 2015

IAS 2015: PREVENTION

## **The PrEP experience: IAS 2015 and beyond**

**Simon Collins, HIV i-Base**

**Oral pre-exposure prophylaxis (PrEP) was a major conference theme at IAS 2015 and featured in numerous plenary talks, oral abstracts and dozens of posters.**

Apart from a few notable exceptions discussed below, the integration of PrEP into many overview talks was perhaps more significant than the new data from individual studies. PrEP is now expected to play a key role in reducing HIV incidence globally, being included as a recommendation in WHO treatment guidelines and as part of the UNAIDS 90:90:90 campaign. [1, 2]

In one of the first plenary talks at the conference, Francois Venter from the University of Witwatersrand, gave a compelling perspective from a doctor on the comparative roles for different biomedical prevention options. He described the new data on PrEP as an “electrifying moment” remarkable for working far better in real life settings than in the randomised regulatory studies: the higher someone’s risk of HIV, the more likely they are to take PrEP and benefit. The earlier preoccupation about risk compensation has now been largely debunked and drug resistance occurred at very low rates in studies. With the more realistic acceptance that condoms alone are clearly not enough for many people at high risk, the cost of PrEP is now a major barrier to wider access, especially in higher income countries. [3] In the UK, this has partly been overcome by increased off-label use of generic PrEP over the last year - imported for personal use from internet pharmacies - that is both cheap and legal.

Given that the potential for using tenofovir disoproxil fumarate (TDF) before exposure to prevent HIV infection has been known for more than two decades, [4] the timeline for PrEP has been very slow.

Irrespective of scientific questions of efficacy, several studies at IAS 2015 also touched on why historical attitudes to HIV prevention, including HIV-related stigma, continue to block access to this option for better health.

PrEP research also involves more difficult challenges than treatment research. On the one hand, with good adherence, daily or near-daily dosing achieves greater than 99% protection against HIV infection. This is a remarkable fact. On the other hand, the unpredictability of real life, and the short but important delay before oral PrEP offers protection, highlights the urgency of finding alternatives to daily dosing that will have comparable close-to-100% efficacy.

The two drugs used in current oral PrEP – TDF and emtricitabine (FTC) – have different absorption times, for different body sites, that includes important dosing differences between men and women. The difficulty with interpreting pharmacokinetic (PK) data was nicely understated by Dave Glidden from University of California in a talk at IAS 2015 that looked at how quickly PrEP becomes protective: “We don’t totally understand how much drug there needs to be, where it needs to be, and when it needs to be there”. [5]

The main dosing difference is driven by the 10- to 100-fold higher intracellular tenofovir diphosphate levels in rectal compared to vaginal tissue. This translates to guidance for optimal adherence to daily dosing as requiring 4-7 doses a week for men and 6-7 doses a week for women. However, this is based on a modelled target IC90 for tenofovir of  $\geq 15.6$  fmol/million viable PBMCs, which still needs to be confirmed in clinical studies. It is also unclear how to interpret the wide confidence interval for this target (95%CI: 3.0 to 28.2). [6]

### **Importance of different dosing strategies based on different HIV risk**

On a population level (rather than individual protection), whether or not PrEP has a long-term impact on reducing rates of transmission might be dependent on having options of different dosing strategies that can be flexible and adapted to individual risk and changes in risk.

Someone who is at risk several times a week has different needs from PrEP compared with someone whose HIV risk might be less than once a month. Individuals commonly change their degree of risk, so dosing needs to be adaptable to the dynamic of changing personal circumstances.

For all the best supporting data, daily PrEP is unlikely to be sustainable for many years for someone at very low risk when the risk:benefit ratio might not support broad use based on safety, adherence and cost. But demand for PrEP might actually be highest from people with relatively few risks. This might relate to quality of life issue for people who want to be able to have sex without the fear of HIV, irrespective of whether they use a condom.

Patterns of PrEP taking varies greatly in efficacy studies. Both IPREX and IPERGAY demonstrated this when adherence was shown as median numbers of pills taken by each individual for each 1-3 month period during the studies. Only a minority of people showed either consistently high or constantly low adherence throughout. Variation in adherence was far more common: consistent high adherence for several months, followed by a break with low or minimal use of PrEP. Both studies suggest that it is common for periods of risk to vary considerably for many people.

### **HPTN 067 - three dosing strategies to achieve PrEP protection in relation to risk**

Several different analyses from the HPTN 067 ADAPT study were presented at IAS 2015 in symposia, oral abstracts and posters. This study is important because it randomised three socially distinct groups of people at high risk of HIV infection, each to three different PrEP dosing strategies.

The primary outcome of the study was adherence based on drug coverage in relation to risk - ie not just as a measure of pills taken. This combined adherence endpoint was measured using electronic pill boxes and weekly phone calls from a researcher. Coverage was defined as someone having taken one or more pills in the four days before sex and one or more pills in the 24 hours after sex. Partial coverage was when only one of the components were taken.

The three groups were: gay men and transgender women in Harlem (US), gay men and transgender women in Bangkok (Thailand), and heterosexual women in an informal settlement near Cape Town (South Africa). Median age was approximately 30 years in all studies with up to one third of participants younger than 25. All three groups were at high risk, with 12%, 19% and 7% of potential participants testing HIV positive during screening in the Harlem, Bangkok and Cape Town groups respectively. A small number of transgender women were enrolled in the Harlem and Bangkok sites.

The dosing strategies were: daily PrEP (D); time-based PrEP (T) - defined as two pills a week, plus one pill after sex; and event-based PrEP (E) - defined as one pill before sex and one after. The study design included: a four week lead-in period where once weekly (ie suboptimal) dosing was directly observed (DOT); a two week PK and washout period; 24 weeks of self-administered dosing; and a final 4 week washout period that included quantitative research. Participants were told that efficacy for PrEP had only been proven for daily dosing.

Bob Grant from UCSF presented the overall study design, [7] including the results from Cape Town, previously presented earlier this year at CROI 2015 [8].

Results from the Harlem and Bangkok groups were presented for the first time at IAS 2015, both in the symposium on PrEP (that was webcast) and later the same afternoon as oral late breaker abstracts (that were not). PK sub-studies were only included for the Cape Town and Bangkok sites.

Although HPTN 067 was not powered for efficacy, the few infections that occurred were all in people with either very low or no detectable drug levels at seroconversion. There were 1, 2 and 2 new infections at the Harlem, Bangkok and Cape Town sites respectively during the suboptimal lead-in DOT phase and 1, 0 and 5 new infections during the 24-week main study.

For the women in Cape Town, daily dosing regimen resulted in greater drug coverage – in relation to times someone had sex – than either time-based or event-based dosing (75% vs 56% vs 52% of events covered,  $p=0.0006$  D/T,  $p<0.0001$  D/E,  $p=NS$  T/E). In the PK sub-study, daily dosing resulted in a higher percentage (of participants who had sex in the previous seven days) with detectable intracellular tenofovir (in 81% vs 52% vs 54% by group at week 10 and 56% vs 46% vs 32% at week 30). This was defined as levels  $>9.1$  fmol/million PBMCs, which approximating to two doses/week. [7]

In the Harlem group, daily PrEP again resulted in significantly greater coverage for the times people had sex (66% vs 47% vs 52%,  $p=0.001$  D/T and D/E,  $p=NS$  T/E). [9, 10] As in the Cape Town site, when people reported partial coverage, it was the post-dose that was generally missed.

In contrast, the Bangkok group reported much higher drug coverage for all strategies (85% vs 84% vs 74%). For people reporting partial coverage, the pre-dose was taken more often than the post-dose. In the PK sub-study, intracellular tenofovir was detectable in  $>85\%$  of participants who had sex in the previous seven days, (in 100%, 87% and 93% at week 10 and 91%, 95% and 86% at week 30, in the D, T and E groups respectively). In the context of high adherence,

the long intracellular half-lives of both drugs (40 to 60 hours), probably contributed to showing similar protection to daily dosing. In this context, event-based dosing achieved similar coverage with significantly fewer doses. [11, 12]

Although not explicitly reported, the difficulty with the post-sex dose reported in all three sites, might have been related to a misunderstanding that this dose does not have to be immediately afterwards, but anytime over the subsequent 24 hours.

Qualitative results from all three sites provided important insight into some of the social determinants relating to PrEP. HIV-related stigma against people who were HIV negative was commonly reported based on the false assumption that having HIV meds meant they were positive. [13, 14, 15]

Stigma and misconceptions were reported in all countries, again when people were taking PrEP at the time of sex – which misses a key benefit of PrEP actually being better if taken the day before, at any time on the day of sex and anytime the day after.

### **Unanswered questions relating to IPERGAY event-based dosing**

The French/Canadian IPERGAY study set out to look at event-based dosing using a randomised placebo-controlled design that was powered for efficacy. The IPERGAY dosing is increasingly important because it is currently being used in the UK as a basis for taking PrEP, even though the study itself produced only limited data from people who only had sex infrequently.

IPERGAY has some similarities to the UK PROUD study. Both studies were in a similar high-risk population of gay men, and both reported 86% reductions in HIV infection from PrEP in presentations at CROI 2015 following a DSMB recommendation to offer immediate PrEP to all participants. [16, 17]

But while PROUD used daily dosing, IPERGAY used event-based dosing that involved a minimum of four pills from having sex once. This schedule was:

- A double pre dose (2 x coformulated TDF/FTC taken 24 to 2 hours before sex).
- A single TDF/FTC taken within 24 hours of having sex - and also on each subsequent day if they had sex for a few days - and
- A final single TDF/FTC taken the day after the last sex.

Lead investigator, Jean-Michel Molina from Saint-Louis Hospital Paris covered some of the outstanding issues about the IPERGAY dosing in an oral symposia session. This talk provided background information about PK evidence supporting event-based dosing together with new PK results. [18]

The results from IPERGAY need to be interpreted knowing that study participants were generally a sexually active cohort. The median number of pills taken per month in IPERGAY was 16 (IQR: 12 to 24 pills). Someone having sex once every week therefore more closely approximated someone taking four doses a week, rather than just relying on starting from zero drug levels using the dosing strategy in isolation. The iPrEX study has already shown that four doses a week achieves >95% protection in a similar high-risk group of gay men [6]. This means that the results from IPERGAY cannot (yet) be extrapolated to less frequent PrEP use.

Evidence used when planning IPERGAY, included macaque data using TDF/FTC with a 2-hour pre-dose and 24-hour post dose. Over 14 weeks, 5/6 animals were protected from weekly rectal exposure, with one infection occurring at week 5. By comparison, all 6/6 animals in the control group became infected. The same study showed that drug levels of tenofovir were detectable in plasma after two hours but not in rectal tissue until 24 hours. Levels of FTC were detectable at the 2-, 5- and 24-hour time points in both plasma and rectal secretions. With only these three time points, we do not know when tenofovir became detectable between the 5- and 24-hour time points. [19]

New data from IPERGAY was presented from a PK sub-study involving 12 participants who received a single double-dose (2 x TDF/FTC) with plasma, PBMC, dried blood spot, saliva and rectal tissue samples taken at 0, 0.5, 1, 2, 4, 8 and 24 hours (2 participants per time point). Similar to data from HIV positive people on ART, drug levels of FTC triphosphate were rapidly detected in rectal tissue after 30 minutes, but tenofovir diphosphate was still not detected after 8 hours and was only detectable at 24 hours.

As with the earlier macaque study, there is no information from between the 8- and 24-hour time points - something that clearly would have practical importance when recommending dosing strategies. It might also be important that levels following the single double-dose were significantly lower compared to control participants at steady state from daily dosing (approximately 5 vs 10 ng/mg).

Another point is that the double-dose approximately doubles the C<sub>max</sub>, AUC and C<sub>min</sub> drug levels of both tenofovir and FTC compared to historical single dose controls. But the double-dose has little if any impact on the T<sub>max</sub> - ie how quickly levels are reached. Although the double-dose intuitively implies a faster potency, it is unlikely to overcome the 24-hour time for tenofovir to achieve protective levels in rectal tissue. This is a critical parameter when recommending minimum timing for the pre-exposure dose.



When the pre-dose is taken less than 24 hours before sex, ie 2-8 hours before, it is difficult to know how much FTC alone contributes to PrEP. Macaque data supports partial protection from FTC alone [20] but the results from the Partners PrEP study reported no significant difference between TDF monotherapy and TDF/FTC dual therapy. [21]

In the PK subsidy of IPERGAY, a trend to partial protection at early time points from using the double-dose was reported from ex vivo rectal tissue using a quantitative infectivity score, but this had no control group using a single TDF/FTC dose for this indirect marker for protection.

Also, although it did not directly inform the IPERGAY strategy, an HIV negative study was also referenced to show that daily dosing achieves EC90 drug levels in rectal PBMCs associated with >90% protection (95%CI: 60% to 96%) after three days and >99% (95%CI 69% to 100%) after 5 days. After achieving steady state with daily dosing, levels remained high for seven days after stopping PrEP, but this would not be the case with less than daily dosing. [22]

This is important practical information for people using daily dosing, as clinical studies including PROUD have previously recommended daily dosing for 1 to 2 weeks before assuming protective drug levels are achieved.

Jean-Michel Molina concluded his talk with an important clarification: "Clearly the effectiveness of the IPERGAY dosing strategy in people having frequent sex taking multiple pills cannot yet be extrapolated to people who have less frequent sex". He also noted that he hoped that additional follow-up from the ongoing open label phase might provide additional data to address this issue.

