

13 March 2019: no 3

CROI 2019: first reports

CONTENTS

EDITORIAL	2	
SUPPLEMENTS	2	
• U=U resources for UK clinics: free posters, postcards and factsheets		
i-BASE APPEAL	2	
• i-Base 2019 appeal: we need your help....		
CONFERENCE REPORTS	3	
Conference on Retroviruses and Opportunistic Infections, 4–7 March 2019		
• Introduction		
• UK patient likely to be the second person cured of HIV: two further cases at CROI 2019 of HIV remission after allogenic stem cell transplants		
• Phase 3 results with dual therapy cabotegravir/rilpivirine long-acting injections: ATLAS and FLAIR studies		
• Viral reservoir can explain persistent low level viraemia with good adherence on ART		
• Dolutegravir suppresses viral load faster than efavirenz in late pregnancy: results from DoIPHIN-2		
• Raltegravir achieves swifter viral load suppression in pregnancy than efavirenz		
• New option for PrEP – TAF/FTC is non-inferior to TDF/FTC: results of phase 3 DISCOVER study		
• Dolutegravir can be given with 3HP to prevent TB without dose adjustment		
• Double doses of darunavir given with rifampicin lead to high rates of hepatotoxicity		
• Shared housing compared to living alone: higher CD4, lower viral load and reduced inflammation in macaques		
• Selected webcasts from CROI 2019		
• i-Base Fit for Purpose report launched at CROI 2019		
• Pre-CROI community HIV cure workshop 2019		
OTHER NEWS	14	
• US requires informed consent forms for clinical studies to be posted online		
ON THE WEB	15	
• Report from cure strategies meeting		
FUTURE MEETINGS	15	
• Conference listing 2019		
PUBLICATIONS AND SERVICES		
FROM i-BASE	16	
ORDER FORM	18	

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 online:

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

or by sending an email to: subscriptions@i-Base.org.uk

Editor: Simon Collins

Contributing Editor: Polly Clayden

Medical consultants:

Dr Tristan Barber, Royal Free Hospital, London.

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

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, ILVC, UK.

Prof. James McIntyre, Chris Hanani Baragwanath Hosp. S 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.

HTB is a not-for-profit community publication. It reviews the most important medical advances related to clinical management of HIV including access to treatment. We compile comments to articles from consultant, author and editorial responses.

We encourage i-Base originated material to be reprinted for community use but copyright remains with HIV i-Base. A credit and link to the author, the HTB issue and the i-Base website is always appreciated. Copyright for other articles remains with the credited source. We thank other organisations for this use and encourage readers to visit the linked websites.

HIV i-Base receives educational grants from charitable trusts, individual donors and pharmaceutical companies. All editorial policies are strictly independent of funding sources.

HIV i-Base, 107 The Maltings,

169 Tower Bridge Road, London, SE1 3LJ.

T: +44 (0) 20 8616 2210.

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

HIV i-Base is a registered charity no 1081905 and company reg no 3962064. HTB was formerly known as DrFax.

EDITORIAL

This issue of HTB includes first ten reports from the Conference on Retroviruses and Opportunistic Infections (CROI 2019).

This year the meeting was particularly important and lively with headline news on the UK case of HIV remission released before the study was even presented.

Other news in this issue includes phase 3 results for long-acting cabotegravir/rilpivirine injections and the data showing that tenofovir alafenamide (TAF) is effective as PrEP.

We include two studies showing faster viral suppression from using integrase inhibitors during pregnancy and drug interaction studies between HIV and TB medications.

We also highlight several CROI webcasts and include a review of a community cure workshop held just before the conference.

Further articles will continue to be published online as we report them, and they will also be compiled for the next issue of HTB.

SUPPLEMENTS

U=U resources for UK clinics: free posters, postcards and factsheets

Please continue to order these free resources.

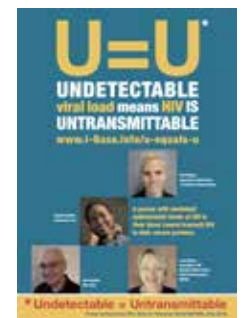
Customise U=U posters for your clinic

i-Base can customise U=U posters to include pictures of your doctors, nurses, pharmacists, peer advocates or any other staff that would like to help publicise U=U.

Personalising these for your clinic is easy and might be an especially nice way to support U=U.

For further information please contact Roy Trelvelion at i-Base:

roy.trelvelion@i-base.org.uk



i-Base 2019 appeal

This year we are continuing a funding appeal to help i-Base continue to provide free publications and services.

Your help has been inspiring – and we hope this support will continue during 2019. If 1000 people support us with £5 a month we will be on course to meet our funding shortfall.

All help is appreciated.

<http://i-base.info/i-base-appeal-we-need-your-help>

CONFERENCE REPORTS

Conference on Retroviruses and Opportunistic Infections (CROI 2019)

4–7 March, 2019

Introduction

This year the Conference on Retroviruses and Opportunistic Infections (CROI 2019) was held in Seattle from 4–7 March.

The meeting had an exciting programme that we will report over at least the next three issues of HTB.

Headline news included:

- Breakthroughs in cure research including two new cases of potential cures – defined as sustained remission off-ART. One case is from the UK and another from Germany. Limited case details were reported in a New York times article before the CROI presentations.
- HIV and pregnancy including numerous studies looking at risk of neural tube defects at conception with integrase inhibitors.
- Urgently-needed information on dosing dolutegravir in paediatric populations.
- Strategies for treating MDR-TB as well as treating and preventing TB in people receiving ART regimens.
- Pipeline HIV drugs, including bNAbs and long-acting formulations and new classes of capsid inhibitors and maturation inhibitors.
- PrEP (including first results with TAF).
- Numerous complications, including obesity, cardiovascular risk and bone health.
- Side effects, including whether integrase inhibitors are linked to weight gain.

CROI is notable for providing same-day or next-day webcasts for most talks and comprehensive online access to abstracts and PDF files for posters.

This year HTB will include summary highlights for each day of the conference, with links to key studies.

<http://www.croiconference.org>

Articles included in this issue are:

- UK patient likely to be the second person cured of HIV: two further cases at CROI 2019 of HIV remission after allogenic stem cell transplants
- Phase 3 results with dual therapy cabotegravir/rilpivirine long-acting injections: ATLAS and FLAIR studies
- Viral reservoir can explain persistent low level viraemia with good adherence on ART
- Dolutegravir suppresses viral load faster than efavirenz in late pregnancy: results from DolPHIN-2
- Raltegravir achieves swifter viral load suppression in pregnancy than efavirenz
- New option for PrEP – TAF/FTC is non-inferior to TDF/FTC: results of phase 3 DISCOVER study
- Dolutegravir can be given with 3HP to prevent TB without dose adjustment
- Double doses of darunavir given with rifampicin lead to high rates of hepatotoxicity
- Shared housing compared to living alone: higher CD4, lower viral load and reduced inflammation in macaques
- Selected webcasts from CROI 2019
- i-Base Fit for Purpose report launched at CROI 2019
- Pre-CROI community HIV cure workshop 2019

CROI 2019: CURE RESEARCH

UK patient likely to be the second person cured of HIV: two further cases at CROI 2019 of HIV remission after allogenic stem cell transplants

Simon Collins, HIV i-Base

One of the headline reports from CROI 2019 is a case where a stem cell transplant is likely to have cured a second person of HIV.

Although the results were due to be presented on the first day of the conference, other publications, including Nature made details available before the CROI presentations. The New York Times notably published their article before the CROI presentations without contacting people who had contributed to the article. As a result the study was reported before the study has even been presented.

Lead author Ravindra Gupta from the University of Cambridge is also interviewed in the NYT article and the study is on behalf of an international team from the Netherlands, Spain and the UK. [1] Further details of the UK case are included from the paper that is due to be published in Nature, but which has also had a broken embargo. [2]

The results reproduce the circumstances that cured Timothy Ray Brown (the Berlin patient) ten years ago [3] but are notable for achieving HIV remission with less aggressive treatment.

