ISSN 1472-4863

HTB: vol 24 no 10/11: October/November 2023

hiv treatment bulletin (e)

Uganda and IAS 2023 reports (1 October 2023)

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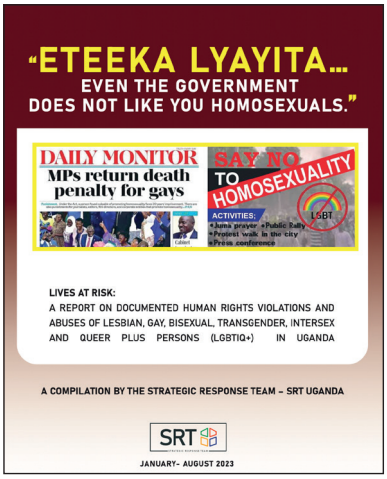


Contents continued inside...

Contents cont...

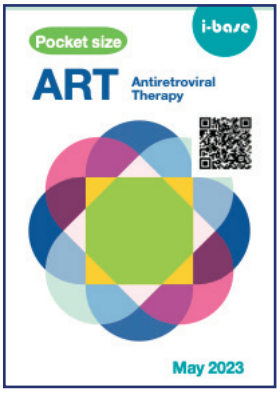
New i-Base pocket leaflets

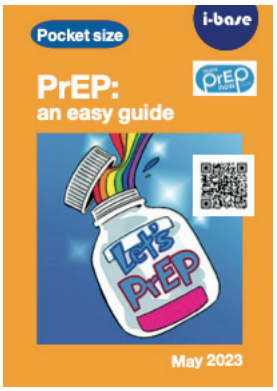
Four new pocket leaflets were recently updated and reprinted.

Each leaflet is 10 x 7 cms and they use minimal text and QR codes to summarise and link to more detailed A5 booklets.

All leaflets are free - please order online:

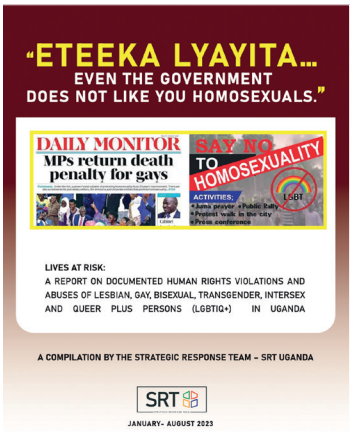
https://i-base.info/forms/order.php





EDITORIAL

We lead this HTB with a special report on the dramatic increase in human rights abuses in Uganda against LGBTQI+ communities and individuals, or anyone who supports them, as a result of the Anti-Homosexual Act (AHA) legislation earlier this year.



The impact of this new law, passed in March 2023 and slightly modified in May, is much wider than HIV or other healthcare issues, but the impact on both HIV prevention and treatment certainly justifies the numerous statements issued against the AHA, including from UNAIDS, IAS, BHIVA and others.

Even before the law was passed, HIV clinics experienced a significant decrease in people falling out of care, for fear of attending services. We reported this in the summary of Track D studies at IAS 2023 in the September issue of HTB. (https://i-base.info/htb/46249)

As international global health goals are used as a structure for financial support, including the 95:95:95 cascade targets, the threat of losing funding is one of the few ways that international pressure could overturn the AHA. It is a significant achievement that in August the World Bank suspended international loans to Uganda, largely because activist pressure made this a global political issue.

Politics and healthcare overlap with issues of migration and the right to have freedom from persecution, which by definition includes the right to claim asylum.

As background, the strategy to marginalise and persecute LGBTQI+ communities in Uganda was to deflect attention away from issue of political corruption in Uganda. Funding for this policy has also been directly linked to religious extremists based in the US.

The particularly cruel speeches recent given by the UK Home Secretary Suella Braveman MP stating that she wants to deny LGBTQI+ persecution as a factor in claiming asylum in the UK, even faced with the death penalty in their own country, makes this a healthcare issue in the UK.

The persecution in Uganda is directly linked to human rights in the UK and internationally and we need to collectively engage in protecting these rights or we risk them being steadily eroded.

The rest of HTB continues with six further reports from IAS 2023 focused on new and pipeline ARVs (lenacapavir, bNAbs and CAB/RPV injections), viral resuppression in the ADVANCE study, and on the safety of tenofovir-based oral PrEP in pregnancy, and bictegravir use in pregnancy (more data needed).

We report recent peer-reviewed papers on ART-related weight gain, resistance to dapivirine rings and changes in renal function in women using alcohol and/or cannabis.

Plus the welcome decision by the EU to approve injectable cabotegravir as PrEP.

As an admin note for the sharp-eyed reader, even though the previous HTB was September/October we have dated this new issue October/November because we compiled enough reports over the last week or so.

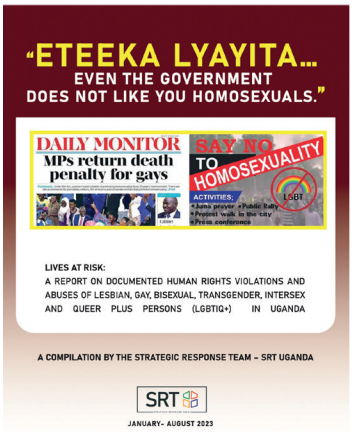
A **non-technical summary of HTB** is also now available: https://i-base.info/htb/46493

SPECIAL REPORT

Uganda report: Increase in LGBTQI+ assaults and human rights violations need urgent activist responses

Simon Collins, HIV i-Base

On 28 September 2023, Strategic Response Team (STG) in Uganda published a new report documenting 306 cases of abuse and discrimination this year when criminalisation laws were publicised and passed against LGBTQI+ people. [1]



These figures are likely to be an underestimate, as many people are too frightened to report these assaults.

The new law, the Anti Homosexuality Act, includes the death penalty for same-sex activity and 10-year prison sentences for people who support LGBTQI+ people or who do not report them.

The 48-page report details an increase in cases of people being exposed, tortured, beaten, arrested and outed and who have suffered physical, sexual and psychological violence, including evictions and banishments, blackmail, loss of employment and health service disruptions.

