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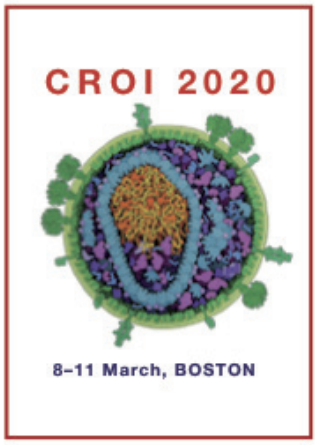
First reports from virtual CROI 2020

CONTENTS



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EDITORIAL

This edition of HTB includes first reports from CROI 2020, which in response to the fast-changing health implications of coronavirus, this year became a virtual meeting.

This kept more than 95% of the programme, with speakers broadcasting from their laptops at home and webcasts available to delegates in real time and only slightly later than usual online. Abstracts and posters also now online as open access.

The first reports in HTB cover the special session on SERS-CoV-2 (the coronavirus associated with COVID-19), new information on long-acting pipeline drugs (that really have the potential to revolutionise both treatment and PrEP), an update on weight gain with dolutegravir, and two reports on the London Patient, who is not only the second person cured of HIV, but who has also decided to talk openly about his experience.

Thanks to those readers who have completed the short online feedback survey for HTB. If you haven't yet done this already, please take five minutes to help us plan for the future...

https://www.surveymonkey.co.uk/r/KCXXT3F

HTB reader's survey 2020

htb reader survey

Please could you spend five minutes to help with a short HTB reader's survey.

This only includes 10 short questions with space for additional comments.

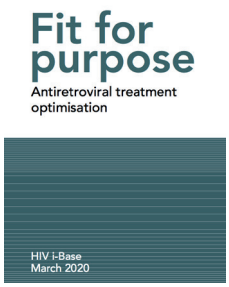
Your feedback will help us develop HTB this year.

Online link

https://www.surveymonkey.co.uk/r/KCXXT3F

SUPPLEMENTS

Fit For Purpose: antiretroviral treatment optimisation (March 2020)



HIV i-Base produces Fit for Purpose – a review of antiretroviral therapy (ART) optimisation – annually for distribution at the International AIDS Society (IAS) conferences, with updates to coincide with other key HIV meetings.

http://i-base.info/htb/37244

HIV pipeline 2020: new drugs in development (March 2020)

This report is based on new developments over the last eight months since the pipeline report produced for the IAS conference in July 2019.

This includes the move towards simplified ART and long-acting compounds in several drug classes that allows less frequent dosing than daily oral ARVs.

It is available in two version - a detailed and reduced 'litr' version.

http://i-base.info/htb/37221

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.

For further information please contact Roy Trevelion at i-Base: roy.trevelion@i-base.org.uk

i-Base 2020 appeal

This year we are continuing a funding appeal to help i-Base continue to provide free publications and services during 2020.

i-Base now recieve more than 12,000 questions each year and the website has more than 500,000 view each month. We also distribute more than 80,000 booklets and leaflets free to UK clinics every year.

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

Subscriptions

To join the email list for HTB please register free online:

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CONFERENCE REPORTS

Conference on Opportunistic Infections and Opportunistic Infections (CROI 2020)

8 – 11 March 2020, Boston

This year, a last minute decision changed the CROI 2020 meeting from a physical to a virtual meeting.

Although the preceding week included several announcements that even with the concerns about COVID-19, CROI would proceed as normal, many delegates arrived in Boston for pre-meetings to find that the main meeting had been cancelled.

The final decision – clearly a difficult one – was only made on Friday 6th March. This was after three confirmed cases of COVID-19 earlier in the week in 150 participants at a medical meeting in Boston, that had strained the local medical system - and also based on 13 cases that had been confirmed in the state. A single diagnosis among thousands of delegates at CROI would have not been manageable.

However, even before the official decision from CROI, many participants, including European doctors, had already decided not to attend and some countries had prevented health workers from travelling (including Australia and Italy). These concerns were not from risk from COVID-19 itself, but from the implications of two weeks quarantine.

CROI are therefore to be congratulated on pulling a virtual conference together so quickly.

Abstracts are already available on the CROI website and most posters should now be uploaded as PDF files.

Nearly alll talks were streamed in real time, and oral presentations will be available as webcasts, perhaps the week after the conference.

www.croiconference.org

Webstreaming (real time and post-presentation access for delegates only)

https://croilive.capitalreach.com

If this virtual CROI is successful it might reduce the need for other international meetings in the future, perhaps still supported by reduced registration costs and better environmental outcomes from fewer flights.

The short term economic implications from coronavirus in general are likely to be more difficult if the decision made by CROI is taken by other conferences, concerts and sports events etc.

Even if things COVID-19 is resolved within a few months (UK predicts 50% of cases within three weeks and that 90% will have been seen within nine weeks, based on effective control measures) it will be difficult for airlines, hotels and supporting businesses given financial margins might already be slim.

The opening ceremony explained the reasons for making this year's conference virtual. It highlighted the difficulties and challenges now faced to contain the coronavirus epidemic - including stigma, prejudice and misinformation – when the response should focus on the science, learning from the global response to HIV.

Also on a positive note, the expected highlights for CROI 2020 (and there will be many) include:

- At least 30 studies will be presented on new drugs for treatment and PrEP, including integrase inhibitors, bNAbs, maturation inhibitors and capsid inhibitors, many with long-acting formulations.
- Many studies looking at HIV cure, including tackling the HIV reservoir, and including an update on the London Patient who will have passed the two-year cautionary period suggested by researchers at CROI last year as being needed before this case could be called a cure.
- Additional analyses of side effects, including weight gain with some HIV drugs.
- New results about options for treating HIV positive children.
- Basic science studies on the early stages of the HIV lifecycle.

i-Base early reports will still be published during the conference week with links below.