The UK case is an HIV positive man with CCR5-tropic HIV who was diagnosed in 2003 and who started HIV treatment (efavirenz/TDF/FTC) in 2012. Shortly after starting ART he was also diagnosed with advanced Stage IVB Hodgkin's Lymphoma (HL) that failed to respond to either first line chemotherapy (ABVD) or several salvage combinations.

This patient underwent allogenic hematopoietic stem cell transplantation (HSCT, 3.6 million CD34+ cells/kg) as treatment for advanced HL using cells from a donor from an international registry who was also homozygous for the CCR5 delta-32 deletion. The donor was a close but not complete match (9/10 - with one allelic mismatch at HLA-B). Induction therapy continued with lomustine, cyclophosphamide, cytarabine and etoposide (LACE) and T cells were depleted with reduced intensity conditioning using anti-CD52 (alemtuzumab). Cyclosporine-A and short-course methotrexate were used as prophylaxis for graft versus host disease (GvHD).

During chemotherapy, ART was switched to raltegravir/TDF/FTC and then to rilpivirine/dolutegravir/3TC (after K65R and M184V developed during a short period of viral rebound).

Unlike the Berlin patient, the UK patient did not undergo full body irradiation but he also experienced only mild GvHD (grade 1), in this case fever and gastrointestinal symptoms at day 77. ART was maintained throughout and continued for 16 months post-transplant. Following detailed consultations with the patient including ethical approval and informed consent, the decision was made to stop HIV treatment.

Viral load was monitored weekly for the first three months then monthly and HIV has remained undetectable HIV DNA (< 1 copy/mL) in peripheral T-cells for 18 months. No reactivatable HIV has been recovered from more than 24 million cells using viral outgrowth assay. Post-transplant, total PBMC associated HIV DNA dropped to below the limit of detection after transplant and total DNA in CD4 T cells was undetectable at 29 months by ultra-sensitive qualitative PCR. Ex vivo, CD4 cells could be infected by CXCR4- but not CCR5-tropic HIV.

Similar to reports with the Berlin patient, a single low level signal was reported in one sample - cellular DNA from blood - which was interpreted as a likely false-positive DNA result.

Both antibody and T cell responses were similar to that reported for the Berlin patient, leading the investigators to tentatively suggest that this might be a second case of HIV remission, while emphasising that this can only be confirmed with longer follow-up.

Also at CROI 2019, a third case of HIV remission/cure following HSCT was reported in a late-breaking poster, but with much less follow-up off-ART.

This case was presented by Björn-Erik Jensen from Heinrich Heine University Hospital, Düsseldorf and colleagues and involved HSCT to treat relapsed AML in February 2013, again using a matched donor (10/10) that was homozygous for CCR5 delta-32. [4]

AML relapsed for a second time in June 2013 and remission was re-achieved after eight courses of 5-azaC chemotherapy and 4 donor lymphocyte infusions.

HIV remained undetectable throughout post-transplant period, with ART maintained for more than 5.5 years. Proviral DNA was not detected by qPCR in PBMCs at different time points in plasma, CSF, rectal tissue, ileum and bone marrow. Low signals failed to confirm HIV replication.

After discussions on risk and with informed consent, ART was stopped as part of an analytic treatment interruption in November 2018 and HIV has remained undetectable in plasma for the last three months.

While concluding that the results were optimistic for this to be another case of HIV remission, the researchers emphasised that longer follow-up was still essential.

Table 1: Summary regimens of UK, Dusseldorf and Berlin patients

	UK patient	Dusseldorf patient	Berlin patient
Underlying condition	HL	AML	AML
ASCT, donor CCR5-d32/d32	Once	Once	Twice
Conditioning	reduced intensity: anti-CD52 (alemtuzumab)	reduced intensity: fludarabine/ treosulfan	Total body irradiation (twice)
GvH disease	Grade 1	Grade 1	Grade 1
ART post-transplant	16 months	66 months	None
Time with HIV remission	18 months	3 months	> 10 years

C O M M E N T

These optimistic results provide hope to millions of people globally - even though this is only a modification of last-stage treatment for advanced cancer.

Previous attempts to reproduce the Berlin patient were not successful, often due to rebound with CXCR4-tropic virus that was later found to have been present at baseline. [5, 6, 7]

Although there have been other cases of HSCT in HIV positive patients, many are still on ART and the UK case is the longest reported remission after a treatment interruption.

They are also optimistic for HIV remission cases at CROI 2019 being achieved with a less aggressive treatment compared

to the Berlin patient whose treatment included total body radiation twice and two courses of HSCT to treat acute myeloid leukaemia; and a less than perfectly matched donor.

The way that such important scientific research was released by mainstream media before presentation at an peer reviewed scientific conference undervalues the work of the researchers and of the individuals in these two studies.

References

Unless mentioned otherwise, references are to the programme and abstracts of the Conference on Retroviruses and Opportunistic Infections, 4 – 7 March 2019, Seattle.

1. Gupta RK et al. Sustained HIV-1 remission following homozygous CCR5 delta32 allogeneic HSCT. CROI 4 – 7 March 2019, Seattle. Late breaker oral abstract 29 LB.
2. Gupta RK et al. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem cell transplantation. *Nature*. DOI: 10.1038/s41586-019-1027-4. <https://www.nature.com/articles/s41586-019-1027-4>
3. Hutter, G. et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med* 360, 692-698, doi:10.1056/NEJMoa0802905 (2009). <https://www.nejm.org/doi/full/10.1056/NEJMoa0802905>
4. Jensen B-E O et al. Analytic treatment interruption (ATI) after allogeneic CCR5-d32 HSCT for AML in 2013. CROI 4 – 7 March 2019, Seattle. Late breaker oral abstract 394 LB.
5. Hayden EC. Hopes of HIV cure in 'Boston patients' dashed. *Nature*. doi:10.1038/nature.2013.14324 (6 December 2013). <https://www.nature.com/news/hopes-of-hiv-cure-in-boston-patients-dashed-1.14324>
6. Henrich TJ et al. Antiretroviral-free HIV-1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases. *Ann Intern Med* 161, 319-327, doi:10.7326/M14-1027 (2014). <https://annals.org/aim/article-abstract/1889547/antiretroviral-free-hiv-1-remission-viral-rebound-after-allogeneic-stem>
7. Kordelas, L. et al. Shift of HIV tropism in stem-cell transplantation with CCR5 Delta32 mutation. *N Engl J Med* 371, 880-882, doi:10.1056/NEJMc1405805 (2014).

CROI 2019: ARVs

Phase 3 results with dual therapy cabotegravir/rilpivirine long-acting injections: ATLAS and FLAIR studies

Simon Collins, HIV i-Base

Two oral presentations at CROI 2019 showed that dual therapy with long-acting monthly injections resulted in very low levels of virological failure with high participant preference for injections compared to oral combinations.

Although results from cabotegravir/rilpivirine (CAB/RPV) long-acting injectable ART has included more than three years follow-up from phase 2 studies, these are the first phase 3 results.

The international randomised open-label ATLAS and FLAIR studies were therefore highly awaited and were presented in two

consecutive oral presentations on the last day of the conference. [1, 2]

Both studies have a similar design, but with different participant characteristics for the control arms. Both are randomised, open-label, non-inferiority studies, based on 6% non-inferiority margin. Both have a primary endpoint of the percentage of participants with detectable viral load (>50 copies/mL) at week 48 by FDA snapshot analysis - which is unusual for reversing the more standard endpoint of the percentage of participants with viral suppression (which is now a key secondary endpoint).