The report documents:

- 180 cases of evictions, displacement and banishment from villages and family homes.
- 176 cases of violating and abusing the right to freedom from inhuman, and degrading treatment or punishment.
- 159 cases of violation and abuse of the right to equality and freedom from discrimination, including 25 by the state.
- 102 cases of of mental health conditions directly linked with violations, abuse and the general climate of fear. Most of these presented with anxiety and panic attacks, suicidal ideation, and depression.
- That since 2022, many organisations that supported LGBT+ rights have been evicted and raided or closed by the police.
- That the climate of fear has disconnected people from health care, including for HIV and sexual health.

Each case is documented by notes, police bond forms, bail forms, medical forms, rulings, and judgments. Additional verification involved interviews with clients, witnesses, paralegals, community responders, and lawyers directly involved. Cases of sexual assault however were particularly difficult to assess.

The report explains: "Queer people are routinely attacked by family members, neighbours, friends and co-workers, accusing them of being a disgrace to themselves and society" and that many assaults "have been mob attacks mobilised by neighbours, family members or community members."

These cases breach human rights that should be protected under Articles 24 and 44 of the 1995 Constitution of the Republic of Uganda, Article 5 of the African Charter on Human and Peoples' Rights, Article 7 of the International Covenant on Civil and Political Rights, and the Convention Against Torture and Cruel, Inhuman or Degrading Treatment or Punishment. These rights are also stressed in Articles 1 and 5 of the Universal Declaration of Human Rights.

The report includes specific recommendations for the following individuals and organisations in Uganda and internationally.

- The Constitutional Court of Uganda.
- The President of Uganda.
- The Parliament of Uganda.
- The Uganda Police Force.
- The Uganda Law Reform Commission.
- The Uganda Human Rights Commission.
- The Equal Opportunities Commission (EOC).
- The National Bureau for NGOs (NGO Bureau).
- The Civil Society Organisations.
- The US, the EU, the UK and other donor governments.

These include a call for the impact of the law to be documented and for the law to be repealed.

COMMENT

Once established, human rights are usually difficult to take away and the decision to withdraw rights from LGBT+ people in Uganda is an urgent issue that needs to be challenged until the law is overturned.

Failure to achieve this risks other countries copying Uganda, already threatened by Kenya and Tanzania. Legislation seeking to outlaw LGBT+ people have been proposed in Kenya, but have since been thrown out by the Supreme Court in Kenya, with activists calling for trade negotiations between the US and Kenya to be a linked issue. [2, 3]

Health activists, including Uganda's Convening For Equality and HealthGAP, have been lobbying to make this a political issue in Western countries. In August, a significant outcome was achieved when the World Bank put any current loans to Uganda on hold. [4]

The Supreme Court in Mauritius also recently declared that discrimination against LGBT+ people is unconstitutional. [5]

In the UK however, a recent speech by Home Secretary Suella Braverman MP when visiting the US, supported the discrimination in Uganda by saying that these abuses against LGBT+ people are not sufficiently serious to enable international migration. Braverman's parents emigrated to the UK from Kenya and Mauritius. [6]

BASHH has issued a statement in response to the speeches. [7]

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CONFERENCE REPORTS

12th IAS Conference on HIV Science (IAS 2023)

23 – 26 July 2023, Brisbane, Australia

Introduction

Simon Collins, HIV i-Base

This issue of HTB includes further reports from IAS 2023 was held in Brisbane, Australia, and as a hybrid conference.

The meeting had a strong programme that included latest scientific progress in HIV treatment.

The open access programme links to abstracts online and includes rapporteur summaries. It doesn't currently link to any webcasts, and satellite and plenary sessions don't include abstracts for these talks:

https://programme.ias2023.org

Abstracts are also available from a separate URL:

https://programme.ias2023.org/Abstract/Index

Abstract book (PDF):

https://www.iasociety.org/sites/default/files/IAS2023/abstract-book/IAS_2023__Abstracts.pdf

The following reports are included in this issue of HTB.

- Lenacapavir studies at IAS: weekly oral dosing and baseline sensitivity in non-clade B settings
- LA-CAB/RPV as first-line ART and implementation studies
- bNAbs for prevention and cure: antiviral and vaccine-like responses
- High rates of re-suppression with dolutegravir in the ADVANCE study
- Bictegravir use in pregnancy: more data needed
- In-utero tenofovir-based PrEP has no effect on children's bone mineral density

IAS 2023: ANTIRETROVIRALS

Lenacapavir studies at IAS: weekly oral dosing and baseline sensitivity in non-clade B settings

Kirk Taylor, HIV i-Base

IAS 2023 included one oral abstract, two posters and four e-posters on lenacapavir (LEN).

- Oral bridging with shown to maintain virologic control during interruption of SC-LEN. [1]
- Pharmacokinetic (PK) data show that plasma LEN levels remain within the therapeutic range during oral bridging on CARISEL and CAPELLA. [2]
- Recommendations on catch-up dosing for people who miss oral LEN loading doses and the prevalence of resistance associated mutations (RAMs) in Uganda were also presented. [3-4]

Weekly oral lenacapavir effectively covers delated access to long-acting injections

Jean-Michel Molina rom Saint Louis Hospital, Paris, delivered an oral presentation on weekly oral LEN bridging for people who miss a Q6M dose of SC-LEN. [1]

LEN (300mg) has a plasma half-life of 10 to 12 days allowing for weekly oral dosing. Between December 2021 and May 2022 the FDA imposed a clinical hold on SC-LEN formulations due to a concern regarding glass vials. Participants on the CAPELLA and CALIBRATE studies were switched to oral LEN to bridge therapy during the hold period. Oral bridging began within two weeks of the next scheduled injection and follow up occurred at 10 to 12 week intervals.

CAPELLA enrolled participants (n=85) who were female (21%), Asian (27%), Black (29%), white (45%) with a mean BMI of 26.7 kg/m^2 (SD ±5.82) and mean age was 50 years (SD ±13.2). Participants enrolled on CALIBRATE (n=82) were female (7%), Black (45%), white (50%), mean BMI was 28 (SD ±7), and mean age was 34 years (SD ±9).

At the onset of oral bridging, virological suppression rates were 100% in CALIBRATE and 81% in CAPELLA. Across both studies, oral bridging was not given to participants due to discontinuation (n=4) or oral bridging was not required due to their injection schedule (n=6). Median duration of oral dosing was 18 weeks.

Viral load remained stable for participants that were virologically suppressed at baseline. In addition, 3/11participants with viraemia at baseline achieved viral suppression by week 10.

