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hiv treatment bulletin (e)

IAS 2023: further reports (1 September 2023)

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Published by HIV i-Base

Contents cont...

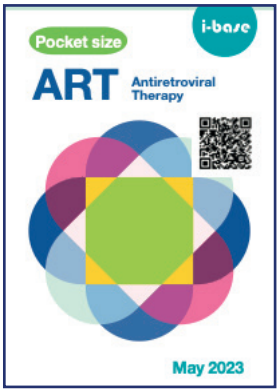
New i-Base pocket leaflets

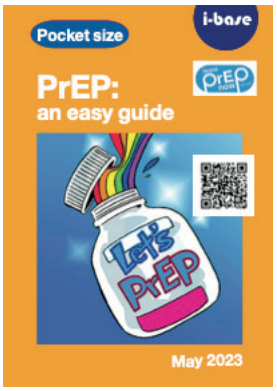
Four new pocket leaflets were recently updated and reprinted.

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

This issue of HTB continues our reports from the 12th IAS conference held in Brisbane in July, covering more than 65 presentations.

The CHAPAS-4 study provided important results to support better second-line ART options for children and we include comments about practical issues related to treatment access.

We also report on the use of semaglutide and other GLP-1 agonists in people living with HIV from a poster that has small numbers but reports significant weight loss when only using the lower dose used to manage diabetes. Again, we include comments that discuss the lack of data on this drug class as part of HIV care.

We also include three review articles based on the rapporteur summaries for basic science, prevention and social science – conference Tracks A, C and D.

Even though the primary focus of HTB is clinical science (Track B, reported last month) the conference included important breakthrough science in these other areas.

Track A includes important advances in cure-related research and Track D includes the difficult and disturbing legal changes in Uganda threatening LGBT people, and anyone who supports them.

The rest of HTB includes five short reports on recent peer-reviewed papers that cover immune inflammation, cannabis use, mpox, cryptococcus and timing of ART, and CSF complications.

CONFERENCE REPORTS

12th IAS Conference on HIV Science (IAS 2023)

23 – 26 July 2023, Brisbane, Australia

Introduction

This issue 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 following reports are included in this issue of HTB.

- Update to navigate the programme and online access
- CHAPAS-4 supports better second-line options for children
- Metabolic and weight changes using GLP-1 agonists in people living with HIV: need for more data
- IAS 2023 rapporteur summaries: tracks A, C and D
- IAS 2023: Rapporteur summaries: track A basic science
- IAS 2023: Rapporteur summaries: track C prevention
- IAS 2023: Rapporteur summaries: track D social science

IAS 2023: Update to navigate the programme and online access

Simon Collins, HIV i-Base

The abstract database should be open access to non-delegates shortly after the conference finishes, but the full programme, including webcasts and pdf posters, is still restricted.

The open access programme does link 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

There is also an electronic abstract book (PDF):

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

For registered delegates and IAS members, access to webcasts seems to be linked using this URL:

https://conference.ias2023.org/programme-live-1

This brings another version of the programme, selected by each day, with the window opened for each session, includes a 'watch now' link.

Open access to all conference material, including webcasts and posters is usually made available within four weeks to all IAS members and within eight weeks for everyone else.

IAS 2023: PAEDIIATRIC CARE

IAS 2023: CHAPAS-4 supports better second-line options for children

Polly Clayden, HIV i-Base

Tenofovir alafenamide (TAF)/emtricitabine (FTC) and dolutegravir (DTG) were virologically superior to abacavir (ABC) or zidovudine (AZT)/lamivudine (3TC) and boosted lopinavir (LPV/r) and atazanavir (ATV/r), respectively, in the second-line paediatric CHAPAS-4 trial. These findings were shown at IAS 2023.

There are limited options and formulations for second-line ART available for children living with HIV. The current LPV/r-based standard of care needs to be taken twice daily. And although TAF has been highlighted as a priority agent for children (who cannot use TDF because of renal and bone toxicity), this has been based on limited evidence.

CHAPAS-4 (Children with HIV in Africa: Pharmacokinetics and Acceptability of Simple novel second-line antiretroviral agents) looked at long-term outcomes for children switching from NNRTI-based first-line to second-line ART. The trial evaluated a number of options.

It was a 4X2 factorial open-label trial, conducted in Uganda, Zambia and Zimbabwe.

A total of 919 children and adolescents, aged 3–15 years, failing first-line ART, were randomised to TAF/FTC vs ABC or AZT/3TC (standard of care) and in turn to DTG vs DRV/r vs ATV/r vs LPV/r (standard of care). All were dosed according to WHO weight bands.