- CROI 2020: special session on COVID-19
- Monthly islatravir for PEP and PrEP could cover unmet global need for HIV prevention in billions of people globally: 12 pills a year
- Long-acting cabotegravir and rilpivirine injections non-inferior to two-monthly dosing
- Safety and PK of bNAb elipovimab (GS-9722) support two-weekly dosing
- First results with long-acting capsid inhibitor GS-6207: oral and subcutaneous formulations for use in naïve and multidrug resistance
- Predicted diabetes risk with first-line ART regimens: results from the ADVANCE trial
- Postpartum weight gain is higher with dolutegravir- compared with efavirenz-based ART among African women
- London patient is second person to be cured from allogeneic stem-cell transplant: updated results from tissue samples
- The London Patient tells his story as second person cured of HIV

CROI 2020: SPECIAL REPORT

CROI 2020: special session on COVID-19

Simon Collins, HIV i-Base

The special session on coronavirus at CROI yesterday is posted for open-access on the CROI website. [1]

https://special.croi.capitalreach.com

The 75-minute overview includes four talks and a Q&A at the end.

A few selected key points include:

- It still emphasises that highest risk of more serious illness and outcome (risk of dying) are older age (80>70>60 years old), and having other health conditions (heart, lung/breathing, diabetes, cancer). The risk of the most serious outcomes is 5-30 times higher than with seasonal influenza ('flu).

- Implications for HIV positive people are not known, other than for general population. One speaker included low CD4 as a possible caution. Due to lack of evidence so far a low CD4 count has not been included as a risk in the recent UK (BHIVA) statement. [2]
- Transmission is largely from microdroplets in air after someone during the infectious period (generally from 1 day before symptoms to average 5 days, but up to 14 days after). These can remain infectious on hard surfaces for an unknown time (possibly hours) which is why hand-washing and not touching your face is important.
- Best ways to minimise risk of infection include washing your hands more carefully and frequently and not touching your face.
- Soap and water is better than hand sanitisers (and more readily available).
- Best candidate treatment (so far) is remdesivir (a Gilead compound). This has good activity against a range of viruses in in vitro studies and is already in at least four large randomised studies.
- Studies with candidate vaccines are expected shortly - within two months of the virus being isolated - fastest time for vaccine development.
- The response in China after the first cases were reported was probably much faster than it would have been in the UK. This included:
- Within four days of the first reported cases, the suspect source was identified and closed (a seafood market).
  - Within a week, the new virus was identified (SARS Cov-2).
  - The viral sequence was then shared with WHO and on databases in the public domain for other global scientist to use.
  - Within three weeks of the first confirmed cases, Wuhan and 15 other large cities in China were shut down as part of containment measures.

One of the questions after the main talks asked whether SARS was now extinct. The answer explained that SARS is a bat virus, and only 50 out of about 1300 species of bats have been studied so far. So SARS is very likely still around.

References
1. Special session on COVID-19. CROI 2020, 8–11 March 2020. https://special.croi.capitalreach.com
2. BHIVA. Comment on COVID-19 from the British HIV Association. 27 February 2020. https://www.bhiva.org/comment-on-COVID-19-from-BHIVA

CROI 2020: HIV PREVENTION

Monthly islatravir for PEP and PrEP could cover unmet global need for HIV prevention in billions of people globally: 12 pills a year

Simon Collins, HIV i-Base

The most important study at CROI 2020 could easily one that looks at using the NRTTI islatravir (EFdA) for HIV prevention.

Islatravir has the potential to change the way we think about PrEP and PEP due to its high potency and long-acting formulations (that include daily, weekly and monthly oral dosing and an annual implant).

Animal studies already showed 100% efficacy using weekly doses (at >0.43 mg/kg) at preventing SHIV infection after rectal challenge.

This is now further supported by results from CROI 2020 of a macaque study, presented by Martin Markowitz from the Aaron Diamond AIDS Research Center that looked at whether islatravir could work as PEP.

The study included 12 rhesus macaques that were challenged rectally with high dose SHIV. Then, 24 hours later, half received a total of four weekly doses of islatravir (3.9 mg/kg) and half were untreated controls.

This was a multistage study using the same animals. After seven weeks follow-up from the last dose, animals were rechallenged with SHIV and stepped down to three weekly doses, then two, then a single dose, all with the same seven week washout.

Islatravir produced 100% protection when 4, 3, or 2 weekly doses were given. However, all control animals quickly became infected. After the single dose, 4/6 animals were still protected, but 2/6 became viraemic (at days 14 and 49). However, lowest intracellular drug levels achieved in these animals were significantly lower than levels seen in human studies (using a 60 mg once-monthly dose).

This led the presenters to speculate that a single PEP dose 24 hours after exposure in human might still provide very high levels of protection.

C O M M E N T

These early results present a strong case for fast track development and regulatory review of the monthly oral formulation of islatravir for PreP. It is possible to go further to say there is actually a public health urgency for this.

Once-monthly oral PrEP could cover a vast unmet need for HIV prevention for people unable or unwilling to use daily PrEP. People who are reluctant to use daily PrEP – 365 pills a year – might rethink their decision if HIV was prevented by taking only 12 pills over a year.

Phase 3 efficacy studies should be run in regions of the world and in populations where HIV incidence is still highest. Following the FDA decision on F/TAF, they will clearly need to include women.

Also, and it is never too early to plan for pricing and access, a highly effective single pill that could be used as PEP or for monthly protection as PrEP, has a potential market that includes multiple billions of people globally who are sexually active.

A market this size can plan for pricing similar to that for current daily generic PrEP.

Reference

Markowitz M et al. Weekly oral islatravir provides effective PEP against IV challenge with SIVMAC251. Oral late breaker abstract 89LB.

http://www.croiconference.org/sessions/weekly-oral-islatravir-provides-effective-pep-against-iv-challenge-sivmac251

CROI 2020: ART

Long-acting cabotegravir and rilpivirine injections non-inferior to two-monthly dosing

Simon Collins, HIV i-Base

In one of the first oral presentations, 48-week results from the ATLAS-2M study provided first data reporting that two-monthly injections of long-acting cabotegravir and rilpivirine are non-inferior to monthly dosing. [1]

Although phase 3 ATLAS and FLAIR studies used monthly dosing, the pharmacokinetics of both long acting injections supported looking at extended dosing. If effective, this would halve the number of annual clinic visits that are currently needed, and also reduce administration costs.