After a 4-week induction with oral CAB plus oral RPV (30 mg/25 mg), the first intramuscular injection uses a 3 mL loading dose of CAB LA 600 mg + RPV LA 900 mg followed by 2 mL injections every four weeks from week 8 using a 400 mg/600 mg dose.

The ATLAS study, in treatment-experienced participants, randomised 705 HIV positive people on stable PI- NNRTI- or INSTI-based ART plus 2NTRIs to either CAB/RPV long-acting (LA) injections (after 4 week induction) or to remain on their current oral ART. At week 48, participants in the control arm switched to the injections for follow-up to week-96.

The FLAIR study, in treatment-naive individuals, enrolled 629 participants who all started first-line ART with dolutegravir/abacavir/3TC for 20 weeks, before randomising those with undetectable viral load to either the same experimental strategy as ATLAS (4-week oral then switch to injections) or to continue on DTG/ABC/3TC. FLAIR continues for 96 weeks when participants in the control arm are able to switch to injections for extended follow-up.

The results from ATLAS were presented first, by Susan Swindells from University of Nebraska.

Baseline characteristics included median age 42 (range 18–82), with 26% older than 50. Approximately one third of participants were women with 68% white, 23% black and 9% other. Although median CD4 count was 653 cells/mm³, this ranged from 150 to >2500 cells/mm³. Median duration on ART was 4 years, and ranged from 1 to >20 years. BMI at baseline was 26 kg/m² with a similarly wide range (from 15 to 58 kg/m²). Approximately half the participants were on NNRTI-based ART, with 33% on INSTI and 17% using PIs.

Overall, both groups had high levels of viral suppression with low discontinuations due to viral failure or missing data.

For the primary endpoints, there were very low rates of viral non-responders, with 1.6% vs 1.0% of participants having viral load >50 copies/mL at week 48 in CAB/RPV vs oral ART. This met criteria for non-inferiority with a difference of 0.6% (95% CI: -1.2 to +2.5).

The secondary endpoint of treatment success (<50 copies/mL) was reported for 92.5% vs 95.5% for the same arms respectively with 5.8% vs 3.6% with missing data. These results numerically favoured the oral therapy arm. Only 3 vs 2 participants in the CAB/RPV vs oral therapy arms discontinued for lack of viral efficacy: and 2/3 in the CAB/RPV arm were later found to have had integrase inhibitor resistance at baseline. Although drug levels were lower than average in the cases of viral failure, median drug levels were consistently well above the protein adjusted IC90 at all time points.

Of the participants without data at week 48, 3.6% vs 1.3% (n=11 vs 4) in the CAB/RPV vs oral therapy arms discontinued due to side effects. The single death (in the oral therapy arm) was an overdose from methamphetamine and judged unrelated to study drugs.

Overall, drug related side effects were reported more frequently for the dual injections (29% vs 3%, nearly all grade 1 or 2): mainly fatigue, fever, headache and nausea (each reported at 4%) but only 3% vs 2% of participants discontinued due to side effects.

Injection site reactions were common following the first treatment (~70%, 98% grade 1 to 2) but reduced to approximately 20% by week 20 and 10% by week 48. Only four participants (1.3%) discontinued due to injection site reactions.

Finally, in the single question survey for patients in the dual therapy arm, 97% (266/273) preferred the injections to their previous oral combination.

The FLAIR study was then presented by Chloe Orkin from Queen Mary University of London.

Baseline characteristics compared to ATLAS included younger age and lower BMI with a slightly lower percentage of women. Inclusion criteria included being HBV negative and not having NNRTI resistance (other than K103N).

Median age was 34 years (range 18–68), with 11% older than 50. Approximately one-fifth of participants were women with 74% white, 18% black and 8% other. Although median CD4 count was 444 cells/mm³ (IQR: 320 to 604), with 7% <200 cells/mm³. Median viral load was approximately 32,000 copies/mL with 20% >100,000 copies/mL. BMI at baseline was 24 kg/m² with a similarly wide range (from 13 to 47 kg/m²).

Virological results were similar to ATLAS, with only 2.1% vs 2.5% reporting virology non-response (>50 copies/mL) at week 48 in the CAB/RPV vs oral therapy groups. This again met criteria for non-inferiority with -0.4% in favour of CAB/RPV (95%CI: -2.8 to +2.1). Viral suppression to <50 copies/mL was reported by 93.6% vs 93.3% respectively, with missing data for 4.2% in each group.

Again, there were few discontinuations for virological failure (1.4% vs 1.1%; n=4 vs 3). All 3/3 patients with genotype samples failed with both NNRTI and integrase resistance (two with Q148R and one with G10R - and all with L74I, which was present at baseline).

Drug exposure results were similar to those reported for ATLAS at all time points.

Side effects were very similar to ATLAS in range, frequency and severity with similar incidence of injection site reactions, also reducing over time.

In the single question survey after the study, 91% of participants preferred injections to oral treatment, with only 1% (n=2) preferring oral pills (and the remainder not responding).

C O M M E N T

Taken together, both studies show that for people who are interested in alternatives to daily tablets (this was a self-selecting criteria for people to enroll in these studies) there were high rates of viral suppression, a broadly tolerable range of side effects and a very high level of overall satisfaction.

References

- Swindells S et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: atlas week 48 results. CROI 4 – 7 March 2019, Seattle. Oral abstract 139.
<http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-maintenance-therapy-atlas-week-48-results> (abstract)
<http://www.croiwebcasts.org/console/player/41308> (webcast)
- Orkin C et al. Long-acting cabotegravir+rilpivirine for HIV maintenance: FLAIR week 48 results. CROI 4 – 7 March 2019, Seattle. Late breaker oral abstract 140LB.
<http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-hiv-maintenance-flair-week-48-results> (abstract)
<http://www.croiwebcasts.org/console/player/41309> (webcast)

Viral reservoir can explain persistent low level viraemia with good adherence on ART

Simon Collins, HIV i-Base

The dynamics of HIV proliferation in the viral reservoir might be the explanation for why viral load fails to become undetectable, especially when adherence is good.

Such cases are often reported as a management challenge in the absence of drug resistance at baseline and when ART is started in very early infection. Anecdotally, replication in the viral reservoir has been suggested as a possible mechanism to explain this and this hypothesis is now supported by results from an oral presentation at CROI 2019.

Elias Halvas from the University of Pittsburgh and colleagues presented results that amplified HIV in 10 participants with persistent low level viral load for >6 months on ART (>50 to <200 copies/mL).

Median viral load and CD4 count was 98 copies/mL and 542 cells/mm³, and at baseline (pre-ART) was 189,000 copies/mL and 212 cells/mm³, respectively. Median cell associated HIV DNA and RNA at the time of the analysis was 1458 and 166 copies/million PBMCs respectively and was detectable in all ten participants.

The study used single-genome sequencing on plasma RNA, cell-associated DNA, and p24+ culture supernatants from quantitative viral outgrowth assays (qVOA). Phylogenetic analysis and integration site analysis was able to show the lack of viral evolution or variation in integration sites.

The showed that low level viral load was not the result of ongoing viral replication linked to suboptimal ART but was due to cell proliferation in the viral reservoir.

The study also concluded that the finding might have implications for cure-related research as this clonal reservoir might lead to more rapid viral rebound if ART is stopped in context of an analytic treatment interruption.

C O M M E N T

These findings have important clinical implications as management of such cases often focuses on intensifying treatment or other modifications to ART.

These results are also important for HIV positive people as intermittent adherence is often proposed as the likely cause.

It is also important to explain that low level viral load (<200 copies/mL) is not seen as a risk from HIV transmission (as this threshold was used in the PARTNER studies).

Reference

Halvas EK et al. Nonsuppressible viremia on ART from large cell clones carrying intact proviruses. CROI 4 – 7 March 2019, Seattle. Oral abstract 23.

