

## march–april 2017

### CONTENTS

#### EDITORIAL

- **i-Base funding appeal: we need your help**

#### CONFERENCE REPORTS

23rd Annual Conference of BHIVA, 4-7 April 2017, Liverpool

- Introduction
- Drop in HIV incidence in gay men: frequent testing, early ART and PrEP
- Prompt/early ART: Dean Street pilot project reports 75% uptake
- Initiatives for earlier HIV diagnosis: opt-out ER and home testing
- Potential for phylogenetic analysis to show direction of HIV transmission
- Community presentations: dental care, HIV awareness and access to formula milk
- PrEP in practice: no new HIV diagnoses over 8 months among 398 PrEP users
- Other selections and webcasts

#### CONFERENCE REPORTS

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

13-16 February 2017, Seattle

- Introduction
- Dose reduction potential of nanoparticle ARV formulations confirmed in humans
- VRC01 in HIV-exposed newborns: first results support monthly injections for those at risk through breastfeeding
- Raltegravir pharmacokinetic targets met in high-risk HIV-exposed infants
- Tenofovir alafenamide exposure is modestly higher in children than adults

2	• New HIV diagnoses in children in UK and Ireland continue to decline	
3	• World Health Organisation paediatric dosing tool	
	• Pre-ART drug resistance in rural South Africa but limited clinical impact with good adherence	
	• Immune-based therapy canakinumab reduces inflammatory markers in HIV positive people on ART	
	• Significant interaction between once-weekly isoniazid/rifapentine and daily dolutegravir: study stopped due to toxicity	
	• Increased risk of IRIS with integrase inhibitors reported in two studies	
	• Breakthrough for treating XDR-TB and ameliorating TB-IRIS	
	• PREP in pregnancy does not increase poor birth outcomes	
	• HIV cure research and basic science: capsules from CROI 2017	
	<b>TREATMENT GUIDELINES</b>	<b>22</b>
	• EACS guidelines: seven translations now online	
	<b>CURE RESEARCH</b>	<b>23</b>
	• Flagging the HIV reservoir: a potential new marker for CD4 cells hiding HIV	
	<b>HIV PREVENTION</b>	<b>24</b>
	• PrEP approved in Scotland but not Wales	
	<b>EVENTS &amp; TRAINING</b>	<b>24</b>
	• HIV: is victory in sight? - Brighton talk	
	• Introduction to cost-effectiveness analysis for infectious diseases	
	• Clinical management of HIV: EACS online course	
	<b>ON THE WEB</b>	<b>25</b>
	• RITA: dyslipidemia with HIV	
	<b>FUTURE MEETINGS</b>	<b>26</b>
	<b>PUBLICATIONS AND SERVICES FROM i-BASE</b>	<b>26</b>
	<b>ORDER FORM</b>	<b>28</b>

## ***h-tb***

### HIV TREATMENT BULLETIN

HTB is published in electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered using the form on the back page or directly from the i-Base website:

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

or by sending an email to: [subscriptions@i-Base.org.uk](mailto:subscriptions@i-Base.org.uk)

Editor: Simon Collins

Contributing Editor: Polly Clayden

#### Medical consultants:

Dr Tristan Barber, Chelsea & Westminster Hosp, London.

Dr Karen Beckerman, Albert Einstein College of Medicine, NYC.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Prof. Diana Gibb, Medical Research Council, London.

Dr Gareth Hardy, PhD.

Prof. Saye Khoo, University of Liverpool Hospital.

Prof. Clive Loveday, International Laboratory Virology Centre.

Prof. James McIntyre, Chris Hani Baragwanath Hosp. South Africa

Dr Graeme Moyle, Chelsea & Westminster Hosp, London.

Dr Stefan Mauss, Düsseldorf.

Prof. Caroline Sabin, UCL Medical School, London.

Dr Graham P Taylor, Imperial College, London.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

Dr Edmund Wilkins, Manchester General Hospital, Manchester.

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**HIV i-Base, 107 The Maltings, 169 Tower Bridge Road, London, SE1 3LJ. T: +44 (0) 20 8616 2210. F: +44 (0) 20 8616 1250**

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

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## EDITORIAL

### **For the first time in 17 years, we are sorry that this issue of HTB is only being produced in digital format.**

This is because i-Base is faced with reduced funding for 2017 and we have to restructure some services to enable the project to continue.

Although more than half our regular readers already receive HTB by email, more than 2500 subscribers still get the print edition. And while it only costs less than 50 pence to print (yes, two for a pound), postage more than doubles these costs.

If you currently receive HTB by post, please register for electronic subscriptions to continue to receive HTB and other i-Base publications.

<http://i-base.info/htb/about/subscribe>

Please also consider helping with our 2017 funding appeal to support i-Base for the next year.

### **New resources**

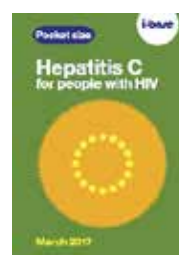
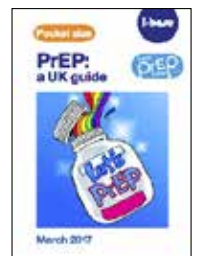
- Pocket guides - concertina leaflets (March 2017)

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

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

All free to UK clinics.

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



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

**HTB is the UK's longest running activist HIV treatment publication - starting as DrFax from 1996-2000 and relaunched as HTB from 2000-2017.**

We have maintained HTB as an independent publication and now need your help for this to continue.

**This year, i-Base needs to raise £100,000 in 2017 to match last year's funding.**

Your regular support can make this happen.

We could reach this target if:

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

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

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

If you would like to support this work, all contributions are appreciated and make a difference.

i-Base does not have the luxury of financial reserves and we make every penny count.

Moving to electronic distribution will help, but by itself will not be enough.

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

This link includes the option to securely donate online or offline.

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

**Thank you for your help.**

## CONFERENCE REPORTS

### 23rd Annual Conference of BHIVA

4-7 April 2017, Liverpool

#### Introduction

**This year, the annual BHIVA spring conference was held in Liverpool, and the programme included six special lectures, 30 oral abstracts, 130 posters and numerous additional workshops.**

The conference does an excellent job for making most PDF and PowerPoint slides available online as the conference closes, including a PDF of the abstract book, with webcasts from the oral session available within a week or so.

A summary of selected themes and highlights is included in the reports below.

- Drop in HIV incidence in gay men: frequent testing, early ART and PrEP
- Prompt/early ART: Dean Street pilot project reports 75% uptake
- Initiatives for earlier HIV diagnosis: opt-out ER and home testing
- Potential for phylogenetic analysis to show direction of HIV transmission
- Community presentations: dental care, HIV awareness and access to formula milk
- PrEP in practice: no new HIV diagnoses over 8 months among 398 PrEP users
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### Drop in HIV incidence in gay men: frequent testing, early ART and PrEP

**Simon Collins, HIV i-Base**

**The conference included the first chance for the recent exciting data on reduced HIV incidence among gay men attending five London clinics, in a joint presentation from Valerie Delpech and Monica Desai from Public Health England (PHE). [1]**

This was the first formal presentation for this data, although top-line results from several London clinics were released at the end of 2016. [2]

The presentation noted that based on PHE overall national data, HIV incidence in gay men started to fall from late 2014 when approximately 550 men were diagnosed in the last quarter of 2014, to about 370 for the last quarter of 2016, with the steepest decline coming throughout 2016.

This dramatic drop was shown most strongly in five high incidence London clinics (more than 40 diagnoses a year) where incidence fell by more than 20% between 2015 and 2016: Dean St, Mortimer Market, Homerton, St Mary's, Guy's and St Thomas'.

Although a decline was reported by clinics outside London, the drop was more gradual (from about 220 to 180 from 4Q 2015 to 4Q 2016).

Over the same time, testing rates significantly increased at the five steep decline clinics (from 7500 to 9500 test per quarter), mainly driven by people who were repeat (rather than first-time) testers. New diagnoses fell in both new and repeat testers, but most new diagnoses were still in people testing for the first time.

Although earlier use of ART was considered as a factor behind the drop in incidence, median time to starting ART was stable at just over 100 days during 2014-2015 (compared to approximately 220 days at clinics outside London).

The study concluded that the impact of combination prevention methods was having an unprecedented impact of reducing HIV incidence and showed the need to consolidate scaling up of testing and early ART across all parts of the country for all groups at greatest risk of HIV.

### Update on planned UK PrEP IMPACT study

The second part of this presentation included information about the planned PrEP Impact study - that proposes to enrol 10,000 people over three years using generic PrEP.

Even though there are no further scientific questions that would prevent PrEP being used immediately, NHS England has deferred a decision on approving PrEP for at least another three years by requiring this "implementation study".

The primary objective is to measure PrEP eligibility and uptake, and duration of eligibility and use among people attending sexual health clinics.

Inclusion criteria are to offer PrEP to all people at high risk of HIV due to higher risk sexual behaviour, having an HIV positive partner or having partner of unknown status and at high risk of HIV. This includes cis and transgender men who have sex with men and transgender women.

The study will be based on 3-monthly visits for prescriptions and monitoring. Daily and event-based dosing will be included as appropriate. Follow-up will include HIV and STI testing including HCV according to standard of care, kidney monitoring and sexual health information.

The study will include more than 200 STI clinics across the UK for wider geographical access with first enrolment planned for late summer 2017.

### C O M M E N T

**The contribution from PrEP to reduction in HIV incidence might have been underestimated during this presentation.**

**PROUD was running through 2013 to October 2014 when early results enabled all participants to access PrEP. Anecdotally, PrEP was being accessed at PEP clinics throughout, and online access greatly expanded from August 2015, when importing generic PrEP was confirmed as legal for personal use.**

**i-Base published information on buying PrEP online in August 2015 and the two leading community PrEP sites, I want PrEP Now and Prepster, were launched in October 2015.**

**The plans for the IMPACT study have not yet explained what will happen if the study enrolls rapidly within the first of the planned three years. While this would be much better for the study and participants – greater with earlier PrEP access and faster study results – it doesn't explain how further demand for PrEP will then be met.**

**Several analysts, including Andrew Hill in his lecture at BHIVA on generics, have pointed out that 10,000 might be far too small. [3] If the background incidence for this study is 2%, then the study might only prevent 200 infections and that 150,000 people would need to be using PrEP to cover the roughly 3000 gay men who are diagnosed each year.**

**in Australia, which has a smaller population than the UK and lower HIV incidence, similar open-label studies (PrEPX, EPIC and QPrEP'D), enrolled more than 8,000 participants within one year.**

**It is notable that NHS Scotland has already approved PrEP, without the need for any further costly studies.**

### References

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## Prompt/early ART: Dean Street pilot project reports 75% uptake

Simon Collins, HIV i-Base

**Several studies reported successful results from new testing initiatives, and importantly, a new model for early access to ART.**

The most important of these was from a pilot study at 56 Dean Street to routinely offer ART in the same week that someone is diagnosed. This service is closely based on the model developed in San Francisco that has become routine care for all patients.

Gary Whitlock presented an update from 56 Dean Street clinic in London, which has the highest number of annual HIV diagnoses. Since July 2016, the clinic restructured services so that people with newly diagnosed HIV could have a first medical review within 48 hours compared to within two weeks. The protocol included offering

immediate PI-based ART (prescribed as TasP), changing from the PI as soon as resistance test results confirmed this would be safe.

A retrospective case note review was presented for 127 individuals, all gay men, diagnosed during the first five months of this service. Approximately 60% were retesting and 40% were first patients.

Mean age was 34 years with median baseline CD4 and viral load of 466 cells/mm<sup>3</sup> (IQR: 310 to 578) and 72,000 copies/mL (IQR: 24,000 to 290,000), respectively. Just under one-third (29%) had a CD4 count <350 cells/mm<sup>3</sup> and half were recent infections (< 4 months based on RITA testing).

Notably, 14% had viral load > 1 million copies/mL indicating likely very early infection. Also a concern, 24% (28/118) had transmitted drug resistance. This included 11 samples with primary PI mutations (L90M, n=9; M46I, n=2) and 9 with primary NNRTI mutations (E138A, V179E, n= 3 each; V179D, n=2; and K103N, n=1). Six samples included two or more mutations.

Of 127 new diagnoses, 11 had no further follow-up (5 moved away, 6 lost to follow-up) and 118 attended first doctor appointment, all were offered ART. Of these, 76% (89/118) started ART at their first doctor appointment. Of those starting ART at first appointment, 31% (28/89) did so within two days of diagnosis. Of those not choosing immediate ART, most (26/29) had started by January 2017.

Although PI-based ART was recommended, only 62/115 (54%) started with a PI, including seven people who were later found to have significant PI mutations. Other combinations included integrase-based (n=33, 29%) or NNRTI-based (n=12, 10%) ART.

Of both measure of time to first appointment and time to starting ART, the pilot programme was significantly shorter than historical control data from the same clinic a year earlier (both p<0.05).