ATLAS-2M is a phase 3, open-label, non-inferiority study that randomised 1045 treatment-experienced participants (including approximately 33% from the original ATLAS study) to injections either every 8 weeks (Q8W, n=522) or every 4 weeks (Q4M, n=523) dosing schedules.

The primary endpoint is detectable viral load (>50 copies/mL) at week-48 by ITT-E snapshot analysis, based on non-inferiority margin of 4%, with the option for all participants to continue with either dosing schedule after week-100.

Baseline characteristics included median age 42 years (range: 19 to 83); 28% women; 73% white, 18% black/African American, 9% other; median BMI 26 kg/m2 (IQR: 23–29) and median CD4 count 661 cells/mm3 (IQR: 508 to 849).

At week-48, viral load was detectable in 1.7% vs 1% of the Q8M vs Q4M groups respectively (adj diff: 0.8% [95%CI: –0.6 to +2.2]) showing non-inferiority on the primary endpoint.

Non-inferiority was also achieved based on secondary endpoint of viral suppression to < 50 copies/mL (adj diff: 0.8% [95%CI: –2.1 to +3.7]). This included 6 (1.1%) vs 2 (0.4%) participants in the Q8W vs Q4W arms who discontinued for lack of efficacy. This was balanced by slight fewer discontinuations in the Q8W group due to side effects (n = 9 vs 13) or for other reasons (n=12 vs 16).

Overall, there were 10 confirmed virologic failures: 8 vs 2 in the Q8M vs Q4M arms; with RPV resistance in 6/8 vs 1/2 and INSTI resistance in 5/8 vs 2/2, respectively.

A post-hoc analysis of baseline resistance of HIV DNA in PBMCs in the Q8W arm showed: 5/8 had pre-existing major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L); 1/8 had pre-existing major INI RAM (G140G/R) and 5/8 had L74I polymorphism (3 subtype A or A1, 1 subtype C, 1 complex subtype). Resistance data were not presented for the Q4W arm and further analyses are underway.

Side effects were similar in both groups and overall, 96% of drug-related events were grade 1–2

Drug-related side effects led to withdrawal in 5 vs 8 participants in the Q8W arm vs Q4W arms.

Injection site reactions were also similar in both groups, despite the fewer number of injections in the Q8W group (8,470 vs 15,711 injections respectively overall).

Approximately 94% of participants with experience of both dosing regimens, preferred Q8W dosing.

C O M M E N T

Although the higher reports of drug resistance were at least partially explained by baseline resistance, this aspect of the study requires greater analysis.

Otherwise, the option to halve the number of injections would clearly benefit both participants and health systems. It should also cut the proposed price for CAB/RPV LA which anecdotally has been discussed as being considerably more expensive than oral ART. This study certainly justifies a more affordable price.

Cabotegravir LA and rilpivirine LA are currently still being evaluated by the FDA and EMA based on results of the phase 3 ATLAS and FLAIR studies that used monthly dosing.

Although an FDA decision was expected by the end of December 2019, a manufacturing problem relating to scale-up led to an FDA complete response letter. The letter has not raised safety or efficacy concerns, but will delay approval until these issues are resolved. [2]

References

1. Overton ET et al. cabotegravir + rilpivirine every 2 months is noninferior to monthly: ATLAS-2M study. CROI 2020. Oral abstract 34. http://www.croiconference.org/sessions/cabotegravir-rilpivirine-every-2-months-noninferior-monthly-atlas-2m-study (abstract)
2. Collins S. FDA decision on long-acting cabotegravir/rilpivirine (Cabenuva) injections delayed due to scale-up manufacturing problems. HTB (January 2020). http://i-base.info/htb/37064

Safety and PK of bNAb elipovimab (GS-9722) support two-weekly dosing

Simon Collins, HIV i-Base

Elipovimab (GS--9722) is a broadly neutralising monoclonal antibody (bNAb) that targets the V3 glycan motif of the HIV envelope.

It was engineered from the bNAb PGT-121 to have an improved formulation that includes reduced immunogenicity and a longer half-life. It is given by infusion and has the potential to be used as treatment and PrEP. It has also been studied in combination with the TLR7 agonist vesatolimod to target the reservoir in cure-related research.

An oral presentation at CROI 2020 included results from an HIV negative phase1a single- (SAD) and multiple (MAD) ascending dose study and an HIV positive phase 1b study.

In the first, 49 HIV negative participants received single doses of 150 mg, 500 mg and 1500 mg and then multiple doses of 150 mg, 500 mg and 1000 mg or matching placebo (n=6 in each group). All participants were Hispanic/Latinx/Black and the group included 7 women.

Safety results were generally very good, with only two grade 3 events and two discontinuations – both in the 1000 mg MAD group (a grade 2 infusion-related event and grade 3 thrombocytopenia). Pharmacokinetics (PK) was linear and dose-proportional (AUC, Cmax and Cmin). A half-life of 26 hours using a target Cmin >50 ug/mL (3 x IC95 cut-off was used to determine in vitro breadth). Although 9/37 (24%) participants had antidrug antibodies, this didn't affect PK (note: though it would expect to affect efficacy).

In the phase 1b study, 32 HIV positive people on suppressed ART were randomised to SAD and MAD doses of 150 mg and 500 mg (or matching placebo). This was a predominantly male cohort (only two women) and was 60% white.

PK results were similar to the HIV negative study (including 9/24; 37%) with anti-drug antibodies and no new safety signals. One participant had a grade 3 small intestinal obstruction (150 mg; SD) that was judged unrelated.

The study concluded that doses up to 500 mg were safe to take forward into phase 2 studies and that the long half-life supports dosing every two weeks.