One participant from CAPELLA who missed two non-consecutive oral doses had increases in viral load at weeks 10 and 20 with the LEN-associated mutation (RAM; N74D) but who resuppressed when switched back to SC-Len.

The safety profile of the two formulation was comparable. The one death of unknown cause during oral dosing in CAPELLA was not judged related to the study drug.

LEN PK during this bridging study was presented as a poster. [2]

Mean plasma LEN concentrations in CAPELLA increased from 46.1 ng/mL (%CV 56.3) to 74.8 (%CV 116.1) following 20 weeks of oral LEN. Concentrations returned to baseline following transition back to SC-LEN (Q6M) and the lower 90% CI values did not fall below the therapeutic threshold (15.5 ng/mL).

In CALIBRATE, baseline plasma concentrations were lower at 27.8 ng/ml (%CV 47.4) but remained 4-fold above the protein-ajusted inhibitory quotient (IQ4).

Modelling pharmacokinetics following missed SC-LEN doses

Another poster at IAS 2023 included population PK (Pop-PK) study to guide recommendations for missed doses of during the initial oral LEN loading dose period. [3]

The model recommended taking the missed oral LEN (600 mg) dose as soon as possible, with a second 300 mg dose on day 8 (<6 days since missed dose) or day 15 (≥6 days since missed dose).

If the day 8 dose is missed, then a 300 mg dose should be taken as soon as possible (<6 days since missed dose) or on day 15 (≥6 days since missed dose), followed by the planned SC-LEN on day 15.

The long half-life of LEN gives a wide dosing window and a degree of missed dose forgiveness.

Pre-existing LEN mutations in a non-clade B Ugandan cohort

One of the e-posters looked at the prevalence of pre-existing natural polymorphism associated with reduced sensitivity to LEN in the Uganda AIDS rural treatment outcomes (UARTO) cohort (n=546) with largely A1, C, D, and intersubtype recombinant HIV-1. [4]

Lenacapavir-associated resistance mutations were taken from the 2022 IAS-USA drug resistance database including L56I, M66I, Q67H, K70N/S/R, N74D/S, A105T and T107N. Additional mutations reported in other studies were also included: Q67K/N, K70H, N74H, A105S, and T107A/C.

Median pre-treatment viral load and CD4 count were 5.2 log copies/mL (IQR: 3.7 to 5.7) and 127 cells/mm^3 (IQR: 64 to 196), respectively.

Only 6/546 participants had pre-ART polymorphisms associated with reduced sensitivity to LEN (1%; 95% CI: 0.4 to 2.4%)/ these were T107A (1%, 7/546) and K70R (0.2%, 1/546).

The poster concluded that these data support LEN being used in regions where non-B are dominant.

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Unless stated otherwise, all references are to the Programme and Abstracts of the 12th IAS conference (IAS 2023), 23–26 July 2023, Brisbane, Australia.

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LA-CAB/RPV as first-line ART and implementation studies

Kirk Taylor, HIV i-Base

IAS 2023 included an oral abstract, four posters and seven e-posters on the injectable combination of cabotegravir/rilpivirine (LA-CAB/RPV). [1]

- Most notably, Monica Gandhi from the University of California San Francisco presented a pilot study using LA-CAB/RPV off-label as first-line ART. [1]

  The current indication for LA-CAB/RPV is as a switch combination in people who have maintained undetectable viral load of six months on oral ART, despite the potential for long-acting formulations to have specific advantages for people who have difficulty adhering to oral meds..

- Week 48 data from the JABS implementation study shows high levels of virologic suppression for Australian participants who received LA-CAB/RPV. [2]

- Data from other implementation studies high levels of participant satisfaction and discussed barriers to implementation. [3, 4, 5]

LA-CAB/RPV as first-line ART to enable easier adherence

Monica Gandhi presented an oral symposium presentation on the implementation of long-acting ART for people in hard-to-reach populations. [1]

The original registrational trials of LA-CAB/RPV (FLAIR, ATLAS and ATLAS-2M) evaluated efficacy and safety in treatment-naive and -experienced participants. These studies all reported high levels of virologic suppression (>80%), but inclusion criteria required baseline virologic suppression on oral ART. Virologic failure rates across these trials was low (1.4%) and linked to INSTI and/or NNRTI resistance associated mutations (RAMs). This has widespread implications for alternative therapy options for these participants.

However, LA-CAB/RPV has specific advantages over daily oral meds for populations where adherence is low.

This demonstration study was run at Ward 86 at San Francisco General Hospital. The majority of participants were on public health insurance (96%), had high rates of mental ill-health complication (45%), recreational drug ise (35%) and/or had an insecure housing (34%). Inclusion criteria did not require an undetectable viral load, but participants needed to be willing to attend monthly clinics.

Results were available for the first 133/194 participants enrolled into the study. Baseline demographics included women (12%), Black (16%), Latinx (38%), median age 45 years (range: 38 to 45) and 43% of participants had detectable viral load. Participants with virologic suppression at baseline (n=76) maintained undetectable viral load through a median period of 26 weeks (range 2 to 42 weeks).

LA-CAB/RPV injections were given on time for 74% of participants.

Mean baseline viral load was 4.21 log copies/mL (SD ± 1.3) for 57 participants. Viral load decreased after a median of 33 days, with virologic suppression anticipated within 26 weeks. Early virologic failure (n=2) included drug resistance to INSTI and NNRTIs.

An interim analysis reported virologic failure in 1.5% of participants, comparable to the Phase 3 switch studies.

The protocol has since been updated to exclude people with baseline RAMs.

Other implementation studies

Other studies (OPERA, CARLOS and CARISEL) had low numbers of participants with baseline viraemia.

In OPERA 21/183 participants had baseline viremia with 91% (n=19) achieving virologic suppression. Both CARLOS and CARISEL reported virologic suppression for >87% participants at months 6 and 12, respectively. Across both studies there were four confirmed virologic failures.

Practical and clinical considerations for implementation of LA-CAB/RPV include a small number of participants who develop virological failure despite perfect adherence to the injection schedule. The risk factors for viral failure in these cases include having two or more of the following:

- Baseline resistance to RPV.
- Low trough levels of rilpivirine.
- HIV-1 subtype A6/A1.
- BMI ≥25 kg/m^2.