## Conclusions

PrEP is a fast changing field and many more studies at IAS 2015 were presented than could have been included in this report.

Numerous posters were notable for reporting little or no evidence that access to PrEP increased high-risk behaviour. These studies often noted that risk factors among the people using PrEP are already high and that resources might be more appropriately focused on increasing awareness of PrEP and supporting adherence (including perhaps with text messaging). [23, 24, 25, 26, 27, 28, 29, 30]

Several of these studies also looked at barriers to PrEP in different populations, including transgender people, who although included in some PrEP studies are still under represented. [31]

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## C O M M E N T

**These studies show not only continued efficacy and safety but that flexibility for dosing is likely to be essential if PrEP is to become widely used.**

**While the NHS has been deciding on criteria for free access, off-label generic use has already become common in the UK. [32]**

**Doctors are therefore increasingly likely to be asked for advice about PrEP and about access to monitoring. This advice is likely to be different depending on whether cost is a factor that limits daily use.**

**The NHS clinic at 56 Dean Street should be commended for responding to demand by offering a PrEP service. Initial costs have already been reduced and services include an option of drug level testing to confirm that internet-sourced drugs are genuine. [33]**

**Off-label use is also currently destabilising HIV post-exposure prophylaxis (PEP) services in London. [34] Given the inconvenience of "clinic hopping" this could be reduced by better awareness that buying generic PrEP online for personal use is both legal in the UK and is dramatically cheaper than Gilead's Truvada at £400 a month. Cipla's Tenvir-EM costs approximately £40 to £70 for 30 tablets, depending on online supplier. [32]**

**Buying generic PrEP online makes it more affordable - approximating to condoms and lube or a few pints - even using daily dosing. As access to PrEP on the NHS, when it becomes available, is likely to be very limited while TDF/FTC remains patent protected, this model approximates that for access to sildenafil. This drug was not available on the NHS when it was first approved but the huge demand was managed by private prescriptions (for the licensed drug).**

**When daily generic dosing is not affordable, alternate day dosing to achieve four doses a week, is likely to produce similar (>95%) reductions in risk and enable a month supply to cover two months. This dosing strategy halves the generic costs.**

**Infrequent event-based dosing is supported by less data, but aiming for a 24-hour rather than 2-hour pre-dose, will enable tenofovir to be active in rectal tissue. Post-exposure doses are essential: daily dosing through the period of sexual activity, plus additional doses in the day or days afterwards. This should be included in information about PrEP, until new data shows otherwise.**

**It is unclear how much the double pre-dose of TDF/FTC in IPERGAY contributes to protection. Although FTC rapidly reaches rectal tissue it is difficult to estimate the level of protection this provides in absence of tenofovir.**

**Although the post-dose is essential, HPTN 067 and other studies have reported that this is more likely to be missed than the pre-dose. This should be a focus for community education and support, given that intuitively it should be easier to do something after an event, because the event itself should be the prompt, and it is more difficult to successfully plan for something that has yet to happen. Communication about the timing of the post dose seems to require further research.**

**HPTN 067 showed that in the context of good adherence (>85%), both time- and event-based dosing strategies provided similar coverage/protection to daily dosing, but with significantly fewer pills, therefore reducing both drug exposure and cost. But for people with lower (<65%) adherence, daily dosing is a significantly better strategy, probably due to greater flexibility to miss doses and still retain coverage. Although in HPTN 067 none of the HIV infections occurred in people with drug levels that supported recent adherence, it was not powered to show efficacy. In the context of lower adherence, any cost saving from using fewer drugs using time- or event-based dosing is likely to be cancelled out by the poorer efficacy.**

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IAS 2015: PAEDIATRICS & PMTCT

## **Raltegravir for neonates will require a complicated dosing regimen**

**Polly Clayden, HIV i-Base**

**A complex dosing regimen will be required to give raltegravir (RAL) to neonates according to data from the International Maternal, Paediatric, Adolescent, AIDS Clinical Trials (IMPAACT) Group presented at IAS 2015.**

There are limited antiretrovirals with appropriate formulations and pharmacokinetic (PK) data to guide their use in neonates.

RAL is approved for infants down to four weeks of age. A formulation of granules for oral suspension is available for this age group. A comprehensive development plan is ongoing with the IMPAACT Group that will inform dosing in neonates less than four weeks of age:

- IMPAACT P1097 was conducted to look at washout PK in neonates born to mothers receiving RAL in late pregnancy. This study showed that RAL crosses the placenta well. There was variable and prolonged elimination of RAL in the first days of life compared with older infants and children. P1097 is now assessing washout PK in a cohort of low birth weight (including preterm) neonates.
- IMPAACT P1110 is an ongoing two-part PK and safety study of RAL in term neonates at high risk of vertical HIV infection, informed by P1097 results.

RAL has the potential for use in prophylaxis and treatment of neonates at high risk of vertical HIV infection. The drug is primarily metabolised by UGT1A1, which has low activity at birth but increases over the first weeks of life and will influence neonatal dosing.

IMPAACT P1110 aims to evaluate the PK and safety of RAL and find an appropriate dose for neonates and infants up to six weeks of age. The study has a two cohort adaptive design: PK data from cohort 1 are included in PK modelling to inform dosing in cohort 2. It is a phase I multicentre PK study of in full-term, HIV-exposed, high-risk neonates.

Cohort 1 participants received a single oral dose of RAL within 48 hours of birth added to standard of care antiretrovirals for PMTCT prophylaxis, and a second dose at 7-10 days old. The initial dose was 3 mg/kg and doses were adjusted as the study progressed. RAL-exposed infants born to mothers receiving the drug during pregnancy and delivery were excluded at the beginning of the study. Later their enrollment was permitted with a lower initial dose.

The investigators performed intensive PK sampling around the initial dose: pre-dose and 1-2 hours, 4-8 hours, 12 hours, 24 hours post-dose and a random sample at 3-4 days old. Sampling was at three time points around the second dose: pre-dose and 1-2 hours and 24 hours post-dose. A validated HPLC-MS-MS method with a lower limit of quantification of 22.5 nM was used to analyse the samples. Protocol specified exposure limits from non-compartmental analysis for each participant were:  $C_{max} \leq 19.6 \mu\text{M}$  and  $AUC_{12} \leq 63 \mu\text{M}\cdot\text{hr}$ .

Cohort 1 comprised 13 neonates: 10 were born to mothers who did not receive RAL before delivery (RAL-naive) and 3 to mothers who received RAL before and during delivery (RAL-exposed). Neonates were 54% female with a median gestational age of 39.0 weeks (range 36.0 to 39.6) and birth weight of 3.02 kg (2.39 to 4.20). Evaluable initial dose and week 1 dose concentration data were available for 12/13 neonates.

The interim analysis of PK data from the first 6 RAL-naive neonates who received 3 mg/kg initial doses found none exceeded the  $C_{max}$  upper limit but two exceeded the  $AUC_{12}$  upper limit. Following this analysis, the initial dose was reduced to 2 mg/kg for RAL-naive and 1.5 mg/kg for RAL-exposed neonates. Table 1 shows RAL PK parameters for cohort 1 following initial doses.

**Table 1: RAL PK parameters – cohort 1 initial doses non-compartmental analysis**

RAL dose	Age at initial dose (hr)	$C_{max}$ ( $\mu\text{M}$ )	$AUC_{12}$ ( $\mu\text{M}\cdot\text{hr}$ )	$T_{1/2}$ (hrs)	$T_{max}$ (hrs)	$C_{24h}$ ( $\mu\text{M}$ )	$V_z/F$ (L/kg)	$Cl/F$ (L/kg/hr)
3mg/kg RAL-naive (n=6)	17.2 (9.9-25.4)	7.56 (4.51-11.96)	66.3 (42.5-104.1)	11.8 (7.9-15.7)	6.5 (4.1-24.0)	3.25 (1.49-8.22)	0.56 (0.35-0.80)	0.033 (0.021-0.053)
2mg/kg RAL-naive (n=3)	27.1 (24.2-33.1)	7.66 (5.01-9.73)	63.3 (39.2-99.0)	17.2 (6.3-32.8)	4.4 (4.3-4.7)	1.81 (0.38-5.60)	0.68 (0.43-0.86)	0.074 (0.039-0.109)
1.5mg/kg RAL-exposed (n=3)	34.1 (22.8-44.9)	3.31 (1.98-25.4)	29.0 (17.5-78.0)	8.7 (6.0-11.7)	4.6 (1.8-11.0)	0.95 (0.17-3.33)	0.62 (0.32-1.31)	0.049 (0.019-0.151)

Geometric mean (range)

All neonates received 3 mg/kg for the second dose at 7-10 days old.

When the investigators looked at protocol specified exposure limits, all 12 evaluable neonates had a  $C_{max} \leq 19.6 \mu\text{M}$ . But, 3/6 infants who received 3 mg/kg; 2/3 infants who received 2 mg/kg; and 1/3 RAL-exposed infants who received 1.5 mg/kg initial dose exceeded  $AUC_{12} \leq 63 \mu\text{M}\cdot\text{hr}$ .

RAL was well tolerated: one infant had a low absolute neutrophil count –considered possibly related to RAL – and none of the infants had elevated bilirubin that needed phototherapy.

The investigators then developed a population PK model including the initial cohort 1 PK data from 6 neonates and RAL concentration data from 24 infants and children ages 4 weeks to <2 years from IMPAACT P1066 – a phase 1/2, multi-centre, open-label, non-comparative intensive PK study in infants and children. They performed population modelling of the combined data set using NONMEM software.

This revealed a change in absorption rate from 16% of maximum at birth to 90% within 2 weeks. Clearance changed from almost nil to a maximum at approximately 6 months of age.

PK parameters including absorption and clearance were estimated and using this population model, simulations were run of various dosing regimens in the first 6 weeks of life.

In the final model the dosing regimen through 6 weeks of age that best met the following revised PK exposure targets (defined for safety and efficacy from recent studies in older infants, children and adults) was selected for use in cohort 2:  $C_{max} < 19.63 \mu\text{M}$ ,  $C_{min} > 75 \text{nM}$ ,  $AUC_{12}$  (twice a day)  $< 45 \mu\text{M}\cdot\text{hr}$  and  $AUC_{24}$  (one a day)  $< 90 \mu\text{M}\cdot\text{hr}$ .

Cohort 2 will begin enrolling RAL-naive neonates with the dose selected from the PK modelling and simulations: 1.5 mg/kg once a day from birth to day 7, followed by 3 mg/kg twice a day until 4 weeks of age, then 6 mg/kg twice a day to age 6 weeks.

Additional PK data need to be obtained before RAL-exposed neonates are enrolled. The investigators noted that PK results for cohort 2 will be evaluated on a rolling basis and dosing adjusted based on these results.

#### C O M M E N T

**The RAL development programme in collaboration with the IMPAACT network is excellent and will provide comprehensive data to inform dosing of young infants for both treatment and prophylaxis.**

**The current granules for the suspension formulation is complicated to administer and generic versions will need to be simpler to use in low- and middle-income countries.**

**Neonates exposed to RAL in utero might require a different dosing strategy and are also being studied in P1110.**

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IAS 2015: CURE RESEARCH

## **News and notes on HIV cure research from IAS 2015**

**Richard Jefferys, TAG**

**The IAS 2015 conference and related satellite meetings in Vancouver produced a slew of research news. Below are links to some presentations of possible interest and information on how to find materials online.**

### **2015 Towards an HIV Cure symposium**

On July 18 & 19, immediately preceding the main conference, the fifth IAS Towards an HIV Cure Symposium took place. Most of the presentations (divided into day 1 and day 2) and posters are now posted, along with the abstract book, with audio pending. [1]

Among the most talked about presentations (beyond Asier Sáez-Cirión's widely publicised description of long-term virological remission in a teenager, covered on the blog previously) [2] was Jonathan Karn's report that estrogen receptors appear to play a role in HIV latency in CD4 T cells. Karn also presented his results at IAS 2015 and a webcast of the talk is available. [3]

Karn showed results from laboratory studies indicating sex differences in responses to latency-reversing agents; specifically, reversal of HIV latency by a variety of different compounds was profoundly inhibited by the hormone estradiol in women but not men. Conversely, compounds that antagonise the estrogen receptor—such as the breast cancer treatments tamoxifen and fulvestrant—enhanced latency reversal. Karn's research is part of an ongoing amfAR-funded effort to better understand HIV latency and reservoirs in women. [4]

During the Q&A after Karn spoke, Brigitte Autran mentioned a French study (by Lise Cuzin and colleagues) of men and women on long-term ART that found that HIV DNA levels were significantly lower in women; these results have just been published in the journal AIDS. [5]

John Mascola from the Vaccine Research Center at the National Institutes of Health offered a glimpse at the viral load reductions obtained in a phase I trial of the broadly neutralising antibody (bNAb) VRC01 in HIV positive individuals not yet on ART. [6] After a single VRC01 dose viral load fell by around 1-1.5 logs, with six out of eight participants experiencing a 10-fold or greater drop. The two individuals who did not see a viral load decline turned out to have VRC01-resistant virus at baseline, suggesting that bNAbs will need to be combined to maximise their effects. These data are due to be published soon and are not included in the version of Mascola's presentation that has been posted online.

The results looked generally compatible with those obtained with the bNAb 3BNC117. [7]

Andrés Finzi discussed the possibility of exploiting the antibodies that are already present in HIV positive people as a means to eliminate virus-infected cells. Finzi's group has identified compounds known as CD4 mimetics that can alter the state of the HIV envelope in a way that allows common non-neutralising antibodies to induce antibody-mediated cellular cytotoxicity (ADCC) and thereby mediate killing of HIV-infected CD4 T cells.