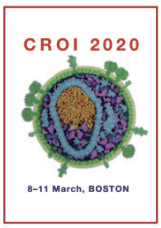
Reference

Ruane P et al. Safety & pharmacokinetics of gs-9722 in HIV-negative participants and people with HIV. CROI 2020, 8–11 March 2020, Boston/virtual. Oral abstract 39.
http://www.croiconference.org/sessions/safety-pharmacokinetics-gs-9722-hiv-negative-participants-and-people-hiv (abstract)

First results with long-acting capsid inhibitor GS-6207: oral and subcutaneous formulations for use in naïve and multidrug resistance

Simon Collins, HIV i-Base

Several posters at CROI 2020 – surprisingly none of them included as oral presentations – included new information about a new capsid inhibitor called GS-6207. This is a highly potent compound which works at multiple stages of the viral lifecycle, including early uncoating, viral assembly and maturation.



First results on viral efficacy were presented from an ongoing phase 1b dose-finding study in 39 HIV positive people not on ART. Participants were randomised to receive a single infusion of one of five doses (20, 50, 150, 450, or 750 mg) or placebo. At day 10, all participants started ART with bictegravir/F/TAF.

Each group included 8 participants (6 active and 2 placebo), except for the highest dose (where only five people received active drug).

Baseline characteristics included: median age 33 years (range: 19 to 65); 10% were women (n=4); 54% were white, 31% black, 8% Asian and 8% other. Median (IQR) CD4 and viral load at baseline were 463 cells/mm3 (IQR: 359 to 614) and approximately 31,000 copies/mL (20,000 to 50,000), respectively.

Median BMI was 25 kg/m2 (range: 19 to 35). Seven participants had previously used ART (18%), but not during the previous 12 months.

Mean reductions in viral load at day 10 were 1.3, 1.8, 1.8, 2.1 and 2.3 log copies/mL in the 20, 50, 150, 450, or 750 mg groups respectively compared to 0.2 with placebo. Maximum reductions were seen with the 450 and 750 doses (ranges: –2.9 to –1.6 and 3.0 to –1.5, respectively).

Trough levels at day ten were generally very good. Across all doses, means levels of GS-6207 were reported as being 0.7 to 22.5-fold higher than the protein adjusted EC95 for wild-type HIV (although at 0.7 this technically means at least one person would have been below this level).

However, PK modelling reported that mean concentrations >4.4 ng/mL were predicted to achieve near maximal activity, and these were reached by all but the lowest 20 mg dose group.

Pooled safety data (still blinded) were from a median follow up of 225 days (median: 156 to 227; range 16 to 247). Although side-effects were commonly reported (in 85% or participants) these were nearly all grade 1 or 2 with only one grade 3 - mainly injection site reactions (58%, n=22). The two participants with serious adverse events were not judged related to the study drugs and did not lead to discontinuations. One was a small intestine obstruction at day 57 and another was a participant with preexisting cardiovascular risk who had multiple cardiovascular events after methamphetamine use.

A second poster presented results from two phase 1 studies in HIV negative participants (n=8 for each study). One looked at PK and safety from a single escalating dose (50, 300, 900, 1800 mg) and the second reported the impact of food interactions from a single 300 mg dose with either a high or low fat meal compared to fasted. [2]

Side effects/adverse events for both studies were all mild (grade 1) and none were judged related to study drug.

PK results included maximal concentrations achieved between 4 to 8 hours and median half-life of 11 to 13 days, allowing “less frequent dosing”, though further details were not specified.

Mean concentrations of GS-6207 for fasted, low fat and high fat meals were similar and overlapping with the conclusion that the compound can be taken with or without food.

A third poster looked at the activity of GS-6207 in-vitro in presence of 19 single or double Gag cleavage site mutations (including naturally occurring polymorphisms associated with resistance to maturation inhibitors), and with mutations associated with resistance to NRTI, NNRTI, PI and INSTI classes. [3]

Phenotypic fold-changes in EC50 with GS-6207 compared to wild-type (WT) ranged from 0.3 to 2.1 with Gag mutants, similar to the control drug, and from 0.3 to 1.1 against mutations associated with current four classes. These results suggest that GS-6207 would provide life-saving options for people with multidrug HIV resistance.

Two phase 2 studies are already recruiting using 900 mg SC dose, one in treatment-naïve (n=175) and one in heavily treatment-experienced (n=100) participants. All sites are in the US or Puerto Rico. [4, 5]

The oral formulation is being used in a two-week lead-in period in these studies and is being developed to be used in association with the infusion or separately in combination with other antiretroviral drugs.

C O M M E N T

These data support the importance of future development GS-6207 both in naïve and heavily treatment experienced people.

Future studies should therefore expand to include participants in other countries who have no other options for treatment.

Although the exact mechanisms of action are not yet understood, other presentations at CROI 2020 included data supporting capsid that capsid remains largely intact until integration into the cell nucleus. [6, 7]

If this is the case, the majority of reverse transcription must also occur in the nucleus, challenging the prevailing view for decades that this occurs in the cytoplasm soon after cell entry.