People with high BMI are recommended to use longer 2-inch needles for the injections, based on pharmacokinetic data showing higher CAB Cmin and drug penetration to target tissues. A study at IAS 2022 last year reported on injecting LA-CAB/RPV into the thigh rather than buttocks, providing alternative injection sites and reducing the chance of injection fatigue. [2]

HPTN 077 trial data show that LA-CAB has a longer tail in women (median: 66.3 weeks, range: 17.7 to 182 weeks) than men (median: 42.7 weeks, range: 20.4 to 134 weeks), suggesting there may be more forgiveness for delayed doses in women.

An open-label single centre implementation study of LA-CAB/RPV conducted in Perth called JABS, included 48-week results in an e-poster. [3]

Baseline characteristics of the 60 participants included: women (15%), mean age 41 years (range: 18 to 63) and mean BMI 26.2kg/m^2 (range: 18.8 to 39.9).

The majority of injections were administered within the target window period (97%) and there were no confirmed virologic failures. Week 48 data included 98% viral suppression with no adverse events relating to the drug formulation. Low-grade injection site reactions were common (30%), and participants reported high levels of treatment satisfaction.

The ILANA (implementing long-acting novel antiretrovirals) implementation study explored the feasibility and acceptability of LA-CAB/RPV in the UK. [4]

Participants received their first dose in clinic and opted to receive future doses in clinic or at a community-based settings (at home or at community-based HIV support NGO). Healthcare professionals (HCP) were interviewed on barriers and facilitators to LA-CAB/RPV implementation at sites in London (n=8), Brighton (n=3) and Liverpool (n=2).

HCP reported concerns relating to clinic attendance, potential for drug resistance and effective dosing. Meanwhile, people living with HIV were concerned that they may be forced to switch to injectables, potential for RAMs and side-effects. Other barriers included increased visit frequency, longer appointments and more complex prescribing and medication stock levels.

LA-CAB/RPV was preferred compared to oral ART because it increased treatment privacy and reduced pill fatigue. Ongoing communication between people living with HIV and HCPs built confidence and trust in treatment. HCP capacity is a major implementation challenge and additional funding is required to support service provision.

Updates from the phase 3b SOLAR study

A poster included data on Inflammatory markers in the phase 3b SOLAR study. [5]

Participants were randomised (2:1) to either LA-CAB/RPV (n=454, Q2M) or daily oral BIC/FTC/TAF (n=227, QD).

Baseline characteristics were matched between groups and participants were women (17%), white (69%), Black (21%) or Asian (5%) and median age was 37 years (range: 18 to 74). Median BMI was 26.0 kg/m^2 (IQR: 23.2 to 29.6) and 22% of participants had BMI ≥30 kg/m^2 at baseline.

This study measured inflammatory markers (IL-6, CRP, D-dimer, CD4/8 ratio, sCD14 and sCD143) at baseline and a year later, with no changes or differences between groups, likely reflecting high levels of virologic suppression.

Another poster presented participant reported outcomes in SOLAR. [5]

Overall, 402/447 participants who switched to LA-CAB/RPV reported a preference for injectable (Q2M) vs oral (QD) therapy. The primary reason for LA therapy preference was not needing to remember to take their ART (85%). Flexibility, convenience and overall treatment satisfaction increased from baseline. Injection tolerance increased across one year and participants reported improved wellbeing benefits, including removal of disclosure fear and adherence anxiety.

C O M M E N T

Much of the Q&A discussion related to practical considerations for implementation of injectable ART. Some of these included the limited options to giving injections out of the clinic due to cold chain needed for rilpivirine-LA. This will not be the case if cabotegravir-LA is used with alternative long-acting drugs, such as bNAbs ir lenacapavir.

We also heard that cabotegravir had been used off-label with lenacapavir in some individuals but that this combination could only be formally studied outside the US.

Although the discussion included concerns in people broadly defined hard-to-reach, phone calls and messages to remind people about visits achieved very high levels of adherence. For many participants. this was the first time that they had experienced an undetectable viral load, and this also motivated them to return for subsequent visits.

There might also be a potential for therapeutic drug monitoring to reduce the chance of vrial rebound. There is high interpatient variability of RPV levels and CAB point of care tests are in development. The PK CAB tail is longer for women compared to men and early data (from PrEP studies) might support quarterly injections.

Using longer (2-inch) needles was reported to be effective in people with higher BMI, but so far this is limited to up to 40 kg/m2.

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bNAbs for prevention and cure using antiviral and vaccine-like effects

Kirk Taylor and Simon Collins, HIV i-Base

IAS 2023 included many presentations that reviewed the different ways that broadly neutralising antibodies (bNAbs) are being used in prevention and treatment studies, many of which are now available as webcasts.

These made up for the few clinical studies.

Duration of antiviral effect of 3BNC117 and 10-1074

IAS 2023 included a PK study that modelled the maximum time that a single dose of two broadly neutralising antibodies (bNAbs) would be expected to have antiviral activity. [1]

This is relevant for cure-related research such as the RIO study which involves interrupting ART to see how long viral load remains suppressed due to these bNAbs. [2]

The bNAbs 3BNC117 (TAB; teropavimab) and 10-1074 (ZAB; zinlirvimab) bind to distinct regions of the HIV envelope. bNAb infusion leads to rapid reduction of viral load and delay of viral rebound for people with an undetectable viral load.

A pharmacokinetic (PK) model was generated with data points (n=265) from six efficacy studies conducted in people living with HIV and three PK studies. Estimated half-lives were longer in people who had undetectable vs detectable viral load for both 3BNC117 (62 vs 46 days) and 10-1074 (79 vs 55 days).

The poster concluded that these data suggest that a 48-week washout period after bNAb infusion is required to evaluate their efficacy in HIV cure studies.