Unfortunately Finzi's powerpoint presentation [8] seems to have been mangled by the translation into PDF form but the work was published recently in PNAS. [9]

Finzi believes the CD4 mimetics will be amenable to testing as oral drugs, and might provide an alternative to injectable bNAbs for the purposes of inducing ADCC against HIV-infected cells after latency reversal.

Christopher Peterson won the IAS young investigator award for his work demonstrating that stem cells genetically modified to abrogate expression of the CCR5 receptor can be successfully transplanted in the pigtailed macaque model. Peterson showed that the approach gave rise to gene-modified immune cells of multiple lineages, both in normal pigtailed macaques and SHIV-infected animals on ART. Results of studies evaluating the anti-SHIV effects of the transplants will be available soon. [10]

## IAS 2015

The main conference website does not have the most user-friendly system for accessing presentations and abstracts. The portal is called the programme-at-a-glance, but you may find yourself doing more squinty-eyed poring and clicking than glancing. There is a helpful section called roadmaps that lists conference sessions by topic area, such as “HIV Pathogenesis,” “Towards an HIV Cure” and “Vaccine.” Slides and webcasts (where available) are accessed via the conference session where the presentation occurred. [11]

The abstracts page allows browsing of different categories and the filtering option can be used to limit browsing to just posters. As far as I can tell, there is no way of searching abstracts using keywords. An IAS 2015 abstract book has been published by the Journal of the International AIDS Society (both in PDF and HTML format), but it only includes the few posters presented in oral discussion sessions. [12]

Additional cure research presentations at IAS 2015 included an excellent overview of the field by Nicolas Chomont, available as a webcast. [13]

Jake Estes described a potentially important new technology capable of visually identifying SIV-infected cells in macaque tissues. Both viral RNA and DNA can be visualised, which has the potential to shed light on the locations of the latent virus reservoir in ART-treated animals. The technology is called RNAscope and DNAscope in situ hybridisation. Estes's slides can be downloaded (but due to the many images it is a huge 64MB file). [14]

Susana Valente discussed how Tat inhibition may lockdown latent HIV, impeding its ability to reactivate – the opposite strategy to latency reversal (Valente describes it as “silencing the HIV reservoir”). The work was published recently in the open access journal mBio [15] and Valente's talk is webcast. [16]

On the HIV vaccine front, two excellent overview presentations are available via webcast: Tony Fauci discussed the state of the field in a talk titled “Progress and challenges in HIV prevention,” while Glenda Gray delivered a plenary talk that focused on plans for the next round of efficacy trials. [17, 18]

### Source

TAG basic science blog. News and Notes on HIV cure research from IAS 2015 (31 Jul 2015).

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## CONFERENCE REPORTS

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### **16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy**

**26-28 May 2015, Washington DC**

#### **Introduction**

**This important annual pharmacology (PK) workshop always includes studies that are not presented elsewhere.**

The slides from the oral abstract presentations are available as pdfs at:

<http://www.infectiousdiseasesonline.com/16th-hivhep-pk-presentations/>

The direct link for the abstract book PDF is:

[http://regist2.virology-education.com/abstractbook/2015\\_4.pdf](http://regist2.virology-education.com/abstractbook/2015_4.pdf)

Reports in this issue of HTB include:

- Reducing efavirenz dose is unlikely to overcome interaction with levonorgestrel
- Doravirine and cabotegravir do not affect the pharmacokinetics of oral contraceptives
- Pharmacokinetics of four antiretrovirals in pregnancy: data from the PANNA network
- Dolutegravir placental transfer moderate in ex vivo model
- Paediatric dosing of DRV/r

### **Reducing efavirenz dose is unlikely to overcome interaction with levonorgestrel**

**Polly Clayden, HIV i-Base**

**The drug-drug interaction between efavirenz (EFV) and levonorgestrel (LNG) cannot be overcome with an EFV dose reduction from 600mg to 400mg per day according to data presented at the 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. [1]**

LNG is a progestin-releasing sub-dermal implant with a contraceptive failure rate of <1%. It is primarily metabolised by the cytochrome P450 (CYP) 3A isoenzyme.

Investigators from Uganda, USA, UK and Ireland, led by Kimberley Scarsi from the University of Nebraska Medical Center, recently identified a significant drug-drug interaction between LNG and EFV. [2,3] In this study, LNG concentrations were reduced by 45-57% over 48 weeks of concomitant use with EFV compared with a control group of women not yet receiving ART. Three out of 20 (15%) women became pregnant during the 48-week study period.

Characterising this interaction is essential for HIV positive women worldwide, particularly as sub-dermal implants are one of only two preferred forms of long acting reversible contraception included in World Health Organisation (WHO) guidelines and many national recommendations.

So the group looked at whether or not decreasing EFV exposure by reducing the dose from 600mg to 400mg per day, would overcome the interaction between EFV and LNG in their study cohort.

This study defined the therapeutic range for EFV 12-14 hour post-dose concentrations as 1-4 mcg/mL. Non-adherence was defined as EFV 12-14 hour post-dose concentrations <1 mcg/mL.

Any LNG concentration that fell below the highest concentration at which there was a pregnancy in the cohort (303 pg/mL) was considered to be suboptimal LNG exposure.

The investigators assessed associations between LNG and EFV concentrations by Pearson's correlation ( $r$ ) and multiple linear regression analysis.

Twenty Ugandan women participated: median age 31 years (range 24-40), weight 59.5 kg (range 45-88) kg, and CD4 534 cells/mm<sup>3</sup> (range 284-853), at study entry. Participants received EFV for a median 10 months (range 5-66) before entry; all had an undetectable viral load <200 cells/mm<sup>3</sup>. The median EFV C12-14h over the study period was 2.3 (0.1-20.0) mcg/mL.

The investigators observed 4 participants with EFV concentrations >6 mcg/mL; 3/4 had the lowest LNG AUC of the study group. All LNG concentrations >900 pg/mL were observed in participants with EFV concentrations <1 mcg/mL. In bivariate analysis LNG was inversely correlated with EFV concentrations:  $r = -0.42$ ,  $p < 0.001$ . This relationship persisted after removing paired samples where the EFV concentration was consistent with recent study defined non-adherence (10 samples from 6 women):  $r = -0.40$ ,  $p < 0.001$ .

A significant regression equation was found in multivariate analysis with an  $R^2$  of 0.39,  $p < 0.001$ . For every 1 mcg/mL increase in EFV plasma concentration, the LNG plasma concentration decreased by 31 pg/mL. Increased age, body weight, and time since implant insertion were also inversely associated with LNG plasma concentrations.

Including the three women who became pregnant during the study, 18 (90%) receiving EFV had at least one suboptimal LNG concentration  $\leq 303$  pg/mL. Of those 18 participants, 7 (39%) had an EFV concentration >4 mcg/mL ( $p = 0.52$ ), including 1 of 3 who became pregnant. The 2 without a suboptimal LNG concentration who became pregnant both had EFV concentrations <2 mcg/mL. LNG concentrations were inversely related to EFV concentrations after adjustment for other confounders.

Participants who had consistently supratherapeutic EFV exposure (four with EFV concentrations >6 mcg/mL) had persistently low LNG concentrations throughout the study. Those with non-adherence to EFV had the highest LNG concentrations. But approximately half of the participants with suboptimal LNG exposure – at high risk for unintended pregnancy – had EFV concentrations within the therapeutic range: 1-4 mcg/mL.

The investigators wrote: "Without further evidence, these data suggest that the drug-drug interaction between EFV and LNG cannot be overcome with a 33% EFV dose reduction from 600 mg to 400 mg per day."

#### C O M M E N T

**In a related poster the investigators described LNG concentrations in women receiving nevirapine (NVP)-based ART in the control group over 48 weeks. [4] (24-week data had been previously presented) [5]**

**At this time point LNG concentrations were 6-35% higher in women using a LNG implant with NVP. The investigators explained that this difference was partly due to the higher baseline weight in the control group and is unlikely to have clinical significance.**

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## **Doravirine and cabotegravir do not affect the pharmacokinetics of oral contraceptives**

**Polly Clayden, HIV i-Base**

**Neither doravirine nor oral cabotegravir alter the plasma pharmacokinetics (PK) of levonorgestrel (LNG) and ethinyl estradiol (EE) containing oral contraceptives, according to manufacturers' data presented at the 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. [1,2]**

Antiretrovirals are likely to be co-administered with oral contraceptives in HIV positive women. Some antiretrovirals also have the potential to be used for prevention in HIV negative women. Drug-drug interactions causing sub-therapeutic concentrations of the estrogen or progestin in oral contraceptives can result in contraceptive failure.

It is good practice for originator manufacturers to include oral contraceptives interaction studies with those for other commonly used medicines during antiretroviral drug development. Two posters showed no effect of the phase 3 clinical doses of the investigational drugs doravirine or oral cabotegravir.

### **Doravirine**

Doravirine is an NNRTI primarily metabolised through oxidation via CYP3A4. It has not demonstrated inhibitory or inductive potential on CYPs in either in vitro or clinical studies or shown an interaction with enzymes that metabolise EE or LNG.

Merck investigators evaluated the effect of 100 mg doravirine, on the plasma PK of an oral contraceptive containing EE and LNG.

This study was open-label, 2-period, fixed sequence of multiple doses of doravirine on the single oral dose PK of a combination of EE/LNG (Nordette-28) in HIV negative women. Period 1: participants received a single dose of 0.03 mg EE/0.15 mg LNG. Period 2: participants received 100 mg doravirine once daily for 17 days, with a single oral dose of 0.03 mg EE/0.15 mg on day 14. There was a washout of at least 7 days between the two periods.

Twenty postmenopausal or oophorectomised women were recruited. Plasma samples were taken for up to 96 hours post-dose in each period.

The investigators reported geometric mean ratio (GMR) EE (Nordette-28 + doravirine/ Nordette-28): AUC 0.98 (90% CI: 0.94 to 1.03), and C<sub>max</sub> 0.83 (90% CI: 0.80 to 0.87). GMR LNG: AUC 1.21 (90% CI: 1.14 to 1.28), and C<sub>max</sub> 0.96 (90% CI: 0.88 to 1.05).

They concluded that multiple dosing of doravirine does not alter the plasma PK of EE or of LNG to a clinically meaningful extent. There are no restrictions on the use of oral contraceptives in phase 3 trials of doravirine.

### **Oral cabotegravir**

Cabotegravir is an integrase inhibitor in development as an oral tablet and a long-acting injectable for treatment and pre-exposure prophylaxis.

Previous in vitro data suggest that the potential for interaction with LNG and EE-containing oral contraceptives is minimal and the study aimed to demonstrate this.

It was an open-label, fixed-sequence crossover study in HIV negative women. There were two consecutive treatment periods that spanned a single menstrual cycle. Period 1: participants received Microgynon (LNG 0.15 mg/EE 0.03mg) once daily days 1-10 with serial PK sampling of LNG and EE on day 10. Period 2: Participants received oral cabotegravir 30mg once daily with Microgynon on days 11-21 and underwent serial PK sampling of LNG, EE, and CAB on Day 21.

Twenty women were enrolled. The ViiV investigators reported that the PK profile of LNG/EE was unaffected by cabotegravir.

The GMR for LNG (LNG + cabotegravir relative to LNG alone): AUC 1.11 (90% CI: 1.06 to 1.16) and C<sub>max</sub> 1.05 (90% CI: 0.96 to 1.15). GMR EE: AUC 1.05 (90% CI: 0.98 to 1.13), and C<sub>max</sub> and 0.92 (90% CI: 0.83 to 1.03).

Similarly in this study multiple doses of oral cabotegravir had no effect on the PK of LNG and EE suggesting it can be administered in combination with LNG/EE oral contraceptives without clinically significant drug-drug interactions.

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

**A related poster authored by researchers from the US FDA showed findings from a database of drug-drug interactions of antivirals (including HIV and HCV treatment) trials conducted to evaluate the effect on oral contraceptives. The study was designed to understand the main design features of such trials. [3]**

The authors collected design features and results of oral contraceptive/antiviral drug-drug interaction trials from labels and clinical PK reviews available at [drugs@fda](mailto:drugs@fda).

The database includes information on trial design (number of menstrual cycles, population, type of oral contraceptive) and results (PK parameters, pharmacodynamic markers, and clinical recommendations in labels).

The investigation revealed that 30% of drug-drug interaction trials with oral contraceptive submitted to 341 new drug applications (NDAs) of new molecular entities (NMEs) approved between 2000 and 2014 were with antivirals. Twenty-seven drug-drug interaction trials with oral contraceptives were conducted among approved antivirals.

The majority (82%) were open-label with a fixed sequence design. Five trials used a double-blind, cross-over design. Almost half of these (37% overall) were conducted within one 28-day ovulatory cycle, 33% over the course of three ovulatory cycles and 30% over two ovulatory cycles.

In most (85%) trials oral contraceptives were give in multiple doses. Almost all (96%) enrolled healthy women – including one trial that recruited postmenopausal women and another surgically sterilised women. Only one trial enrolled HIV positive women.

Almost half (44%) the participants were receiving stable doses of oral contraceptives before enrolling in 12 trials. Median number of women in a trial was 20 (range 12 to 52) and mean 24.