The primary endpoint was viral load <400 copies/mL at week-96. The investigators hypothesised: TAF/FTC would be non-inferior to standard of care (10% margin); ATV/r non-inferior to LPV/r (12% margin); DRV/r and DTG superior to LPV/r and ATV/r arms combined (superiority threshold p=0.03, as multiple comparisons). The primary analysis was intention-to-treat.

Participants were 54% male, median age 10 years, CD4 669 cells/mm3 and viral load 17,573 copies/mL. They had been on first-line ART for a median of 5.6 years: 53% received ABC and 47% AZT and 57% efavirenz (EFV) and 44% nevirapine (NVP0.

Over 96 weeks only 11 (1.2%) participants were lost to follow up and 98% of time was spent on the original allocated regimen; 5 (0.5%) started third-line ART.

At week-96, TAF/FTC was superior to ABC or AZT: 89.4% vs 83.3% respectively viral load <400 copies/mL (p=0.004). ATV/r was non-inferior to LPV/r (p=0.33). DTG was superior to LPV/r and ATV/r: 92% vs 82.5% respectively viral load <400 copies/mL (p<0.0001). DRV/r showed a trend to superiority to LPV/r and ATV/r (p=0.04).

These effects were similar for viral load <60 copies/mL, at weeks 48 and 144, by per-protocol analysis and by subgroup analyses (first-line NRTIs and NNRTIs, sex, weight and CD4)

CD4 count improved in all participants – there was no difference by arms.

There was no difference in adverse events (AE) between NRTIs. There were more grade 3/4 AE, mostly hyperbilirubinemia, ATV/r vs LPV/r (p<0.0001). DTG had fewer AE vs LPV/r (p=0.02).

There was increased total and LDL cholesterol in LPV/r vs other arms (p<0.001 and p=0.0002, respectively)

Improvement in growth parameters were greater with TAF and with DTG. Participants on LPV/r had the least weight gain.

There was no excess weight gain with DTG and TAF.

COMMENT

A generic formulation containing TAF for children has been on the WHO PADO priority list for some time now, so these supporting data from CHAPAS are very welcome. [2]

This needs to be either a dual formulation combined with 3TC or FTC or a fixed dose triple combination with additional DTG, to be used over WHO weight-bands 3–25 kg. These formulations would give alternatives to ABC-based regimens and

mean that all age groups have access to a tenofovir-based regimen. The triple fixed-dose combination could be used in both first- and second-line paediatric treatment and both formulations would be good news as the dual combination could also be used with DRV/r.

The ongoing UNIVERSAL project includes pharmacokinetic (PK) modelling and bioavailability studies of TAF and DTG/TAF/3TC dose ratio. [3]

A recent announcement from Gilead stated that the company (originator manufacturer of F/TAF) will provide a technology transfer of currently available data for a dispersible formulation of F/TAF and supporting PK data. [4]

PENTA (within the UNIVERSAL project) will develop the PK modelling and clinical studies, and CHAI, will be in charge of the global access strategy, in collaboration with two generic manufacturers.

Progress has also been made in developing a DRV/r fixed-dose combination (120 mg of DRV plus 20 mg of ritonavir) for second-line treatment in children with resistance to DTG, within this initiative.

These plans are aligned with the WHO Global Accelerator for Pediatric Formulation (GAP-f). [5]

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IAS 2023: HIV COMPLICATIONS

IAS 2023: Metabolic and weight changes using GLP-1 agonists in people living with HIV: need for more data

Kirk Taylor and Simon Collins, HIV i-Base

Glucagon-like peptide 1 (GLP-1) agonists have been used for more than 15 years to manage type-2 diabetes but more recently have shown a much wider range of potential indications, including to reduce weight.

However, data in people living with HIV as so far extremely limited.

A poster at IAS 2023 from the University of Cincinnati Medical Centre, compared the weight changes after using GLP-1 agonists to treat type-2 diabetes mellitus (T2DM) in adults with (n=15) vs without (n=30) HIV. [1]

This was a retrospective analysis from 2017 to 2022 that matched participants 2:1 by gender, race/ethnicity, GLP-1 RA, and dose.

Baseline demographics included mean age 57 years (±8), 13% women, 52% Black, 48% white, and mean weight 118 kg (±35) and was balanced between groups. Almost half (46%) had the GLP-1 dose titrated up during the study period. Approximately 70% used dulaglutide, with 15% using semaglutide and 15% liraglutide.

The mean changes in weight were –10.4 (±12.4) kg vs –1.7 (±8.4) kg in the HIV+ vs HIV– groups respectively (p=0.0085). The mean percentage difference in weight was –8% (±9.9%) vs –1.4% (±6.8%), (p=0.013).