## C O M M E N T

**Part of the success of the San Francisco same-day ART is likely to be linked using integrase-based ART for the first combination, based on lower risk of side effects.**

**The resistance results from Dean Street would further support using integrase-based ART, given very low risk of transmitted integrase resistance and the high barrier to developing drug resistance, certainly with dolutegravir.**

**This approach to shortening time between diagnosis and seeing a doctor could easily become the model of care across the UK, and high uptake of early ART from this relatively informed treatment-aware patient group probably minimises the anxiety and stress associated with learning you are HIV positive.**

### References

- Whitlock G et al. Rapid initiation of antiretroviral treatment in newly diagnosed HIV: experience of a central London clinic. 23rd BHIVA 4-7 April 2017, Liverpool. Oral abstract O14.  
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<http://www.bhiva.org/170406GaryWhitlock.aspx> (webcast)

## Initiatives for earlier HIV diagnosis: opt-out ER and home testing

Simon Collins, HIV i-Base

### Several studies presented important and sobering results about HIV testing.

Sarah Parry reported on the importance of routinely moving to opt-out testing for blood borne viruses (HIV, HBV and HCV) for people accessing the emergency department the Royal London Hospital, a high prevalence setting. [1]

From November 2015 to August 2016, more than 6,200/24,900 attendees were tested (25% uptake), of which 257 (4.1%) were positive for one virus and 15 people had coinfection. Of these, 86 people (33%) required linkage to care (n=16 HIV, 26 HBV and 44 HCV) as either new diagnoses (n=10, 7 and 13 respectively) or in people who were disengaged from care (n=5, 11 and 17 respectively). Data was not available for all patients. See Table 1.

A high proportion of linkage patients (29%, 25/86) had advanced disease (CD4 <350, APRI >1 or FibroScan F3/4) including five people with AIDS-defining infections and three people with hepatocellular carcinoma (HCC).

Engagement in care was easiest for HIV and most difficult for HCV (where 11% of cases were in people without permanent housing).

Unfortunately, there were seven deaths, five of which were directly BBV-related.

**Table 1: HIV, HBV and HCV prevalence**

	HIV n=71	HBV n=54	HCV n=147
Prevalence, % (95% CI)	1.2 % (0.92 to 1.5)	0.9 % (0.69 to 1.2)	2.4 % (2.0 to 2.8)
M/F %	80/20	67/33	71/29
Required linkage, n	16	26	44
Informed to date, n (%)	11 (69)	17 (65)	30 (68)
Av. contact attempts and time, minutes	1 4 mins	2 8 mins	6 20 mins

A second study on opt-out HIV testing in an ER setting was also presented by Hannah Alexander from King's College Hospital.

This included almost 50% uptake during the first 31 weeks from August 2016 (more than 12,600 HIV tests out of >25,600 people overall). Of these, 102 were HIV positive, with 19/102 being new diagnoses, 77/102 were known positive, with 5/77 having disengaged from care and 6/102 were not traceable.

Of the new diagnoses, 18/19 are now engaged in care. Mean CD4 count was 233 cells/mm<sup>3</sup> (range 13 to 738) including six people with AIDS-defining illnesses (toxoplasmosis, 3; cryptococcal meningitis, 1 and PCP, 2) and two people were in seroconversion.

Notably, HIV had been considered as a differential diagnosis in only 2 cases.

By comparison, over the same period, 15 people were newly diagnosed at the sexual health clinic for the same hospital (out of almost 6000 tests). People diagnosed in the ER setting were more likely to have lower CD4 count (mean 233 vs 522 cells/mm<sup>3</sup>) and less likely to be gay men (4/19 vs 9/15).

Results from a home testing programme were reported by Michael Brady from the Terrence Higgins Trust. [3]

During a six-week pilot study from June to August 2016, almost 5,000 home tests (Biosure) were sent out, with results reported by just over 3,000 people (62%) - despite two text message prompts. Most tests (98%) went to men, 99% of whom identified as gay, with 96 tests requested by cis women, with 16 requests from trans women and 6 from trans men. Only 168 people (3.4%) were Black African and 91% were from urban settings (ie where access to GUM testing would be easier).

Most test requests were generated in response to social media marketing (34% from Grindr, 34% from Facebook, 24% of other and 7% from the THT website) - with 85% accessed by a mobile phone.

Of the 25 new HIV diagnoses reported (0.5%), one was a false-positive. Of the remaining 24 with positive results (all gay men), contact was made with 22 (92%) to confirm access to care.

Of the approximately 600 people completed an evaluation survey (12%), satisfaction was high, with 98% saying they would use the service again.

#### C O M M E N T

**NICE guidance recommends routine testing when prevalence is greater than 0.5% (>2 to 5 per 1000) and is clearly warranted in many urban ER settings.**

**The high rates of undiagnosed and late-stage infections is clearly upsetting, given the UK has both free testing and treatment.**

**Home HIV testing appears to be very acceptable for some people. A new national self-testing study called SELPHI, with funding to distribute 10,000 tests is just starting. [4]**

#### References

1. Parry S et al. Routine blood-borne virus testing for HIV, hepatitis B and hepatitis C in the emergency department: the 'new normal'? 23rd BHIVA 4-7 April 2017, Liverpool. Oral abstract O8.  
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## Potential for phylogenetic analysis to show direction of HIV transmission

Simon Collins, HIV i-Base

**Tentative results presented in a poster at BHIVA 2017 suggest that a new approach to phylogenetic testing might have the potential to show the direction of HIV infection between two individuals.**

While the results are exciting from a scientific perspective, if the approach proves to be robust, this will raise many ethical and legal questions.

Until now, phylogenetic analysis, where sections of two viruses are compared for similarity, has been able to show similarity but crucially not direct infection (a third person could be involved) or direction of infection. Phylogenetic analysis is most useful for showing when transmissions are definitely not linked, when the two strains are unrelated. When linkage is shown, direction of infection cannot be inferred nor the possibility that both infections originated from intermediary partners.

The current study, presented as a poster by Kate El Bouzidi and colleagues from Brighton and Sussex University Hospitals Trust, used whole genome sequencing (WGS) to look at genetic diversity at each of the >9000 individual nucleotide sites in two linked viruses, with heterogeneous samples being interpreted as being the source virus for the sample which had homogeneity at the same nucleotide site.

WGS performed on 170 samples from a UK MSM cohort identified five linked pairs and these were compared to four control pairs where linkage was already established and direction inferred from clinical notes.

The direction of travel was able to be inferred using WGS for 3/4 control pairs, with the single indeterminate result linked to a sample that was taken so long after transmission took place that natural divergence was too great to determine direction.

WGS-inferred direction was consistent with clinical data for 2/5 case pairs. The lack of a signal in two further case pairs with indeterminate was able to be interpreted as not supportive direct transmission, but missing intermediary partners from whom samples were not available.

Finally, the case where WGS-inferred transmission did not match clinical route, was when the sample from the source partner was taken during primary infection (when HIV is likely to be homogenous at most points) several years before likely transmission to the second partner (whose sample was only taken during chronic infection (when heterogeneity is more likely)).

This study is funded by both BHIVA and Public Health England as part of the COMPARE-HIV Study (Comparison of Molecular & Phylogenetic Approaches to Reconstruct an Epidemic of HIV), based at Brighton and Sussex University Hospitals NHS Trust.

#### C O M M E N T

**The results are preliminary and clearly the timing of samples is likely to be important when interpreting the results from this approach.**

**WGS may improve our understanding of transmission networks at a population level but it cannot be used to confirm direct transmission at an individual level and sequence data should always be interpreted cautiously in conjunction with clinical information.**

**However, if the methodology is supported in larger analyses, the results will raise important ethical and legal concerns, especially in countries where HIV transmission is still criminalised.**

#### Reference

El Bouzidi K et al. Insights into the dynamics of HIV-1 transmission using whole genome deep sequencing. 23rd BHIVA, 4-7 April 2017, Liverpool. Poster abstract P31.

## No new HIV cases in 398 people using PrEP at Dean Street clinic

Simon Collins, HIV i-Base

**Compelling results on the real world efficacy of generic PrEP by gay men in London were presented in a poster by Issac Aloysius and colleagues from the 56 Dean Street clinic in Soho.**

Since February 2016, this NHS clinic has been providing free routine HIV, STI and renal monitoring for people using generic PrEP that they buy online. More than 700 people have been using this service over the last year, and data was presented for 371. Median time since starting PrEP is 17.2 months.

Baseline characteristics include 99% men and 82% white, with median age 37 years (IQR 30 to 43). Overall, 90% were using daily PrEP and 10% using event-based dosing. Baseline eGFR was >60 in 96% of samples, with reduced renal function on PrEP only reported for 1 person who had pre-existing renal problems.

The TDM monitoring in the service confirmed all generic drugs were genuine. Overall, 97% were using Tenvir-EM from Cipla, with 88% of first TDM sample and all repeat samples showing comparable drug levels to branded formulations.

Most importantly, from 223 patient years of follow-up (data was included up until the last HIV negative test) there were no new HIV diagnoses (0%, 95%CI: 0 to 1.6%). This was despite participants having high likely exposure risk for HIV.

For example, 30% reported ChemSex while on PrEP (use of methamphetamine, mephedrone or GHB) and there were high rates of STIs during follow-up: 26% chlamydia (92/348), 23% gonorrhoea (79/348), 3% syphilis (11/348). However, there were no cases of HBV and only three cases of hepatitis C (1%), which given the cohort could easily have been higher.

The poster showed monthly HIV diagnoses at Dean Street falling from 71 in June 2015 to approximately 20 a month for the last six months to January 2017.

#### Reference

Aloysius I et al. InterPrEP (II): internet-based pre-exposure prophylaxis (PrEP) with generic tenofovir DF/emtricitabine (TDF/FTC) in London: analysis of safety and outcomes. British HIV Association Conference, abstract P32, Liverpool, April 2017.

## Community presentations: dental care, HIV awareness and access to formula milk

Simon Collins, HIV i-Base

**Although BHIVA conferences always include community-based research, usually covered by many posters, this year the Friday morning oral research presentation were all focused on living with HIV. [1]**

### HIV and dental services

Alasdair Hudson from the Family Planning Association presented an analysis on experience that HIV positive people have over dental care. The results were from more than 1,500 responses to the 2015 Stigma Survey, roughly matching the UK demographics in terms of gender, age, race and time since diagnosis.

This is a community-based project with surveys distributed by organisations and clinics across the UK and supported with analyses from Public Health England.

In the age of ART, the historical issues linked to dental care: stigma, denial of service, the need for HIV as a special needs service, should have largely been resolved, especially as the ban on HIV positive dentists was lifted years ago.

However, on the first question of awareness of HIV status, only 58% of respondents felt in control of HIV disclosure to dentists, only 35% disclosed and only 27% felt supported in the disclosure process.

Compared to GP services, people were more worried about dental care (40% vs 27%) with 14% of respondents reported avoiding seeking care at both services and 13-15% reported being treated differently at both services.

Worrying about receiving a different level of treatment, having received poorer treatment and refusal or delayed treatment were all significantly associated with avoiding dental care in the future (all  $p < 0.001$ ).

### HIV awareness among the general public

Alex Sparrowhawk from the Terrence Higgins Trust presented results from an independent commissioned three-question survey about HIV awareness from 2000 members of the general public.

On HIV transmission, 30% of respondents (including 30% of gay and bisexual men) thought this could come from sharing a toothbrush, 20% from kissing (including 10% of gay and bisexual men) and around 5% from sharing other household items.

On the impact of ART, only 29% knew HIV positive people could have children without passing on HIV and only 59% that living to old age was possible. However, almost 40% knew that ART meant HIV positive people could have sex without the risk of HIV transmission. On these questions responses were broadly similar between the general population and gay/bisexual men.

Many transmission myths were still widespread in London, with little difference in results by geographical region. Awareness was slightly lowest in those either under 24 or older than 55.

Very few people (~3%) strongly agreed "there is currently an HIV epidemic in the UK", with 53% of the general public and 68% of gay/bisexual men broadly disagreeing with this statement.

## Affordability and access to formula milk

Bianca Karpf presented results on experiences of affording formula milk from a telephone survey of 42 HIV positive mothers (given birth within three years) who were service users at London-based Body and Soul.

Overall, 71% spent more than £10/week on formula milk with 7% spending more than £20. Over 50% admitted there were times when they or a family member went hungry in order to buy formula milk. Approximately half had no access to public funding.

Most women were strongly advised not to breastfeed, although one woman was given no advice. Most women were strongly committed to using formula milk even when breastfeeding was suggested as an option, as even with ART there is still a small risk of HIV transmission.

The presentation focused on lack of choice and support for many women and recommended that prescription of free formula milk should be provided to all HIV positive mothers, with most women (75%) preferring the option of vouchers that could be used in supermarkets.

### References

Unless stated otherwise, all references are to the programme and abstracts of the 23rd BHIVA conference, 4-7 April 2017, Liverpool.