Norethindrone/EE combination was most commonly used in the trials (55%), followed by norgestimate/EE (31%). The primary objective of all trials was to evaluate the changes in the exposure of OC components with the co-administration of antivirals. Pharmacodynamic evaluation was performed in 37% of trials. Two antivirals (atazanavir and boceprevir) had drug-drug interaction studies with two different oral contraceptives. Labeling recommendations were based on exposure changes in 92.5% cases.

The investigators noted that there is no preferred study design and the answer to the exposure question can be achieved using any design, taking into consideration aspects such as safety considerations and logistical issues.

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## **Pharmacokinetics of four antiretrovirals in pregnancy: data from the PANNA network**

**Polly Clayden, HIV i-Base**

**The European PANNA network – established to study the pharmacokinetics (PK) of antiretroviral drugs during pregnancy – showed data from women receiving antiretrovirals as part of routine care, at the 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy.**

Physiological changes take place in pregnancy, which can influence the PK of antiretrovirals and might lead to decreased drug exposure. Results from four PANNA analyses – of darunavir/ritonavir (DRV/r), ritonavir (RTV), rilpivirine (RPV) and abacavir (ABC) – were presented as posters at the meeting. [1, 2, 3, 4]

### **Darunavir/ritonavir**

Limited PK data from clinical studies to date show that the exposure to DRV/r is reduced during pregnancy: AUC<sub>0–tau</sub> and C<sub>trough</sub> reductions range from 17% to 31%.

The PANNA investigators used a population PK approach to characterise DRV/r PK with 800/100 mg once daily and 600/100 twice daily dosing during pregnancy.

The study included HIV positive pregnant women receiving DRV/r as part of their antiretroviral therapy (ART).

The investigators obtained a 12 or 24 hour PK curve after two weeks or more DRV treatment during the third trimester (ideally week 33) and at least two weeks post-partum (4–6 weeks post-partum). Blood sampling was pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12 and (if applicable) 24 hours post-dose at both time points.

They performed a population analysis using NONMEN software. The final PK model was used to simulate 1000 DRV concentration-time profiles during the third trimester of pregnancy with DRV/r 800/100 mg once daily or 600/100 mg twice daily dosing. DRV concentrations were compared with the DRV protein binding-adjusted inhibitory concentration (IC) for HIV strains with or without DRV resistance mutations.

A two-compartment model with an absorption lag-time (LAG), inter-individual variability (IIV) terms on clearance (CL/F) and V1/F, and proportional residual error best described DRV PK. The investigators noted that pregnancy influenced LAG as well as CL/F, and IIV in CL/F and in V1/F.

In the final model the population estimates of CL/F were 8.71 L/h for the third trimester and 4.18 L/h for postpartum. All DRV concentrations in the simulation with DRV/r 800/100 mg once-daily dosing during the third trimester of pregnancy were above the protein binding-adjusted IC for wild-type HIV (0.055 mg/L). And just 0.9% of simulated DRV trough concentrations with twice-daily DRV 600/100 mg were below the IC of HIV with DRV resistance mutations (0.55 mg/L).

The investigators concluded that the final population PK model described DRV concentrations with no systematic bias and adequate precision. They recommended that no DRV dose adjustment seems to be necessary in pregnancy for HIV positive women fully susceptible to DRV, despite noting that pregnancy had been identified as a major covariate influencing CL/F, explaining lower DRV concentrations in plasma during third trimester than postpartum.

### **Ritonavir**

For RTV the investigators used data from women treated with boosted saquinavir (SQV), atazanavir (ATV) and DRV during pregnancy with 12- or 24-hour PK profiles in the third trimester and at least 2 weeks postpartum.

Cord blood and matching maternal blood samples were taken at delivery where possible in order to evaluate placental transfer. The investigators used a validated UPLC method and a lower limit of quantification of 0.045 mg/L to measure RTV concentrations.

A total of 49 women were included in the analysis: 5 receiving DRV/r 600/100mg twice daily, 9 DRV/r 800/100mg once daily, 26 ATV/r 300/100mg once daily and 9 SQV/r 1000/100mg twice daily.

Geometric mean ratios of third trimester/post-partum RTV (100 mg booster) AUC<sub>tau</sub> were: 0.74 (90% CI: 0.65-0.84) for DRV twice daily; 0.59 (90% CI: 0.42-0.83) for DRV once daily; 0.45 (90% CI: 0.37-0.53) for ATV; and 0.57 (90% CI: 0.39-0.82) for SQV.

The investigators noted an effect of pregnancy on RTV PK parameters, with decreases in exposure of 26 to 55%. They looked at the correlation between the effect of pregnancy on the AUC of the protease inhibitor used and the effect of pregnancy on the AUC of RTV using a Spearman Correlation test. This test revealed a correlation coefficient of 0.590,  $p < 0.01$ .

RTV concentrations were below the lower limit of quantification in all but one cord blood sample (25/26). The cord blood/maternal ratio was 0.05 (0.05/1.06 mg/L) for this participant. Almost half (12/25) the samples had RTV concentrations below lower limit of quantification with detectable maternal concentrations (range: 0.058-0.416 mg/L) at the same time point. The remaining 13 samples had both cord blood and maternal concentrations below the lower limit of quantification.

In conclusion it appears that pregnancy has a substantial influence on RTV concentrations and this is independent of the protease inhibitor being boosted. Less RTV boosting can contribute to lower protease inhibitor exposure in pregnancy. RTV appears to hardly reach the foetus during pregnancy, the investigators noted.

### **Rilpivirine**

The group presented preliminary data on third trimester exposure to RPV with the same study design.

RPV plasma concentrations were determined with a validated UPLC method with a lower limit of quantification of 0.0063 mg/L. Based on an analysis of ECHO/THRIVE PK data the minimum effective concentration of RPV was defined as 0.040 mg/L.

There were 7 participants included in this interim analysis: 4 black, 1 white, 1 Asian and 1 other. They were a median age of 29 years (range: 19-32). All received RPV with FTC/tenofovir; one participant also received lopinavir/ritonavir.

Evaluable, paired PK curves third trimester/postpartum were available for 6 participants. Median PK values in the third trimester and post partum respectively were: AUC<sub>0-24h</sub> (mg\*h/L) 1.73 (range 1.25-3.66) and 2.82 (range: 1.77-6.32); C<sub>max</sub> (mg/L) 0.13 (range: 0.074-0.20) and 0.16 (range: 0.11-0.32); T<sub>max</sub> (h) 3.0 (range: 0.5-4.2) and 4.00 (range: 0.0-0.6); and C<sub>trough</sub> (mg/L) 0.056 (range: 0.041-0.14) and 0.11 (range: 0.066-0.25).

Median ratios of PK parameters third trimester/post-partum were: AUC<sub>0-24</sub> 0.63 (range: 0.29-1.16); C<sub>max</sub> 0.69 (range: 0.37-1.20); and C<sub>trough</sub> 0.54 (range: 0.27-1.07). Three participants had a C<sub>trough</sub> of or below 0.04 mg/L in the third trimester.

In 2 participants with available data, the ratios of cord blood/maternal plasma RPV concentrations were 0.74 and 0.81 respectively.

The investigators wrote that in this small study exposure to rilpivirine was lower during pregnancy (third trimester) than postpartum, and possibly inadequate in 3/7 participants. RPV has good placental transfer and they suggested the drug might have potential for pre-exposure prophylaxis. Data from a larger group are needed.

### **Abacavir**

The final poster showed an analysis using the same study design of 9 participants receiving ABC 600 mg once daily in their ART regimen. They were a median age of 34 years (range: 25-39); 4 black and 5 white. All participants also received 3TC; 7 a protease inhibitor, 1 an NNRTI and 1 received 3 NRTIs.

Geometric mean for AUC<sub>0-24h</sub>, C<sub>max</sub> and T<sub>1/2</sub> in the third trimester were: 13.7 mg\*h/L (95% CI: 10.1-18.6), 3.83 mg/L (95% CI: 3.17-4.64) and 3.8 h (95% CI: 2.4-6.0), respectively. Geometric mean for AUC<sub>0-24h</sub>, C<sub>max</sub> and T<sub>1/2</sub> postpartum were: 12.6 mg\*h/L (95% CI: 10.5-15.1), 4.11 mg/L (95% CI: 3.44-4.92) and 3.2 h (95% CI: 2.1-4.9), respectively. Third trimester/postpartum ratios AUC<sub>0-24h</sub>, C<sub>max</sub> and T<sub>1/2</sub>: 1.08 (90% CI: 0.92-1.28); 0.93 (90% CI: 0.75-1.17); and 1.19 (90% CI: 1.03-1.37), respectively.

Ratio of cord blood /maternal ABC concentration ratios in 2 participants were 0.73 and 1.01 respectively.

The investigators concluded that ABC PK parameters are not influenced by pregnancy so 600 mg once daily is an appropriate dose in pregnancy. Placental transfer of ABC is substantial.

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

**Like IMPAACT 1026s, PANNA enrolls pregnant women receiving new antiretrovirals. Pregnancy can effect drug disposition significantly and originator companies do not always investigate new drugs in pregnant women.**

**Placental drug transport is another important aspect of PK for which few data exist for many antiretrovirals. Transport of antiretrovirals from mother to foetus might provide protection from vertical transmission of HIV across the placenta and at the time of birth.**

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Unless stated otherwise, references are to the programme and abstracts 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, 26-28 May 2015, Washington DC.

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## **Dolutegravir placental transfer moderate in ex vivo model**

**Polly Clayden, HIV i-Base**

**Modest placental transfer of dolutegravir (DTG) shown in an ex vivo human placenta perfusion model was presented in a poster at the 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy.**

Clinical data showing placental transfer of DTG is not yet available. Dual perfusion of a single placental lobule (cotyledon) is an experimental model used to predict placental drug transfer.

Investigators from the Departments of Pharmacy, Pharmacology and Toxicology, and Obstetrics and Gynecology, Radboud University Medical Center, Nijmegen, The Netherlands, developed a placenta perfusion model to estimate foetal exposure to DTG pregnancy.

The method involves cannulating a foetal vein and artery of an intact cotyledon ex vivo. The foetal circulation (6 mL/min) and the maternal circulation (12 mL/min) were initiated by inserting four cannulas into the intervillous space.

The perfusion medium was Krebs-Henseleit buffer supplemented with 10.1 mM glucose, 30 g/L HSA and 0.5 mL/L heparin 5000IE (to avoid coagulation of any remaining blood). DTG was administered to the maternal circulation (approximately 4.2 mg/L). Samples from the maternal and foetal compartment were collected at fixed time points for a maximum of three hours and analysed using validated UPLC-MS/MS.

The investigators used antipyrine (a marker of passive diffusion) to demonstrate successful perfusion in six placentae. This model showed placental transfer to steady state with a mean foetal-to-maternal concentration ratio of 0.96 (SD 0.04).

After three hours of perfusion the mean foetal-to-maternal ratio of DTG was 0.48 (SD 0.02) and the DTG concentrations in the maternal and foetal compartment were 2.4 (SD 0.6) and 1.1 (SD 0.3) mg/L, respectively. When the investigators applied this DTG foetal-to-maternal ratio to the average C<sub>trough</sub> of 1.18 (SD 0.71 mg/L) in HIV positive adults, they estimated that disposition in the foetal circulation would be 5-10 times higher than the EC<sub>90</sub> 0.064 mg/L found in vitro.

They noted that DTG did not reach steady state in the foetal and maternal circulation after three hours, which limits interpretation of the foetal-to-maternal ratio and extrapolation to in vivo.

These preliminary results (which need to be confirmed with clinical data) suggest DTG crosses the placenta ex vivo and that transfer is low to moderate. The investigators wrote that these findings "might also reflect the in vivo situation, which implicates exposure to DTG of the newborn". They suggested that because of immaturity of the main metabolising enzyme UGT1A1, a relatively long washout period of DTG from the neonatal circulation is expected.

The poster included a comparison of DTG with the in vivo cord-to-maternal blood concentration ratios of other antiretrovirals, obtained from PANNA studies. The comparison showed placental transfer of DTG to be relatively moderate and is summarised in Table 1.

**Table1: Cord-to-maternal blood concentration ratios of antiretrovirals from PANNA network**

Antiretroviral	Ratio	Range	n
FTC	1.63	0.46-1.82	10
RAL	1.21	0.13-4.53	9
TDF	0.82	0.64-1.10	14
RPV	0.74		1
DTG*	0.48	0.27-0.79	
ATV	0.20	0.06-3.05	12
DRV	0.13	0.08-0.35	8
RTV	<0.05		26

\* Perfusion model.

Key: FTC - emtricitabine; RAL - raltegravir; TDF - tenofovir disoproxil fumarate; RPV - rilpivirine; DTG - dolutegravir; ATV - atazanavir; DRV - darunavir; RTV - ritonavir.

**C O M M E N T**

**The PANNA network has begun enrolling pregnant women receiving DTG.**

Reference

Schalkwijk S et al. First human data on placental transfer of dolutegravir using an ex vivo perfusion model. 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, 26-28 May 2015, Washington DC. Poster abstract 34.

**Paediatric dosing of DRV/r**

**Polly Clayden, HIV i-Base**

Small changes to the current World Health Organisation (WHO) recommended darunavir/ritonavir (DRV/r) dosing could improve DRV exposure in children at the same time maintaining the number of weight bands and a standard dosing ratio, according to modeling presented at the 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy.

DRV/r is approved for children three years old and above and 10 kg and 15 kg and above in the US and EU respectively. Approved paediatric dosing regimens for DRV/r are different from WHO-recommended ones because different weight bands have been used. When considering a co-formulation for children, generic manufacturers will likely use a darunavir:ritonavir (DRV:RTV) fixed ratio and the WHO paediatric weight bands.