Approximately 60% (9/15) vs 33% (10/30) achieved >5% loss in body weight (p=0.1158).

There were no significant differences between groups in haemoglobin A1c: –1.3% (±2.39%) vs –0.49% (±2%), respectively (p=0.2415).

COMMENTS

This study only has a small number of participants and a larger study is underway. The signal of greater changes in participants with HIV supports the suggestion in the poster that HIV might reduce GLP-1 and/or that integrase inhibitors might affect metabolic pathways directly, or indirectly due to increased appetite.

This increases the importance of understanding more about the potential use of GLP-1 agonists in management of both HIV-associated weight gain and metabolic changes from lipodystrophy.

Although general reductions in systemic fat might reduce visceral abdominal fat. intramuscular and pericardial fat but might jave less impact on localised fat deposits including lipoma, buffalo hump and gynaecomastia. There is also the potential to worsen HIV-related lipoatrophy and a concern that lean mass might be reduced. [2]

HIV was a likely exclusion criteria not only for registrational studies but also for many of the newly proposed studies.

SEMAGLUTIDE

In 2021, the US FDA approved a higher dose of semaglutide with an indication to manage weight, in combination with diet and exercise. [3]

NHS England also recently agreed to provide semaglutide for weight loss in the UK. [4]

On 8 August 2023, top-line results from the SELECT study included a 20% reduction in cardiovascular events using semaglutide compared to placebo. [5]

However, semaglutide has also been associated with a diverse range of potential off-target events that range from reducing hepatic steatosis and reducing use of alcohol and cigarettes to possible signals for increased risks of cancer and suicide. [6, 7, 8, 9]

RETATRUTIDE

Early results from other GLP-1 agonists, including retatrutide are also impressive. In June 2023, the New England Journal of Medicine published results from a randomised double-blind trial on retatrutide to treat obesity and type 2 diabetes. [10]

Retatrutide is a novel three hormone receptor agonist cocktail developed by Eli Lilly that contains a GLP-1 agonist, GIP (glucose-dependent insulinotropic polypeptide) and a glucagon receptor antagonist.

Participants receiving the highest weekly dose of retatrutide (12 mg) experienced a 24% reduction in body weight over 48 weeks. A 5% reduction in body weight was reported for participants on intermediate doses (4 or 8 mg) across the same period.

Pre-diabetic status was reversed for >70% of participants in the retatrutide group.

Participants (n=338) were female (48%), Black (8%), Asian (4%), Hispanic/Latinx (35%), mean age was 48.2 ± 12.7 years and mean BMI was 37.3 ± 5.7 kg/m^2. At baseline participants were pre-diabetic (36%), hypertensive (43%) and had dyslipidaemia (33%). Participants were randomised in this double-blind trial to receive weekly injections of retatrutide (1 mg, 4 mg, 8 mg or 12 mg) or placebo control for 48 weeks.

Weight loss was reported for all groups that received retatrutide. Weight loss at 48 weeks was dose-dependent with a 2% loss in the placebo group compared to 5% for intermediate doses (4 and 8 mg) and 24% for those in the 12 mg group. The magnitude of weight loss at week 48 for people in the 12 mg group was greater for women (28.5%) than men (21.9%).

A sub-study of 98 participants investigated the impact of 8 mg or 12 mg retatrutide on non-alcoholic fatty liver disease (NAFLD). [11]

Participants had MRI imaging of their livers and biomarkers were measured from their blood. Reduced liver fat was reported for 90% of participants at week 48 for those that received ither 8 or 12 mg of retatrutide.

Participants that received retatrutide had improved blood pressure, lipid levels and 72% of participants that had pre-diabetes at baseline returned to normoglycaemia. Gastrointestinal side effects (e.g. diarrhoea, vomiting) were common in the retatrutide group. Serious adverse events (n=15) occurred with similar frequency in the placebo and treatment groups. A single case of acute pancreatitis was reported in the retatrutide group but did not lead to discontinuation.

These studies indicate that retatrutide has potential to reduce obesity and NAFLD in people in non-diabetic and pre-diabetic individuals.

FURTHER HIV RESEARCH

Only two studies are currently registered in US clinicaltrials.gov registry that evaluate semaglutide in people living with HIV following, including one with sites in Dublin and Liverpool. [12]

There are five registered trials of retatrutide with two that will recruit participants from the UK. [13]

Most reports of GLP-1 agonists in HIV care are limited to single cases or very small cohorts, with only one study listed for lipodystrophy, despite potential benefit. [14, 15, 16, 17, 18, 19]

But it is difficult to understand the lack of data from larger observational cohorts on the use of GLP-1 agonists in people living with HIV. These drugs have been widely used to treatment diabetes for over 15 years were approved in the US for weight loss in 2021.