<http://www.croiconference.org/sessions/nonsuppressible-viremia-art-large-cell-clones-carrying-intact-proviruses> (abstract)

<http://www.croiwebcasts.org/console/player/41059> (webcast)

CROI 2019: PREGNANCY

Faster viral suppression in women starting dolutegravir late in pregnancy: results from DoIPHIN-2

Polly Clayden, HIV i-Base

Women living with HIV starting dolutegravir (DTG)-based ART after presenting in late pregnancy achieved more rapid virological suppression before delivery than those who started with an efavirenz (EFV)-based regimen – according to findings from the DoIPHIN-2 study, shown at CROI 2019.

But, late presentation in pregnancy is associated with poor outcomes despite ART and regardless of ART regimen.

DoIPHIN-2 (NCT03249181) is an open label study, randomising pregnant women from Uganda and South Africa starting ART from 28 weeks' gestation to DTG vs EFV plus 2NRTIs.

The primary endpoint is viral load <50 copies/mL at delivery (up to 14 days postpartum) for efficacy, and drug-related adverse events in mothers and infants.

Professor Saye Khoo from the University of Liverpool presented data on behalf of the study group.

All 268 randomised mothers were included in the safety and 237 (122 DTG, 115 EFV) in the efficacy analyses. Data were censored 31 January 2019.

Baseline characteristics were similar between arms: median maternal age was 28 years; viral load 4.5 log₁₀ copies/mL, CD4 count 446 cells/mm³ and gestation 31 weeks.

Viral load was measured at baseline, 1 week and 4 weeks after starting ART, then at 36 weeks' gestation and delivery, and 6 weeks postpartum.

Median time on ART at delivery was 55 days (IQR 33–77): DTG 52 days (IQR 30–74) vs EFV 59 (IQR 38–82).

By ITT analysis, viral load <50 copies/mL at delivery was significantly higher with DTG (90/122, 73.8%) vs EFV (49/115, 42.6%): RR 1.66 (95% CI 1.32 to 2.08), p<0.0001. Viral load <1000 copies/mL was also higher with DTG (113/122, 92.6%) vs EFV (95/115, 82.6%): RR 1.11 (95% CI 1.00 to 1.23), p=0.05.

There were three vertical transmissions – all in the DTG arm. Mothers had received 35, 32 and 24 days of ART pre-delivery, which they started at respectively 32, 32 and 30 weeks' gestation. Their respective infants had 4, 3 and 2 positive PCRs with the first at 5, 3 and 11 days after delivery. Maternal viral load at delivery was 29, 20 and 200 copies/mL for the respective cases. All four were judged likely to be in-utero transmissions.

DTG was well-tolerated in pregnancy with no differences with EFV in frequency or organ class of severe adverse events.

There were four stillbirths – all in the DTG arm. These were judged not related or unlikely to be related to ART or maternal IRIS.

Among 242 evaluable live births, median gestation at delivery was 39.9 weeks in both arms with similar rates of preterm and very preterm deliveries: 16% and 5% respectively overall.

About half of the infants had at least one SAE. There were 7 infant deaths (DTG 4 and EFV 3) also judged not related or unlikely to be related to ART or maternal IRIS.

Overall 38% of infants had congenital, familial and genetic anomalies. But excluding congenital umbilical hernia (29.8%) and birthmark (15.3%) these were in the normal range and there were no neural tube defects.

In conclusion, DTG achieves faster virological suppression before delivery compared with EFV and is well tolerated.

The three infant infections were likely to be in-utero transmissions. The four still births in the DTG arm were associated with known risk factors and unlikely to be related to ART.

Polly Clayden is on the trial steering committee of DoIPHIN-2.

C O M M E N T

As previously reported, HIV positive women who start ART in late pregnancy are a vulnerable group with a higher risk of adverse outcomes and vertical transmission of HIV than those who start earlier. Infant deaths, stillbirths and infant infections seen in DoIPHIN-2 corroborate this.

Such women are difficult to reach (and to recruit in to studies) but efforts must be made to ensure that they receive care and treatment earlier in pregnancy.

Mothers and infants in DolPHIN-2 will be followed to 72 weeks after delivery.

Reference

Kintu K et al. RCT of dolutegravir vs efavirenz-based therapy initiated in late pregnancy: DolPHIN-2. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 40LB.

<http://www.croiconference.org/sessions/rct-dolutegravir-vs-efavirenz-based-therapy-initiated-late-pregnancy-dolphin-2> (abstract)

Raltegravir achieves swifter viral load suppression in pregnancy than efavirenz

Polly Clayden, HIV i-Base

Viral load reduction with raltegravir (RAL)-based ART was faster than with an efavirenz (EFV)-based regimen started during pregnancy in HIV positive women.

These data, shown at CROI 2019, from the first large randomised trial in pregnant women comparing an integrase inhibitor to EFV support the use of RAL during pregnancy, especially for women starting ART late in gestation.

NICHD P1081 is a phase 4 multicentre, randomised, open-label trial comparing viral suppression (<200 copies/mL near delivery), tolerability (remaining on study drug through delivery), and safety (maternal and infant adverse event grade 3 and above) of ART when started in pregnancy.

The study began in September 2013 and enrolled women at 28 to 37 weeks' gestation. This was reduced to 20 weeks after 22% of the women were enrolled. Enrolment was completed in February 2018.

ART-naive pregnant women were randomised to RAL or EFV-based ART with AZT/3TC (a change in NRTIs was permitted if indicated). Women and their infants were followed through 24 weeks after delivery.

Mark Mirochnick presented findings from the study on behalf of the NICHD P1081 study group.

A total of 408 pregnant women (206 RAL; 202 EFV) were enrolled at sites in Brazil, Tanzania, South Africa, Thailand, Argentina and US.

Participants were similar across the arms at baseline: median age 27.2 years; median viral load 3.9 log copies; 6% <200 copies/mL; CD4 435.3 cells/mm³; 84% AZT/3TC backbone; gestational age 26.9 weeks with 50% each 20–28 and 50% 28–37 weeks' gestation. No participant had integrase inhibitor resistance at entry and 9% had RTI resistance.

Overall 84% and 94% women in the EFV and RAL arm respectively, with entry viral load >200 copies/mL and no resistance at entry (n=307), had viral load <200 copies/mL at delivery, p=0.001.

These respective proportions were 97% and 96% in the 20–28 weeks' gestation group and 71% and 93% in the 28–37 weeks' gestation group for the EFV and RAL arm respectively, p=0.04.

High proportions of women remained on their assigned study drug: 97% and 99% for EFV and RAL respectively.

A greater proportion of women receiving RAL achieved the secondary composite outcome of rapid and sustained response while remaining on study drug through delivery: 84/131 (64%) vs 121/132 (92%) in the EFV vs RAL arms respectively, p<0.001.

Viral decline was swifter in the RAL arm: median time to viral load <200 copies/mL, 15 vs 8 days for EFV vs RAL, respectively

There were no significant differences in occurrence of adverse events grade 3 and above among women or infants, stillbirth, or preterm birth.

C O M M E N T

BHIVA (and other) guidelines recommend RAL for pregnant women presenting late in gestation. These data confirm this recommendation.

Reference

Mirochnick M et al. Randomized trial of raltegravir-ART vs efavirenz-ART when initiated during pregnancy. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 39LB.

<http://www.croiconference.org/sessions/randomized-trial-raltegravir-art-vs-efavirenz-art-when-initiated-during-pregnancy> (abstract)

<http://www.croiwebcasts.org/console/player/41080> (webcast)

CROI 2019: HIV PREVENTION

New option for PrEP – TAF/FTC is non-inferior to TDF/FTC: results of phase 3 DISCOVER study

Simon Collins, HIV i-Base

The results from the large international phase 3 DISCOVER study are notable showing that a new version of PrEP is at least as effective at protecting against HIV infection as the currently approved formulation.