To simplify administration, WHO recommends five weight bands from 10 kg to > 35 kg and a 6:1 ratio of DRV:RTV. US approved dosing uses eight weight bands from 10 kg to >40 kg, and varying DRV:RTV ratios that range from 7.5:1 to 5.8:1.

Investigators from Janssen, the originator manufacturer of DRV, conducted a pharmacokinetic (PK) simulation to look at a regimen that conforms with the WHO weight bands and 6:1 ratio, and reaches DRV exposures comparable to those in adults.

A population PK model of DRV/r had been previously established based on pooled, richly sampled data from adult (DUET) and paediatric (DELPHI, ARIEL and DIONE) studies.

Paediatric twice daily dosing regimens using WHO weight bands and a 6:1 DRV/RTV ratio (240/40mg co-formulation) were determined, targeting 80 to 130% the exposure (AUC) achieved in ART-experienced adults receiving DRV/r 600/100mg twice daily. The investigators also compared these to the exposures predicted with the approved regimen and weight bands with DRV and RTV as single agents.

Applying current WHO recommended DRV/r dosing, the simulation revealed an AUC below 80% of the adult reference value of 62.3 ug\*h/mL in the lower weight band 14 to <20kg (1 paediatric tablet 240/40mg) and above 130% the adult reference value in the weight band 25 to <35kg (1 adult tablet 600/100mg). The other weight bands were comparable.

After further simulations of AUC and PK profiles, following administration of DRV/r as 240/40mg tablets, the investigators selected a new dosing schedule that gave DRV exposures 80% to 130% the adult reference value in all WHO weight bands. This new dosing schedule is: 1 tablet (240/40mg) for 10kg to <14kg; 1.5 tablets (360/60mg) for 14kg to <20kg and 20kg to <25kg; 2 tablets (480/80mg) for 25kg to < 35kg; and adult dose as of 35kg.

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#### C O M M E N T

**These simulations by the originator manufacturer suggest that DRV dosing according to current WHO weight band recommendations might lead to either under-dosing in a lower weight band or over-dosing in a higher weight one.**

**The investigators suggest that simple changes to the current WHO dosing schedule could improve DRV exposure in children while still keeping to the number of weight bands and a standard DRV/r dosing ratio.**

**Would it be too much to ask for this work on aligning with WHO weight bands to be done as originator manufacturers conduct their paediatric investigation plans? This would help generic manufacturers develop co-formulations and FDCs that allow dosing aligned with recommendations across the WHO weight bands. It could help close the gap between when new drugs and regimens are available in low- and middle-income countries for adults and children**

#### Reference

Brochot A et al. Model-based pediatric dosing of ritonavir-boosted darunavir: an alternative to WHO guidelines. 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, 26-28 May 2015, Washington DC. Oral abstract 15.

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## TREATMENT ACCESS

### **Why the 5000% price hike for pyrimethamine in the US is relevant in the UK**

**Simon Collins, HIV i-Base**

**The 5000% increase in price in the US for an off-patent drug by a company with a monopoly license was widely reported earlier this month. This was based on a very good article on Monday 21 September in the New York Times (NYT). [1]**

The least interesting aspect of the story however, was the company responsible for increasing the price or its noxious CEO. The real story was that the US has a system that allows this to be legal – and that the US is currently driving new trade agreements (TTIP) that threaten similar restrictions globally.

The news story related to pyrimethamine which has been off patent for decades. This is an important drug. It is used to treat toxoplasmosis which affects people with suppressed immune systems (transplant recipients, and HIV positive people) but also women during pregnancy (irrespective of HIV and immune status) and children who are infected with toxoplasmosis at birth.

However, most of the story is about US-access and is US-based. It relates to a regulatory and licensing system that allows any single manufacturer to have a license for a drug that is already off patent. The NYT article referred to other widely used off-patent medicines that have undergone similar monopoly-based investment pricing, including the antibiotics doxycycline (multiple use, including treatment for some common STIs) and cycloserine (for drug-resistant TB). It is about a broken system that needs fixing.

The story raises issues about:

- Monopoly licenses and importance of competition for drug pricing.
- How monopoly licenses can be granted for off-patent drugs.
- Monopoly licenses to drugs on the WHO list of Essential Medicines for citizens of all countries. Pyrimethamine is listed as an essential medicine for both adults and children to treat pneumocystosis, toxoplasmosis and malaria. [2]
- Use of online pharmacies to import generic medicines for personal use. This is perfectly legal in many high income countries, including the UK, if this for personal use, irrespective of drug patent. [3]
- Lack of any regulation between drug approval and drug pricing. For any drug, in-patent or off-patent, the manufacturer can set any price that the market will pay.

For people in the US, the option to access import generic medicines for personal use should also be available. US citizens widely use Canadian and other online pharmacies, although this may complicate reimbursement costs for those on insurance-based care. But while access to online suppliers might overcome the short-term cost issue for individuals, this probably excludes health providers who will be stung by monopoly price increases. A challenge to the license should therefore be an advocacy issue strengthened by the option for public health providers to also be able to do this for their patients.

From the 1970s, the Indian generic manufacturer Cipla led generic access to medicines for 90% of the world's population living in low and middle income countries. As with other generic companies, Cipla are a for-profit commercial company and they list pyrimethamine as one of their current products. Based on the cost of co-formulated pyrimethamine plus sulfadiazine at less than \$0.45 a tablet from online suppliers, the earlier US price of \$13.50 a tablet seems steep even before the hike to \$750. [4, 5]

This story highlights the risk for monopoly licenses for medicines in any situation. It especially highlights the risk for medicines that are off-patent, without linking this to a requirement for pricing. The move to further strengthen and restrict global patents for medicines has been an ongoing concern for at least the last decade.

For people outside the US, this news story on pyrimethamine might appear to have little direct impact – so long as generic manufacturers continue to manufacture pyrimethamine, including as a separate drug. Most use for pyrimethamine however is in a two-drug coformulation of pyrimethamine plus sulfadiazine in a single tablet, which is still widely available from many generic manufacturers. [6]

But the continued access to generic medicines outside the US, including in the EU, is directly threatened by proposed changes to EU legislation - the Transatlantic Trade and Investment Partnership (TTIP) - that would extend and strengthen patent rights globally for all medicines. [7, 8, 9, 10]

Given that 65-85% of all prescribed medicines in the UK are generic, fighting to retain access right to medications is an issue that does and will affect us all.

Check out the links below to the MSF Essential Medicines campaign for why this is such an important issue in the UK.

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#### C O M M E N T

**On Tuesday 22nd September, Martin Shkreli, founder and head of the small opportunistic Turing Pharmaceuticals, and personally responsible for the public relations wreck that generated his widespread vilification, announced that the original price of primethamine would be restored.**

**However, as this issue of HTB went to press in mid October, the US price had still not been lowered.**

**Unless legal changes are made to the system that allows such approaches to pricing of medicines, this example highlights vulnerability to similar practice in the US in the future.**

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## **Proposed TTIP trade agreement in Europe: Report shows European Commission's access to medicines commitments are 'empty gestures'**

### **MSF and HAI press release**

**On 14 October 2015, Médecins Sans Frontières (MSF) and Health Action International (HAI) published a new report that outlines the threats to global access to medicine in low- and middle-income countries (LMICs) from the proposed new TTIP trade agreement.**

Both organisations now urge the European Union to close the gap between its public position to support access to affordable medicines and the current reality of its trade policies, calling EU commitments 'empty gestures'.

The call comes as MSF and HAI today publish the report, "Empty Gestures: The EU's Commitments to Access to Medicines", which outlines clear recommendations for the EU to ensure its policies support access to affordable, safe and effective medicines in LMICs.

MSF and HAI have continuously criticised the EU for imposing intellectual property (IP) rules and measures that go further than the internationally-agreed rules on IP for pharmaceuticals in trade agreements with LMICs, as specified in the World Trade Organization's Agreement on Trade-related Aspects of Intellectual Property Rights ('TRIPS agreement'). Measures such as those being imposed by the EU have been shown to increase medicine prices by limiting generic competition, thereby reducing access to affordable medicines.

This is in clear contradiction with the Commission's stated support for the Doha Declaration on TRIPS and Public Health, which reaffirms that WTO members can make use of the public health related flexibilities of the TRIPS Agreement to promote access to medicines.

"The EU's long history on pushing LMICs to accept intellectual property protection that exceeds international obligations shows that the Commission's stated support for access to medicines have so far been empty gestures," said Tessel Mellema, Policy Advisor with Health Action International. "Instead of putting LMICs on trade watch lists and threatening them with financial sanctions for making use of TRIPS flexibilities to improve access to medicines, the EU should actively support these countries in making effective use of these policy flexibilities."

The European Commission's recent decision to support the world's poorest countries in their request for an indefinite exemption from implementing intellectual property rules on medicines until they are no longer classified as a least-developed country could, however, promise a new, more positive direction for EU trade policies under Commissioner Malmström.

The trade and investment policy review is a long-awaited opportunity for the EU to adopt the necessary corrective measures to ensure that the EU's trade policy supports, instead of undermines, access to medicines. Given that access to affordable medicines is increasingly also a problem in EU Member States, the HAI/MSF report recommends that a comprehensive 'access to medicines policy' that covers areas such as trade, R&D, development and public health should urgently be developed by the Commission. This is needed to ensure that future necessary reforms to the current patent-based innovation model in the EU and elsewhere are not impeded by excessive intellectual property rules in international trade agreements.

The EU is currently engaged in free trade negotiations with the United States and numerous LMICs, including India, Thailand, Mexico, Vietnam, as well as the MERCOSUR region.

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

**As this issue of HTB went to press the 11th round of talks for TTIP were underway in Miami.**

**The secrecy over the proposals precludes any effective public discussion over the outcome until after they have been signed.**

**Two examples for how TTIP will strengthen multinational companies over the interest of citizens are: i) the UK would become vulnerable to legal challenges for state-provided NHS services that are not put out to commercial tender; and ii) national health initiatives such as the successful Australian anti-tobacco campaign that led to plain packaging - and reductions in smoking - would be increasingly difficult.**



Reference

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## PAEDIATRIC CARE

### FDA approve additional weight band dosing for children using atazanavir powder

#### FDA press notice

**On 24 September 2015, the US FDA approved revisions to the atazanavir oral powder label to include dosing recommendations for patients three months and older weighing at least 5 kg.**

This represents the addition of a new paediatric weight band. Previously the oral powder formulation was for patients three months and older weighing at least 10 kg.

Atazanavir oral powder must be taken with ritonavir and is not recommended for use in children who weigh less than 5 kg.

For children weighing 5 kg to less than 15 kg the daily dosage of atazanavir oral powder is 200 mg (4 packets) plus 80 mg ritonavir oral solution once daily. Only patients weighing 5 to less than 10 kg who do not tolerate the 200 mg (4 packets) dose of atazanavir oral powder and have not previously taken an HIV protease inhibitor, may take 150 mg (3 packets) atazanavir oral powder with close HIV viral load monitoring.

The safety profile of atazanavir in paediatric patients taking atazanavir oral powder was generally similar to that observed in clinical studies of atazanavir in paediatric patients taking atazanavir capsules. The most common Grade 3–4 laboratory abnormalities occurring in paediatric patients weighing 5 kg to less than 35 kg taking atazanavir oral powder were increased amylase (33%), neutropenia (9%), increased SGPT/ALT (9%), elevation of total bilirubin ( $\geq 2.6$  times ULN, 16%), and increased lipase (8%). All other Grade 3–4 laboratory abnormalities occurred with a frequency of less than 3%.

The pharmacokinetic parameters for atazanavir at steady state in paediatric patients taking the powder formulation are summarised in Table 1 below.

Atazanavir is marketed in the US by Bristol Myers-Squibb with the trade name Reyataz.

Source

FDA HIV email list-serve (24 September 2015).

**Table 1: Steady-state pharmacokinetics of atazanavir (powder formulation) with ritonavir in HIV-infected paediatric patients**

Body weight (range in kg) (n)	atazanavir/ritonavir Dose (mg)	C <sub>max</sub> ng/mL Geometric Mean (CV%)	AUC ng*h/mL Geometric Mean (CV%)	C <sub>min</sub> ng/mL Geometric Mean (CV%)
5 to <10 (n=20)	150/80	4131 (55%)	32503 (61%)	336 (76%)
5 to <10 (n=10)	200/80	4466 (59%)	39519 (54%)	550 (60%)
10 to <15 (n=180)	200/80	5197 (53%)	50305 (67%)	572 (111%)
15 to <25 (n=32)	250/80	5394 (46%)	55687 (45%)	686 (68%)
25 to <35 (n=8)	300/100	4209 (52%)	44329 (63%)	468 (104%)

## TREATMENT GUIDELINES

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### **UK BHIVA 2015 guidelines for HIV positive adults**

**Simon Collins, HIV i-Base**

**The 2015 BHIVA guidelines are now posted online to the BHIVA website.**

These guidelines provide guidance on best clinical practice in the treatment and management of adults with HIV infection on antiretroviral therapy (ART).

The scope includes:

- Guidance on the initiation of ART in those previously naive to therapy.
- Support of people living with HIV (PLWH) on treatment.
- Management of individuals experiencing virological failure.
- Recommendations in specific populations where other factors need to be taken into consideration.

Five appendices are included together with comment received during the consultation period:

- Summary of the modified GRADE system.
- PICO questions and search strategies.
- Grade tables.
- Food considerations for antiretrovirals.
- Considerations for antiretrovirals in renal impairment.