A recent analysis of GLP-1 pricing also suggests that generic manufacturers would be able to make oral version of semaglutide affordable in low- and middle-income countries. [20]

A recent review in JAMA reported on the extended patent life of these drugs, with each compound also being linked to numerous patents related to the delivery system. [21]

Thanks to Dr Graeme Moyle for additional comments.

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IAS 2023: Rapporteur summaries Track A - basic science

Simon Collins, HIV i-Base

The following report is based on an edited transcription of rapporteur summary at the end of the conference, with additional original content added for some of the selected studies.

This issue of HTB includes summaries from Tracks A and C as Track B was included in the previous issue.

The Track A summary was presented by Professor Lishomwa Ndhlovu, from Weill Cornell Medicine in the US who included 12 key talks or studies, covering bNAbs, vaccine developments, potential cures and cure-related research, HIV and the microbiome and measuring and targeting the viral reservoir. [1]

- bNAbs in vaccine and cure-related research
- A potential HIV cure from wild-type CCR5 donor
- Role of microbiome in HIV transmission
- Measuring antibody responses and viral escape
- Obatoclax selectively induces cells with intact but not defective HIV
- In vivo CCR5 gene-editing produces ART-free HIV control in mice
- HIV controllers
- New approaches to measuring the reservoir

bNAbs in vaccine and cure-related research

An early plenary session included two talks looking at how monoclonal antibodies (bNAbs) are being used in vaccines and cure research. [2]

In the first talk, Wilton Williams, from Duke University School of Medicine gave an overview of HIV vaccine research that aims to induce bNAbs that target HIV surface proteins to block infection.

This included new data from the exciting HTVN133 vaccine study that induced HIV-1 neutralising B cell lineages in humans, showing late, intermediate and early bNAbs that were maturing and showed progressive neutralisation capacity. [3]

The second plenary, from Katharine Bar, University of Pennsylvania, reviewed use of bNAbs in cure-related research, and as a component of combination immunotherapy, including at ART initiation and as therapeutic vaccination.

Exciting data demonstrated that on ART the neutralisation capacities of bNAbs can increase, providing optimism for vaccine approaches that could enhance autologous neutralisation antibodies. This included a phenomenal overview of this field that also gives us optimism for vaccines. [4]

A potential HIV cure from wild-type CCR5 donor

Asier Saez-Cirion from the Pateur Institute in France. presented results of another case of potential cure following autologous stem-cell transplant. [5]

This case is a man in his 50s, diagnosed in 1990, now referred to as the Geneva patient (number 34 in the ICISTEM register). He had continuous viral suppression on ART since **2005** and who was diagnosed with biphenotypic sarcoma (extramedullary myeloid tumour) in 2018. Total body irradication (4x2 Grays) + chemotherapy

This case is ICISTEM patient number 34, named as the Geneva patient, who notably had a stem cell transplantation with a wild-type CCR5 donor. This person has now shown undetectable viral load off-ART for over 20 months. This case had several regions of graft vs host disease (GVHD) across his therapy, and was also on PrEP during the time of remission.

Role of microbiome in HIV transmission

In back-to-back sessions on the same day J Victor Garcia from the University of North Carolina, presented results on the importance of the gut microbiota in HIV transmission. Working with the germ-free BLT humanised mouse model, these animals were unable to be initially infected, after both oral and rectal HIV exposure. After subsequent doses, a few animals did show viraemia, suggesting an important role for the microbiota enhancing HIV acquisition. This model can now be used to better understand the role of the microbiome in HIV pathogenesis and cure. [6]

The following day, Karsten, Eichholz from the Fred Hutchinson Cancer Center presented results showing that anti-PD-1 CAR-T cells can efficiently target SIV-infected CD4 cells in rhesus macaques. showing complete removal of these cells. There seemed to be SIV replication, the T cells suggesting potentially an impact on immune responses. An important caution however, is that a couple of the animals developed lymphoma, showing the importance of finding better ways to better develop these CAR T cells targeting the receptor in combination with others to improve the efficiency of these approaches. [7]

Also, following ART interruption, there was a higher viral rebound in CAR T treated animals and accelerated disease progression, associated with the acute depletion of CD8+ memory T cells after CAR T infusion in SIV+ animals on ART.