References

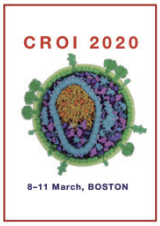
1. Daar E et al. Dose-response relationship of subcutaneous long-acting HIV capsid inhibitor GS-6207. CROI 2020. Poster abstract 469. http://www.croiconference.org/sessions/dose-response-relationship-subcutaneous-long-acting-hiv-capsid-inhibitor-gs-6207 (abstract and poster)
2. Begley R et al. PK, food effect, and safety of oral GS-6207, a novel HIV-1 capsid inhibitor. CROI 2020. Poster abstract 470. http://www.croiconference.org/sessions/pk-food-effect-and-safety-oral-gs-6207-novel-hiv-1-capsid-inhibitor (abstract and poster)
3. Margot NA et al. Absence of GS-6207 phenotypic resistance in HIV Gag cleavage site and other mutants. CROI 2020. Poster abstract 529. http://www.croiconference.org/sessions/absence-gs-6207-phenotypic-resistance-hiv-gag-cleavage-site-and-other-mutants (abstract and poster)
4. ClinicalTrials.gov. Study to Evaluate the Safety and Efficacy of GS-6207 in Combination With Other Antiretroviral Agents in People Living With HIV (CALIBRATE) https://clinicaltrials.gov/ct2/show/NCT04143594
5. ClinicalTrials.gov. Study to Evaluate the Safety and Efficacy of GS-6207 in Combination With an Optimized Background Regimen in Heavily Treatment Experienced Participants Living With HIV-1 Infection With Multidrug Resistance (CAPELLA) https://clinicaltrials.gov/ct2/show/NCT04150068
6. Burdick RC et al. Nuclear uncoating of HIV-1 occurs near sites of integration. CROI 2020. Oral abstract 23. http://www.croiconference.org/sessions/nuclear-uncoating-hiv-1-occurs-near-sites-integration (abstract)
7. Munshi MH et al. HIV-1 capsid-nuclear envelope interactions that facilitate nuclear import. CROI 2020. Oral abstract 165. http://www.croiconference.org/sessions/hiv-1-capsid-nuclear-envelope-interactions-facilitate-nuclear-import (abstract and poster)

CROI: SIDE EFFECTS

Predicted diabetes risk with first-line ART regimens: results from the ADVANCE trial

Polly Clayden, HIV i-Base

Increased risk of diabetes predicted for people receiving tenofovir alafenamide (TAF), emtricitabine (FTC) and dolutegravir (DTG) in the ADVANCE trial – according to an analysis presented at CROI 2020. [1]



In ADVANCE 1053 treatment-naive people in South Africa were randomised to one of three first-line ART regimens. More participants taking first-line TAF/FTC/DTG developed clinical obesity compared to tenofovir disoproxil fumarate (TDF)/FTC/DTG and TDF/FTC/efavirenz (EFV). [2]

The analysis of predicted risks associated with obesity in the study set out to answer the following research questions:

1. What changes are seen in markers of cardiovascular risk and diabetes?

2. Can we use risk equations to predict the risk of cardiovascular disease or diabetes from these changes?

At baseline characteristics were balanced across the three study arms, participants were 99% black and 59% women. The median age was 31 years, approximately 20% had viral load above 100,000 copies/mL and CD4 was about 350 cells/mm3.

Women weighed more and had higher BMI than men: approximately 27 vs 21 kg/m2. Just over half the participants had a normal BMI at baseline, and approximately a quarter were overweight.

Mean change in weight at week 96 was greater in women than men. Mean weight increase for women in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms was 8 kg, 5 kg and 3 kg, respectively. For men, mean weight increase for the respective regimens was 5 kg, 4 kg and 1 kg.

Treatment-emergent obesity occurred in 28%, 17% and 12% of women in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms, respectively. Compared to 7%, 5% and 3% of men in the respective treatment arms.

There was less increase in cholesterol in the TDF/FTC/DTG arm than in the other two arms (see Table 1). Total cholesterol and LDL increased in the TAF/FTC/DTG arm. Fasting glucose increased more in the TDF/FTC/EFV arm than the other two.

Table 1: Changes in laboratory parameters to week 96: median (IQR)

ART regimen/ comparison	1.TAF/FTC/DTG (n=185)	2.TDF/FTC/DTG (n=187)	3.TDF/FTC/EFV (n=191)	Arm 1 vs 3	Arm 1 vs 2	Arm 2 vs 3
Total cholesterol (mg/dL)	10.4 (-5.4 to 24)	1.5 (-13 to 19.7)	13.1 (-1.9 to 33.3)	p=0.022	p=0.007	p<0.001
LDL (mg/dL)	8.5 (-6.2 to 20.5)	2.3 (-10.8 to 12.4)	6.2 (-5.0 to 22.0)	p=0.82	p=0.007	p=0.013
HDL (mg/dL)	4.6 (-2.3 to 12.0)	3.9 (-2.3 to 12)	9.7 (2.3 to 19.3)	p<0.001	p=0.73	p<0.001
Fasting glucose (mg/dL)	19.3 (7.7 to 34.8)	19.3 (0.0 to 34.8)	27.1(11.6 to 42.5)	p=0.0049	p=0.21	p<0.001
Systolic BP (mmHg)	3.0 (-7.0 to 11.0)	-1.0 (-12.0 to 8.0)	0.5 (-9.0 to 8.0)	p=0.19	p=0.03	p=0.35

Metabolic syndrome (International Diabetes Federation definition – clinical obesity plus at least two of: raised triglycerides; reduced HDL cholesterol; raised blood pressure; raised fasting glucose) emerged in 8%, 6% and 3% of participants in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively. There were statistically significant differences between TAF/FTC/DTG and TDF/FTC/DTG at week 96 (p=0.031).

The investigators used three risk equations to calculate the risk of cardiovascular events or diabetes in ADVANCE participants.

The Framingham risk equation estimates the 10-year risk of heart attack or coronary death. According to this equation, the investigators reported no significant difference and low risk across arms at baseline: 2.37%, 2.53% and 2.24% in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

At week 96 there was a similar and very modest increase in risk: +0.43%, +0.22% and +0.28 across the respective treatment arms.

The QRISK equation estimates the 10-year risk of developing heart attack or stroke. This equation looks at a larger number of variables than Framingham – including black African ethnicity.

According to QRISK, the baseline 10-year risk of heart attack or stroke was very low: 0.6%, 0.6% and 0.5% in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

At week 96 there was a slightly lower borderline significant risk with TDF/FTC/EFV compared with TAF/FTC/DTG (p=0.027)

The QDiabetes score estimates the 10-year risk of developing diabetes. Black African ethnicity is also included among the variables in this equation.

The baseline 10 year risk score of developing diabetes was: 0.30%, 0.40% and 0.30% in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

At week 96, this increased to 0.90%, 0.50% and 0.70% in the respective arms. Compared with TDF/FTC/DTG, the risk of diabetes was significantly higher with TAF/FTC/DTG (p=0.004) and with TDF/FTC/EFV (p=0.005). There were no significant differences between TAF/FTC/DTG and TDF/FTC/EFV.