The guidelines are aimed at clinical professionals directly involved with and responsible for the care of adults with HIV infection, and at community advocates responsible for promoting the best interests and care of HIV positive adults.

They should be read in conjunction with other published BHIVA guidelines.

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#### C O M M E N T

**This 2015 update includes the most dramatic changes in treatment and care for at least the last ten years. [2]**

**This includes the removal of a CD4 threshold for initiating ART. The change is based on results from the START study finding that HIV-related complications occur at CD4 counts above 500 cells/mm<sup>3</sup> and that earlier use of treatment reduces the risk of both HIV and non-HIV related serious events.**

**The guidelines also relegate efavirenz from a preferred to an alternative drug when starting treatment.**

**The i-Base patient guide *Introduction to ART* and new Pocket ART leaflets have already been updated to include the changes in these new guidelines. [3, 4]**

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## **WHO guidelines for when to start ART and use of PrEP (September 2015)**

**Simon Collins, HIV i-Base**

**On 30 September 2015, the World Health Organization (WHO) issued a new 78-page guideline document on two important changes to current treatment and prevention recommendations. [1, 2]**

The first change is that antiretroviral treatment (ART) is to now be recommended for all HIV positive people. Previous guidelines included the option to monitor people in early infection until their CD4 count dropped to 500 cells/mm<sup>3</sup>.

The second change is that pre-exposure prophylaxis against HIV infection (PrEP) should be widely available to HIV negative people who are at substantial risk of infection, in order to reduce their risk of infection.

Currently, PrEP is most widely used as a daily pill that contains two HIV drugs (tenofovir DF plus emtricitabine).

These recommendations have been announced ahead of the full guidelines which are still in press and expected to be released by 1 December 2015. [3]

Both recommendations are significant for their impact on global health to reduce HIV-related illnesses and deaths and to reduce new infections.

The recommendations are also controversial in being aspirational goals to increase access to both ART and PrEP, which is still limited for many people and in many countries.

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

**The lead shown by WHO is based on evidence from clinical studies that show the both benefits of earlier ART and the effectiveness of PrEP.**

**In practice, current access to both ART and PrEP means that these goals are unlikely to be immediately achieved in many country, however well resourced.**

**Both changes, together with the publicity that the news will generate, are likely to contribute to both reducing late and undiagnosed HIV and to normalise HIV by reducing stigma and fear that currently remains high.**

**In the UK, 40% of the 6250 people diagnosed in 2013 were late - defined as having a CD4 count had already dropped to less than 350 cells/mm<sup>3</sup>.**

**UK BHIVA 2015 guidelines now include the recommendation for all HIV positive people to be treated, including at higher CD4 counts.**

**UK availability of PrEP on the NHS is in the late stages of review, and will be based on the results of the UK PROUD study, that reported PrEP dramatically reduced the risk of HIV infection in gay men and transgender women who were at high risk of HIV infection.**

**WHO-approved generic formulations of PrEP are easy to buy online at greatly reduced prices compared to the current in-patient version used for HIV treatment. It is legal in the UK to buy online medication for personal use (defined as a three month supply). A recent Q&A on the i-Base website includes further information. [4]**

**People in the UK are increasingly using these sites to buy generic medicines. This shows the importance for the NHS to provide a setting where the essential monitoring can be easily provided.**

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## SIDE EFFECTS AND COMPLICATIONS

### **Neurocognitive disorder, persistent inverted CD4:CD8 ratios and immune activation in the CNS**

**Gareth Hardy, HIV i-Base**

**Given the concerns that HIV positive people commonly have about neurocognitive changes, a recent paper published in the *Annals of Clinical and Translational Neurology* is important to review in HTB as the suggested link to residual immune activation did not appear to be supported by the research. [1]**

Oliver Grauer and colleagues at the Department of Neurology at the University Hospital Muenster, Germany, investigated whether HIV-associated neurocognitive disorders (HAND) are associated with residual immune activation during antiretroviral treatment (ART), and whether immune activation markers may have utility in identifying those at risk of developing HAND.

HAND generally presents as a subcortical dementia with cognitive, behavioural, and motor decline that occurs over weeks or months, and interferes with activities of daily living and cannot be explained by any other cause of dementia. There are three levels of HAND: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HAD (HIV-associated dementia). Severe cognitive disorders are rare in HIV positive people on ART who have controlled viral loads, however subtle cognitive impairments can be found in as many as 50% of HIV positive people on ART and are particularly associated with CD4 count nadir.

Factors that might be involved in development of neurocognitive dysfunctions during ART include failure of ART to fully suppress HIV replication in the central nervous system and potential toxic effects of anti-retrovirals on the central nervous system. These factors may contribute to a slow, progressive process of brain infection, inflammation and injury that can be characterised by increased levels of inflammatory cytokines in the cerebrospinal fluid (CSF). In an attempt to identify biomarkers that may be predictive of risk for HAND, the researchers assessed whether immune activation markers on CD4 and CD8 T cells in peripheral blood and CSF showed any relation with viral load, the grade of neurocognitive dysfunction or the severity of MRI signal abnormalities.

Grauer and colleagues conducted clinical evaluations that consisted of medical history, standardised neurologic examinations and a neuropsychological assessment for the presence of HAND that were classified according to the following Frascati criteria:

Grade 0: HIV patients with normal test performances.

Grade 1: patients with HIV-associated ANI that does not interfere with everyday functioning.

Grade 2: patients with HIV-associated MND with mild interference in daily functioning.

Grade 3: patients with HAD with marked interference with day-to-day functioning. MRI scans were also graded according to the severity of cerebral signal abnormalities and abnormalities in the periventricular white matter and the basal ganglia.

Over two years, 86 participants were recruited (male = 71, female = 15) with a median age of 49 years (range 19 to 72 years). 89% of participants were on ART and most had suppressed viral load (<37 copies/mL) in blood (69.8%) and CSF (75.6%) with a median CD4 count of 552 cells/mm<sup>3</sup> (range 3 to 1327). The control group consisted of participants who had been suspected of having a neurologic disorder but who were retrospectively found to be suffering from a somatisation disorder. In these participants there was no evidence of elevated inflammatory markers in the CSF. The 17 control participants had a median age of 45 years (range 23–59 years).

The researchers found that the ratio of CD4:CD8 T cells, both in peripheral blood and CSF, was associated with the grade of neurocognitive impairment. The more inverted the CD4:CD8 ratio, the greater the grade of impairment. The researchers next found significant upregulation of the activation marker HLA-DR on CD4 and CD8 T cells in peripheral blood and CSF of HIV positive people in comparison to the control group. The percentage of CD4 T cells that express HLA-DR in peripheral blood and CSF of HIV positive participants was significantly greater than in controls ( $p < 0.0001$  for both blood and CSF). The difference in HLA-DR positive CD8 T cells between HIV positive participants and controls was not as strong, though still statistically significant ( $p < 0.01$  in peripheral blood and  $p < 0.05$  in CSF).

Though there did not appear to be a difference in the percentage of HLA-DR positive CD4 and CD8 in peripheral blood or CSF according to whether viral load was detectable or not, in virologically suppressed participants the percentage of HLA-DR positive T cells in blood and CSF significantly increased with the severity of neurocognitive impairment. In addition, the percentage of HLA-DR positive CD4 T cells was higher in virologically suppressed participants with more severe cerebral MRI scan signal abnormalities. While the researchers found some relationships between T cell expression of HLA-DR and neurocognitive impairments, they do not at any point justify their choice of HLA-DR as a single activation marker. Most studies that assess pathological T cell activation in HIV infection use HLA-DR in conjunction with CD38, or

CD38 in conjunction with memory cell markers. The role of HLA-DR as a single marker of pathological immune activation is contentious and the role of this molecule on the surface of T cells is still not known.

In order to assess whether the associations between neurocognitive dysfunction and immune activation translated into any changes in the distribution of memory and naive T cell populations, the researchers assessed their frequencies in peripheral blood and CSF. While results in peripheral blood confirm population perturbations that have long been known in HIV infection, in CSF only the frequency of naive CD4 T cells was significantly reduced in HIV positive people in comparison to controls ( $p < 0.0001$ ) and terminally differentiated CD4 T cells ( $p < 0.01$ ). Lastly the researchers assessed levels of the immune check-point molecule, programmed death receptor-1 (PD-1), which is associated with antigen-driven T cell exhaustion and chronic activation. In comparison to controls, participants with grade 2-3 (mild or severe) neurocognitive impairment had significantly elevated expression of PD-1 on peripheral blood effector memory CD4 T cells ( $p < 0.01$ ) and central memory CD4 T cells ( $p < 0.05$ ).

This study aimed to identify potential new biomarkers for HAND. CD4:CD8 ratio and the cell surface immune activation marker HLA-DR, in peripheral blood and CSF, may be informative in understanding the pathology of HAND. However their utility as new markers for HAND will have to be determined in larger, more comprehensive studies.

#### C O M M E N T

**The unsubstantiated claims in this paper includes reporting a correlation between grade of neurocognitive dysfunction and naive and effector cells numbers in the CSF. Although the authors emphasise this point, they show no such correlation, merely that if you take one or two of the most severe grades of impairment as a single group there was a relationship within that group between the numbers of naive and effector cells.**

**HIV is clearly linked to all sorts of neurological complications, even in the context of ART, but although many studies report associations, the interpretation of the clinical importance of tentative results is more complex.**

**Neurological problems will - and are - certainly affecting some HIV positive people - just like they affect some HIV negative people - with ageing and other factors being primary risks. HIV positive people might even be at a higher risk for some of these complications - and this study is trying to see whether we can find markers for increased risk.**

**However, current evidence doesn't suggest neurological complications will broadly affect all HIV positive people, especially in the context of having undetectable HIV RNA in CSF on ART. Having a lower CD4:CD8 ratio has long been linked to poorer outcomes, so there is plausibility but no interventions that can directly improve the ratio other than earlier diagnosis and earlier use of ART which is already now in guidelines. It is also difficult to know whether this association is just a bystander marker or causally linked - as with the other immunological responses.**

**Even when studies report small or marginal increased risks in HIV positive people, this is remarkably good news given how extensively HIV is distributed within weeks of infection and that many people have years of unsuppressed infection before starting ART. It is also reassuring that increased rates of Parkinson's or Alzheimer's disease, which might plausibly have been expected, have not been reported. [2]**

**It will be interesting to see the results from the START neurological substudy. This is an ideal group to see whether either HIV or ART affects cognitive function as it includes a large randomised group with several years uncontrolled HIV, including presumably in the CSF, and a comparison group where ART is likely to have suppressed this to undetectable very early in infection.**

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## HIV PREVENTION

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### **i-Base Q&A resources on PrEP: increased use of off-label PrEP in the UK shows need for NHS support and risk to PEP services**

**Simon Collins, HIV i-Base**

**Since the announcement of the early results of the PROUD study in October 2014, the i-Base information service has received an increasing number of enquiries about PrEP.**

This includes requests for information about accessing generic TDF/FTC from online suppliers and on the data for different ways that PrEP can be taken. [1]

Over the last year i-Base has increasingly heard about people accessing PrEP through PEP services, a practice that was highlighted again in a recent popular community blog. [2]

This level of demand supports anecdotal reports that PrEP has been increasingly accessed and used with little or no medical support.

In response, there are now five online Q&A pages that cover most of the questions that have been asked about PrEP. These may be useful referral links for clinics that are getting similar enquiries.

#### **Where can I buy PrEP or HCV meds online and is it legal in the UK?**

<http://i-base.info/qa/10734>

#### **How to take PrEP: daily dosing and other options?**

<http://i-base.info/qa/10743>

#### **How do I safely use PrEP if I buy it online?**

<http://i-base.info/qa/10528>

#### **Can I check PrEP from the Internet is genuine?**

<http://i-base.info/qa/10695>

#### **Can I get PrEP privately in the UK?**

<http://i-base.info/qa/10696>

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#### C O M M E N T

**Many people accessing PrEP via PEP services are likely to be unaware that buying generic PrEP online is both legal and dramatically cheaper than a private prescription.**

**There is an urgency for routine monitoring of PrEP to be provided as part of NHS sexual services.**

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1. i-Base Q&A service: recent question on PrEP.  
<http://i-base.info/qa/category/prep>
2. Owens G. Get free P(r)EP on the NHS – NOW. Web blog (12 October 2015).  
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### **Two new UK community PrEP websites**

**Simon Collins, HIV i-Base**

**Two new community websites have been launched in UK aimed at increasing awareness of PrEP among gay men.**

Both sites have been developed and funded by independent activists to raise the issues of PrEP as an effective option.

Both sites also include practical information about how to buy generic PrEP online, although neither site was available for full pre-launch preview before we went to press.

[www.iwantprepnnow.co.uk](http://www.iwantprepnnow.co.uk) (live from 19 October)

[www.PrEPster.info](http://www.PrEPster.info) (live from 21 October)

## First UK NHS PrEP support service launched at 56 Dean Street, Soho

Simon Collins, HIV i-Base

**In October 2015, the NHS sexual health clinic at 56 Dean Street in Soho London made important changes to the private PrEP clinic that was launched two months earlier. This is the first clinic in the UK to run a free PrEP support service. [1]**

The clinic is an appointment only service that runs from 11 am to 3 pm on Saturdays.

The free service includes the monitoring tests that are essential for anyone using PrEP. This includes testing for HIV, hepatitis B, liver and kidney monitoring and the option to test for other STIs. The clinics also includes advice and information on how to take PrEP and follow up visits.