Despite this modelling, cases have been reported where viral suppression is maintained for longer than a year, and after bNAb concentrations are no longer detected or active, suggesting that in addition to antiviral properties, bNAbs might induce through the FC domains a vaccine-like effect. [3]

Vaccine-like properties of bNAbs

The evidence for a vaccine effect, both anti-viral and anti-tumour, was discussed in more detail by Carey Hwang in a satellite meeting on the development of bNAbs for prevention and cure, organised by IAS and available as a webcast. [4, 5]

bNabs for prevention, vaccine and cure

Another IAS satellite, organised with IAVI, looked at the potential for bNAbs used as post-natal prophylaxis for infants. [6]

In the main conference programme, Wilton Williams and Katharine Bar reviewed bNAbs research for an HIV vaccine and cure, respectively, and although the slides are available online, these talks do not seem to be webcast. [7, 8]

IAS 2023 also included an oral presentation and e-poster on bNAb studies conducted in non-human primates and methods for bNAb production. [9, 10]

C O M M E N T

3BNC117 and 10-1074 were both developed by Michel Nussenzweig and colleagues at Rockefeller University and were licensed to Gilead Sciences in January 2020. [11]

The RIO study is still currently enrolling in the UK. [2]

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IAS 2023: TREATMENT STRATEGIES

High rates of re-suppression with dolutegravir in the ADVANCE study

Polly Clayden, HIV i-Base

With enhanced adherence counselling, 95% of people re-suppressed on dolutegravir-based ART after viral rebound to over 1000 copies/mL. These findings from the ADVANCE study were presented at IAS 2023.

WHO guidelines currently recommend switching NNRTI-based ART for people with sustained viral load above 1000 copies/mL.

For people receiving dolutegravir (DTG)-based treatment, the alternative recommendation is to provide enhanced adherence counselling and then repeat viral load testing after three months.

The study tested this approach by comparing rates of viraemia and re-suppression in the ADVANCE trial of first-line ART in South Africa.

In ADVANCE, 1053 treatment-naive people were randomised to tenofovir alafenamide (TAF)/emtricitabine (FTC)/DTG, tenofovir disoproxil fumarate (TDF)/FTC/DTG or TDF/FTC/efavirenz (EFV) for 192-weeks. This analysis combined the two DTG arms.

Viral load was tested at four weeks, 12 weeks, then every 12 weeks to week 96, and after that every six months up to week 192. Presenting author Andrew Hill noted that this was probably a lot more than in a standard African treatment programme.

This study used the following definitions to describe viral load values:

- Viral suppression – viral load less than 50 copies/mL
- Virologic failure (or rebound) – one viral load result of 1000 copies/mL or more at least 24 weeks after randomisation
- Re-suppression – one viral load result less than 50 copies/mL in people with virologic failure who previously achieved suppression (only the first incidence of virologic failure per person is considered)

The analysis used Kaplan-Meier methods to look at time to viral suppression, virologic failure and re-suppression.

This revealed that time to suppression was significantly shorter in the combined DTG arms (4 weeks) compared to the EFV arm (12 weeks). And time to re-suppression was also significantly shorter for DTG (12 weeks) than EFV (26 weeks). (Both $p<0.001$).

The proportion of participants with virologic failure was similar across arms: combined DTG 12% vs EFV 9% ($p=0.343$).

Week 24 re-suppression rate was: 88% (95% CI 79 to 95) for DTG vs 46% (95% CI 25 to 72) for EFV. Week 48 rate was respectively: 95% (95% CI 87 to 99) vs 66% (95% CI 40 to 90).

Fewer people stayed on EFV after viral rebound though and a proportion of these switched to a protease inhibitor – Dr Hill explained in questions after the presentation.

There was no integrase inhibitor resistance observed in ADVANCE, nor in a meta-analysis of first-line studies that the investigators performed to compare to this study. When they looked at second-line studies, a small proportion of people developed resistance but the outcomes were unknown.

Limitations of the study include a significant number of people lost to follow up with viraemia and not everyone with viral load greater than 1000 copies/mL was genotyped.

COMMENT

These results are important and have practical implications for people experiencing viral rebound with DTG and for ART programmes. Already, the new South African guidelines recommend that people only switch from DTG if resistance testing shows integrase inhibitor mutations. This is an excellent approach but will clearly rely on access to the tests. This is variable

in South Africa and rare in some African settings.

Dr Hill also raised the question of how much adherence counselling and repeated viraemia is needed before it becomes better for someone to switch?

Because phase 3 industry studies switch people with viral rebound fairly rapidly (usually two consecutive viral load tests 400 copies/mL), they don't look at the potential for re-suppression, and this aspect of an investigator-led study in a close to real-life setting (that likely will simplify treatment delivery) is also worth highlighting.

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IAS 2023: PREGNANCY

Bictegravir use in pregnancy: more data needed

Polly Clayden, HIV i-Base

Despite comparatively lower exposure to bictegravir, emtricitabine and tenofovir alafenamide during pregnancy, compared with postpartum, all participants remained undetectable in a small study presented at IAS 2023. [1]

Bictegravir (BIC), emtricitabine (FTC) and tenofovir alafenamide (TAF) is available as an adult fixed-dose combination (B/F/TAF) from the originator company and is widely used in high-income countries.

But there are limited data on B/F/TAF PK, safety and efficacy in pregnancy and although these data are reassuring and suggest B/F/TAF does not need a dose adjustment, information to guide its use is still lacking.

BIC is highly protein bound and metabolised by UGT1A1 and CYP3A4. Increased activities of these enzymes, as well as alterations in protein binding and other physiological changes, have been reported in pregnancy.

Investigators from Gilead conducted a dedicated, open-label study in 33 pregnant women living with HIV. All participants had an undetectable viral load (less than 50 copies/mL) at the start of the study.

The primary objective was to evaluate steady state of BIC and confirm the dose of B/F/TAF (50/200/25 mg once-daily) in the second and third trimesters of pregnancy. The study also evaluated steady state PK of FTC and TAF and the maintenance of an undetectable viral load during the second and/or third trimesters.

Steady-state intensive plasma samples were collected over 24 hours post-dose of B/F/TAF during second and/or third trimesters of pregnancy and 6 and 12 weeks postpartum.

BIC and TAF, plasma protein binding was measured. As was tenofovir diphosphate in PBMCs. Cord blood was collected at delivery (BIC and TAF).

BIC concentrations were lower during pregnancy vs postpartum but similar within each period: second vs third trimester and 6 vs 12 weeks postpartum.

Individual Ctrough values were greater than IQ1 (0.162 ug/mL) across each of the four periods, apart from in one participant during the second trimester (who remained undetectable). Median Ctrough was 6.9- and 6 -fold of IQ1 during the second and third trimesters, respectively.