- 10-100 higher viral setpoint in CAR-expanded animals.
- Viral setpoint comparable to historical controls in animals treated with anti-CD8 antibodies (Okoye et al, 2021, JCI).
- Additional signs of immunodeficiency included opportunistic infections (lymphocryptovirus; LCV), LCV-associated lymphomas and loss of germinal centre Ki67+ B cells; due to absence of TFH cells.

Measuring bNAb responses and viral escape

Alejandro Balazs from the Ragon Institute, talked about using a recombinant AAV vector to deliver immunotherapy using several different bNAbs and expanded on the mechanisms for viral escape. Earlier animals studies Previously studies showed that a single shot can generate antibody expression for many years in both immunocompetent and immunocompromised animals. [8]

Human studies conducted using an NIV constructed vector using VRC603 showed the a single shot produced bNAb for over three years. However, levels are not as high as in animals and occasionally result in aniti-drug antibodies.

New data were presented on how vectored antibody delivery is being used for functional cure research in humanised BLT mice infected with HIV and then given VRC07 and compared to controls. About half the treated animals continued to suppress vireamia and half initially suppressed but later rebounded. However, repeating the experiment using two different bNAb - PGM1400 and N6 - resulted in high levels and antibody expression but without any impact on reducing viral load.

The different responses within the VRC07 groups was explained by different patterns of resistance, mainly requiring multiple mutation before viral load rebounded. In contrast, the lack of viral effect with PGM1400

and N6 occurred due to a single mutation that generated complete resistnce. The group then developed an escapability indexto categrorise and score responses across different antibodies under different viral selective pressure, that might be more appropriate than comparing in vitro potency.

Obatoclax selectively induces cells with intact but not defective HIV

An oral abstract session on viral persistence included a presentation from Steven Yukl from UCSF on differential susceptibility of cells infected with intact or defective HIV when presented within small molecule therapies. [9]

This group identified Obatoclax, a Bcl-2 inhibitor, which was able to reduce HIV DNA in this in vitro ex vivo assay of PBMCs from ART-suppressed individuals.

It was exciting that this particular drug was able to selectively deplee cells with intact proviruses but not those with defective DNA. Further studies will test combinations with Obatoclax in animal and human models.

Obatoclax (Bcl-2 inhibitor) reduces intact HIV DNA

- Goal: new therapies that promote selective killing of infected cells.
- Screening in ex vivo PBMCs from up to nine ART-suppressed individuals.
- Obatoclax induced selective depletion of cells with intact proviruses.
- No reduction of total of defective HIV DNA.
- Future studies should test combinations ex vivo and in animal of human trials.

In vivo CCR5 gene-editing produces ART-free HIV control in mice

In an oral abstract session on immune-based interventions towards an HIV cure, Priti Kumar from Yale School of Medicine presented results from in vivo genome editing of human T cells to edit CCR5 using CRISPR technolog. [10]

This process used non-infectious virus-like particle (VLPs) coated with antibodies to human CD7, administered by IV injection. Direct gene editing overcomes the need for stem-cell transplants to develop CCR5-delta 32 changes in immune function.

Although viral load rebounded several weeks after ART was stopped in this mouse study, with some loss of CD4 cells, immune responses quickly rebounded, also reducing and controlling HIV. Control animals all experienced rapid viral load rebound after stopping ART and dramatic CD4 loss, Upwards of 80% of T celles were edited for CCR5 which contained very little HIV DNA and the group were unable to generate out-growth virus by the end of the study. The process was therefore highly effective in changing humanised cells and that produced ART-free HIV control in humanised mice

The plenary on the final morning of the conference included two important talks - on the phenomenon of ntural HIV controllers and on new ways to measure the viral reservoir.

HIV controllers

Asier Saez-Cirion reviewed how a better understanding of the viral and genetic mechanisms that might contribute to the as-yet unexplained mechanism of natural viral control without ART could be used to inform cure strategies. [11]

This small group of people includes both elite and post-treatment controllers, some of whom have seroreverted after many years (decades) and may be candidates for remission or cure. However, HIV control can also be a transient state for controllers who maintain residual or intermittent viremia, with CD4 declines that still need use of ART.