As NHS England has not yet agreed to pay for PrEP, medication is currently only available as a private prescription (at £400 for 30 tablets).

However, generic PrEP is already becoming widely available, as it is easy, legal to buy generic tenofovir/FTC online, at much lower prices (£40 to £80 for 30 tablets, depending on supplier). Several community websites already provide excellent advice on how to do this. [2, 3]

The Dean Street PrEP clinic also offer drug level tests as a private service at £230. This is a blood test that can confirm whether someone taking generic PrEP has active drug levels of tenofovir DF.

It is important to note that there is little need for everyone using generic PrEP to have a drug level test, once an internet supplier has been confirmed as a genuine. The option for this service is nevertheless important.

As neither of the private services are needed, the service will enable people to access the appropriate care on the NHS.

This clinic was set up in response to the growing demand for PrEP services following the results from the UK PROUD study and the French/Canadian IPERGAY study a year ago. Both studies reported dramatic reductions in HIV transmission from PrEP in gay men and transgender women at high risk of HIV. Both studies were presented as late breaker oral abstracts at CROI 2015. The PROUD study was published in the Lancet last month. [4]

Two prices are currently listed depending on whether medication is included as part of the service. The initial consultation, plus HIV, hepatitis B, kidney and liver tests are provided free.

- 30-day TDF/FTC prescription – £400 flat fee.
- For patients sourcing TDF/FTC elsewhere who want a drug level test – £230 flat fee.

For further details please see the clinic website.

<http://getprep.uk>

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### C O M M E N T

**It is significant that 56 Dean Street have developed this service in response to the growing use of off-label use of generic PrEP, as it provides essential safety support in an NHS setting.**

**Although this shows the need for the NHS to decide on criteria for free access to PrEP for people at high risk, the relatively low cost of generic PrEP is likely to encourage many people to source PrEP independently.**

**Raising awareness of low cost generic PrEP might also reduce use of PEP services as a source of PrEP.**

#### References:

1. PrEP services at 56 Dean Street.  
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2. i-Base Q&A. Where can I buy PrEP or HCV meds online and is it legal in the UK?  
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## **UK PROUD study published as open access article in The Lancet: PrEP dramatically reduces risk of HIV**

**Gareth Hardy, HIV iBase**

**Results from the UK PROUD study are now published as an open access article on 9th September in the Lancet. [1]**

This follows their earlier presentation at in February 2015 at CROI [2] showing that oral pre-exposure prophylaxis (PrEP) dramatically reduces the risk of HIV infection in gay men and transgender women by who are at significant HIV risk. In addition, there were no cases of HIV transmsion in people actively using PrEP and no evidence of increased high risk sex.

PrEP consists of two antiretroviral drugs, tenofovir and emtricitabine (FTC), coformulated in a single pill (Truvada).

PROUD is an open label, randomised clinical trial conducted at 13 sexual health clinics in England. Participants were randomised to receive PrEP either immediately, or after one year deferral. Entry criteria included being at high risk of infection defined as recent receptive anal sex without a condom in the previous 90 days. Participants were prescribed PrEP on a rolling 90 day basis, after an initial 30 day prescription and asked to attend clinic every three months in which they would be tested for HIV and bacterial STIs. In addition, participants were asked to complete monthly questionnaires and daily diaries about sexual behaviour and PrEP adherence.

PROUD used an open label design to test the effectiveness of PrEP in a real-life setting. The results in the Lancet paper are from a pilot phase of PROUD, intended to assess feasibility of recruitment and retention for an efficacy trial. The larger study was estimated to need 5000 participants to detect a 50% reduction in new HIV infections. However, the unexpectedly large difference in HIV infections between the immediate and deferred arms of the study, driven by higher HIV incidence overall, meant that efficacy could be demonstrated.

In October 2014, while still in the pilot phase, the trial steering committee recommended that the study design was changed to close recruitment and give immediate access to PrEP to all participants in the deferred PrEP group (n=163). PROUD will continue to follow all participants until the final enrolled participant has completed 2 years follow up.

The study recruited 544 participants, of which 275 were in the immediate group and 269 were in the deferred group. At the time of reporting, HIV incidence follow up data was complete for 243 (94%) of 259 patient years in the immediate group and 222 (90%) of 245 patient years in the deferred group.

Three HIV infections occurred in the immediate group (1.2/100 person years) as compared to 20 in the deferred group (9/100 person years), representing a relative a reduction of 86% (90% CI 64-96,  $p = 0.0001$ ). These figures mean that 13 individuals in a similar group would need to be taking PrEP for one year to avert one new acquisition of HIV.

The new infections in the deferred group occurred despite 174 prescriptions of post-exposure prophylaxis (PEP). Of the twenty participants who became newly infected in the deferred group, six had received a total of 12 courses of PEP. Of the three participants who became infected in the immediate group, one had a positive HIV test at week 4 of the study and is thought to have been infected before enrolment. The other two participants tested HIV positive much later in the study after many months of not returning for PrEP prescriptions. These results suggest that no HIV infections occurred in people who were actively taking PrEP.

Sexual behaviour questionnaires at year one of the study revealed that 21% of participants randomised to the immediate group reported receptive anal sex without a condom with 10 or more partners versus 12% in the deferred group ( $p = 0.03$ ). Regardless of this, diagnoses of bacterial STIs occurred in 152 (57%) of 265 participants in the immediate group and 124 (50%) of 247 participants in the deferred group. After adjustment for the number of study screens in each group, no significant difference was found between the groups for incidence of bacterial STIs. Importantly the incidence of rectal gonorrhoea or chlamydia, indicators of receptive anal intercourse without condoms, were similar in both groups.

None of the participants of either group who became HIV positive, had resistance mutations to either emtricitabine or tenofovir, apart from the participant who tested positive at week 4 and was suspected to have been infected before enrolment. This person had the M184V mutation associated with resistance to FTC.

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

**PROUD showed that PrEP is highly effective in a real-life setting and importantly is not associated with increased risk-taking in this group. Economic modelling based on the UK epidemic in MSM suggests that PrEP would be cost effective at current drug pricing in a similarly risk-matched group and that wider use by people with lower HIV risk would also be cost effective if the current price of Truvada was dropped by 50%. [3]**

**The reduced dosing used in the French IPERGAY study would lower costs further but data on efficacy is still needed before this can be routinely recommended. [4]**

**The earlier report on PrEP studies at IAS 2015 in this issue of HTB includes a discussion of PrEP dosing.**



#### References

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## HEPATITIS COINFECTION

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### **Gilead to provide free hepatitis drugs to treat all people living with hepatitis C in Iceland**

**Simon Collins, HIV i-Base**

**On 7 October, the Icelandic Ministry of Health announced that an agreement with Gilead Sciences would enable all people with hepatitis C in Iceland to receive free treatment with new direct acting antiviral (DAA) oral treatment.**

This will initially involve at least 1200 people, but people who are diagnosed over the next few years will also have access to treatment

In exchange, Gilead will use the results from the programme to study the potential for reducing HCV on a population level.

Earlier this year a similar plan was announced to provide treatment to 25,000 people with hepatitis C in Georgia, which at 7% of the population has one of the highest prevalence rates for HCV (coming third after Egypt and Moldova). [2]

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1. Icelandic Ministry of Health. Efforts to eliminate hepatitis C in Iceland (7 October 2015). <http://www.velferdarraduneyti.is/frettir-vel/nr/35288>  
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### **Australian Medical Society issues guidelines for personal importation of generic oral hepatitis C drugs including sofosbuvir**

**Simon Collins, HIV i-Base**

**On 8 October 2015, the professional association for doctors and other health workers that specialise in HIV, hepatitis and sexual health in Australia (ASHM) issued guidance on the importation of generic HCV drugs. ASHM is similar to the British HIV Association (BHIVA) in the UK.**

This guidance is important as the cost of some medications - notably tenofovir/FTC for PrEP and sofosbuvir and other DAAs (for hepatitis C) - are prohibitively expensive for the NHS to provide widespread access that would meet current medical need.

Australia has similar flexibility to the UK for buying and importing medication online for personal use.

The guidance is printed below in full as a model to aid UK doctors in a similar position.

#### **ASHM Advice for HCV Clinicians**

This communique is for clinicians experienced in the management and treatment of Hepatitis C using Direct Acting

Antivirals (DAAs), who may be consulted by their patients who are considering importation of generic DAAs. It assumes an understanding of HCV management and new treatments.

Overview of the current status of DAAs in Australia:

All PBS subsidised treatment for hepatitis C in Australia currently consist of pegylated interferon and ribavirin with the addition of a DAA for genotype 1. These combinations are now not widely used due to side effects, duration of treatment and relatively poor cure rates.

Newer DAA regimens that are interferon-free, well tolerated and have shorter duration of treatment are available in the USA and Europe. They are detailed in the current evidence-based guidelines produced by EASL and AASLD.

A number of DAAs have been approved in Australia by the TGA. In 2015, several interferon-free regimens for the treatment of hepatitis C were recommended by the PBAC for inclusion on the PBS, however they are not yet listed. For HCV genotype (G) these include:

- sofosbuvir + ledipasvir (G1).
- sofosbuvir + daclatasvir (G1 and 3).
- sofosbuvir + ribavirin (G2).
- sofosbuvir + pegylated interferon/ribavirin (G1).
- paritaprevir/r + ombitasvir + dasabuvir (+/- ribavirin) (G1).

Consumers in Australia can currently access DAAs through a number of mechanisms:

- Purchase the drug without subsidy.
- Participate in a clinical trial.
- Apply under a compassionate access program (limited places).
- Import drugs into Australia for private use under the Personal Importation Scheme.

ASHM recommends that any individual considering DAA therapy discuss their options with a clinician experienced in HCV management and treatment with the new DAAs.

Patients may approach clinicians to write them a script for DAAs so that they can purchase them overseas or via the internet due to their current high cost in Australia without subsidy. In these circumstances, it is important they understand that it is the patient that is the personal importer. The Doctor should document fully the patient's request and understanding and that the doctor is supporting the patient to personally import the medicines. More information on this process is discussed below. Doctors should not advertise or promote these methods of acquisition to patients.

### **Evidence for the effectiveness of DAAs**

The efficacy of DAAs in the treatment of hepatitis C has been widely established in the international literature and is detailed in the EASL and AASLD evidence-based guidelines.

### **Discussing importation of generic DAAs with patients**

Patients are allowed to import up to 3 months of medication for their own use under the Commonwealth Government's Personal Importation Scheme. It is important that patients know that the safety and quality of medicines purchased overseas or over the internet cannot be guaranteed.

It is a legal requirement of this scheme that a patient has a prescription from an Australian registered medical practitioner.

Refer patients to the Hepatitis Australia factsheet Importing Medicines into Australia (May 2015).

### **Establishing HCV status**

When a patient requests a script for a generic DAA, it is essential to establish their current HCV status. This should be done using a conventional blood sample and laboratory testing.

Current HCV infection is confirmed when the test results are HCV antibody positive and HCV RNA is positive.

### **Patient HCV assessment**

Once the presence of chronic HCV (HCV RNA positive) has been confirmed, it is very important in patient assessment to:

- Establish HCV genotype (as this determines the treatment regimen)
- Determine the degree of liver fibrosis (as this influences treatment choice and duration)

- Determine the presence of comorbidities that may affect treatment (e.g. renal disease)

Patients with cirrhosis need ongoing specialist monitoring for complications, including HCC and oesophageal varices. They also need different treatment combinations and more prolonged treatment.

### **Drug interactions**

The potential for drug interactions with other medication must be considered when DAAs are prescribed. For up to date drug-drug interaction information, go to: <http://www.hep-druginteractions.org/> or download the App: HEP iChart.

### **Compliance with dosing regimen**

It is essential that patients take the right combination of medications for their HCV genotype and stage of fibrosis. They must also take the medication consistently for a sufficient duration in order to optimise the likelihood of viral clearance (SVR or sustained virological response).

### **Safe injecting strategies**

Patients should be counselled to use safe injecting practices. This will prevent the acquisition of other blood-borne infections and reinfection with hepatitis C.

### **Monitoring and side effects**

DAAs are generally very safe. Patients should be monitored according to evidence-based guidelines. The key issues are in initial patient assessment (as discussed above).

Patients will also need post treatment assessment including 2 HCV RNAs (PCR) to determine viral clearance. Note that patients with cirrhosis will need lifelong monitoring.

### **Accessing DAAs through the Personal Importation Scheme**

Patients have a number of options to access DAAs, including their purchase in Australia without subsidy. Patients can also personally import the drugs in person or via mail. Details of how to do this can be obtained on the TGA website. A patient can import up to 3 months supply at the one time into Australia using the Personal Importation Scheme.

Generic drugs can be purchased via a number of websites. These drugs have not been evaluated by the TGA. Generic drugs use alternative trade names and packaging and may be a different colour or shape so you must be sure that the drug being purchased is the correct formulation.

Self-importation has some risks associated with it. You do not have the quality protection provided by drugs evaluated and listed on the ARTG. You need to be careful about the veracity of the website. Supply time may vary and the postage time could be delayed if customs investigates the package. Self-importation is legal, but not routine. Having a valid Australian prescription completed by a registered medical practitioner is essential, and completing all the paper work will facilitate the process but patients should allow up to eight weeks for delivery.

### **How to order Generic DAAs for HCV online**

ASHM does not endorse any specific websites or products. It is up to the individual personally importing the drugs to locate an appropriate website and test the veracity of the supplier. The following are shown as examples only.