Total mean (%CV) AUCtau h*ug/mL was 62.8 (32.2), 60.2 (29.1), 135 (26.9) and 148 (28.5) in second and third trimester and week 6 and 12 postpartum, respectively. Exposure levels in pregnancy were closer to those in non-pregnant adults: mean (%CV) 102 (26.9). Mean total BIC AUCtau in the third trimester was approximately 41% lower than in non-pregnant adults.

Plasma FTC exposures were lower in pregnancy than postpartum: %GLSM ratio for total AUCtau ranged from 64.3% to 69.2%.

Plasma TAF exposures were also lower in pregnancy than postpartum: %GLSM ratio for total AUCtau ranged from 56.5% to 77.6%. When adjusted for changes in protein binding, %GLSM ratio for unbound AUCtau ranged from 83.6% to 89.3%. Trough tenofovir diphosphate levels in PBMCs were generally similar (but variable) during pregnancy and postpartum.

The investigators noted that US pregnancy guidelines state that no dose adjustment is require for TAF or FTC during pregnancy.

For BIC mean (%CV) cord blood to maternal blood plasma concentration ratio was 1.4 (35%). Median t1/2 in neonates was 43.1 hours, which is longer than that in adults (approximately 18 hours across postpartum). The investigators noted that other BIC PK parameters in neonates were not calculable or meaningful.

All adult participants (n=32) had undetectable viral load at delivery and through 18 weeks postpartum. CD4 and CD4% remained stable for adult participants throughout.

B/F/TAF was generally well-tolerated in adults and neonates (n=29). The majority of AEs were grade 1/2. There were no discontinuations due to AEs.

The investigators concluded: "Data from this study and available evidence suggest the suitability of once-daily B/F/TAF use throughout pregnancy, including the second and third trimesters, and indicate that no dose change is needed."

C O M M E N T

The "available evidence" to which this conclusion refers is one poster presentation at CROI earlier this year, from the BIC study arm of IMPAACT 2026. This is an ongoing, open-label, parallel-group, multi-centre phase 4 prospective study of antiretroviral PK in pregnant women living with HIV.

Data from the 27 mother-infant pairs in this study similarly reported lower total BIC exposure in pregnancy but all C24 concentrations were above the estimated BIC protein-adjusted EC95 value of approximately 0.162 mcg/mL and 90% of participants were virally suppressed at delivery.

Apart from this, the Antiretroviral Pregnancy Registry (APR) reports 14/324 birth defects with first trimester BIC exposure prospective cases with follow-up data through 31 January 2023: prevalence 4.3% (95% CI 2.4 to 7.1%). [3] This is slightly higher than most antiretrovirals (and the upper bound of the confidence interval is the same as ddI).

For the US perinatal guidelines, the panel uses a longstanding, systematic approach to evaluating birth defect risk for all antiretrovirals. [4]

In order to determine whether a drug has an increased risk of a rare birth defect, data from more than 2,000 periconception exposures are needed to rule out a threefold increase in risk. Data from more than 1,000 first-trimester exposures are needed to rule out a 1.5-fold increase in the risk of overall birth defects and a twofold increase in the risk of the most common classes (cardiovascular and genitourinary) of birth defects.

So the conclusion above that: "Data from this study and available evidence suggest the suitability of once-daily B/F/TAF use throughout pregnancy, including the second and third trimesters…" seems like over-interpretation of what is currently available on the safety of BIC in pregnancy.

Surely the experience with dolutegravir (and before that efavirenz) emphasised the importance of obtaining sufficient data about antiretroviral drugs in pregnancy.

Although BIC is not a priority for low- and middle-income countries, where most pregnancies in women living with HIV occur, according to Fierce Pharma in 2022 (based on sales): "If it weren't for COVID-19, Gilead Sciences' HIV triplet Biktarvy would still be the world's best-selling pharmaceutical product for an infectious disease", and " the highest level of market share any complete regimen has ever achieved in the US". [5]

So it doesn't seem unreasonable to ask why there is so little information to guide its use in pregnancy, considering B/F/TAF was approved over five years ago. [6]

And bictegravir is far from an isolated case.

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In-utero tenofovir-based PrEP has no effect on children's bone mineral density

Polly Clayden, HIV i-Base

There were no differences in bone mineral density among children of women using and not using tenofovir-based PrEP during pregnancy. These findings from the PrIMA study (an ongoing evaluation of perinatal PrEP use in Western Kenya) were presented at IAS 2023.

Previous studies found that tenofovir disoproxil fumarate (TDF)-based ART use during pregnancy among women living with HIV may be associated with lower bone mineral density (BMD) in infants.

The SMARTT study found TDF-exposed infants had lower BMD, but no differences in height or weight z-scores, compared with unexposed infants. And the Partners Demo Project found lower z-scores for length at one month but no difference at one year for exposed infants compared to unexposed, but the sample size was small.

Overall there are limited available data on bone outcomes among TDF exposed infants, no study has evaluated bone outcomes beyond infancy, or infants born to HIV-negative women taking TDF-based PrEP.

The aim of this was to evaluate the association between in-utero TDF-based oral PrEP exposure and BMD at 36 months of age.

The investigators used data from mother-child pairs enrolled in PrIMA (PrEP Implementation for Mothers in Antenatal Care). The parent study is a cluster RCT that offered TDF-based PrEP to HIV-negative pregnant women at 20 maternal and child health clinics. Participants were followed through nine months postpartum.

The study includes an extension cohort, PrIMA-X, that is evaluating longer-term infant safety outcomes. This has completed enrollment and is actively following up participants. They are followed until 60 months postpartum.

Birth and growth outcomes are obtained by trained study nurses. About 40% pregnant women in the cohort used PrEP during their pregnancy.

The investigators randomly selected a subset of singleton children aged 36 months with in-utero PrEP exposure. These children were matched (1: 2) to those without in-utero PrEP exposure by: maternal age, education level, and child sex and age.

Whole-body BMD was measured by DEXA scan at Aga Khan University Hospital in Nairobi, Kenya.

A total of 111 children were included in the analysis: 36% PrEP exposed and 64% PrEP unexposed.

The median maternal age at delivery was 28 years and the median duration of PrEP in pregnancy was 12 weeks. The majority of women started PrEP during the 2nd (52%) and 3rd (43%) trimesters.

The median age at DEXA scanning was 37 months. The median height of children at scanning was similar between those with and without PrEP exposure: 94.3 cm vs 94.0 cm, p=0.455.