1. Oral Research Presentations: Session 4: Living with HIV. 23rd BHIVA 4-7 April 2017, Liverpool. Friday 7 April 2017, 11-12am.
2. Hudson A et al. Experiences of HIV disclosure and stigma in the dental setting: findings from the people living with HIV Stigma Survey 2015. 23rd BHIVA 4-7 April 2017, Liverpool. Oral abstract O25.  
<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170407/AlastairHudson.pdf> (PDF)  
<http://www.bhiva.org/170407AlastairHudson.aspx> (webcast)
3. Sparrowhawk A et al. Perceptions of HIV within the general public. 23rd BHIVA 4-7 April 2017, Liverpool. Oral abstract O26.  
<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170407/AlexSparrowhawk.pdf> (PDF)  
<http://www.bhiva.org/170407AlexSparrowhawk.aspx> (webcast)
4. Karpf B et al. Affording formula: HIV - positive women's experiences of the financial strain of infant formula feeding in the UK. 23rd BHIVA 4-7 April 2017, Liverpool. Oral abstract O27.  
<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170407/BiancaKarpf.pdf> (PDF)  
<http://www.bhiva.org/170407BiancaKarpf.aspx> (webcast)

## Other selections and webcasts

### Simon Collins, HIV i-Base

**In addition to the studies reported above, many other studies included important results. A selection of these are included below.**

### Generics: the facts

Andrew Hill from the University of Liverpool in the first of five BHIVA invited lectures, argued that now many widely used HIV drugs have come off patent, incremental cost from newly approved ARVs such as dolutegravir and tenofovir alafenamide need to be reduced to remain cost-effective relative to the new price of generic-based combinations.

The talk covered HIV and hepatitis C comparing the more ambitious Australian government programmes for broader access to both PrEP and direct acting antivirals for hepatitis C.

Ref: Hill A. Generics: the facts. BHIVA invited lecture 1, Thursday 6 April 2017.

<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170406/JohnFrater.pdf> (PDF)

<http://www.bhiva.org/170406AndrewHill.aspx> (webcast)

### Suicide in HIV positive people

Sara Croxford from Public Health England presented an analysis of suicide deaths in HIV positive people compared to the general population.

From 1997 to 2012, 96 suicide deaths in HIV positive people accounted for 1.8% of the 5302 deaths, representing a mortality rate of 2.1 per 10,000 patient years (95%CI: 1.8 to 2.6).

This was more than double the rate for the general population, matched by sex and age (SMR 2.0; 95%CI 1.6 to 2.4), driven by significantly higher rates in men.

Rates were highest within the first year of diagnosis.

Ref: Croxford S et al. Suicide among people diagnosed with HIV in England and Wales compared to the general population. Oral abstract O16.

<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170406/SaraCroxford.pdf> (PDF)

<http://www.bhiva.org/170406SaraCroxford.aspx> (webcast)

### Acute hepatitis C in HIV negative gay men

Laura Midgely presented results from a case review of acute HCV diagnoses from patients attending the Mortimer Market sexual health services between April 2015 to April 2016.

The study was prompted by increasing reports of sexual HCV transmission, when condomless sex was reported as the only risk factor. Risk factors were assessed based on case notes and included ChemSex, injecting or snorting drugs, STI history, PrEP use, fisting, and condomless sex.

Of the 48 cases identified, 81% were gay men (including 16 gay men who were HIV negative), 13% women and 6% heterosexual men. Overall, two-thirds of the diagnosis were in HIV positive patients.

Condomless sex was reported as the only risk factor for 19% of the HIV positive group compared to none of the HIV negative group. ChemSex, use straws and IV drug use in the positive vs negative men was reported by 53% vs 38%, 53% vs 38%, and 31% vs 44% respectively. STIs were significantly higher in the HIV positive group (59% vs 6%), but fisting was low in both groups (3% vs 6%).

Although there are limitations for assessing risk factors from retrospective case notes, this signal confirms previous reports that HCV can be sexually transmitted from condomless sex, especially for HIV positive men.

Ref: Midgely L et al. Acute hepatitis C infection in lower risk MSM: an evolving picture. Oral abstract O24.

<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170406/LauraMidgely.pdf> (PDF)

<http://www.bhiva.org/170406LauraMidgely.aspx> (webcast)



## Scientific advances - including cure research

The potential for new technological advances to affect HIV research was given by John Frater from the University of Oxford. These include:

- Advances in single cell technologies that enable massive scale up of research capacity with simpler lab facilities, for example in screening compounds and in rare cell populations.
- Gene editing technologies, including CRISPR/Cas9 and advances in HIV broadly neutralising monoclonal antibodies.
- The recent discovery of a new marker for latently infected CD4 cells (CD32a) that could be a key step in HIV cure research.

Ref: Frater J. An overview of basic science discoveries that will impact upon clinical practice. BHIVA invited lecture 1, Thursday 6 April 2017.

<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170406/JohnFrater.pdf> (PDF)

<http://www.bhiva.org/170406JohnFrater.aspx> (webcast)

## HIV and neurological complications

Two presentations at BHIVA 2017 focused on neurological symptoms and HIV associated neurological disorders (HAND) in HIV positive people.

Tristan Barber, from the Chelsea and Westminster Hospital presented a practical approach to the complexity of interpreting neurological symptoms and clinical management of HAND, including a stepped-care model for psychological wellbeing.

Paul Holmes from St Thomas' Hospital gave an overview of the pathobiology of HAND, the role of CSF biomarkers and other causes of neurological impairment.

### References

1. Barber T. Neurocognitive symptoms in people with HIV. BHIVA invited lecture 5, Friday April 2017.  
<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170407/TristanBarber.pdf> (PDF)  
<http://www.bhiva.org/170407TristanBarber.aspx> (webcast)
2. Holmes P. Neurocognitive symptoms in people with HIV. BHIVA invited lecture 5, Friday April 2017.  
<http://www.bhiva.org/documents/Conferences/2017Liverpool/Presentations/170407/PaulHolmes.pdf> (PDF)  
<http://www.bhiva.org/170407PaulHolmes.aspx> (webcast)

## CONFERENCE REPORTS

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

13-16 February 2017, Seattle

#### Introduction

**This issue of HTB includes further reports from the 24th Conference on Retroviruses and Opportunistic Infections (CROI 2017) held in Seattle from 13-16 February 2017.**

CROI is one of the leading scientific HIV meetings and the exciting news is that there was much to report.

The conference also provides free access to the conference materials online, including comprehensive webcasts of all oral presentations, available immediately after each session.

The programme for the meeting and abstract books can be downloaded as PDF files.

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

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

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

New CROI reports for this issue of HTB include:

- Dose reduction potential of nanoparticle ARV formulations confirmed in humans
- VRC01 in HIV-exposed newborns: first results support monthly injections for those at risk through breastfeeding
- Raltegravir pharmacokinetic targets met in high-risk HIV-exposed infants
- Tenofovir alafenamide exposure is modestly higher in children than adults
- New HIV diagnoses in children in UK and Ireland continue to decline
- World Health Organisation paediatric dosing tool
- Pre-ART drug resistance in rural South Africa but limited clinical impact with good adherence
- Immune-based therapy canakinumab reduces inflammatory markers in HIV positive people on ART
- Significant interaction between once-weekly isoniazid/rifapentine and daily dolutegravir: study stopped due to toxicity
- Increased risk of IRIS with integrase inhibitors reported in two studies
- Breakthrough for treating XDR-TB and ameliorating TB-IRIS
- PREP in pregnancy does not increase poor birth outcomes
- HIV cure research and basic science: capsules from CROI 2017

CROI 2017: NEW DRUGS

## Dose reduction potential of nanoparticle ARV formulations confirmed in humans

Polly Clayden, HIV i-Base

### First in-human trial results of nanoformulations of efavirenz and lopinavir confirmed the potential for a 50% dose reduction to the current standard oral dose of both antiretrovirals.

Andrew Owen presented these findings at CROI 2017 on behalf of colleagues from the University of Liverpool, St Stephens AIDS Trust, Chelsea and Westminster Hospital, London, Clinton Health Access Initiative, Boston, and the Medicines Patent Pool, Geneva.

Professor Owen explained that the group's solid drug nanoparticle (SDN) formulations of efavirenz (EFV) and lopinavir (LPV) have previously shown preclinical potential for dose reduction while maintaining pharmacokinetics (PK).

The aims of the human study were to: investigate the PK of the EFV and LPV SDN formulations in HIV negative participants; construct population PK models to describe the available data and compare PK to historical data from the originator products; and investigate multiple dosing and safety of the two SDN formulations.

The SDN formulations were powder filled capsules.

The investigators obtained consent from and screened five participants who then received 200mg nano-LPV (boosted with 100 mg originator ritonavir [RTV]) twice daily for seven days. A 12-hour PK profile was generated after the first dose, followed by steady-state PK after the last dose with 56-hour decay. A single plasma concentration was measured on day 3. Participants were assessed for safety at screening, day 1 (before morning and afternoon dose and 4 hours after afternoon dose), day 7, and at completion.

Four participants received 50mg nano-EFV once daily over 21 days ("to err on the side of caution"). A 72-hour PK profile was generated after the first dose, followed by steady-state PK profile after the final dose with 228-hour decay. Single plasma concentrations were measured on days 7, 14, and 17. Safety assessments (including physical examination with vital signs, ECG, urinalysis, laboratory testing) were made at screening, day 1, 2, 14, 21 and at completion.

Professor Owen reported that both SDNs were well tolerated at the studied doses, with no grade 3–4 adverse events.

The investigators used population PK models to analyse PK (one compartment model for LPV and two compartment for EFV), and the resulting models to simulate 1000 HIV negative participants dosed at 200/100 and 300/100 mg LPV/r twice daily, and 200 and 300 mg EFV once daily. These results were compared with simulated 400/100 mg twice-daily originator LPV/r and 600 mg or 400 mg once daily originator EFV.

The simulations predicted that 200mg nano-LPV twice daily (with 100mg originator RTV) would be bioequivalent to twice-daily originator LPV for AUC<sub>0-12</sub>, C<sub>max</sub>, and C<sub>12</sub>. See Table 1.

For nano-EFV, the simulations predicted that 300mg once daily would provide bioequivalence to 600mg once daily originator EFV for AUC<sub>0-24</sub>, C<sub>max</sub> and C<sub>12</sub>. For C<sub>24</sub> bioequivalence not achieved because concentrations were predicted to be higher than those for originator EFV. Simulations were also made for 200mg nano-EFV vs 400mg originator EFV. See Table 1.

Dr Owen noted that there was an indication of an extended tail for both SDN formulations compared to originator formulations.

**Table 1: Simulated comparisons of SDN and originator formulations of LPV and EFV**

Drug/PK parameter	Geometric mean		Geometric mean ratio
	LPV SDN 200 mg	LPV originator 400 mg twice daily	GMR (90% CI)
C <sub>12</sub> (mg/L)	4.16	4.02	1.04 (0.99–1.08)
AUC <sub>0-12</sub> (mg.h/L)	72.35	79.07	0.92 (0.89–0.94)
C <sub>max</sub> (mg/L)	10.69	9.97	1.07 (1.05–1.10)
Efavirenz	Geometric mean		Geometric mean ratio
	EFV SDN 300 or 200 mg	EFV originator 600 or 400 mg once daily	GMR (90% CI)
AUC <sub>0-24</sub> (mg.h/L)	51.56	58.61	0.88 (0.86–0.90)
C <sub>12</sub> (mg/L)	2.03	2.51	0.81 (0.78–0.83)
C <sub>24</sub> (mg/L)	1.90	1.44	1.32 (1.26–1.37)
C <sub>max</sub> (mg/L)	2.99	3.36	0.89 (0.87–0.91)

He explained that limitations to the study were small sample size, use of historical data rather than direct comparison with conventional formulations (stage 2 is ongoing), and dose prediction above studied doses assumes linear PK across adult doses.

Dr Owen concluded that these data confirm the potential for 50% dose reductions using a novel approach to formation of LPV and EFV SDNs. If confirmed in larger studies, this approach has the potential for estimated savings of up to US \$243 million a year while also freeing up significant manufacturing capacity up to 930 tons a year.

He added that more formulation development is needed for future clinical translation: co-formulation, tableting, stability etc. And that this approach has wide applicability for drugs from various classes for numerous indications.

#### C O M M E N T

**This group are currently working on a number of other antiretroviral development programmes for oral and long-acting SDN formulations: darunavir, atazanavir, ritonavir and dolutegravir.**

**If 400 mg EFV becomes the recommended dose SDN formulations can be targeted accordingly. The same applies to lower dose darunavir, if these dose reduction studies are successful.**

**There also might be benefits with SDN formulations for paediatric ART (particularly for infants and young children) as nanoparticles can be dispersed in water, which might mitigate the need for organic solvents.**

#### Reference

Owen A et al. Human confirmation of oral dose reduction potential of nanoparticle ARV formulations. CROI 2017. Oral abstract 39.