The talk also interestingly referred to a recent ANRS survey reporting that quality of life wasn't necessarily better for controllers compared to non-controllers on ART. [12]

New approaches to measuring the reservoir

Ya-Chi Ho from Yale University, reviewed the 25-year history of measuring the viral reservoir and what it contains and the problem of the one-in-a-million challenge to find a needle in a needlestack. [13]

Exciting new approaches to measure and map the heterogenetic cells in the reservoir are now using single cell and multiomic tools – instead of using bulk RNA sequencing that measures the >99% of uninfected cells. Early attempts, since 2016, still relied on activating cells in order to count them, which destroyed the latent profile. However, over the last year, several platforms reported this new approaches to identify DNA containing sleeping cells (including FINDseq, PhePseq, ASAPseq, ECCITEseq and DOGMAseq). Barcoded cells can then show the development of the reservoir during the first year of ART and describe the development of the diverse range and behaviour of reservoir cells. These tools can now identify HIV infected cells at a single cell level that are not actively expressing HIV RNA,

The final study highlighted was a plenary talk given by Guido Ferrari from Duke University, who looked at using antibody-dependent cellular cytotoxicity (ADCC) responses to increase vaccine protection against HIV infection. [14]

This involved using the traditional ALVAC vaccine backbone and adding additional envelope sequences to this prime boosting strategy. Results from human studies showed that we may need to improve the maturation responses by using multiple dosing and delayed boosting, but also that the antigenic diversity of these vaccine immunogens will allow for broad ADCC responses.

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IAS 2023: HIV PREVENTION

Rapporteur summary: Track C prevention

Simon Collins, HIV i-Base

The following report is based on an edited transcription of rapporteur summary at the end of the conference, with additional original content added for some of the selected studies.

This issue of HTB includes summaries from Tracks A and C as Track B was included in the previous issue.

The rapporteur summary for Track C was given by Nyaradzo Mavis Mgodi from the University of Zimbabwe, provided an overview of the programme rather than selecting the most important and significant studies, included more than 30 talks and presentations. [1]

- Towards HIV elimination
- Long-acting PrEP: HIV testing and estimating HIV incidence.
- Preventing HIV and related co-infections.
- Sexual reproductive health and STIs.
- Human-centred approaches.

Towards HIV elimination

Many presentations related to global health goals to effectively reduce HIV transmissions and prevent HIV-related deaths by 2030 with some countries reporting optimistic results and others highlighting significant problems.

The oral abstract session 'Progress towards HIV elimination, are we there yet?' focussed on indicators and metrics for ending HIV transmission. [2]

This session included optimistic progress towards 95:95:95 targets in Australia (currently 92:92:98) and from the increased use of rapid/same-day ART in Thailand. [3, 4]

Difficult challenges were reported in two studies from South Africa: the increased incidence of HIV in people who use drugs (reduced by access to harm reduction packs and earlier ART) and a 200% increased risk of mortality from unplanned treatment interruptions (see Table 1 below). [5, 6].

Table 1. Increased risk of mortality linked to unplanned treatment interruption (Moolla et al) [5]

Interruption status	Adjusted hazard ratio (95%CI)
No interruption	1 (reference)
Early interrupters	2.32 (2.06 to 2.61)
Late interrupters	1.90 (1.68 to 2.15)

An oral late-breaker included results from a systematic review and meta-analysis showing the benefits of using social networks to increase the uptake of HIV testing to reach the first 95 target. [7]

Plenary session PL05 focussed on elimination of HIV in two talks. [8]

Andrew Grulich focussed on how prevention programmes measure elimination, and on progress at a global, regional and country level, with detailed results from Australia. East and Southern Africa are on track to meet elimination targets (57% reduction), but other regions lag or are seeing substantial increases on new cases. Although Australia is a low-incidence country, the 88% reduction reported in inner Sydney compares to only 31% reductions in outer suburbs where access to prevention follows different patterns. [9]

Natalia Laufer looked at the implications of U=U on HIV prevention in the context of pregnancy and breast/chest feeding. This included questions about the duration and need for neonatal PEP if ART is started before conception when French data now report the risk of transmission as zero? So far, only the Swiss guidelines say that neonatal PEP in not needed in the context of optimal ART. Will guidelines always remain regional rather than universal? The low risks of transmission from breast/chest feeding are still based on two cases from each of the PROMISE and KIULARCO studies (with low adherence, notably difficult post-partum, complicating all four cases). What happens with INSTI-based ART (where drug concentrations in milk are lower)? Is the earlier concern about mixed feeding still relevant? What happens in the context of mastitis? What is the role of cell-associated HIV DNA? [10]

The benefits of a community-based primary healthcare at scale, showed that Brazil's family health strategy (FHS) has a substantial impact on reducing the incidence advanced HIV and mortality, using data from a linked longitudinal cohort of >3.4 million people (see Table 2). [11]

Table 2. Incidence and mortality rates using Family Health Strategy, Brazil, 2007-2015

Outcome	Untreated N=605,890	Treated N=2,829,178	Total N=3,435,068
AIDS incidence	25.57 (23.71 to 27.58)	13.21 (12.65 to 13.80)	15.00 (14.45 to 15.58)
AIDS mortality	8.28 (7.25 to 9.45)	3.88 (3.58 to 4.20)	4.51 (4.22 to 4.83)