The median whole-body BMD for children with and without in-utero PrEP exposure was respectively: 418.5 mg/cm2 and 423.0 mg/cm2, p=0.649. The adjusted mean difference was -21.6 mg/cm2, p=0.27.

C O M M E N T

The investigators concluded that their findings suggest that in-utero PrEP exposure may not affect BMD in early childhood – which would be very good news.

This evaluation is continuing. The next steps include quantifying PrEP exposure during pregnancy using more objective measures such as in hair and dried blood spots. The current analysis is limited by measuring PrEP exposure using self-reported PrEP use.

The study is also currently conducting DEXA scans on the same group of children at 52 months as well as their mothers at both time points.

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SIDE EFFECTS

Help needed: UK surveys on access to New-Fill for facial lipoatrophy

Simon Collins, HIV i-Base

New-Fill has been available and commissioned from the NHS for over 15 years as a way to correct for facial fat loss caused by early HIV drugs, principally stavudine (d4T) and zidovudine (AZT).

It is an injectable non-permanent filler that works by generating new collagen growth rather than being used as a traditional filler. The higher volumes used to correct HIV-related lipoatrophy requires specialist services.

Some clinics already have either have an in-house service or a commissioned referral routes to a local clinic. However, access to New-Fill still seems to vary by hospital and region. These services were put on-hold during COVID-19 which also reduced the number of people who can be treated.

A pilot project is looking to map current access to services to help understand the demand for New-Fill in order to support more stable and equitable access.

There are two short surveys - one for community and one for health professionals

Community survey via the UK-CAB:

https://www.surveymonkey.co.uk/r/LWVRK35

BHIVA use a similar short survey for doctors and HIV clinics.

https://www.surveymonkey.co.uk/r/YXBF9YD

Thank you for your help.

>10% weight gain during first two years of ART linked to double the risk of cardiometabolic disease

Kirk Taylor, HIV i-Base

A major article in Clinical Infectious Diseases reports associations between weight gain and metabolic consequences during the first two years on first-line ART. [1]

Combined data from two US cohort studies collected between 2000 and 2013 show that people who gained >10% weight were two-fold more likely to develop cardiometabolic disease.

As background, weight gain as part of the return-to-health phenomenon is a positive indicator for people who at baseline are underweight or have normal BMI. The opposite is true of those who are overweight or obese.

Two observational ACTG cohorts were used to recruit 2624 participants. Demographics included: women (19%), Black (35%), Hispanic (22%) and mean age was 38 years (SD +/– 10). BMI at baseline was classified as normal for 47%, whilst 33% were overweight and 17% were obese.

Mean weight change in year one was +3.6 kg (SD: 7.3 kg) and was greater in women than men (4.2 kg vs 3.5 kg). This trend continued at 10 years with a mean weight change of +7.1 kg (SD: 10.7 kg).

Over the first year, 22% of participants gained >10% of their baseline weight in the first year, and after ten years this increased to 40%. The paper noted that the 10-year increase was similar to the general US population (36%).

Baseline CD4 count below 200 cells/mm^3 was associated with weight gain (HR: 5.02; 95% CI: 4.23 to 5.95) and emergent obesity (HR: 2.76; 95% CI: 2.25 to 3.39). Metabolic markers shifted per kilogram of weight gain, with small increases of fasting glucose, total cholesterol and LDL, whilst HDL decreased.

Weight gain of >10% was associated with doubling the rate of incident diabetes (HR 2.01; 95% CI: 1.30 to 3.08, n=130) and metabolic syndrome (HR 2.02; 95% CI: 1.55 to 2.62, n=360) and increasing cardiometabolic events 1.5-fold (HR 1.54; 95% CI: 1.22 to 1.95, n=424).

However, cardiovascular events were not associated with weight gain (HR 0.62, 95% CI 0.22 to 1.67, n=28).

Weight loss of >5% was associated with a reduced risk of metabolic syndrome (HR 0.60, 95% CI 0.37 to 0.98).

C O M M E N T

The results were not stratified by ART use and the study design did not include matching. Data also predates both TAF and second-generation integrase inhibitors that are currently linked to weight gain.

The authors do not report an increase in cardiovascular events which is probably due to the young mea age of the cohort (38 ± 10 years). The increased signal for cardiometabolic complications suggests that CVD incidence might easily increase in the future.

An overview of weight gain and ART use by Prof Andrew Carr was included in the 2023 BHIVA conference and reported in HTB. [2]

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Altered kidney function associated with alcohol and cannabis use by women living with HIV

Kirk Taylor, HIV i-Base

The June issue of AIDS included a prospective cohort study of the effect of substance use (e.g. alcohol and cannabis) on kidney function for women living with or without HIV.

Participants were recruited from a US multicentre prospective cohort study and were living with (n=1043) or without (n=469) HIV. Median age was higher for people with HIV compared to HIV negative participants (46 years (IQR: 41 to 52) vs 42 years (IQR: 35 to 50). People living with HIV had CD4 counts ≥200 cells/mm^3 (86%), undetectable viral load (54%) and art regimens included TDF (60%).

Substance use data was collected at bi-annually and eGFR (estimated glomerular filtration rate) data calculated across a decade (2009 to 2019). Linear regression analyses were adjusted for HIV factors and kidney disease to identify associations between substance use and kidney function.

Using cannabis for up to 14 days per month decreased eGFR by 3.34 ml/min per 1.73m^2 (95% CI: -6.63 to -0.06 ml/min per 1.73m^2), compared to those that did not report cannabis use.

Having ≥7 alcoholic drinks per week increased eGFR by 5.41 ml/min per 1.73m^2 (95% CI: 2.34 to 8.48 ml/min per 1.73m^2), relative to non-drinkers.

There was no association between tobacco use and eGFR. The study did not report any differences between women living with HIV and those that were HIV negative.

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HIV PREVENTION & TRANSMISSION

EU approves cabotegravir as injectable PrEP

Simon Collins, HIV i-Base

On 19 September 2023, ViiV Healthcare issued a press release that the European Union had approved cabotegravir as HIV pre-exposure prophylaxis (PrEP).

Approval includes both the two-monthly injection and oral tablet formulations of cabotegravir. Injections are given every two months.

The indication is for use by adults and adolescents (age 12 and older), weighing at least 35 kg who are at high risk of sexual exposure to HIV.