The study was also able to do this despite much lower numbers of people becoming positive than were predicted when the research was first planned. [1, 2]

For ethical reasons, this study did not include a placebo control arm with all participants taking both one active and one placebo pill each day. These two active arms comparing the new formulation of tenofovir alafenamide/emtricitabine (TAF/FTC) to already approved tenofovir DF/FTC (TDF/FTC). And while the study was running, rates of new HIV infections are likely to have become lower (due partly at least to the wider availability of PrEP).

The results were given as a late-breaking oral presentation at CROI 2019 by Charles Hare from the University of California San Francisco.

From September 2016 to May 2017, the study enrolled 5387 gay/bisexual men or transgender women who were randomised 1:1 to either daily TAF/FTC or TDF/FTC plus appropriate placebo.

Baseline demographics included median age 34 years (range 18 to 76), and 74 participants were transgender women. Ethnicity was reported as 84% white, 9% black and 5% Asian – but also referred to 24% of participants being Latin/Hispanic.

During the study 17% vs 16% (n = 452 vs 430) participants discontinued treatment, in the TAF vs TDF arms respectively. This was mainly because of loss to follow-up (LTFU) (n=201 vs 170) or participant decision (n=193 vs 175, with much fewer participants (36 vs 49) stopping due to side effects.

Entry criteria also included being at high HIV risk, with a definition that included one or more risk factors: having had receptive sex without condoms at least twice in the previous three months (60%), having had rectal chlamydia or gonorrhoea in the previous six months (each for >10% participants), recent syphilis, recreational drug use (67%), binge drinking (22%) or to be already taking PrEP at baseline (16%).

The primary endpoint was the number of HIV infections per 100 patient years of follow-up (PYFU) after all participants have a minimum of 48 weeks follow up and 50% of participants have follow-up for 96 weeks.

After a total of 8756 PYFU there were only 22 new HIV infections: 7 vs 15 in the TAF/FTC vs TDF/FTC arms respectively, none of which were in transgender women. This gave an incidence of 0.16 vs 0.34 and an incidence rate ratio (IRR) of 0.47 (95%CI: 0.19 to 1.5) numerically in favour of TAF/FTC (though not statistically significant) and meeting criteria for non-inferiority.

However, of the people diagnosed HIV positive during the study, 5 participants were found to have been HIV positive at baseline (1 vs 4) and 15 had low drug levels (5 vs 10) suggesting suboptimal adherence. This left only one participant in each arm who became HIV positive with medium or high drug levels suggesting good adherence. Non-inferiority was also maintained in a sensitivity analysis that excluded participants who were likely to be HIV positive at baseline (0.55; 95% CI: 0.20 to 1.48).

In 18 samples that were genotyped (n=6 vs 13), the 4 cases of M184V were all in the TDF/FTC arm with no tenofovir resistance in either arm.

Overall, 95% of participants reported adverse events (AEs), with only 20% with a possible link to study drug, nearly all grade 1 or 2. Grade 3 side effects (6% in each arm) with 0.1% vs 0.2% linked to serious drug-related side effects. Only 1% vs 2% of the TAF/FTC vs TDF/FTC arms respectively stopped treatment due to side effects.

There were 3 deaths (n= 1 vs 2: one case of traffic accident and carcinoma and one unknown). Most AEs were symptoms related to sexually transmitted infections (STIs) - reported in about 15% of participants in both arms at all 3-monthly study time points. These include rates of 1.45/100 and 1.38/100 PYFU for TAF/FTC vs TDF/FTC respectively.

Mean percentage change in bone density include + 0.50% vs -1.12 at the spine at spine and +0.18 vs 0.99 in the hip at week 48 in TAF/FTC vs TDF/FTC arms respectively, both (p<0.001).

Renal safety was also better in TAF/FTC group with eGFR changes of +1.8 vs -2.3 mL/min at week 48 (p<0.001). Similar benefits were reported for sub-clinical markers for proximal tubular protein to creatinine ratios.

Finally, given the low number of HIV diagnoses, even with very high rates of STIs linked to HIV risk, the group calculated the background HIV incidence for gay men who not on PrEP in the US cities where the study was running. This was estimated as 4.02 /100 PY (95%CI: 3.96 to 4.09) and was compared to observed rates of 0.08 (95%CI 0.01 to 0.28) and 0.45 (95%CI: 0.23 to 0.78) in the TAF/FTC and TDF/FTC group respectively.

The study concluded that TAF/FTC had high efficacy and good tolerability in high risk gay men and transgender women.

C O M M E N T

These results are positive in supporting that TAF/FTC is non-inferior to TDF/FTC with safety benefits that might be clinically important both for people <30 years old at a time when bone density is still growing and in older people who are more susceptible to loss of both BMD and renal function.

Drug pricing will be critical for both access and use in nearly every setting, especially with TDF/FTC now off-patent in the EU (though not, apparently, in the US for several years).

References

- Hare CB et al. The phase 3 discover study: daily F/TAF or F/TDF for HIV preexposure prophylaxis. Oral abstract LB 104LB. <http://www.croiconference.org/sessions/phase-3-discover-study-daily-ftaf-or-ftdf-hiv-preexposure-prophylaxis> (abstract) <http://www.croiwebcasts.org/console/player/41210> (webcast)
- clinicaltrials.gov. Safety and efficacy of emtricitabine and tenofovir alafenamide (F/TAF) fixed-dose combination once daily for pre-exposure prophylaxis in men and transgender women who have sex with men and are at risk of HIV-1 infection (DISCOVER) <https://clinicaltrials.gov/ct2/show/NCT02842086>

CROI 2019: TB COINFECTION

Dolutegravir can be given with 3HP to prevent TB without dose adjustment

Polly Clayden, HIV i-Base

Dolutegravir (DTG) can be given with short-course TB preventive therapy of 12 once-weekly rifampentine/isoniazid (3HP) without dose adjustment, according to data from the DOLPHIN trial, presented at CROI 2019. [1]

Both DTG and 3HP are recommended by WHO. DTG is metabolised by CYP3A and UGT1A1 that are induced by rifamycins, including rifampentine. So giving them together could be tricky.

A previous study in HIV negative volunteers found a modest reduction in DTG trough concentrations. [2] But this was stopped early due to adverse events in two out of four participants.

DOLPHIN was a single arm phase 1/2 study of 3HP and DTG in HIV positive adults receiving ART, conducted to characterise safety, drug interactions, and viral suppression.

60 participants with undetectable viral load on efavirenz (EFV)-based regimens were recruited into 3 groups. All participants received DTG in place of EFV for 8 weeks, then started 3HP; after completing 3HP, all were followed for 4 more weeks.

Viral loads were measured at baseline and weeks 11 and 24. Groups 1A (n=12) and 1B (n=18) had intensive DTG pharmacokinetic (PK) sampling at week 8 (pre-HP), then weeks 11 and 16 following the 3rd and 8th doses of HP. Group 2 (n=30) received the same regimen and had sparse DTG PK sampling at weeks 8, 11 and 16.

Primary objectives were to: evaluate the effect of RPT and INH given at doses of 990 mg once weekly on the PK of DTG; and to assess the safety of DTG and 3HP co-administration.

The study took place in South Africa, it was conducted by the Aurum Institute and the Johns Hopkins University Center for TB Research as part of the IMPAACT4TB project. Enrollment was January to September 2018 and the last scheduled visit February 2019. Kelly Dolley presented the findings on behalf of the DOLPHIN trial team.

Of the 60 participants, 70% were women, median age was 40 years, all were black African, median CD4 was 683 cells/mm³, and median BMI was 28.9 kg/m². All 60 completed the 12 HP doses.

There were three grade 3 adverse events (2 elevated creatinine, 1 hypertension).