FHS coverage	AIDS incidence N=3,435,068 RR (CI 95%)	AIDS mortality N=3,435,068 RR (CI 95%)
<20%	1	1
100%	0.76 (0.68 to 0.84)	0.68 (0.56 to 0.82)

Long-acting PrEP: HIV testing and estimating HIV incidence

Although long-acting PrEP and treatment is highly effective many talks referred to ongoing inequity in access and practical concerns including caution about drug resistance that has slowed scale-up. Three talks in symposium 11 looked at the challenges associated with testing in the background of long-acting PrEP using CAB-LA or the dapivirine ring. [12]

This included Urvi Parikh discussing how the fear of resistance should slow down the scale-up of long-acting interventions. [13] Also, discussions on the technical challenges of testing for HIV testing when using long-acting PrEP. [14, 15]

Another set of invited talks in symposium 05 looked at the technical challenges of estimated background incidence of HIV and overcoming efficacy challenges now that oral PrEP is standard of care, including a talk by Deborah Donnell on use of HIV recency tests (detuned, RITA) and counterfactual placebo. [16, 17, 18, 19]

Preventing HIV and related co-infections

An oral abstract session on colliding epidemics covered other infectious diseases and the importance of person-centred public health interventions and integrated care in people living with HIV or at risk for HIV. [20]

Joseph Puyat's presentation showed the need for flexible and adaptable guidelines for COVID vaccinations among people who inject drugs, people who are living with HIV, and those with fast waning of vaccine effectiveness. [21] Claire Pederson described the first integration of a HIV PrEP service in sub-Sahara Africa with an assisted partner notification programme in STI clinics in Malawi. [22] Thomas Carpino also described the mpox vaccination policy in the US. [23]

Sexual reproductive health and STIs

Two talks and a Q&A in a plenary session on STI and HIV prevention included a talk about STU prevention using DoxyPEP and HIV prevention using bNAbs. [24]

Jean-Michel Molina reviewed accumulating data supporting the short-term benefits of doxycycline PEP among gay and bisexual men with strong reductions on the incidence of syphilis and chlamydia (though lower and conflicting effects on gonorrhoea). The challenges with DoxyPEP include the risk or resistance and the impact on the microbiome makes continued research important in different populations but also that cautious implementation might also be possible where close monitoring can track the risks. [25]

Nyaradzo Mgodi reviewed options for HIV prevention, including using bNAbs as PrEP. This included the different timelines for developing binding, early neutralising and then broadly neutralising antibodies (in a minority of people). The potential of bNAbs for prevention, for example in the large AMP studies, is limited by evolution of modern circulating strains and the challenges of testing for bNAb sensitivity, even using PT80 as a surrogate marker for efficacy. There are now seven classes of bNAbs and use of combinations or multi-specific compounds will be essential. [26]

A useful review of future developments was also just published by Malhotra et al in PIAS. [27]

Session OAC04 included four presentations related to reproductive health in different populations, mainly focussed on the safety of PrEP in low-income settings, especially in Kenya and Thailand. [28, 29, 30, 31]

The Thai study showed a lack of interactions between TAF-based PrEP and gender affirming hormones in 20 transgender women who had not undergone orchiectomy. The new data reporting similar drug levels in PBMCs and urine with and without hormone treatment supported earlier data showing no differences in plasma levels. [32]

Human-centred approaches

The importance of human-centred approaches was included in many of the presentations that are already reported above, but also in the session of late-breaking abstracts. [33]

It also included results on preferences for PrEP formulations in women in HPTN 082 study. This included a greater preference for injectable PrEP, although a significant minority preferred oral PrEP, with choice related to initial PrEP experience. See Table 3.[34]

Table 3: Participant preferences for PrEP formulation in HPTN 084 (n=2472)

Prefer injectable - n=1931 (78%)	
Overall prefer injections and/or don't like pills	78%
In those using injections (n=1253)	89%
In those first using oral pills (n=1219)	67%
Convenient, discreet and/or easier to adhere	11%
CAB was shown to be superior to TDF/FTC	8%
Want to avoid side effects of TDF/FTC	1%
No response	2%

Prefer oral PrEP n=536 (22%)	
In those using injections (n=1253)	11%
In those first using oral pills (n=1219)	33%
Concern about injection site/other side effects	5%
Clinic visits more efficient	1%
Pregnancy	1%
Other	1%
No response	11%

Perhaps most notable in the review was the insistence throughout that prevention science should be a human-centred approach that includes the choices and perspectives of the people who are most directly affected.