<http://www.croi-conference.org/sessions/human-confirmation-oral-dose-reduction-potential-nanoparticle-arv-formulations> (Abstract)

<http://www.croiwebcasts.org/console/player/33376> (Webcast)

CROI 2017: PAEDIATRIC CARE

## VRC01 in HIV-exposed newborns: first results support monthly injections for those at risk through breastfeeding

Polly Clayden, HIV i-Base

**Preliminary results suggest that VRC01 – an investigational HIV neutralising monoclonal antibody – administered subcutaneously to neonates is safe and well tolerated. Its half-life would support monthly injections for those at risk of HIV through breastfeeding. These data from IMPAACT P1112 were presented at CROI 2017.**

IMPAACT P1112 is an ongoing, prospective, open label, dose escalating study of VRC01, given to infants at increased risk of HIV transmission as a single 20 or 40 mg/kg subcutaneous dose within 72 hours of birth. Study sites are in US, Puerto Rico, and South Africa.

Increased risk of infant HIV infection is defined as one or more of the following maternal risk factors: no antiretrovirals (ARV) in pregnancy;

began or restarted ARV in third trimester; detectable viral load; prolonged ruptured membranes; two class ARV resistance.

Eligible infants were 36 weeks of gestation or more weighing at least 2 kg at birth. All infants received ARV prophylaxis according to local standard of care. After VRC01 immunisation they received safety assessments for 4 hours followed by safety and pharmacokinetic (PK) measurements at 24 hours, days 3, 7, 14, 28, weeks 8, 16 and 24. Target VRC01 level is 50 mcg/mL on day 28.

The study enrolled 27 infants: 52% male, 61% black, median age 2 days and birth weight 3105 grams. One infant in the 20 mg/kg group was incorrectly enrolled and one in the 40 mg/kg group was under dosed and excluded from the PK analysis.

VRC01 was well tolerated with no grade 3 and above systemic adverse events. Local injection site reactions were common, occurring in 6 and 11 infants in the 20 mg/kg and 40 mg/kg groups respectively. These resolved in four hours for 100% and 55% of infants in the respective dosing groups. The PK results are shown in Table 1.

These preliminary results showed persistent levels of VRC01 through day 28 of life. The 40 mg/kg dose achieved the target level at day 28 compared with adults receiving 20 mg/kg intravenously.

The investigators suggest that the half-life of VRC01 supports monthly injections for infants at ongoing risk of vertical transmission of HIV through breastfeeding.

#### C O M M E N T

**Despite the massive success in preventing vertical transmission of HIV with ARVs, children still become infected for a number of reasons. A long acting monoclonal antibody might further prevent transmission during breastfeeding.**

#### Reference

Cunningham CK et al. Safety & pharmacokinetics of the monoclonal antibody, VRC01, in HIV-exposed newborns. CROI 2017. 13-17 February 2017. Seattle. Poster abstract 760.

<http://www.croi-conference.org/sessions/safety-pharmacokinetics-monoclonal-antibody-vc01-hiv-exposed-newborns> (Abstract and poster)

**Table 1: Infant PK of VRC01 after single 20 or 40 mg/kg subcutaneous dose**

VRC01	Dose	Mean	SD	Median	Range
C <sub>day28</sub> (mcg/mL)	20 mg/kg	39.33	14.94	39.19	16.71 to 76.56
	40 mg/kg	75.22	21.38	74.79	47.61 to 122.59
C <sub>max</sub> (mcg/mL)	20 mg/kg	226.64	30.78	233.32	153.63 to 260.64
	40 mg/kg	378.37	79.20	390.27	247.44 to 536.60
T <sub>max</sub> (d)	20 mg/kg	2.7	2.2	2	1 to 7
	40 mg/kg	1.4	0.8	1	1 to 3
Half-life (d)	20 mg/kg	19.73	4.99	20.17	13.11 to 28.60

## Raltegravir pharmacokinetic targets met in high-risk HIV-exposed infants

Polly Clayden, HIV i-Base

**Daily raltegravir was safe and well tolerated at six weeks of life and met pharmacokinetic targets in HIV-exposed infants, according to data from IMPAACT P1110 presented at CROI 2017.**

Previous studies have shown raltegravir (RAL) elimination to be highly variable in the first weeks of life due to low UGT1A1 activity.

IMPAACT P1110 is a phase I multicentre study in full-term HIV-1 exposed neonates at high risk of HIV with or without maternal RAL exposure. It includes two cohorts: cohort 1 infants received two single RAL doses one week apart; cohort 2 infants received daily RAL dosing for first six weeks of life.

The study sites are in Brazil, South Africa and the US.

PK data from cohort 1 and from older infants and children in IMPAACT P1066 were combined in a population PK model. The model included maturation of absorption rate from 16% of max at birth to 90% at two weeks, and clearance from close to nil to max at approximately six months of age.

The model was used to perform simulations of possible daily dosing regimens for RAL-naïve infants in cohort 2 (using oral granules for suspension). See Table 1.

Plasma samples were collected at the following time points. First dose: pre-dose, 1–2, 6–10 and 20–24 hours post dose. Second dose: 3–6 hours post dose. Day 6–9 of life: pre-dose. Day 15–18 of life: pre-dose, 4–6 and 8–12 hours post-dose. Day 28–32 of life: pre-dose. Week 5–6 of life: pre-dose and 3–6 hours post-dose.

Exposure targets are: AUC<sub>24</sub> 12–40 mg\*h/L; AUC<sub>12</sub> 6–20 mg\*h/L; C<sub>12</sub> or C<sub>24</sub> > 33 ng/mL; and C<sub>max</sub> <8724 ng/mL.

Cohort 2 enrolled 26 infants: 46% female; 69% black, 12% white and 19% other; median gestation age 38.5 weeks and birth weight 2.93 kg. Evaluable PK and 6-week safety data were available for 25 infants.

The investigators reported no drug related adverse events. All RAL exposure targets were met; PK parameters are shown in Table 2.

The investigators noted that after the initial dose some infants had AUC<sub>24</sub> slightly above target range – but they considered this to be acceptable given the rapid increase in RAL metabolism over the first week of life.

Infants born to mothers who received RAL and low birth weight infants are to be studied in IMPAACT P1110.

**Table 1: Raltegravir dosing in IMPAACT P1110**

Days of life	Dose mg/kg	Frequency
1–7	1.5	Once daily
8–28	3.0	Twice daily
after 28	6.0	Twice daily

**Table 2: Raltegravir PK parameters IMPAACT 1110**

	After initial dose: 1.5 mg/kg once daily (n=25)		Day 15–18: 3.0 mg/kg twice daily (n=24)	
	Geometric mean (CV)	Target	Geometric mean (CV)	Target
AUC (mg*h/L)	38.2 (38.4%)	11 above 13 met 0 below	14.3 (43.3%)	8 above 14 met 1 below
Trough (ng/mL)	948 (64.2%)	25 above 0 below	176 (93.8%)	22 above 1 below
C <sub>max</sub> (mg/mL)	2350 (35.0%)	0 above 25 below	2850 (41.9%)	0 above 24 below
T <sub>max</sub> (mg/mL)	5.4 (57.5%)		5.4 (57.5%)	
T <sub>1/2</sub> (hours)	15.8 (174.8%)		15.8 (174.8%)	

### Reference

Clarke DF et al. Raltegravir pharmacokinetics and safety in HIV-1 exposed neonates: dose-finding study. CROI 2017. 13–17 February 2017. Seattle. Poster abstract 757.

<http://www.croiconference.org/sessions/raltegravir-pharmacokinetics-and-safety-hiv-1-exposed-neonates-dose-finding-study> (abstract and poster)

## Tenofovir alafenamide exposure is modestly higher in children than adults

Polly Clayden, HIV i-Base

**Tenofovir alafenamide (TAF) and its metabolite tenofovir (TFV) exposures are slightly higher in children aged 6–12 years compared with adults, according to data presented at CROI 2017.**

The original tenofovir formulation, tenofovir disoproxil fumarate (TDF) is not a recommended first-line nucleos(t)ide reverse transcriptase inhibitor in children. This is due to its association with bone and renal toxicity – linked to plasma exposure. TAF provides 91% lower TFV exposure than TDF and is considered to have better renal and bone safety in adults and adolescents. There is interest in the potential benefits of TAF for paediatric HIV.

TAF is currently commercially available for adults and adolescents from the originator manufacturer (Gilead Sciences) within fixed dose combinations (FDC) and co-formulations, which are under investigation for children.

The company showed 24 week findings from a pharmacokinetic (PK), safety and efficacy study of the once daily FDC elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) 150/150/200/10 mg, which is approved for adults and adolescents aged 12 and above.

The study was a phase 2/3, single-arm, open-label, 48 week, switch trial. Eligible children were aged 6–12 years, weighing at least 25 kg

and virologically suppressed (<50 copies/mL) on stable antiretroviral therapy (ART) for six months or more.

PK assessments were made on all the agents in the FDC, as well as TFV, at steady state. These were compared with adult values. Adverse events (AE), laboratory tests, including viral load, were also conducted. Bone mineral density (BMD) z-score was assessed every 24 weeks

The study enrolled 23 children: median age 10 years (range 8 to 11), median weight 31 kg (range 26 to 58), 14 (61%) female, 18 (78%) black, median CD4 count 969 cells/mm<sup>3</sup> (range 603 to 1421).

At 24 weeks mean AUC<sub>tau</sub> were 333 h\*ng/mL (45% coefficient of variation) and 440 (21% coefficient of variation) for TAF and TFV respectively. These were modestly higher than adult values, but within safe and efficacious ranges of adults. Exposures of the other agents in the FDC followed a similar pattern.

No child had a serious AE or one leading to study drug discontinuation. No child had proximal renal tubulopathy. Median per cent change in BMD at 24 weeks was +4.2% for spine and +1.2% for total body less head. Median change in BMD height-adjusted z-score was +0.10 for spine and -0.12 for TBLH.

#### References

Gaur A et al. Pharmacokinetics, safety & efficacy of E/C/F/TAF in HIV-infected children (6–12 yrs). CROI 2017. 13 – 17 February 2017. Poster abstract 424.

<http://www.croiconference.org/sessions/pharmacokinetics-safety-efficacy-ecftaf-hiv-infected-children-6-12-yrs> (Abstract and poster)

## New HIV diagnoses in children in UK and Ireland continue to decline

### Polly Clayden, HIV i-Base

**Numbers of newly diagnosed children in the UK and Ireland are still declining but an increasing proportion are born abroad and ART experienced, according to data presented at CROI 2017.**

All HIV positive children diagnosed with HIV in the UK and Ireland (UK/I) are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC). Those receiving paediatric HIV care are followed in the Collaborative HIV Paediatric Study (CHIPS). Datasets from the two studies were linked for this analysis.

The aim of the study was to describe evolving trends in the characteristics of children at diagnosis in the UK/I from 2000–2015 and in turn project the numbers entering or remaining in care up to 2020.

The analysis revealed 1,528 children were diagnosed from 2000–2015: 529 (35%) born in UK/I and 999 (65%) born abroad.

Overall age at diagnosis declined over time. Median age declined from 9 to 6 to 3 months for those born in the UK/I 2000–2005, 2006–2010 and 2010 or after respectively. The respective median ages for those born abroad were 6, 4.7 and 3 years.

There was a significant decline in the proportion of children with AIDS at diagnosis: 26% 2000–2003 to 2% in 2012–2015. The proportion with CDC B symptoms also fell from 34% to 11% in the respective time periods,  $p < 0.001$ .

Of the children born abroad 23% were diagnosed before entering the UK/I. This proportion increased significantly over time: 8% in 2000–2003 to 55% in 2012 and after,  $p < 0.001$ . By the time they arrived in UK/I 49% were ART experienced. Where ART regimen was known, 76% started on a NNRTI and 14% a boosted-PI based regimen. Of children linked in CHIPS with ART data after entry, 23% switched to a new regimen within one year of arrival.

As the CHIPS cohort grows older, an increasing number of participants are making the transition to adult HIV care. CHIPS investigators estimated that the cohort will halve in size by 2020 assuming that the numbers entering paediatric HIV care remain in decline or standstill. But the need for targeted adolescent services will increase.

#### Reference

Peters H et al. Current trends in children with HIV diagnosed in the UK and Ireland. CROI 2017. 13–17 February 2017. Seattle. Poster abstract 831.

<http://www.croiconference.org/sessions/current-trends-children-hiv-diagnosed-uk-and-ireland> (Abstract and poster)

## World Health Organisation paediatric dosing tool

### Polly Clayden, HIV i-Base

**A paediatric dosing tool developed by World Health Organisation (WHO) might assist in the design of clinical trials for dosing in children.**

When finding a safe and effective dose for children, the approach in anti-infectives is to target drug exposures similar to those in successfully treated adults. Scaling pharmacokinetics (PK) is the first step.

Down to two or three years of age, body size accounts for most of the differences in doses between children and adults.

The paediatric dosing tool – developed by the WHO Paediatric ARV Working Group (PAWG) – uses allometric scaling to help evaluate antiretroviral dosing regimens. The WHO paediatric dosing tool was presented at CROI 2017.

Allometric scaling describes the nonlinear effect of body size on PK parameters. A milligram per kilogram (mg/kg) dose in children and adults causes under-dosing in children. Even without other available information, allometry is a better guess than constant mg/kg. But paediatric dosing regimens still use constant mg/kg dosing as first best guess.