DTG AUC was reduced by 29% at weeks 3 and 8. The geometric mean (GM) trough concentration of DTG in Group 1 (n=30) was: 0.85 (90% CI 0.42 to 1.20); 0.41 (90% CI 0.15 to 0.68); 0.39 (90% CI 0.18 to 0.87); and 0.47 (90% CI 0.29 to 0.88) on days 1, 2, 6 and 7 post-dose, respectively.

The investigators judged DTG levels to be sufficient, based on 96 week outcomes for 10 mg DTG in the original dose finding study SPRING-1. And viral load suppression <40 copies/mL was maintained throughout 3HP/DTG treatment.

References

1. Dooley KE et al. Safety & PK of weekly rifapentine/isoniazid (3HP) in adults with HIV on dolutegravir. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 80LB.
<http://www.croiconference.org/sessions/safety-pk-weekly-rifapentineisoniazid-3hp-adults-hiv-dolutegravir> (abstract)
<http://www.croiwebcasts.org/console/player/41177> (webcast)
2. Brooks KM et al. Cytokine-mediated systemic adverse drug reactions in a drug-drug interaction study of dolutegravir with once-weekly isoniazid and rifapentine. Clin Inf Dis Feb 3 2018.
<https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciy082/4836314>

Double doses of darunavir given with rifampicin lead to high rates of hepatotoxicity

Polly Clayden, HIV i-Base

Adjusted doses of darunavir/ritonavir (DRV/r) with rifampicin (RIF) were associated with unacceptable risk of hepatotoxicity and a reduction in DRV trough concentrations in a pharmacokinetic (PK) study, conducted in South Africa, presented at CROI 2019.

DRV/r is better tolerated and has a higher genetic barrier to resistance than lopinavir/ritonavir (LPV/r) – which is part of standard second-line ART in most low- and middle-income countries (LMICs). Doubling LPV/r leads to therapeutic concentrations when administered with RIF.

Currently, giving DRV/r with RIF is contraindicated as significant reductions in DRV exposures are expected. Switching RIF to rifabutin is recommended but this drug is not available in most LMICs. Not being able to give DRV/r with standard first-line TB treatment is a barrier to its use in such settings.

Investigators from the University of Cape Town performed a study to compare the trough plasma concentrations for double doses of DRV/r given once or twice daily with rifampicin versus standard dose DRV/r without rifampicin. Gary Maartens presented the results on behalf of the study team.

It was an open label, randomised, cross-over, single centre, PK drug interaction study, including HIV positive participants with viral load <50 copies/mL and CD4 >200 copies/mm³, receiving second-line ART of ritonavir (RTV)-boosted PI + 2NRTIs.

In place of their boosted PI participants received two adjusted doses of DRV/r (1600/200 mg once daily and 800/100 mg twice daily) with RIF to compare with plasma exposures with DRV/r 800/100 mg once daily without RIF.

Baseline DRV steady state PK was measured and RIF added for 7 days, then the dose of RTV was increased to 200 mg; 7 days later the dose of DRV was increased; after a further 7 days, participants crossed over to the alternative adjusted DRV/r dose. PK in plasma samples was measured at baseline post-dose and after each dose adjustment.

The study was originally planned to enrol 28 participants in 2 sequential cohorts of 5, 12 and 11 participants, with a DSMC review after each cohort. Stopping rules included DAIDS grade 3/4 events in 2 or more of the first 5 participants or >20% of the following cohorts.

The study was stopped before completion due to high rates of hepatotoxicity.

At baseline participants in cohorts 1 and 2 (n=16) were: 15/16 women; median age 44 years; weight 73 kg; BMI 31 kg/m²; CD4 684 cells/mm³; and median of second-line ART 58 months.

Six (35%) participants were withdrawn for grade 3 (n=3) or 4 (n=3) ALT elevations developing after 9–12 days of RIF. All participants with grade 3/4 ALT were symptomatic.

All case of hepatotoxicity resolved after withdrawal of study treatment and participants successfully returned to their standard of care ART regimen.

DRV trough concentrations were below the protein-adjusted EC50 of 200 ng/mL in 2/4 participants in the once-daily double dose group on RIF (0/4 in the twice daily group).

The investigators concluded that double dose DRV/r with RIF has an unacceptable risk of hepatotoxicity in HIV positive people without TB.

Twice daily but not once daily double dose DRV/r might achieve adequate DRV trough concentrations.

C O M M E N T

Giving RIF with PIs remains complicated.

Reference

Ebrahim I et al. Pharmacokinetics and safety of adjusted darunavir/ritonavir with rifampin in PLWH. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 81LB.

<http://www.croiconference.org/sessions/pharmacokinetics-and-safety-adjusted-darunavirritonavir-rifampin-plwh> (abstract)

CROI 2019: OTHER NEWS

Shared housing compared to living alone: higher CD4, lower viral load and reduced inflammation in macaques

Simon Collins, HIV i-Base

The impact of community contact for research animals might have implications for interpreting the results of these studies.

Researchers from Johns Hopkins University in Baltimore looked for health markers of laboratory macaques used for studies.

SIV-negative animals that are kept in single cages have shown significantly higher signs of stress, including lower CD4 counts and other changes in their immune response compared to socially housed animals.

However, animals that were infected with SIV (as models for HIV research) also had significantly higher viral load compared to animals living together.

This was retrospective data from 35 singly housed and 41 socially housed pigtail macaques, with three pre-SIV infection and two post-infection samples during acute infection.

During acute infection, singly housed macaques had a greater drop in CD4 count ($p=0.0012$), CD8 cells ($p=0.0003$) and total lymphocytes ($p<0.0001$), with significantly higher levels of immune activation (circulating activated CD69+ CD4 and CD8+ cells, both $p<0.0001$).

They also had higher viral loads in plasma and CSF (both $p<0.001$) throughout acute infection and greater variability in plasma viral load.

This study concluded that this factor might not only affect the interpretation of results from animal studies, but also questioned whether a similar effect might be found in HIV positive people.

Reference

Guerrero-Martin S et al. Single housing of macaques increases the immune impact of SIV infection. CROI 2019. Seattle. 4–7 March 2019. Poster abstract 212.

<http://www.croiconference.org/sessions/single-housing-macaques-increases-immune-impact-siv-infection> (abstract)

Selected webcasts from CROI 2019

Simon Collins, HIV i-Base

Comprehensive webcasts from all oral presentations and plenary talks make CROI one of the most accessible conferences.

<http://www.croiwebcasts.org>

Talks are available and video or audio format, with or without slides.

The following presentations are recommended from this years meeting.

The challenges of HIV treatment in an era of polypharmacy

David Back. Oral abstract 120.

<http://www.croiwebcasts.org/console/player/41280> (webcast)

Can two drugs tango: the role of dual therapy

Laura Waters. Oral abstract 161.

<http://www.croiwebcasts.org/console/player/41004> (webcast)

Chemsex and implications for HIV transmission and management

Mark Rohan Pakianathan. Oral abstract 64.

<http://www.croiwebcasts.org/console/player/41152> (webcast)

Tobacco smoking: the silent killer

Lene Ryom. Oral abstract 66.

<http://www.croiwebcasts.org/console/player/41154> (webcast)

Obesity: a growing problem in antiretroviral therapy

John R. Koethe. Oral abstract 158.

<http://www.croiwebcasts.org/console/player/41364> (webcast)

Update on antiretroviral drugs and birth defects

Lynne Meryl Mofenson

<http://www.croiwebcasts.org/console/player/41144>

i-Base Fit for Purpose report launched at CROI 2019

Polly Clayden, HIV i-Base

Fit for Purpose provides an overview of recent developments in antiretroviral treatment (ART) optimisation for HIV positive adults, in low- and middle-income countries (LMICs).

We produce Fit for Purpose annually for distribution at the International AIDS Society (IAS) conferences, with updates to coincide with other key HIV meetings.