FixHepC is a buyers club that states it will assist with buying, testing and delivery of hepatitis C drugs.

<http://fixhepc.com/getting-treated/how-to-do-it/buyers-club.html>

AIDS Drugs Online has been used to source low-cost generic versions of HIV medications from various overseas manufacturers and they also stock hepatitis C medications.

<http://www.aids-drugs-online.com>

Please be aware that the brand names used on AIDS Drugs Online are not the same as the brands in Australia. For example: Australian brand name sofosbuvir has a brand name: sofosbuvir/Hepcinat on AIDS Drugs Online (ADO).

Online suppliers may be only able to supply one of the HCV drugs needed in a regimen, so patients may need to source medicines from more than one source, e.g. the internet and locally through compassionate patient access schemes.

### **Further information and links**

TGA Personal Importation Scheme

<https://www.tga.gov.au/personal-importation-scheme>

Fix Hep C – website supplying further information on personal importation

<http://fixhepc.com>

EASL Recommendations on Treatment of Hepatitis C 2015

<http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/recommendations-on-treatment-of-hepatitis-c-2015>

AASLD HCV Guidance: Recommendations for Testing, Managing and Treating Hepatitis C

<http://www.hcvguidelines.org/full-report-view>

Hepatitis Australia

<http://www.hepatitisaustralia.com/>

Source

ASHM Advice for HCV Clinicians (08 October 2015).

<http://www.ashm.org.au/HCV/management-hepc/importation-of-generic-hcv-drugs>

## BASIC SCIENCE & CURE RESEARCH

### **Combining PKC agonists and bromodomain inhibitors to reverse HIV latency**

**Richard Jefferys, TAG**

**Two recent papers in PLoS Pathogens report that combinations of candidate latency-reversing agents can potentially activate HIV production by latently infected CD4 T cells in laboratory experiments. [1, 2]**

Pairings of the PKC agonists bryostatin-1 or ingenol with the bromodomain inhibitor JQ1 were most effective, generating levels of virus production by latently infected cells similar to those achieved by maximal T cell activation.

The results appear consistent with those published earlier this year by the research group of Robert Siliciano at Johns Hopkins University [3], and are encouraging because there had been some scepticism as to whether any latency reversing strategy could match the effects of maximal T cell activation (which is known to be too dangerous to use in people). But there are caveats: the compounds do affect T cell activation pathways and it is not yet known if they will be safe in HIV positive individuals; currently, they are being tested (and in the case of ingenol, used topically) as cancer treatments.

The two new publications derive from independent research laboratories led by Satya Dandekar at UC Davis and Carine Van Lint at Université Libre de Bruxelles (ULB), respectively. The experimental findings are broadly consistent but involve two different variants of ingenol: ingenol-B, which has previously been reported [4] to have latency-reversing activity, and ingenol-3-angelate (PEP005), the active component of an FDA-approved topical treatment for precancerous actinic keratosis named PICATO. The opinions of the two groups regarding which version of ingenol might be safer for systemic use in humans differ somewhat. Van Lint's group writes: "Importantly, ingenol-3-angelate appears to be more toxic than ing-B when orally delivered to rats and dogs (Luiz Pianowski, Kyolab, Brazil, personal communication)."

While Dandekar states: "Similar to the safety of the topical application of PICATO, the systemic (intravenous) use of PEP005 in small animals (mini pig and rat model) was reported to be relatively safe, with the maximum nonlethal dose >73 µg/kg (See Assessment report of PICATO to European Medicines Agency, Sept 20, 2012) [5]. While additional safety data with systemic administration in non-human primates is needed, these existing data support further investigation of PEP005 as a potential candidate in HIV cure studies."

Further animal model studies should help resolve this uncertainty. The UK website NHS Choices, [6] which provides commentary on research-related stories in the mainstream media, takes a rather dim view of Dandekar's suggestion (reported by the BBC) [7] that the FDA-approved status of PICATO is relevant to the prospects of this approach in people with HIV, countering that "although the drug is being used on patients, it is currently just applied to the skin. The effects may be very different if the whole body is exposed to the drug, as would be required to locate hidden reservoirs of HIV."

The other PKC agonist studied, bryostatin-1, is already being tested in HIV positive people in a small, single-dose clinical trial in Spain [8] supported by a biotech company named Aphios [9]; results are pending. While some researchers have expressed concern about the potential toxicities of bryostatin-1, Van Lint's group is more sanguine, noting that in a phase I trial in children with cancers (published in 1999) "only few patients have experienced myalgia, photophobia or eye pain." [10]

But the report from this trial also states “toxicities of bryostatin-1 occurred days after the infusion and lasted for prolonged periods” and I think it’s fair to say that opinions about the acceptability of these types of side effects in healthy HIV positive people are likely to vary. There are ongoing efforts to develop safer and more targeted analogues of bryostatin-1, notably those led by Paul Wender at Stanford University. [11]

Bromodomain inhibitors are also being studied in cancer. The compound used in these studies, JQ1, has too short a half-life for human use but Van Lint and colleagues note: “Clinical trials with JQ1-derivative called TEN-010 (also called JQ2) and another BETi called GSK525762 have been initiated recently to characterise their safety, tolerability, pharmacokinetics and anti-cancer activity (clinicaltrials.gov).” [12]

Safety information from these trials will be important in determining whether studies in HIV are appropriate.

Source:

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## Estimating how frequently latent HIV reactivates

Richard Jefferys, TAG

**The primary barrier to curing HIV infection is the persistence of the virus in a latent form in long-lived resting memory CD4 T cells.**

The number of latently infected resting memory CD4 T cells in a typical individual on ART is estimated to be in the range of 1 to 60 million. An important strand of HIV cure research involves attempting to reduce the size of this persistent HIV reservoir, in hopes of delaying or – better yet – preventing viral load rebound when ART is interrupted. In order to gain insight into how feasible this might be, researchers have employed mathematical modeling to estimate how the size of the HIV reservoir relates to time to viral load rebound.

A widely cited model created Alison Hill and colleagues [1] has suggested that reservoir reductions on the order of 5-6 logs (100,000 to 1 million fold) would be necessary to delay viral load rebound for 30 years or more in most individuals (an outcome that would approach a lifelong cure), while a yearlong delay would likely require a drop of at least 3 logs (1,000 fold). Last month in *PLoS Pathogens*, a new model was published that argues that significant delays in viral load rebound might be achieved with far more modest declines in HIV reservoir size. [2]

The study draws on data from several different clinical trials in which ART was interrupted and time to viral load rebound assessed. A series of calculations are used to generate an estimate of how often – on average – a latently infected resting memory CD4 T cell would have to start producing virus to explain the kinetics of the rise in viral load observed after ART interruption. The math is complex and opaque to a non-mathematician, but produces a result of one successful reactivation of latent HIV every six days, considerably less frequent than a previous estimate of five times per day based on studies involving drug resistance mutations [3] (this prior estimate is used in the Alison Hill model). A separate analysis in the new paper, using different methodology based on the genetic characteristics of rebounding HIV, arrives at a reasonably similar estimate of once every 3.6 days.

The researchers extrapolate that a yearlong delay in viral load rebound might therefore be achievable with a reduction in the HIV reservoir of 60-70 fold, a more optimistic scenario than proposed previously by Alison Hill et al. But, on the surface at least, the Hill model appears more consistent with the well-publicised cases of the Boston patients, two individuals who were reported to have experienced HIV reservoir reductions of at least 3 logs [4] as a result of receiving stem cell transplants to treat cancers. After a carefully conducted ART interruption, viral load rebound occurred after around three months in one case and eight months in the other. The authors of the new model suggest that this apparent discrepancy might be explained by the presence of a larger, unmeasured HIV reservoir in the tissues of the Boston patients.

The Alison Hill et al PNAS paper also cites a case report by Tae-Wook Chun and colleagues describing an individual with an HIV reservoir approximately 1,500 fold lower than a typical person on ART in whom viral load rebound occurred 50 days after ART interruption. [5]

Although it would be premature to draw conclusions from so few case reports, it has to be noted that a 60 to 70 fold decline in the HIV reservoir doesn't appear to have delayed viral load rebound for a year in anybody as yet. And in three examples where greater reservoir reductions appear to have occurred, viral load rebound was not delayed for a year.

The cautious interpretation would be that additional data are needed to help refine the mathematical modeling and ascertain which models most closely approximate the biological reality. An intervention (beyond stem cell transplantation, which cannot be studied on a large scale) that significantly lowered HIV reservoir levels would also allow for a more direct assessment of the impact on time to viral load rebound.

## Remission definitions

A final comment on the use of the term “remission” in this context: it's important to note the distinction between the type remission being described in this work and the “virological remission” reported in the recent case of the teenage post-treatment controller [6] and the similar VISCONTI cohort participants.

The former involves a complete absence of HIV activity due to remaining latently infected cells staying in a non-activated resting state for the duration of the remission, and any eventual viral load rebound occurring as a result of a latently infected cell becoming activated and producing infectious virus (as best as anyone can tell with available technology, this appears to be the type of remission that occurred in the Boston patients and Mississippi baby).

The latter scenario of post-treatment control of viral load is different because it involves ongoing limitation of HIV replication by immune responses; in other words, low-level HIV replication activity that is kept in check by the immune system.

Current evidence implies that the former type of remission is more likely to be associated with a state of health comparable to being HIV negative (and therefore consistent with most people's understanding of the term remission), whereas post-treatment control might be associated with some degree of inflammation-mediated risk of disease, making it perhaps questionable as to whether the term remission should be applied.

Source:

Jefferys R. Estimating how frequently latent HIV reactivates. TAG basic science blog. (7 Aug 2015).  
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## OTHER NEWS

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### **Professor Clive Loveday awarded a Royal Order of Chivalry**

**The investiture of Professor Loveday as an ‘Officer to the Order of St John of Jerusalem’ for services to International Charities and HIV/AIDS takes place in the City of London on 20<sup>th</sup> October 2015 at The St Johns Church.**

Professor Loveday worked as a volunteer, in a team, for St Johns Ambulance developing the first Division to be associated with motorsport medicine at Snetterton Circuit (1987 onwards) and later became the Chief Medical Officer for British Forces Overseas (2007 onwards).

He has worked for over 33 years in HIV/AIDS patient clinical care and associated translational research; he formed a Charity in 2001 (ICVC Charitable Trust) to deliver economic cutting-edge molecular services to UK patients and published widely in this field. He then developed teaching programmes to support the ongoing training of NHS specialist staff in this field.

He has served a Charity Trustee (2008 onwards) for ‘Saving Lives’, a charity dedicated to the wider testing of HIV in the community.

Professor Loveday is Consultant HIV/GUM Birmingham Heartlands Hospital and Professor of Infectious Diseases UWL.

He has also been on the editorial comment board for HIV Treatment Bulletin since the first edition in April 2000 – and for its forerunner DrFax since 1999.



## ON THE WEB

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### *Study results:*

#### **New music video on results from the START study: “Now we know”**

<https://www.youtube.com/watch?v=tr5b499WzIU>

**Check out the new video on the International START study, written and recorded by Moses Supercharger, the community advocate from Uganda on the START community Advisory Board.**

“Kalabakalambaala (let’s all go for) early treatment”. This is an update to the earlier “Nobody know for sure” video from Moses Supercharger and a great way to publicise study results.

#### **UK PROUD study published as open access article in the Lancet**

**Results from the UK PROUD study showing the dramatic impact of PrEP to reduce risk of HIV transmission have been published in the Lancet as open access publication.**

McCormack S et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *The Lancet*. 2015. (Online 10 September). DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)00056-2](http://dx.doi.org/10.1016/S0140-6736(15)00056-2).

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A separate editorial comment article is also included by Kenneth H Mayer and Chris Beyrer.

Antiretroviral chemoprophylaxis: PROUD and pragmatism. Editorial comment.

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(15\)00153-1/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00153-1/fulltext)

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## FUTURE MEETINGS

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### **Conference listing 2015/16**

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.

#### **BHIVA Autumn Conference including CHIVA Parallel Sessions**

12–13 November 2015, London

<http://www.bhiva.org>

#### **7th International Workshop on HIV Persistence During Therapy**

8 – 11 December 2015, Miami

<http://www.hiv-persistence.com>

#### **European HIV Hepatitis Coinfection (EHC) Conference**

10–11 December 2015, London

<http://www.bhiva.org>

#### **International HIV Drug Resistance Workshop 2016**

20 – 21 February 2016, Boston

<https://www.informedhorizons.com/resistance2016>

#### **6th HIV & Women Workshop**

20 – 21 February 2016, Boston

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

#### **23rd Conference on Retroviruses and Opportunistic Infections (CROI 2015)**

22 – 25 February 2016, Boston

<http://www.croiconference.org>

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

19–22 April 2016

<http://www.bhiva.org>

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

17 – 22 July 2016, Durban

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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>



### New pocket guide to ART

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



We hope this is especially useful as a low literacy resource.

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

### i-Base treatment guides

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

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

- Introduction to ART (September 2015)

The 2015 update to the Introduction to Combination Therapy booklet is now retitled Introduction to ART.

This 48-page A5 booklet includes essential information for anyone starting treatment (or already on treatment), especially if they are recently diagnosed.

- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (November 2013).

### Other publications

- HIV Treatment Bulletin (HTB)
- HTB South
- HTB Turkey
- HTB West Balkans

### Translations

i-Base resources have been adapted in over 35 languages. PDF version of many of these are online.

<http://i-base.info/category/translations>

### Order publications and subscribe by post, fax or online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK.

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

## **htb(e)**

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

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

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