The investigators noted that among women treated with TAF/FTC/DTG, weight is continuing to increase, with no sign of a plateau. The predictive models do not account for additional weight gain after week 96.

C O M M E N T

There is very little additional risk of MI in this young population, but there is a significant increase in the predicted risk of diabetes for people taking TAF/FTC/DTG vs TDF/FTC/DTG.

For every 1000 people treated, these results suggest that an additional 4 people taking TAF/FTC/DTG would develop diabetes. The investigators have checked these results using another predictive equation (Cambridge algorithm) and seen the same.

In South Africa, with its vast HIV epidemic, this would translate into large numbers of additional diabetes cases.

WHO 2019 guidelines recommend TDF/FTC/DTG as first-line treatment. TAF/FTC/DTG is reserved only for special circumstances: people with osteoporosis or impaired renal function. The results from this analysis support the current WHO guidelines.

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http://i-base.info/htb/36879

CROI 2020: PREGNANCY

Postpartum weight gain is higher with dolutegravir- compared with efavirenz-based ART among African women

Polly Clayden, HIV i-Base

Two analyses presented at CROI 2020 show higher weight postpartum among African women receiving dolutegravir (DTG) compared with efavirenz (EFV). [1,2]

Concerns are growing about weight gain with DTG use, but there has been no previous analysis of this phenomenon in pregnancy and the postpartum period.

Data from a randomised controlled study, conducted in South Africa and Uganda and a cohort study in Botswana, found differences also varied by country in the first analysis and weight gain with DTG-based ART was similar to that among negative women in the other.

DolPHIN-2

A secondary analysis of the DolPHIN-2 study showed increased postpartum weight gain in women living with HIV receiving DTG vs EFV. But differences in weight gain also varied by site with higher weight gain in South African compared with Uganda.

DolPHIN-2 is an open label trial randomising pregnant women from Uganda and South Africa starting ART from 28 weeks' gestation to DTG vs EFV plus 2 NRTIs.

The study measured maternal weight at: enrolment, less than 14 days of delivery and at 6, 12, 24 and 48 weeks postpartum.

Women were enrolled between January and August 2018 and follow-up data were censored September 2019. A total of 232 women, with mean age of 28 years, were included. Median follow-up was 60 months.

At enrolment (median gestation 31weeks): mean weight was 73 kg and mean BMI 30 kg/m2. There was higher mean third trimester weight in South Africa vs Uganda: 80 vs 67 kg.

Across arms and sites, mean change in weight from enrolment to 6 weeks post-partum was -6.1 kg. Mean weight change between 6 and 72 weeks postpartum was different by site: Uganda decreased by 0.6 kg; South Africa increased by 2.8 kg.

Mean predicted postpartum weight (mixed effects linear regression model) was higher in the DTG vs EFV arm: 4.3 kg (95% CI 0.64 to 8.06) difference.

This was also higher in South Africa vs Uganda: 13 kg (95% CI 9.28 to 16.72).

The investigators observed similar findings for BMI.

Tshilo Dikotla

Women living with HIV receiving DTG had persistently higher weight through 18 months postpartum than those on EFV but similar weight to HIV negative women, in the Tshilo Dikotla cohort study, conducted in Botswana.

The study enrolled pregnant HIV negative women and positive women receiving either tenofovir (TDF)/emtricitabine or lamivudine (XTC)/DTG or TDF/XTC/EFV started during or before pregnancy.

This analysis included women with weight measurements 1 to 18 months postpartum.

Of 406 women, 170 received DTG and 114 EFV. Women on DTG or EFV were older than HIV negative women: median age 28.5 vs 33.0 vs 25.0 years respectively, p<0.01. And they had more children: 3 vs 3 vs 1, respectively, p<0.01.

Weight gain per week between second and third trimester was highest in HIV negative women vs DTG vs EFV: 0.3 vs 0.2 vs 0.1 kg/week respectively, p<0.01. And duration of breastfeeding was longest: 35.7 vs 19.0 vs 22.6 weeks respectively, p<0.01.

There were no differences in income, gestational diabetes, gestational age at delivery, or BMI at 4 weeks postpartum across groups.

Among women with HIV, no differences in CD4 or log viral load at enrolment were seen between the DTG and EFV groups. More women on EFV were receiving ART at conception: 86% vs 35.3%, p<0.01.

After adjusting for age, gestational diabetes, breastfeeding duration, and weight gain between second and third trimester, compared to HIV negative women, women receiving DTG had similar postpartum weight through 18 months but were about 5 kg heavier postpartum than women on EFV, p<0.01.

This association remained in subgroup analysis of women living with HIV after adjustment for same confounders as above plus CD4, viral load and ART at conception: DTG vs EFV (ref), coefficient 2.4, p=0.04.

C O M M E N T

Long-term follow up of DolPHIN-2 is ongoing and weight will be assessed through 2 years post-partum.

References

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CROI 2020: CURE RESEARCH

London patient is second person to be cured from allogeneic stem-cell transplant: updated results from tissue samples

Simon Collins, HIV i-Base

The second day of the virtual CROI 2020 was due to start with a press conference at 7.30 am that included details on the London Patient – now officially the second person to be cured of HIV by allogeneic haematopoietic stem cell transplantation (HSCT).

Even though the press conferences are no longer part of the virtual conference, the embargo for the presentation later today was still lifted early. This was largely because the case was also just published in the Lancet HIV. [1, 2]

The headline news story from CROI 2020 about HIV cure is important for several reasons.

Firstly, the early reports from CROI 2019 on the results of the HSCT in a London patient have reached and passed the two-year target that researchers set last year for the remission to be called a cure. [3, 4] This case is now supported by extensive tissue sampling using ultrasensitive tests that still show no evidence of active HIV infection.