The objective of the work by the PAWG is to bridge this gap. WHO proposes an easy-to-use tool to assist researchers not familiar with PK modelling to design and evaluate paediatric dosing regimens.

The tool operates in Microsoft Excel and has easy steps to follow with results displayed in real time. It uses allometric scaling to adjust for the effect of a child's body size on clearance and it targets the same area under the time-concentration curve (AUC) as that for adults. The lowest and highest values within a paediatric weight band are shown alongside the target.

The tool can also analyse multiple drugs in a fixed dose combination and used either standardised or customised weight bands. If the effect of maturation is known for a drug this can be specified.

The WHO group note that allometric scaling alone only works well down to two years of age. Below that immature organ function could mean that clearance might be lower than that predicted using only body size. This is specific to individual drugs. Other unaccounted for factors might also have an impact: lower protein binding in children; drug formulation differences; and poor absorption.

Another limitation is that terminal half-life is usually shorter in children so adult AUC targets might lead to higher C<sub>max</sub> and lower C<sub>min</sub> so it might be necessary to dose smaller children twice daily.

The group stress that the tool is to support the design of clinical trials for dosing in paediatrics and is “not a substitute for confirmatory studies”. They add that the use of the tool in study design “would represent a significant step away from the constant mg/kg paradigm, possibly leading to improvements in the efficacy of paediatric dosing trials”.

#### Reference

Denti P et al. An easy-to-use paediatric dosing tool: one mg/kg dose does not fit all. CROI 2017, 13–17 February 2017, Seattle. Poster abstract 809.

<http://www.croiconference.org/sessions/easy-use-paediatric-dosing-tool-one-mgkg-dose-does-not-fit-all> (Abstract and poster)

## CROI 2017: DRUG RESISTANCE

### Pre-ART drug resistance in rural South Africa but limited clinical impact with good adherence

Polly Clayden, HIV i-Base

**Results from the Africa Health Research Institute showed significant pretreatment antiretroviral resistance but this was not associated with reduced viral suppression with good adherence – according to findings from the ANRS 12249 TasP trial presented at CROI 2017.**

Greater use of antiretroviral therapy (ART) in Treat All strategies might lead to higher levels of acquired and transmitted drug resistance (DR) and reduce ART efficacy.

The ANRS 12249 two arm cluster-randomised TasP trial was conducted in KwaZulu-Natal to evaluate the effect of early ART, started irrespective of CD4 count on HIV incidence. Participants were randomised to treat all HIV positive people or treat according to South African guidelines (CD4 350 or 500 cells/mm<sup>3</sup>) at the time of the trial, which took place between 9 March 2012 and 30 June 2016. The study did not show a difference between the two arms.

The second objective of the trial was to look at the prevalence of pre-treatment DR (PDR) and its impact on viral suppression (<400 copies/mL) in ART naive participants starting first-line treatment in the trial. Two presentations at CROI 2017 described these findings. [1,2]

There were sequences available from 1337 participants at trial entry: 189 dried blood spot samples (participants diagnosed HIV positive but did not refer to TasP clinic); and plasma samples from 88 recently infected and 1060 chronically infected participants.

Pol gene Sanger sequencing was performed on dried blood spots with detection threshold 20%. Full or partial HIV genome sequencing

was performed on plasma samples. Low level variants were called at a 2% level.

The overall prevalence for any PDR in majority virus for all participants was 8.7% (95% CI 7.3 to 10.3). Any PDR prevalence in chronic infection and recent infection at >2% threshold was 16.7% and 21.6% respectively.

PDR was predominantly to NNRTI drug class driven by K103N/S; there were low levels of K65R mutation; PI mutations were very rare.

When the investigators looked at antiretroviral susceptibility, 7% of participants would start ART with high level PDR to NNRTIs and only two fully active drugs out of three. But most participants would be susceptible to tenofovir and FTC.

Among participants with PDR, 74% had only one mutation. But 11% participants had three or more (up to seven) – the investigators noted that this was not observed among newly infected participants – suggesting that this group had previously received ART.

A total of 837 participants starting ART in the trial with follow up viral load results contributed to the evaluation of the impact of PDR on viral suppression: 93.3% received a fixed dose combination of efavirenz/tenofovir/FTC.

Participants were a median of 34 years of age at baseline with over one third aged 16–29; the majority (71.6%) were female and about half were eligible for ART according to South African guidelines. The prevalence of PDR mutations was similar to that observed in those starting ART overall (16.5%).

The median time to viral suppression (<50 copies/mL) was 3.61 months (IQR 3.19 to 3.71). The median time on ART was 1.36 years (IQR 0.91 to 2.13). Cumulative probability of suppression at 12 months was 94.5% (95% CI 92.7 to 96.0). Kaplan-Meier estimates showed no difference in viral suppression with or without DR at baseline.

In multivariate analysis adjusted for sex, age, baseline viral and adherence, high baseline viral load (>100,000 vs <10,000 copies/mL) was associated with a decreased rate of viral suppression: RR 0.48 (95% CI 0.39 to 0.59), p<0.0001. Good adherence (≥95% vs <95%) was associated with an increased rate of viral suppression: RR 1.29 (95% CI 1.04 to 1.60), p=0.017.

#### C O M M E N T

**The prevalence of transmitted drug resistance is above the WHO threshold of 5% in this study conducted in rural South Africa. The investigators suggest that this might be overcome with optimal adherence. This study only has 16 months of follow up and longer-term outcomes are needed to confirm these findings.**

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## CROI 2017: TREATMENT STRATEGIES

## Immune-based therapy canakinumab reduces inflammatory markers in HIV positive people on ART

Richard Jefferys, TAG

**Many studies have reported that HIV infection is associated with an increased risk of arterial inflammation and cardiovascular disease.**

The pipeline of therapies that might reduce this risk has been discouragingly dry, but at CROI Priscilla Hsue from UCSF presented results from a trial of an anti-inflammatory antibody targeting the cytokine IL-1 $\beta$  that may augur a change for the better.

The antibody, canakinumab, is FDA-approved for the treatment of certain autoimmune conditions and is being tested as a therapy for cardiovascular disease in a large (10,000-person) randomised study in HIV negative individuals. Hsue's pilot trial recruited ten HIV positive people on suppressive ART with a median age of 59. A single dose of canakinumab was administered at baseline and participants followed for eight weeks.

There were significant declines in inflammatory biomarkers: IL-6 levels declined by 30% and high sensitivity c-reactive protein by 41%. Imaging studies revealed a 10% reduction in arterial inflammation. In terms of safety, Hsue noted a transient drop in absolute neutrophil count that resolved by week four and a single case of shingles that did not appear related to any immunological parameters. No significant changes in any biomarkers of HIV disease were seen apart from a 17% drop in CD8 T cell counts between baseline and week two that was not apparent at any other timepoints. CD4 T cell counts, viral load and T cell activation markers were unchanged. Analyses of measures of the HIV reservoir are ongoing.

"We believe this is one of the first immune-based therapies to show a very profound reduction in inflammatory markers in the setting of treated HIV," Hsue said, noting that a larger randomised controlled trial is planned that will give two canakinumab doses and follow 100 participants for 36 weeks.

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## CROI 2017: TUBERCULOSIS

## Significant interaction between once-weekly isoniazid/rifapentine and daily dolutegravir: study stopped due to toxicity

Polly Clayden, HIV i-Base

**Serious toxicities were seen in participants in a drug-drug interaction study of once-weekly isoniazid and rifapentine with once-daily dolutegravir, leading to its early termination – according to data presented at CROI 2017.**

Once-weekly isoniazid (INH) and rifapentine (RPT) (wHP) is a three-month regimen for latent tuberculosis infection (LTBI). There are limited drug interaction data between wHP and antiretrovirals (ARVs). As with other rifamycins, RPT can induce CYP and UGT enzymes, and in turn reduce ARV drug exposure.

This study – conducted by the US NIH – was designed to look at the effect of wHP on the steady-state pharmacokinetics (PK) of dolutegravir (DTG). It was an open-label, intrasubject drug-drug interaction study in HIV-negative participants. The study had two phases: [1]. DTG once daily alone days 1–4; [2]. DTG once daily with wHP for days 5–19. Plus, safety follow up days 20–34. DTG levels were measured at all PK visits, and RPT and INH levels on day 19.

Four participants were enrolled before the study was stopped: 3 men and 1 woman aged 21–46 years. One participant voluntarily withdrew from the study before day 19.

The study was stopped early due to the flu-like symptoms and transaminase elevations in two out of three participants who received three doses of wHP with DTG. The symptoms started about 8–10 hours after the last dose of DTG, RPT and INH on day 19 and resolved by 72 hours post-dose.

Following start of wHP, DTG C<sub>min</sub> was decreased by 42.7% on day 14 vs day 4; and by 74.4% on day 15. The C<sub>min</sub> was 5.3 x protein-adjusted IC<sub>90</sub> for DTG (0.064 ug/mL) at this time point (range 0.9 to 11.0).

Exposure to RPT and its metabolite were similar to reference PK data, but INH exposure was 67–92% higher than expected in the two participants that developed flu-like symptoms.

### C O M M E N T

**These data suggest that administration of DTG and wHP together should be avoided. The investigators noted that the mechanisms behind these reactions are unknown but cytokine assays revealed increases in a number of inflammatory markers. Additional investigations are underway.**

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## Increased risk of IRIS with integrase inhibitors reported in two studies

Polly Clayden, HIV i-Base

**Two cohort studies – from the Netherlands and France – showed a higher risk of IRIS with integrase inhibitor-based ART than with other regimens. Findings from both studies were presented at CROI 2017.**

HIV treatment with integrase inhibitor (INSTI) based ART is recommended as preferred first-line in most high-income countries and is expected to become standard of care in many low- and middle-income countries over the next few years.

The use of INSTI based ART is associated with an accelerated viral load decline and faster CD4 increase compared with PI or NNRTI based ART.

IRIS is a pathological inflammatory response to antigens of opportunistic infections (OIs). People with CD4 counts of less 200 cells/mm<sup>3</sup> when they start ART are at an increased risk for IRIS. Typically phase 3 registrational studies of new antiretrovirals exclude people with low CD4 counts and active OIs.

### ATHENA cohort

The Dutch findings were from a multicentre, retrospective observational study in the ATHENA cohort. [1] The investigators performed a chart review of all treatment-naïve participants starting ART from 2009 onwards (when raltegravir was registered in the Netherlands) who were at risk for IRIS. This included people with: CD4 200 cells/mm<sup>3</sup> or less at start of ART; on OI diagnosed before or after starting ART; and/or use of corticosteroids up to 12 months after starting ART; and/or died up to 12 months after starting ART.

The study used two definitions of IRIS.

1. According French et al, 2004 (An atypical presentation of an OI or tumour in a patient responding to ART with decline in viral load or increase in CD4 count); and
2. Diagnosed by the treating clinician (IRIS as most likely diagnosis in the patient file or IRIS in the differential diagnosis with initiation of treatment for IRIS – eg corticosteroids).

The primary endpoints were French IRIS and combined clinical or French IRIS in INSTI vs non-INSTI users (the investigators considered French IRIS to be more specific so participants with IRIS according to both definitions were categorised as French). Participants who switched from PI/NNRTI to or from INSTI were censored.

Of 18,355 participants in the ATHENA cohort, 369 met the study criteria and were included at time of analysis: 69 received INSTI based ART and 300 non-INSTI based. At HIV diagnosis, median CD4 count and viral load in the INSTI vs non-INSTI groups respectively was 36 vs 30 cells/mm<sup>3</sup> and 446,694 vs 257,040 copies/mL. The majority of participants were men: respectively 74% and 83%. Median age overall was 43 years.

Incidence of French IRIS in the INSTI group was 19% and clinical IRIS 19%, compared to 9% and 7% in the non-INSTI group, with IRIS being three times more likely in the INSTI group according to either definition (OR: 3.25, 95%CI: 1.83 to 5.8).

Cox regression showed that INSTI use was independently associated with French as well as French/ clinical IRIS: HR 2.62 (95%CI: 1.35 to 5.1),  $p=0.0045$ , and HR 2.69 (95%CI: 1.63 to 4.44),  $p=0.0001$ , respectively.

IRIS was most frequently related to pneumocystis jirovecii pneumonia (PCP), candidiasis and mycobacterial infections.

Sex, age, ethnicity, mode of infection, calendar year, baseline CD4, CD4/CD8 ratio, highest viral load measurement, type of ART regimen, number and type of OI-events, time between start of OI treatment and start of ART and use of steroids for OIs, were not associated with an elevated HR for IRIS.

The investigators did not report any interaction between INSTI-use and any of the other characteristics that were significantly associated with IRIS.

### Dat' AIDS cohort

The French study was from the Dat' AIDS cohort across French HIV centres that share the same electronic patient record system. [2]

The investigators selected participants starting ART with CD4 200 cells/mm<sup>3</sup> or less (2010–2015) and admitted to hospital within six months and compared those receiving INSTI-based with non-INSTI regimens. Three HIV specialists blinded to the ART regimen performed the examination of the patients' medical charts.