This abbreviated version – looking at optimised ART for adults and including the HIV pipeline – was released at the annual Conference on Retroviruses and Opportunistic Infections (CROI) 2019

Key developments since the July 2018 edition include:

- Interim World Health Organisation guidelines recommending dolutegravir (DTG)-based regimens for all adults and children (for whom approved DTG dosing is available) as preferred first- and second-line ART – published December 2018
- Week 48 results from the NAMSAL study – a key ART optimisation trial of first-line DTG vs efavirenz (EFV) in an African setting – presented October 2018
- Week 48 results from a second-line switch study of people stable on a twice-daily lopinavir/ritonavir (LPV/r)-based regimen who switched to a once-daily 400/100 mg darunavir/ritonavir (DRV/r) one – presented July 2018
- Pharmacokinetic data on tenofovir alafenamide (TAF) pregnancy from IMPAACT P1026s – presented July 2018

We will continue to cover key developments in optimised ART and new drugs and strategies in HTB throughout the year.

The July 2019 update will include ART optimisation for both adults and children and a new section on long acting formulations

Download Fit for Purpose (March 2019)

<http://i-base.info/htb/wp-content/uploads/2019/03/iBase-fitforpurpose-march2019.pdf> (PDF)

Pre-CROI community HIV cure workshop 2019

Simon Collins, HIV i-Base

For several years, community advocates focused on cure-related research have organised pre-CROI workshops on latest developments in finding a cure for HIV.

Many of these activists have been reporting on HIV treatment for decades and their experience means that the programme also include leading HIV researchers.

This year the meeting had a larger presence on social media with web streaming of most talks. The morning workshop was held in a meeting room at a hotel close to the conference centre and the afternoon workshop was held at the Seattle Public Library to encourage involvement of both conference delegates and people who live in Seattle.

The meeting included an introduction by Carl Dieffenbach, Director of the Division of AIDS (DAIDS), and responsible for a \$1 billion research budget and the chance to celebrate Timothy Ray Brown's 12th anniversary of being cured (as the Berlin patient).

The agenda and presentations from this workshop together with videos of the talks are on the TAG website.

<http://www.treatmentactiongroup.org/content/pre-croi-community-hiv-cure-research-workshop-2019>

Online videos are also available on the defeatHIV facebook page.

https://business.facebook.com/pg/defeatHIVseattle/posts/?business_id=759362077466728

TAG survey of ongoing studies

The first presentation – from Liz Barr from the Women's HIV Research Collaborative and the ACTG – was of results from a survey of studies in the impressive TAG online database of 128 ongoing cure-related studies.

<http://www.treatmentactiongroup.org/cure/trials>

All studies were sent a short survey and just over half replied (72/128 with completed surveys and 7/128 declining to take part). Most respondents were from the US, many were from other countries or representing multi-country international studies. Of these, at least 32 include an analytic treatment interruption (ATI). As most early studies are short, 69/72 are expecting to have results either during 2019 (38/72) or 2020 (29/72).

Demographic info was limited, perhaps because many studies were still enrolling, but as 113/128 of the studies in the database are phase 1 or 2 they will be exempt from federal requirements that participants reflect appropriate diversity in terms of sex and ethnicity.

With a caveat that the data is far from complete, ethnicity results from 39/72 studies (mainly US) included 52% white and 39% black participants. By sex, 82% of participants are men and 17% women – but this is likely to underestimate the percentage of men because an answer that said "mostly men" was assigned as 51%. Many studies report 100% male participants.

Surprisingly, some studies (n=9) reported no obstacles to enrolling (a common challenge for nearly most research) while others listed having concerns about the type of intervention (n=21) or that there were no direct health benefits (n=15) as reasons given for not taking part.

Discussion after the presentation suggested future surveys could collect more information about financial incentives, treatment interruptions and an upper age limit that excluded people older than 65.

Consensus and disagreements between community and researchers

The second presentation, from Lynda Dee from AIDS Action Baltimore and the DARE collaboration, reported on discussions from a US community meeting held in July 2018 to develop discussions between community activists and researchers about trial design and related ethical concerns.

The meeting recognised a disconnect between researchers who understand that there is little chance of personal benefit for participants in their research and the participants themselves who are drawn to the hope they might be cured. One practical approach that was suggested was to not refer to “cure” in informed consent, where this is still commonly used, but to refer perhaps to drug-free long-term control, viral suppression off-ART or ART-free remission (though the use of remission is not supported by attendees at the meeting).

The need for ATIs was discussed as probably the most difficult ethical issue for cure-related studies - as they contradict HIV treatment guidelines that recommend remaining on ART. However, there is still consensus that there is currently no other option to measure interventions that are looking to maintain viral suppression without the need for ART.

Potential risks from ATIs include seroconversion symptoms, reseeding the reservoir (though also maybe not), ART resistance, inflammation-related events (neurological, cardiovascular, cancer, liver/kidney etc), and more recently, the worry about HIV transmission.

There is with growing consensus on some entry criteria - including that current CD4 count >500 cells/mm³ on effective ART (viral load <50 copies/mL) is equivalent to a so-called ‘healthy’ HIV negative person. This in itself is a community achievement. However, while advocates argue for caution with a higher CD4 nadir of 350 cells/mm³ some studies still allow 200 cells/mm³.

Recent inclusion criteria also include having at least two active drug classes in case the ATI leads to drug resistance.

Two areas where less is less consensus include the criteria for restarting treatment, with community advocates preferring a lower viral load threshold and researchers wanting >100,000 copies/mL when the intervention is hoped to generate post-treatment viral control.

There was no agreement on whether PrEP should be provided in ATI studies. While there was 100% community support for including information about PrEP and also preferably access, the practical difficulties and costs of arranging this in the US meant most researchers see this as not being their responsibility.

Ethical issues: gene editing and respect for participants

A discussion on ethical concerns from approaches that involve gene editing was led by Karine Dubé from University of North Carolina and Michael Louella from defeatHIV. This talk focused on the recent use of CRISPR/Cas-9 in China to try to produce babies with the CCR5-d32 deletion that might offer limited further protection against HIV.

The ethical issues in this example included false informed consent, coercion of study participants, flawed justifications (there is no transmission risk when on effective ART), lack of previous safety results from animal studies and lifelong uncertainty for the two children who underwent these procedures. There were no peer-review input to the study design or results which were released on youtube.

<https://www.youtube.com/watch?v=th0vnOmFltc>

This study would have not been allowed in any other setting, but other ongoing research into gene editing are very carefully designed and controlled to meet good practice for both participants and researchers. These include ZFN editing (using own cells reinfused), TAL effector nuclease, CRISPR/Cas-9 (not yet in humans) and megaTals.

This session also included a discussion of a recent paper published in the Journal of Infectious Diseases that reported a case of heterosexual HIV transmission during an ATI in a French vaccine study. In addition to reporting oral sex as the transmission route (from an HIV positive man), the paper included numerous personal details for the people involved that were not required for medical and scientific concerns, and took a judgemental approach to this event.

<https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiz012/5344456>

Some aspects of the case suggested that participants were improperly enrolled although a community discussion did include support for including a depression scale cut-off for ATI studies, so that more vulnerable participants are not included.

MMF to reduce the reservoir

The morning session concluded with a talk from Seattle-based researcher Joshua Schiffer who is running a small study funded by amfAR to see whether mycophenolate mofetil (MMF) could reduce the viral reservoir.

This hypothesis is based on modelling the dynamics of different cell populations that make up the viral reservoir based on the role that cell proliferation plays in maintaining the reservoir. MMF can target cell proliferation and is used to prevent GvH disease. Although there is significant risk of toxicity at higher doses, MMF is also is teratogenic in pregnancy.

<https://clinicaltrials.gov/ct2/show/NCT03262441>

<https://www.fredhutch.org/en/news/center-news/2018/11/hiv-persistence-cell-proliferation.html>

This study is currently enrolling and plans to run for two years.