However, the long half-life of the injections means that significant levels of cabotegravir can continue at detectable levels for more than a year. People who continue to need PrEP after using cabotegravir injections are recommended to switch to oral PrEP for the following year.

Injectable cabotegravir is produced by ViiV Healthcare and marketed under the trade name Apretude.

No details about pricing were included in the announcement.

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Early phase 1 HIV vaccine study launched in the US and South Africa

NIAID press release

On 20 September 2023, NIAID issued a press release about an early study of a potential HIV vaccine called VIR-1388. [1]

The study aims to enrol 95 people from sites in the US and South Africa with early results by the end of 2024 and an additional three years follow-up. [2]

The study will look for immune responses to the vaccine rather than whether it stops infection. It will also check for safety.

The vaccine uses a cytomegalovirus (CMV) vector, meaning a weakened version of CMV delivers the HIV vaccine to the immune system without the risk of causing disease in participants. NIAID has funded the discovery and development of the CMV vaccine vector since 2004.

This trial is sponsored by Vir and conducted through the NIAID-funded HIV Vaccine Trials Network as study HVTN 142.

HVTN 142 is taking place at six sites in the United States and four in South Africa and will enroll 95 HIV-negative participants. Participants will be randomised to one of four study arms. Three arms will each receive a different dose of the vaccine, and one will receive a placebo.

To reduce any risk from CMV, participants need to already be living CMV, without symptoms.

Further information is online. [2]

C O M M E N T

It is notable that former NIAID-head Anthony Fauci recently commented in an interview with Jon Cohen in Science, that compared to an annual ARV which 'we will have shortly', a CMV-based vaccine with low efficacy 'would not stand a chance'. [3]

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Mutations associated with resistance to dapivirine vaginal ring: reported in 7/38 women seroconverting in the open-label HOPE study

Kirk Taylor, HIV i-Base

A brief report in JAIDS highlights mutations associated with dapivirine (DPV) resistance in seven women who seroconverted during the open-label MTN-025/HOPE trial. [1]

These mutations decreased susceptibility to DPV by three-fold for 6/7 women.

During the open-label study, 38/1456 participants seroconverted and 7/38 women (18%) developed the following DPV-associated resistance mutations: A98G, K103N, V106M, E138A and V179D.

DPV resistance did not increase in people who continued to use DPV rings for more than three months after their HIV diagnosis.

Two DPV-associated mutations (K103N and V179I) were also reported in one woman who did not use the DPV ring, reducing DPV-susceptibility by 9-fold.

As these are either commonly associated with first-line NNRTIs (efavirenz and nevirapine) this was reported

as likely transmission of drug-resistant HIV, rather than recently having developed in relation to DPV use for prevention. [2]

It is unclear how many of the other cases might also have been due to transmitted drug resistance.

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C O M M E N T

These are important findings, given the low overall efficacy of DPV rings, usually due to low adherence.

Retention after four months dropped to only around 60% and was similar to oral PrEP, in a study from Zimbabwe, reported at IAS 2023. [3]

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3. Munjoma M et al. Dapivirine vaginal ring (DPV-R): An acceptable and feasible HIV prevention option. Evidence from Zimbabwe. IAS 2023, oral abstract OAD04023.
   https://programme.ias2023.org/Abstract/Abstract/?abstractid=4452

Introducing the seventh edition of CHAI's HIV Mid-Year Market Memo, a brief covering the latest trends in the HIV space in low- and middle-income countries since the publication of CHAI's annual HIV Market Report in December 2022.

Download the Report

MEETINGS & WORKSHOPS 2023/4

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

Some meetings are in person, some are virtual and others offer both options.

Academic Medical Education (AME) meetings and workshops

Several AME workshops (previously Virology Education) are highlighted below but 35 meetings are planned each year. Many virtual meetings include free registrations for health workers, researchers and community.

https://academicmedicaleducation.com (meetings listings)

2023

19th European AIDS Conference (EACS 2023)

18 – 21 October 2023, Warsaw, Poland

www.eacsociety.org

14th International Workshop on HIV & Aging HIV & Aging 2023

26-27 October 2023, Washington DC, USA and hybrid

https://academicmedicaleducation.com/

6th Southern African HIV Clinicians Society Conference (SAHCS 2023)

8 – 10 November 2023, Cape Town, South Africa

www.sahcsconference.co.za

BHIVA Autumn Conference 2023

Friday 24 November 2023

155 Bishopsgate, Liverpool Street, London EC2M 3YD

www.bhiva.org

PrEP Awareness week: campaign

27th November - 3rd December 2022, London, UK

https://www.getonprep.co.uk/

2024

CROI 2024

3 – 6 Mach 2024, Denver, Colorado

https://www.croiconference.org

5th HIV Research for Prevention Conference (R4P 2024)

6 – 10 October 2024, Lima, Peru, and virtual.

www.iasociety.org/conferences/HIVR4P2024

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.

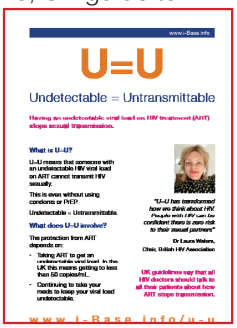
http://www.i-base.info/guides

- Introduction to ART (May 2022)
- HIV & quality of life: side effects & long-term health (Sept 2016)
- Guide to PrEP in the UK (February 2022)
- HIV testing and risks of sexual transmission (June 2021)
- Guide to changing treatment and drug resistance (August 2021)
- Guide to HIV, pregnancy & women's health (April 2019)

Pocket guides

A series of pocket-size concertina folding leaflets that are 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 has 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 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 email: subscriptions@i-Base.org.uk

h-tb

HIV TREATMENT BULLETIN

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

http://www.i-Base.info

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

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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.

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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**

Introduction to ART: *44-page A5 booklet* **quantity** _____

UK Guide To PrEP: *24-page A5 booklet* **quantity** _____

ART in pictures: HIV treatment explained: *32-page A4 booklet* **quantity** _____

Guide to changing treatment: *8-page A5 leaflet* **quantity** _____

Guide to side effects and quality of life: *8-page A5 leaflet* **quantity** _____

Guide to HIV testing and risks of sexual transmission *52-page A5 booklet* **quantity** _____

- **Other resources**

U=U resources:

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

HIV treatment passports - Booklets to record your HIV 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