IRIS was defined as symptoms consistent with an infectious or inflammatory condition associated with a viral load drop of  $>2 \log_{10}$  copies/mL not explained by a new infection, the clinical course of a previous infection, or side-effects, according to adapted ACTG IRIS criteria.

The study included 2287 participants: 398 received INSTI based ART and 1889 non-INSTI. Median age was 45 years and 63% were men. The third drug was a boosted PI in 65%, NNRTI in 12%, and INSTI in 12%. At ART initiation, the median CD4 count and viral load were 34 vs 84 cells/mm<sup>3</sup>, and 5.3 vs 5.2  $\log_{10}$  copies/mL and in the INSTI vs non-INSTI groups respectively.

Median viral load was lower in the INSTI group after three months of ART: 1.7 vs 2.1  $\log_{10}$  copies/mL,  $p<0.001$ .

IRIS occurred in 3% of participants in the INSTI group compared with 1.5% in the non-INSTI: OR 1.99 (95%CI: 1.09 to 3.47),  $p=0.04$ .

IRIS was most frequently related to tuberculosis, Mycobacterium avium and progressive multifocal leukoencephalopathy (PML).

As with the previous study co-factors such as age, sex and mode of infection were not associated with increased risk of IRIS.

### C O M M E N T

**These two reports are from cohorts and not randomised so come with all the associated potential for confounding with cohort studies.**

**The Dat' AIDS investigators noted that the relative infrequency of IRIS events in their study (1.8% overall) might be explained by the strict definition of IRIS they used and that they focused exclusively on severe IRIS needing hospitalisation. They also suggested it might be possible that because of known interactions between**



**PIs and rifampicin that people with a pre-existing mycobacterial disease could be more likely to receive an INSTI based regimen. They did not demonstrate this in the study but probably lacked power to find any significant difference in the choice of first-line ART in IRIS cases.**

**Possible confounding aside, people starting INSTI based ART with a CD4 count of 200 cells/mm<sup>3</sup> or less appear to be at increased risk for IRIS. This is important for low- and middle-income countries for which a dolutegravir based regimen is now recommended as an alternative first-line by WHO, and is predicted to become the preferred regimen as evidence gaps are filled.**

**Two ongoing large randomised trials of first-line dolutegravir vs efavirenz in as-close-as-possible-to-real-life unselected African patients that are likely to include people with low CD4 cell counts – ADVANCE (South Africa) and NAMSAL (Cameroon) – plan to have results in 2019 – but incidence of IRIS should be raised now as an ongoing concern for DSMBs for each study. [3]**

**The ADVANZ-4 Trial (Spain) is comparing first-line ART with dolutegravir and darunavir/ritonavir, both with abacavir and 3TC, in people with very low CD4 counts: below 100 cells/mm<sup>3</sup> before treatment. [4] It is a small study with only 108 participants but is looking at immune reconstitution with results expected at the end of this year.**

**In the meantime, there needs to be careful monitoring of people with low CD4 counts at increased risk for IRIS in early dolutegravir adopter countries such as Botswana and Brazil.**

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## Breakthrough for treating XDR-TB and ameliorating TB-IRIS

Richard Jefferys, TAG

**Several important TB studies were presented as late breaker oral presentations at CROI 2017, on treatment for extensively drug-resistant TB (XDR-TB) and on TB-IRIS.**

Highly promising results from the Nix-TB study were presented by Francesca Conradie of the University of the Witwatersrand in

Johannesburg, on a breakthrough in treating XDR-TB, a condition normally requiring the use of debilitating, toxic injectable drugs. [1]

This small study uses a new combination of three oral drugs (bedaquiline, pretomanid, and linezolid). Of the 72 participants (39 men and 33 women) enrolled so far, 31/72 have reached the primary endpoint of being culture negative after 6 months follow-up. Of these, only two cases of relapse/reinfection were reported (still to be determined, but suspected reinfections), and only one case with XDR-TB. However, four participants died, all within the first eight weeks: 3/4 due to multi-organ TB (on autopsy) and 1 due to gastrointestinal bleed relating to erosive oesophagitis.

Tolerability was good with most side effects (peripheral neuropathy and myelosuppression relating to linezolid) being manageable, even with short dose interruptions.

This greatly shortened all-oral combination therefore provided extremely encouraging results both for safety and efficacy.

A short report by Jon Cohen in Science, included a comment that the combination would have likely efficacy for MDR-TB, whether Nix-TB data would be sufficient for pretomanid to become approved and the issues of cost and access. [2]

Immune reconstitution inflammatory syndrome (IRIS) is a potentially life-threatening consequence of the restoration of immune responses to opportunistic pathogens in people who initiate ART at low CD4 T cell counts.

Evidence suggests that immune responses can become exaggerated and overly inflammatory as a deficient, dysregulated immune system begins to recover due to ART-mediated HIV suppression. In some cases opportunistic infections can get worse before improving, a problem termed paradoxical IRIS. This is a particularly significant concern in tuberculosis (TB), with a reported mortality rate of around 3%. [3]

In an effort to reduce morbidity and mortality from paradoxical TB-IRIS, Graeme Meintjes and colleagues conducted a randomised trial evaluating a four-week course of the corticosteroid prednisone in individuals at risk. The encouraging results were debuted as a late-breaker at CROI, with Meintjes reporting a significant 30% reduction in the incidence of paradoxical TB-IRIS and a trend toward decreased hospitalisations in the prednisone arm. [4]

No evidence of an increase in cancer risk – which had been raised as a potential issue with prednisone - was observed. The evidence from the trial suggests that the approach should be adopted as the standard of care for individuals at risk for paradoxical TB-IRIS.

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CROI 2017: HIV PREVENTION

## PREP in pregnancy does not increase poor birth outcomes

Polly Clayden, HIV i-Base

### No increase in poor birth outcomes with PrEP used throughout pregnancy in the Partners Demonstration project reported at CROI 2017.

There are limited safety data to guide the use of PrEP in pregnancy and women are currently counselled with the option to continue or discontinue it during this period.

Birth outcomes from infants exposed to FTC/TDF PrEP throughout pregnancy in the open label Partners Demonstration PrEP study, conducted in Kenya and Uganda, were compared with unexposed infants born to women randomised to placebo who became pregnant in the Partners PrEP Study (comparator).

Of 334 women receiving PrEP, 30 became pregnant and continued its use. Of 621 women receiving placebo, 79 became pregnant (85 pregnancies).

Women in the PrEP exposed and unexposed groups were a median of 25 and 28 years respectively and had a median of two children before study entry.

The investigators reported similar pregnancy outcomes in PrEP-exposed and un-exposed pregnancies. See Table 1.

**Table 1: Pregnancy outcomes PrEP exposed vs unexposed infants**

	PrEP-exposed	PrEP-unexposed	OR (95% CI) p-value
Preterm delivery	0	5 (7.7%)	0.4 (0 to 2.3) p=0.4
Pregnancy loss	5 (16.7%)	20 (23.5%)	0.8 (0.3 to 2.5) p=0.7
Congenital anomaly	0	5 (7.7%)	Fisher's exact p=0.3

They also reported that infant growth characteristics were similar at 12 months and any early detriment in PrEP exposed infants appeared to catch up by this time.

### C O M M E N T

**Data from this small cohort of PrEP exposed babies provide some reassurance that PrEP can be used safely throughout pregnancy.**

### Reference

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CROI 2017: CURE RESEARCH AND BASIC SCIENCE

## HIV cure research and basic science: capsules from CROI 2017

Richard Jefferys, TAG

**CROI 2017 offered a dizzying parade of new data. Webcasts of presentations and PDF files of posters were rapidly placed online and are accessible via the CROI website.**

### A fillip for kick & kill

On the cure research front, the results that drew the most attention related to a small trial combining a latency-reversing agent (the HDAC inhibitor romidepsin) with therapeutic vaccination – a strategy commonly referred to as “kick & kill.” [1]

Presented by Beatriz Mothe from IrsiCaixa in Barcelona, the crux was that five out of 13 recipients of the interventions have since interrupted ART and displayed control of viral load to low levels for several months (the longest a little over six months). None of the five have yet met the study criteria for restarting ART, which is a viral load over 2,000 copies/mL; the other eight participants quickly rebounded to levels above this cutoff and resumed ART.

Contrary to a slew of erroneous headlines in the mainstream media, [2] none of the five individuals are “virus-free”; based on the slide presentation, three appear to have viral load below the limit of detection of the assay used (20 copies/mL) whereas the other two are oscillating between the limit of detection and approximately 2,000 copies/mL.

The study represented a rollover from a prior trial that administered two therapeutic vaccines to 24 people who had started ART within three months of HIV infection. The vaccine vectors were based on a chimpanzee adenovirus (ChAdV63) and modified Vaccinia Ankara strain (MVA), both encoding antigens designed to focus T cell responses on highly conserved parts of HIV, including elements from the Gag, Pol, Env and Vif proteins. In a poster presented at last year's CROI, Mothe reported that receipt of these vaccines shifted HIV-specific T cell responses toward the intended conserved targets but did not have a measurable effect on the size of the HIV reservoir. [3]

A total of 15 participants from this original trial then agreed to enrol in a follow up study, which provided booster immunisations with the MVA vector before and after three infusions of romidepsin. Eight weeks after the final MVA dose, all participants interrupt ART, and so far 13 individuals have reached this stage and contributed data to Mothe's report at CROI 2017.

Although the numbers are small and follow up still relatively short, Mothe noted that the frequency of viral load containment in the cohort (~38%) is higher than has been observed in any studies involving early initiation of ART (where rates have varied from 0-15%). Ongoing

analyses are exploring potential correlates of control, with Mothe suggesting there are hints of links between the induction of T cell responses to the conserved HIV antigens, lower HIV DNA levels, and the achievement of post-ART viral load control.

The contribution of romidepsin is unclear due to the lack of any control group, but the drug did not have a measurable effect on the size of the HIV reservoir when levels before and after administration were compared. There was evidence of blips in HIV viral load after each romidepsin dose, consistent with a latency-reversing effect. Mothe pointed out that blips also occurred after the MVA immunisations in 60% of the participants, indicating that the vaccine may have activated latently infected CD4 T cells specific for HIV antigens (a number of studies have reported that HIV-specific CD4 T cells can contain a substantial proportion of the latent HIV reservoir). [4]

Romidepsin infusions were associated with an array of side effects known to be caused by HDAC inhibitors—primarily grade 1 and grade 2 headaches, fatigue and nausea—and the drug also caused precipitous but transient declines in peripheral blood CD4 T cell counts of around 300 cells. One participant developed the serious complication of sepsis after the final romidepsin dose.

Additional follow up will be required before the significance of the study can be fully assessed, but it represents the first time that any kick & kill strategy has been associated with an increased frequency viral load control after ART interruption. There is an important caveat that applies to all studies reporting maintenance of low viral load in the absence of ART: while most news coverage assumes that the health benefits of viral load suppression will be the same regardless of whether the suppression is being mediated by immune responses or ART, that assumption remains unproven. [5]

Based on studies of elite controllers, it is possible that even low level viral load may be associated with a slight increase in the risk of morbidity and mortality compared to the stricter control of HIV replication imposed by ART. If post-ART control of viral load can eventually be induced in more significant numbers of people, there will be opportunity to more carefully investigate this issue by comparing clinical outcomes between post-ART controllers and study participants who restart or continue ART.

### Complete suppression of HIV replication by ART

The question of whether low-level HIV replication persists despite ART has been a major issue of debate in the cure research field. The balance of evidence has favoured the conclusion that ART typically completely prevents HIV from reproducing in adherent individuals, but some studies have challenged this view, including a paper published last year in *Nature* which argued that cryptic replication occurs in lymphoid tissues. [6]

At CROI 2017, Mary Kearney from the National Cancer Institute addressed the question with an analysis of HIV evolution in ten children who started ART early (mostly within a few months of birth) and were followed for at least seven years. [7]

Two of the children experienced some lapses in suppression of viral load and served as positive controls, while the remaining eight showed no evidence of any viral load blips during follow up.

Kearney found that the evolution of HIV genetic sequences was readily apparent in the two individuals whose viral load was not continually suppressed. In stark contrast, no evidence of HIV evolution was detectable in the other eight participants, supporting the idea that

ART completely stymies viral replication. Kearney suggested that differences in the types of tools used to analyse HIV evolution may explain some of the conflicting results that have been reported, noting that the Bayesian approach employed in last year's *Nature* paper may mistakenly suggest that the virus has been evolving because the timing of sample collections influences the outcome of the analysis.

Kearney's results were buttressed by a poster presentation from Morgane Rolland of the US Military HIV Research Program (US MHRP). [8]

Rolland studied eight individuals who initiated ART at Feibig I, an extremely early stage of infection estimated to represent the period 10-17 days after HIV acquisition. After an average of around three years, ART was interrupted as part of a protocol assessing whether HIV remission might occur. All eight participants experienced a viral load rebound within a median of 26 days, and Rolland compared the re-emerging HIV genetic sequences with those sampled at the pre-ART baseline. These analyses, like Kearney's, revealed no evidence of HIV evolution during ART.