Secondly, the London Patient has shared his personal experience in an interview in the New York Times yesterday, planned to coincide with the presentation at CROI 2020. [5]

This disclosure – neither easy nor straightforward – is partly a way to acknowledge and thank the many doctors, nurses and other health workers that have contributed to his care over the last eight years – and who also protected his anonymity throughout. It is partly to support Tim Brown (the Berlin Patient) who as the first person cured by similar HSCT treatment 12 years ago, has been the only public face of an HIV cure. And it is partly to give other people hope - not just for HIV but also for cancer – that such successes are possible.

For all the complexity the scientific research is perhaps the easiest data to report. After 30 months since the transplant, HIV viral load has remained undetectable using ultrasensitive tests in blood plasma and CSF (<1 copy/mL) and in semen plasma (<12 copies/mL, at 25 months) and cells (<10 copies/million cells, at 21 months). (See Table 1).

Table 1: Summary of evidence support HIV cure

Test and tissue sample	Lower limit of detection / test sensitivity	Results	Time since transplant and ATI (months)
VL in blood plasma	<1 copy/mL	Negative	30 mo
VL in CSF	<1 c/mL	Negative	25 mo
VL semen plasma	<12 c/mL	Negative	21 mo
Semen cells	<10 c/million cells	Negative	21 mo
HIV-1 DNA in peripheral CD4 memory cells		Weakly positive *	28 mo
HIV DNA in rectum, caecum, sigmoid and terminal ileum tissue (150,000 to 300,000 cells tested for each site)	<10 c/million cells	Negative	22 mo
Long-terminal repeat (LTR) in axilla lymph node tissue	33 c/million cells	Positive *	28 mo
Env in axilla lymph node tissue	26 c/million cells	Positive *	24 mo
Intact packaging signal and integrase in lymph node	30 c/million cells	Negative	24 mo
Proviral DNA (IPDA) in axilla tissue	<0·5 intact proviral DNA c/million	Negative	27 mo
Antibody responses	western blot	Negative (low level positive in Env but persistent loss of bands *	27 mo

* Remnants of HIV-1 sequences were present at levels low enough to be false-positive, and in tissue samples are unlikely to be capable of producing virus and are regarded as so-called fossil virus.

HIV DNA by droplet digital PCR was negative in rectum caecum sigmoid and terminal ileum tissue. Lymph node tissue from the axilla was positive for LTR and Env at around 30 copies/million cells but negative for packaging signal and integrase. These remnants of HIV-1 sequences, also reported for the Berlin Patient, were present at levels low enough to be false-positive or may have survived HSCT but are unlikely to be replicant competent and are regarded as so-called fossil virus.

The intact proviral DNA assay (IPDA) was negative.

Plasma HIV antibodies have remained undetectable by western blot except low level Env reactivity. Donor chimerism has been maintained at 99% in T cells.

The CD4 count, CD4% and CD4:CD8 ratio at 28 months post-transplant were 430 cells/mm^3, 23·5% and 0.86 which are close to pretransplant levels.

There have been no further episodes of graft versus host disease (GvHD) since gut GvHD at 2 months post-transplant, and donor chimerism has also been maintained at 99% in peripheral CD4 T cells.

The researchers also undertook mathematical modelling to firstly simulate the expected distribution of rebound times as a function of reservoir size for latent and active HIV in someone off-ART and secondly to interpret the outcomes from the London Patient. Results were adjusted for the reduced CD4 cell pool.

This was to look at the likelihood of a rebound sometime in the future (compared to lifetime remission) based on 29 months without viral rebound and no viral outgrowth seen in 24 million CD4 cells at 18 months

The models estimates that with 50% and 80% chimerism, the likelihood of full remission is 87% and 98%. For 90% or higher reduction in susceptible cells, that cure is almost certain.

The authors concluded that this represents HIV cure and that this is not affected by low level defective HIV genomes in lymphoid tissue.

The interview in the NYT also included many remarkable personal aspects of this case.[6, 7]

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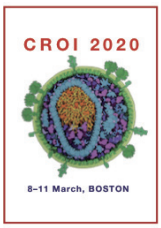
London patient tells his story as second person cured of HIV

Simon Collins, HIV i-Base

Early this morning, on Monday 9 March 2020, the second person to be cured of HIV allowed his story to be included in an interview in the New York Times. [1]



The article is available online (after free registration) and is focused on some of the personal responses from undergoing such difficult and rare treatments. It is also published ahead of a medical update on this case to be presented (virtually) at CROI 2020 tomorrow. [2]

This decision to go public requires a lot of courage - and it is clear from the interview that Adam – who still wants to be known as the London Patient – has been thinking about this for a long time. It is also clear that he is driven by the positive impact that his story can have for people who are undergoing cancer treatment as much as those of us who are HIV positive. It is also the outcome from approximately eight years of fighting cancer, after which, many people might happily retire with their health to lead a private life.

The article is mainly focused on the diagnosis in 2011 with stage 4 lymphoma and how this failed to respond to successive treatments over the next four years. Then, in 2015, after being told that there were no other treatment options, it was Adam, with help from a friend, who contacted the Chelsea and Westminster Hospital after learning online about their experience for treating HIV positive people with cancer.

The haematopoietic stem cell transplantation (HSCT) that then followed was complicated and difficult. This involves first having conditioning treatment to wipe his own natural immune system making someone very vulnerable to many serious infections. The stem cells are a type of bone cell transplant, but from a donor that has an immune system that is resistant to the most common type of HIV. After the transplant the body has to survive a battle against the new cells. This is called graft vs host (GvH) disease and often needs hospitalisation because the symptoms are so difficult.

Two years after the transplant, with full consent and under supervision of his medical team, Adam was able to stop his HIV medication, in order to see whether or not his HIV drugs were still needed.

An important caution, as the article explains, is that HSCT is not a cure for most people living with HIV. For all the news that the case will rightly generate, the ability to repeat this scientific breakthrough might be an outcome for only a few people. This procedure is a secondary outcome for advanced cancer that hasn't responded to multiple treatments with chemotherapy.