MMF was also used as an experimental addition to ART fifteen years ago as a potential booster for abacavir in the context of MDR HIV, and also in early infection, though without convincing evidence that it added benefit in either situation.

Paediatric cure, IciStem collaboration and cure research in Africa

The afternoon session included talks on paediatric cure research, the international IciStem collaboration to support stem cell research and an overview on the importance of cure research in Africa.

Deborah Persaud from Johns Hopkins Children's Center in Baltimore, discussed the differences between cure research in children compared to adults and included an overview of paediatric remission cases including the case of the Mississippi baby from 2013, and a review of ongoing research.

Monique Nijhuis from University Medical Centre Utrecht reviewed the potential for HIV to be cured by stem cell transplant and the work of the IciStem collaboration. This international research group has included developing an international donor database from cord and blood banks that has now identified more than 22,000 potential donors with delta-32 deletion. This group has also developed a database cohort of HIV positive people who have undergone HSCT or who plan to do so. So far, 39/45 people registered from nine countries have already undergone autologous transplants and 26/39 are still living. Median follow-up is >4.5 years and 19/26 are beyond the first year of transplantation. Although most patients received transplants with wild-type cells, nine cases had donors with CCR5 d-32 deletion and 4/9 are still alive.

The consortium have also developed more sensitive tests for measuring HIV reservoirs post-transplant.

The complexities of myths and misconceptions about the HIV cure in Africa were discussed by Moses Supercharger, a Uganda activist who is also a member of the International INSIGHT community advisory board. This included the practical urgency for HIV positive people to limit dependence on international funding for medications, especially given the threats of changes in US political priorities. It also looked at the need for better ART in settings where the benefits of ART are often undermined by false claims of herbal cures.

OTHER NEWS

US requires informed consent forms for clinical studies to be posted online

Simon Collins, HIV i-Base

US studies now require informed consent sheets for clinical studies to be available on as US Federal website as open access documents.

This is an important move for greater transparency in clinical research that should be routinely adopted for all studies.

This change is mainly for new studies (enrolling after 19 January 2019).

The new requirements were published in the electronic Code of Federal Regulations on 20 December 2018.

Unfortunately, this requirement only becomes mandatory after studies have closed to recruitment and no later than 60 days after the last study visit by any participant. It is a good move, but is still a long way from full transparency.

References and further information

Clinical trial informed consent form posting (45 CFR 46.116(h))

<https://www.hhs.gov/ohrp/regulations-and-policy/informed-consent-posting/index.html>

Revised common rule educational materials

<https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/index.html>

Revised common rule Q&As

<https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/revised-common-rule-q-and-a/index.html>

ON THE WEB

Report from Cure Strategies meeting

Kuo L et al. Highlights from the Fourth Biennial Strategies for an HIV Cure Meeting, 10–12 October 2018, Bethesda. *J Virus Erad.* 2019 Jan; 5(1): 50–59.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6362907>

FUTURE MEETINGS

Conference listing 2019

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

25th Annual BHIVA Conference

2 – 5 April 2019, Bournemouth
www.bhiva.org

20th International Workshop on Clinical Pharmacology of HIV, Hepatitis & Other Antiviral Drugs

14 – 16 May 2019, Noordwijk, The Netherlands
www.virology-education.com

17th European Meeting on HIV & Hepatitis

22 – 24 May 2019, Rome
www.virology-education.com

Viruses, vaccines and eradication conference 2019

Thursday 6 June 2019, London
<http://www.vveconference.com>

11th International Workshop on HIV Pediatrics

19 – 20 July 2019, Mexico City
www.virology-education.com

HIV & HBV Cure Forum

20 – 21 July 2019, Mexico City
<https://www.iasociety.org>

International Workshop on HIV & Transgender People

July 2019, Mexico City, date TBC
www.virology-education.com

10th IAS Conference on HIV Science

21 – 24 July 2019, Mexico City
www.ias2019.org

4th European Workshop on Healthy Living with HIV

13 – 14 September 2019, Barcelona
www.virology-education.com

10th International Workshop on HIV & Aging

10 – 11 October 2019 | New York, NY, USA
www.virology-education.com

International Workshop on HIV Drug Resistance and Treatment Strategies

16 – 18 October 2019, Johannesburg
www.hivresistance2019.co.za

21st Intl Workshop on Comorbidities and Adverse Drug Reactions in HIV

5 – 6 November 2019, Basel, Switzerland
<https://www.intmedpress.com>

17th European AIDS Conference

6 – 9 November 2019, Basel
www.eacsociety.org

PUBLICATIONS & SERVICES FROM i-BASE

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 (May 2018)
- HIV & quality of life: side effects & long-term 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 (Dec 2017)
- Guide to HIV, pregnancy & women's health (December 2015)

Pocket guides

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

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

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.



U=U resources for UK clinics: free posters, postcards and factsheets

i-Base have produced a new series of posters, postcards and leaflets to help raise awareness about U=U in clinics.

This project was developed with the Kobler Centre in London.

As with all i-Base material, these resources are all free to UK clinics.

Until our online order form is updated to include the U=U resources, more copies can be ordered by email or fax.

email: subscriptions@i-base.org.uk

Fax: 0208 616 1250

Other i-Base resources can still be ordered online as usual.

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

Customise U=U posters for your clinic

i-Base can customise U=U posters to include pictures of doctors, nurses, pharmacists, peer advocates or any other staff that would like to help publicise U=U.

Personalising these or your clinic is cheap and easy and might be an especially nice way to highlight the good news.

For further information please contact Roy Trelvelion at i-Base: roy.trelvelion@i-Base.org.uk

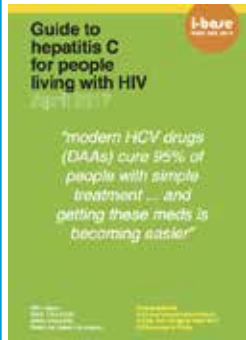
Order publications and subscribe online

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>

i-base
0808 600 8013

Plus FREE guides to treatment.



ask a question

by email, online or phone

questions@i-Base.org.uk

www.i-Base.info/qa

0808 800 6013

take control of your treatment

HIV i-Base, 4th Floor, 57 Great Suffolk Street, London, SE1 0BB. Tel + 44 (0) 20 7407 8488.
Registered charity no: 1081905. Company reg no: 3962064.



Orders and subscriptions

107 The Maltings, 169 Tower Bridge Road, London, SE1 3LJ

Tel: +44 (0) 20 8616 2210



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 _____

Telephone _____ Fax _____

e-mail _____

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

• **HIV Treatment Bulletin (HTB) every two weeks** **by e-mail**

• **Pocket leaflets** - *A7 small concertina-folded leaflets (2017)*

Pocket HCV coinfection	quantity _____	Pocket PrEP	quantity _____
Pocket ART	quantity _____	Pocket pregnancy	quantity _____
Pocket side effects	quantity _____	PrEP for women	quantity _____

• **Booklets about HIV treatment**

ART in pictures: HIV treatment explained (*August 2018*): 32-page A4 booklet quantity _____

Guide to hepatitis C coinfection (*April 2017*): 52-page A5 booklet quantity _____

UK Guide To PrEP (*March 2019*): 24-page A5 booklet quantity _____

Introduction to ART (*May 2018*): 48-page A5 booklet quantity _____

HIV and quality of life: guide to side effects and long-term health (*Sept 2016*): 96-page A5 quantity _____

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

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

Guide to changing treatment: what if viral load rebounds (*Jan 2018*): 24-page A5 booklet quantity _____

• **Other resources**

U=U resources:

A3 posters quantity _____ **A5 leaflets** quantity _____ **A6 postcards** quantity _____

HIV Treatment 'Passports' - Booklets for patients to record their own medical history quantity _____

Phoneline posters (A4) quantity _____

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

subscriptions@i-Base.org.uk