Jintanat Ananworanich also described the results of this US MHRP clinical trial in detail in a separate oral presentation. [9]

### Another case of temporary HIV remission in a stem cell transplant recipient

To date, Timothy Ray Brown remains the only individual considered to have been cured of HIV infection, an outcome achieved as a result of a complex series of treatments for a life-threatening cancer that included stem cell transplants from a donor homozygous for the CCR5 delta-32 mutation (which renders immune cells resistant to most HIV strains). Brown was in attendance at CROI, celebrating reaching a milestone of ten years since those transplants were performed. But it has also been learned—as a result of the experience of two individuals known as “the Boston patients”—that HIV-positive people who receive stem cell transplants for cancer treatment can experience dramatic reductions in the HIV reservoir even when the stem cell donors lack the CCR5 delta-32 mutation.

In the case of the Boston patients, this shrinking of the reservoir ultimately allowed for a temporary period of remission after ART interruption; [10] the individuals were able to go for three and eight months without any signs of HIV activity, respectively, before viral load rebounded (Boston patient Gary Steinkohl has since gone public to discuss the experience of participating in this research). [11]

A poster at CROI 2017 from Nathan Cummins at the Mayo Clinic in Rochester reported another case of HIV remission with broad similarities to the Boston patients. [12]

The individual received a stem cell transplant from a donor without the CCR5 delta-32 mutation as part of his treatments for acute lymphoblastic leukemia. By day 56 posttransplant, HIV DNA was no longer detectable in blood and subsequent sampling of large numbers of cells by leukapheresis showed significant declines in measures of the HIV reservoir. An occurrence of graft-versus host disease (GVHD) was associated with apparent elimination of most of the individual's original CD4 T cells, which were present at a frequency of around 1 in 10 cells at day 142, but had diminished to ~13 per million cells by day 265. HIV-specific antibody responses also waned.

Approval was obtained to interrupt ART on day 784 posttransplant. HIV viral load rebound occurred after a period of remission lasting

288 days (a little over nine months), with levels rising relatively slowly from 60 copies/mL initially to 1640 copies/mL five days later, at which point ART was restarted. No symptoms were associated with the reappearance of viral load, contrasting with the Boston patients who both experienced sharp increases in viral load and symptoms of acute retroviral syndrome at the time they rebounded.

A colleague of Nathan Cummins, Stacey Rizza, presented the poster, and in discussing the case revealed that the individual had the misfortune to experience a car accident shortly before viral load rebounded (without serious injury, thankfully). One speculative possibility under consideration is that inflammation caused by stress might have triggered the activation of a latently infected cell (or cells). Samples were collected throughout follow up and are now being evaluated to try and gain a better understanding of what occurred.

### Remission macaques

The potential for rare latently infected cells to persist in a dormant state for extended periods despite ART interruption was emphasised in a symposium talk by Louis Picker from the Vaccine & Gene Therapy Institute at Oregon Health Sciences University. [13]

Picker's effort to develop a CMV-based vaccine for HIV has attracted considerable publicity due to unprecedented results achieved in the SIV/macaque model: when immunised with a version of the vaccine encoding SIV antigens, half the recipient macaques exert strict control over a pathogenic SIV challenge and appear to eventually clear the infection. [14, 15]

Picker outlined two possible explanations for this outcome:

- Vaccine-induced immune responses limit SIV replication to such an extent that only a very small, unstable SIV reservoir is formed, which eventually decays away over time.
- Vaccine-induced immune responses actively clear the SIV reservoir over time.

To try and discern which explanation is correct, Picker and colleagues conducted a therapeutic study in which the CMV-based vaccine was administered to SIV-infected macaques on ART (a version of the vector encoding TB antigens served as a control). The timing of ART initiation in the experiment was guided by the detection of monocyte activation after SIV challenge, because previous work suggested this coincided with the initial formation of the viral reservoir. The approach allowed the researchers to divide macaques into various groups depending on how many days after SIV challenge ART was first administered.

After 600 days of treatment, ART was interrupted in all animals. Receipt of the CMV vaccine encoding SIV antigens did not affect viral load rebound, indicating it lacked any therapeutic effect. But Picker highlighted that timing of ART showed a major influence: all six macaques started earliest, on day 4 or 5 post-challenge, did not experience any viral load rebound. Necropsy studies were eventually conducted and only rare traces of SIV genetic material could be detected in tissues. Large volumes of cells sampled from these animals were unable to transmit SIV to uninfected macaques. CD8 T cells were depleted to assess if SIV-specific CD8 T cells were suppressing the virus, but there was no return of viral load, arguing against immunological control.

Out of 35 animals administered ART from day 6 or later, only one (initiated on day 6) displayed a similar lack of rebound. But after eight months, shortly before a planned necropsy, this macaque

experienced a rebound in SIV viral load. Picker noted the parallel between this outcome and those observed in the human remission cases of the Mississippi baby and Boston patients.

Picker drew several conclusions from this work:

1. The window of opportunity between infection and the formation of a stable long-lived viral reservoir is tiny – in this experiment, a delay in the initiation of ART of just one day had a huge effect on the risk of rebound when ART was interrupted.
2. As has been observed in human remission cases, latently infected cells can linger in an inactive state for a long time before causing a rebound in viral load. This observation supports the importance of efforts to reverse HIV latency and promote clearance of latently infected cells.
3. The lack of a therapeutic effect of the CMV-based vaccine indicates that, in the preventive context, it likely works by limiting the formation of the SIV reservoir, rather than inducing immune responses capable of progressively clearing the reservoir.

Picker also mentioned that there does appear to be a case of ultra-early ART leading to temporary remission in an adult human; this is an individual who acquired HIV infection in a short period between screening for a pre-exposure prophylaxis (PrEP) demonstration project and starting on the TDF/FTC PrEP regimen. When HIV was detected in the sample taken on the first day of PrEP administration, ART was immediately substituted for PrEP (this occurred within a matter of days). Hiroyu Hatano from UCSF described the case at CROI in 2014, [16] and cited plans to eventually conduct an ART interruption. Early last year, ART was stopped, and the individual displayed no sign of HIV activity for 220 days before rebound was detected and treatment restarted. A full presentation of the data is expected at the International AIDS Society (IAS) conference in July 2017.

### Sex differences in HIV persistence

At the IAS conference in 2015, Jonathan Karn reported that the biology of HIV latency is influenced by the oestrogen receptor on CD4 T cells, leading to sex differences in the activity of candidate latency-reversing agents (LRA). Specifically, the hormone estradiol significantly inhibited the effect of LRAs in women but not men, whereas drugs that antagonise the oestrogen receptor—including the breast cancer treatments tamoxifen and fulvestrant – enhanced latency reversal. [17]

At CROI 2017, Eileen Scully from Johns Hopkins University presented a poster describing results from a study comparing measures of HIV persistence in carefully matched cohorts of women and men. [18]

Contrary to a previously published retrospective analysis, levels of HIV DNA were not significantly different between the groups. [19] However multiple measures indicated that expression of HIV RNA from the viral reservoir was lower in women compared to men. These included cell-associated HIV RNA and low-level viraemia (measured with an assay capable of capturing a single HIV RNA molecule), as well as the ratio between the amount of integrated HIV DNA detected and the ability to induce HIV RNA production from the reservoir (using the TILDA assay [20]). Consistent with the lower HIV expression, markers of T cell activation were also significantly reduced in women compared to men. Scully concluded that biologic sex is an important consideration in cure research, and that the manipulation of sex hormones may have a role to play in efforts to target the HIV reservoir.

Jintanat Ananworanich drew attention to Scully's poster in an excellent plenary overview of the cure research field, and emphasised the need to do more to facilitate increased participation by women. [21]

### Dual bNAbs combo leads to long-term SHIV control

In a symposium on broadly neutralising antibodies (bNAbs), Michel Nussenzweig premiered unpublished results from a collaborative experiment his laboratory has conducted with Malcolm Martin at the National Institute of Allergy and Infectious Disease (NIAID). [22]

The study challenged macaques with a pathogenic SHIV (SHIVAD8) and, starting three days post-infection, administered a combination of two bNAbs, 3BCN117 and 10-1074, thrice weekly for two weeks. Nussenzweig reported that, interestingly, the bNAbs led to prolonged preservation of CD4 T cells and control of viral load in treated animals, with many displaying what he described as an "elite controller phenotype." The depletion of CD8 T cells from some of the macaques led to increased viral load, indicating that the short course of combined bNAbs had positively modulated virus-specific immunity. A paper by Nishimura et al describing the results is now in press at *Nature*. [23]

### Macaque models in HIV/AIDS research

Jeff Lifson delivered an exceptional Bernard Fields Memorial Lecture on the role of non-human primate models in HIV/AIDS research. [24]

Included in the broad survey were a few nuggets of unpublished data from ongoing work: in a collaboration with Louis Picker, the anti-B cell antibody rituximab has been used to disrupt B cell follicles in elite controller macaques, and this led to reductions in SIV viral load and numbers of T-follicular helper cells in the lymph node, consistent with previous reports that B cell follicles can represent a sanctuary site for the virus. A similar study is now being conducted in SIV-infected macaques treated with ART.

As an alternative approach to the same problem, Lifson cited the work of Dave Ott whose laboratory is investigating the genetic modification of CD8 T cells to express CXCR5, a chemokine receptor that can guide the CD8 T cells into B cell follicles. [25]

Lifson showed imaging results demonstrating that this strategy successfully localised CD8 T cells to the follicles, and work is now underway to modify CD8 T cells to express both CXCR5 and T cell receptors targeting SIV antigens.

### Cellular & gene therapy in cancer and HIV

Finally, Carl June from the University of Pennsylvania gave a plenary talk on the dramatic advances that have occurred in the cancer field involving genetically modified T cells. [26]

These approaches typically extract T cells from an individual, genetically modify them in the laboratory to target the desired antigen, then expand and reinfuse the cells, which are described as "chimeric antigen receptor" (CAR) T cells. Impressive results have been obtained against a variety of cancers, although serious safety issues have also emerged in some cases due to the potential for excessively vigorous immune reactions to cause inflammation and pathology. [27]

June highlighted that many different clinical trials of this type of approach are currently underway across the globe in cancer, but none are occurring in HIV. June advocated for the development of

combination approaches that both engineer HIV resistance in CD4 T cells (such as the Sangamo approach, which June has been involved in studying) and modify CD8 T cell antigen receptors to better target HIV-infected cells for elimination. [28]

He also stressed the need to foster engineering innovations to make this type of therapy cheaper, scalable and globally accessible.

#### Source

Jefferys R. TAG basic science blog. (10 March 2017)

<http://tagbasicscienceproject.typepad.com>

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## TREATMENT GUIDELINES

### EACS guidelines: seven translations now online

**EACS guidelines are now available in seven new translations.**

- French - Français - Version 8.1
- Greek - Ελληνικά - Έκδοση 8.1
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- Spanish - Español - Versión 8.1
- Turkish - Türkçe - Sürüm 8.1

The guidelines on the EACS website are also available as a free App downloadable on IOS and Android.

Reference:

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

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

## CURE RESEARCH

### Flagging the HIV reservoir: a potential new marker for CD4 cells hiding HIV

Richard Jefferys, TAG

**The rarity of CD4 T cells containing latent HIV in people on antiretroviral therapy – the typical estimate is around one per million CD4 T cells – makes them extremely challenging both to study and to target with therapies.**

A paper published online yesterday in *Nature* represents a possible breakthrough in this area, reporting that it may be possible to identify many latently infected CD4 T cells due to expression of a particular cell surface protein, CD32a. [1]

The paper's authors, led by Benjamin Descours from the laboratory of Moncef Benkirane at Université de Montpellier, made their discovery using an *in vitro* model they developed that allows for the direct infection of resting CD4 T cells by a modified version of HIV. Descours and colleagues used the system to generate latently infected CD4 T cells and then looked at whether any genes in these cells were behaving differently compared to uninfected CD4 T cells.

Out of 103 genes upregulated exclusively in the infected cells, 16 were selected for further study because they encode cell surface proteins that can be used to rapidly sort cells using a flow cytometer. The gene FCGR2A turned out to be most strongly and consistently upregulated, which encodes the cell surface receptor CD32a.

The researchers found that when resting CD4 T cells sampled from uninfected donors were latently infected with HIV in the laboratory, the expression of CD32a was reliably induced: approximately 90% of the CD32a+ CD4 T cells generated in these experiments contained latent HIV. Furthermore, treatment of the samples with the integrase inhibitor raltegravir before infection prevented CD32a expression, suggesting that the integration of HIV into the CD4 T cell genome was causing the receptor to be expressed.

To try and confirm the relevance of the laboratory findings, CD4 T cells from 12 HIV positive individuals on suppressive ART were sampled and sorted based on CD32a expression. When the amount of HIV DNA was compared between subsets, there was a significant concentration of latent HIV infection in CD4 T cells with the highest levels of CD32a expression (an approximately 1,024-fold enrichment of HIV DNA in CD4 T cells with high CD32a expression versus those lacking CD32a).