Last year, tentative details of the London Patient were presented at CROI (and later published in Nature), with a conclusion that longer follow-up was needed for the remission to be classified as a cure. [3, 4, 5] A third case with less follow-up time off-ART - referred to as the Dusseldorf Patient – was also reported at the same conference. [6]

Although this is now the second case of an HIV cure using HSCT, the first case was reported in 2008 (initially as the Berlin Patient and later as Timothy Ray Brown). [7, 8, 9]

Since then, none of previous attempts to repeat the HSCT in other patients were successful. The important medical differences reported last year for the London and Dusseldorf patients – and that directly help other people in a similar situation – are that these more recent cases used less intense procedures than for Timothy Brown in 2008. They therefore allow for slightly easier approaches for future cases and the lessons will crossover both for cancer and HIV care.

C O M M E N T

Having followed this case from the first tentative presentation of the results at a BHIVA meeting in 2018 [11] to the upcoming results due to be presented at CROI 2020 tomorrow, [2] it is good to be able to report such positive news.

It is clear from the article that by deciding to use his experience as a new advocate, that Adam, the London Patient has a great chance to raise the profile of cure research and HSCT for cancer.

His spirit, resilience and determination to do this publicly are appreciated.

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TREATMENT ACCESS

Dolutegravir/lamivudine FDC recommended by NHS England

Simon Collins, HIV i-Base

On 12 March 2020 the specialised commissioning document for dolutegravir/lamivudine was published.

The was after what is alwasy a long protracted process, even with the best intentions for faster access.

Doctors should now be able to prescriber this single-pill formulation, in line with prescribing guidelines.

Reference

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DRUG INTERACTIONS

Drug-drug interactions and COVID-19

Simon Collins, HIV i-Base

The Drug-Drug Interaction (DDI) services at Liverpool University have put together a summary of likely drug interactions with experimental COVID therapies.

Remdesivir is also completed but awaiting authorisation to use proprietary data.

Continued updates will be posted when available.

Reference

http://www.covid19-druginteractions.org

FUTURE MEETINGS

Conference listing 2020

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

Please check updates with these meeting for whether

26th Annual BHIVA Conference (BHIVA 2020)

27 – 29 April 2020, Manchester

www.bhiva.org

INTEREST 2020

5 – 8 May 2020, Windhoek, Namibia

https://virology.eventsair.com/interest-2020/registration/Site/Register

21st International Workshop on Clinical Pharmacology of HIV, hepatitis, and other antiviral drugs

13 – 15 May 2020 (TBC), New York

www.virology-education.com

International Workshop on HIV Paediatrics 2020

3 – 4 July, San Francisco tbc

www.virology-education.com

Community Reclaiming the Global Response (HIV 2020)

5 – 7 July 2020, Mexico City

https://www.hiv2020.org/registration

23rd International AIDS Conference (AIDS 2020)

6 – 10 July 2010, San Francisco and Santa Barbara

www.aids2020.org

23rd International Workshop on Co-morbidities and Adverse Drug Reactions in HIV (2020)

12 – 13 September 2020, New York

https://www.intmedpress.com/comorbidities/default.cfm?itemtypeid=1&title=The%20Workshop

HIV Glasgow Congress 2020

4 – 7 October 2020

www.hivglasgow.org

HIV Research for Prevention (HIV R4P 2020)

11 – 15 October 2020, Cape Town

https://www.hivr4p.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 (March 2019)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (Jan 2018)
- Guide to HIV, pregnancy & women's health (April 2019)

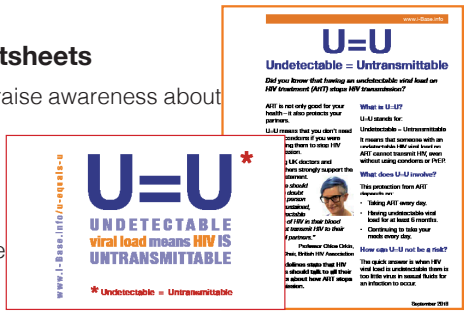
Pocket guides

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 clincs.

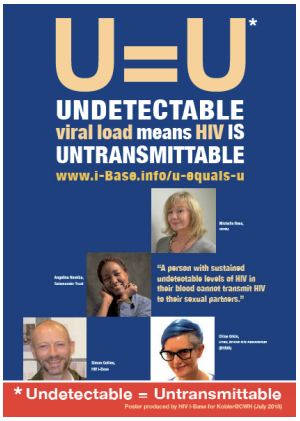
This project was developed with the Kobler Centre in London.

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 orded by email or fax.

email: subscriptions@i-base.org.uk

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

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

roy.trevelion@i-Base.org.uk

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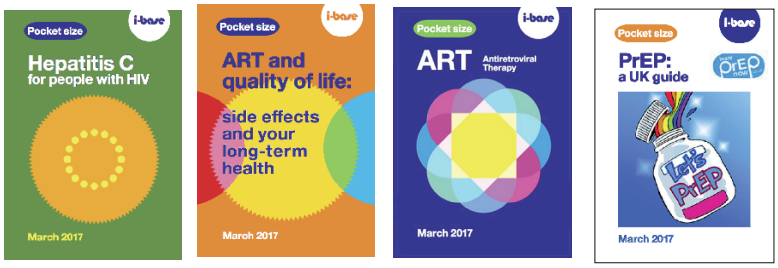

h-tb

HIV TREATMENT BULLETIN

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- **HIV Treatment Bulletin (HTB) every two months** ☐ **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**

NEW: Introduction to ART *(October 2019): 48-page A5 booklet* **quantity** _____

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

ART in pictures: HIV treatment explained *(June 2019): 32-page A4 booklet* **quantity** _____

Guide to HIV, pregnancy and women's health *(April 2019): 36-page A5 booklet* **quantity** _____

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

HIV and quality of life: 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 hepatitis C coinfection *(April 2017): 52-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

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.

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Please complete the above and return to: HIV i-Base, 107 Maltings Place,169 Tower Bridge Road, London, SE1 3LJ

(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.
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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

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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.

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