There was variation between participants, however, with the contribution of the CD32a+ CD4 T cell population to the total HIV DNA reservoir ranging from 26.8% to 86.3% – the average contribution was a little over 50%. A similar concentration of the HIV reservoir in CD32a+ CD4 T cells was also documented with an assay measuring replication-competent HIV rather than HIV DNA.

The researchers highlight several potentially important implications of these findings:

- Sorting CD4 T cells based on CD32a expression should offer an easier means of studying the HIV reservoir than has previously been available, facilitating studies at the single-cell level.

- The normal biological function of CD32a involves recognising antigen-antibody complexes via the Fc region of antibodies and delivering signals capable of activating a broad spectrum of immune responses. This suggests CD32a might have a role in mediating responses to broadly neutralising anti-HIV antibodies, (bNAbs) and the potential to contribute to clearance of reservoir cells by these antibodies (evidence of bNAbs contributing to HIV reservoir depletion has been reported in a mouse model. [2])
- CD32a may allow for direct targeting of a large portion of the HIV reservoir in CD4 T cells with elimination strategies. However, as Doug Richman notes in an accompanying commentary in *Nature* [3], CD32a expression on other cell types (see figure 2 of this 2014 review [4, 5]) raises concerns as to whether this approach could be pursued safely.

The study also raises some technical questions about the mechanism by which HIV latency is established. Under most circumstances, CD4 T cells need to be activated to be susceptible to HIV infection, and viral latency has generally been thought to result from some infected cells returning to a resting state with HIV integrated into their genomes. [6]

But the laboratory model used by Descours et al involves manipulations that allow direct infection of resting CD4 T cells, and the researchers did not see CD32a expression in CD4 T cells that were infected after activation. This poses the question of whether the latently infected CD32a-expressing CD4 T cells sampled from people on ART were infected while they were in a resting state, or if CD32a can eventually be expressed when an HIV-infected, activated CD4 T cell returns to a resting state. Additional investigations will be required to address this issue.

Source

TAG Basic Science Blog (16 March 2017)

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## HIV PREVENTION

### PrEP approved in Scotland but not Wales

Simon Collins, HIV i-Base

**On 10 April 2017, the Scottish Medicines Consortium announced that PrEP has been approved for prescription by the NHS in Scotland. [1]**

Pre-exposure prophylaxis (PrEP) in this context refers to a single pill containing emtricitabine/tenofovir DF (tradename Truvada). The indication is for preventing HIV transmission in people at high risk of HIV.

The announcement noted that patient groups had "highlighted that current prevention methods have not managed to reduce the spread of HIV in Scotland over the last ten years."

Details for availability and prescribing details are still being confirmed but access to PrEP is expected to be available within the next month.

On the same day, NHS England sent an email update about the proposed PrEP Impact Trial. This study will enrol 10,000 people over three years who are at high risk of HIV. It is planned to include more than 200 level-3 STI clinic sites and will start sometime in summer 2017.

On 26 April, NHS Wales decided not to approve PrEP although the National Assembly for Wales can override this decision.

#### C O M M E N T

**NHS Scotland and the advocacy organisations that supported this application are to be congratulated. Enabling doctors to prescribe PrEP to people at highest HIV risk is the right decision.**

**The decision highlights the lack of provision by the NHS England and the current block against any doctor prescribing PrEP irrespective of their patients needs. [2]**

**The data supporting safety and efficacy of PrEP is overwhelming. PrEP clearly works and is already linked to fewer HIV infections in several London clinics where people are using generic PrEP. [3]**

**Even if access is limited in Scotland until generic PrEP becomes available at a dramatically lower price, this new approval will significantly improve healthcare for people directly affected.**

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## EVENTS & TRAINING

### HIV: is victory in sight? - Brighton talk

Martin Fisher Foundation

**A talk that is part of the Brighton festival looks at whether we might really overcome HIV in the UK?**

How can we reduce HIV globally? What are our successes and challenges?

Brighton is set to become the first city in the UK to have United Nations 'Fast Track City' status.

In this it will join 65 other cities worldwide with high levels of HIV working to end the epidemic of HIV/AIDS by 2030.

The panel conversation will be chaired by Baroness Gould and is supported by Brighton and Sussex Medical School in partnership with the Martin Fisher Foundation.

[http://brightonfestival.org/event/11069/hiv\\_is\\_victory\\_in\\_sight](http://brightonfestival.org/event/11069/hiv_is_victory_in_sight)

### Introduction to cost-effectiveness analysis for infectious diseases

**A two-day course on cost-effectiveness analyses is being organised by UCL.**

Thursday 28th and Friday 29th September 2017

*UCL Royal Free Campus, Rowland Hill Street, London, NW3 2PF*

The course is for people working in health care settings, academic environments, industry and governmental and non-governmental organisations who wish to achieve a basic understanding of, and be able to interpret, cost effectiveness analyses in the context of infectious diseases, with particular focus on HIV. It will be assumed that participants have no prior knowledge of cost effectiveness analysis.

The course includes:

- Principles of economic evaluation of health care programmes.
- Basic aspects of infectious disease modelling.
- The use and role of economic evaluations in helping to make decisions, with particular regard to infectious diseases.

The interactive and informal course will be led by Dr Valentina Cambiano and Professor Andrew Phillips from UCL Institute for Global Health.

In addition, specific sessions will be led by Dr Loveleen Bansi (UCL), Professor John Cairns (LSHTM), Dr Tim Colbourn (UCL), Dr Alec Miners (LSHM), Dr Jasmina Panovska-Griffith (UCL), Dr Elena Pizzo (UCL), Paul Revill (University of York), Dr Alison Rodger (UCL) and Professor Mark Sculpher (University of York).

In order to maintain a low participant to tutor ratio, attendee numbers will be limited.

Price: NHS/Academic: £500 Pharmaceutical Industry: £1,000



Lunch and refreshments breaks will be included. Participants will be responsible for their own travel and accommodation costs.

For further information please contact: Pat Withington Tel: 020 7794 0500, ext. 34871; email: p.withington@ucl.ac.uk

<http://onlinestore.ucl.ac.uk/conferences-and-events/faculty-of-population-health-sciences-c09/research-department-of-infection-and-population-health-g16/g16-introduction-to-costeffectiveness-analysis-for-infectious-diseases>

## Clinical management of HIV: EACS online course

**The Clinical Management of HIV online Course, led by Prof Jens D. Lundgren and Prof Manuel Battegay, is an online, flexible, open access course.**

It is available to anyone who wishes to participate, free of charge, but is especially aimed at clinicians in Eastern Europe and Central Asia. The course, sponsored by the European AIDS Clinical Society and supported by WHO Europe, will provide an in-depth understanding of the scope and manifestations of HIV-related diseases, their prevention, management, and care.

Special emphasis will be placed on co-infections and co-morbidities as well as state-of-the-art treatment of HIV according to international guidelines from EACS and WHO.

In February 2016 the EACS online course Clinical Management of HIV was successfully launched for the first time. The online course is now relaunched in an updated version 1 May - 9 June 2017 with a 6 week moderated course period.

The online model promotes more flexibility than a traditional face-to-face approach as participants can join in when their schedule allows and select the modules in the order they desire. Participants should plan on using 1 to 1½ hours per subtopic. Russian and English subtitles will be available for video lectures, while other course materials will be available in English.

The application form for this course is on the EACS website.

<http://www.eacsociety.org/education/clinical-management-of-hiv-online-course/clinical-management-of-hiv-online-course.html>

Please return this completed form to:

HIVonlinecourse@eacsociety.org

In addition to submitting this application form by email, all course participants will be required to register online at the site hosting the course.

<http://www.iversity.org>

For more information please email:

HIVonlinecourse@eacsociety.org

## ON THE WEB

### Community reports

#### RITA: dyslipidemia with HIV

<http://centerforaids.org/pdfs/rita0417.pdf> (PDF)

The issue features an interview with Case Western's Chris Longenecker filled with practical advice on managing dyslipidemia, plus three review articles.

- Prevalence and risk factors.
- Lipid impact on clinical outcomes, and antiretroviral impacts on lipids.
- Screening for and managing dyslipidemia.

## FUTURE MEETINGS

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### Conference listing 2017

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

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

14–16 June 2017, Chicago, (tbc)

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

#### EASL: the International Liver Conference

19–23 June 2017, Amsterdam

[www.easl-2017.org](http://www.easl-2017.org)

#### 12th International Workshop on HIV Transmissions

23–26 July 2017, Paris, France

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

#### 9th IAS Conference on HIV Science

23–26 July 2017, Paris, France

[www.ias2017.org](http://www.ias2017.org)

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

2–3 October 2017, New York, USA

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

#### 19th International Workshop on Comorbidities and Adverse Drug Reactions in HIV

23–25 October 2017, Milan, Italy

[www.intmedpress.com](http://www.intmedpress.com)

#### 16th European AIDS Conference

25–27 October 2017, Milan, Italy

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

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

6–8 November 2017, Johannesburg

[www.HIVresistance2017.co.za](http://www.HIVresistance2017.co.za)

## PUBLICATIONS & SERVICES FROM i-BASE

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### i-Base website

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

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

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

Publications and regular subscriptions can be ordered online.

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

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

### i-Base treatment guides

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

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

- Introduction to ART (September 2016)
- HIV & quality of life: side effects & better health (Sept 2016)
- Guide to PrEP in the UK (November 2016)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (February 2015)
- Guide to HIV, pregnancy & women's health (December 2015)

### New pocket guides

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

The first five pocket leaflets are: Introduction to ART, HIV and pregnancy, ART and quality of life, UK guide to PrEP and HCV/HIV coinfection.

We hope these are especially useful as low literacy resources.

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

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

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

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



## HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

However, any donation that your organisation can make towards our costs is greatly appreciated.

### STANDING ORDER DONATION

### THANK YOU FOR YOUR SUPPORT

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**HIV i-Base, 107 The Maltings, 169 Tower Bridge Road, London SE1 3LJ**

(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.  
Sort Code: 60-12-14. Account Number: 28007042)

#### ONE-OFF DONATION

I do not wish to make a regular donation at this time but enclose a one-off cheque in the sum of £ \_\_\_\_\_ .

#### GIVE AS YOU EARN

If your employer operates a Give-As-You-Earn scheme please consider giving to i-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

Since many employers match their employees donations, a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit [www.giveasyouearn.org](http://www.giveasyouearn.org)

#### REFUNDS FROM THE TAX MAN

From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

**However you chose to donate to i-Base,  
we would like to thank you very much for your support.**



## Fax-back orders and subscriptions

107 The Maltings, 169 Tower Bridge Road, London, SE1 3LJ  
Tel: +44 (0) 20 8616 2210 Fax: +44 (0) 20 8616 1250



Please use this form to amend subscription details for HIV Treatment Bulletin and to order single or bulk copies of publications. Publications are available free, but please contact i-Base if you would like to make a donation.

Name \_\_\_\_\_ Position \_\_\_\_\_

Organisation \_\_\_\_\_

Address \_\_\_\_\_

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e-mail \_\_\_\_\_

I would like to make a donation to i-Base - *Please see inside back page*

- **HIV Treatment Bulletin (HTB) every two months**  by e-mail
- **Pocket leaflets** - *A7 small concertina-folded leaflets (2017)*

<b>Pocket HCV coinfection</b>	quantity _____	<b>Pocket PrEP</b>	quantity _____
<b>Pocket ART</b>	quantity _____	<b>Pocket pregnancy</b>	quantity _____
<b>Pocket side effects</b>	quantity _____		

- **UK Guide To PrEP** (*November 2016*): 24-page A5 booklet  
1  5  10  25  50  Other \_\_\_\_\_
- **Introduction to ART** (*September 2016*): 48-page A5 booklet  
1  5  10  25  50  Other \_\_\_\_\_
- **HIV and your quality of life: guide to side effects and long-term health** (*September 2016*): 96-page A5 booklet  
1  5  10  25  50  Other \_\_\_\_\_
- **Guide To HIV testing and risks of sexual transmission** (*July 2016*): 52-page A5 booklet  
1  5  10  25  50  Other \_\_\_\_\_
- **Guide to HIV, pregnancy and women's health** (*November 2015*): 52-page A5 booklet  
1  5  10  25  50  Other \_\_\_\_\_
- **Guide to changing treatment: what to do if viral load rebounds** (*February 2015*): 24-page A5 booklet  
1  5  10  25  50  Other \_\_\_\_\_
- **HIV Treatment 'Passports'** - Booklets for patients to record their own medical history  
1  5  10  25  50  Other \_\_\_\_\_

*Treatment guides in other languages are available as PDF files on the website*

- **Phoneline support material** (*please specify quantity of each*)

A4 posters \_\_\_\_\_ A5 leaflets \_\_\_\_\_ A6 postcards \_\_\_\_\_ Small cards \_\_\_\_\_

Please fax this form back, post to the above address, or email a request to HIV i-Base:

**020 8616 1250 (fax)**

**subscriptions@i-Base.org.uk**