Whatever the specific interventions, this research should meet the following criteria.

- To reflect diversity, equity and inclusion.
- Target highest prevalence regions and special populations (pregnant and breast-feeding, infants, adolescents, gender diversity, women).
- Begin with the end in mind (access, manufacturing, licensing, delivery methods).
- Be framed by a human rights-based approach and
- Uphold justice and kindness to achieve the best results.

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Rapporteur summary track D: social and behavioural sciences

Simon Collins, HIV i-Base

The following report is based on an edited transcription of the rapporteur summary at the end of the conference, with additional original content added for some of the selected studies.

This issue of HTB includes summaries from Tracks A and C as Track B was included in the previous issue.

The rapporteur summary for Track D was given by Bridget Haire, senior research fellow from the Kirby Institute in Sydney included 18 talks and presentations. [1]

- Overview: Stigma, decolonisation and sex cultures.
- Social life of testing.
- Social life of prevention: PrEP choices.
- Social life of treatment: Uganda after the Anti Homosexuality Act.
- Stigma and decolonisation.
- Sex cultures, sex-positivity and chemsex.

Overview: Stigma, decolonisation and sex cultures

The premise of social research is that we operate in complex and multi-layered relational systems, including the macro or structural level, the meso or the social community level and the interpersonal and intimate. From this premise, although we understand that technologies that address HIV are necessary and valued, they are not in themselves sufficient to change the trajectory of the epidemic without lubricating social pathways. And as this is HIV, there are a lot of complex and intertwining social pathways that need a great deal of lubrication.

This overview covers the key thematic areas of the social and behavioural research presented at IAS 2023,

This includes examples of the social lives of HIV testing, HIV prevention and HIV treatment. It also involves the big thematic issues of stigma and decolonisation, and examples of the context of sex cultures.

Social life of testing

- Simplify, de-medicalise and increase access.
- Optimising use of social networks.
- Removing barriers by providing supportive mechanisms for self-testing.
- Racial inequalities in HIV testing in adolescent MSM and transgender women in Brazil.

On plenary PL03 on combining approaches to community engagement, we heard from Victoria McDonald about the social life of testing and that social networks have been identified as a way of optimising testing to meet HIV elimination goals. This included the critical necessity of removing barriers by providing supportive mechanisms for self-testing – so self-testing alone is not going to solve the issue of getting testing to the people who need it. We need to actually provide the ways to do that. [2]

We also saw a presentation by Marcus França that described racial inequalities in HIV testing, showing in adolescent MSM and transgender women in Brazil. [3]

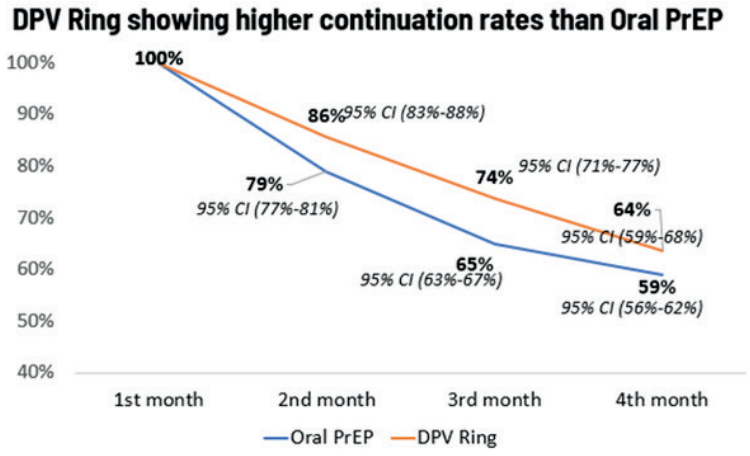
Social life of prevention: PrEP choices

- The dapivirine vaginal ring, with modest efficacy, was roughly as popular as oral PrEP in Zimbabwe – although only 60% were still using either option after only four months.
- Effective harm reduction is also HIV prevention – new data on barriers to methadone services (fears about methadone, lack of access, stigmatising language by service providers).
- Relative ineffectiveness of doxy PrEP in Kenyan women, poorly understood.

In terms of the social life of prevention, one study showed that with modest efficacy, the dapivirine ring was preferred by women in Zimbabwe to oral PrEP. [4].

The answer to the audience question: 'Why was this, what was the difference?' was that the ring is easier to hide from our families, which is incredibly significant in understanding the lived experience and the ways in which people need to work to incorporate HIV prevention into their social lives.

Editorial note: The difference in retention at four months was only 64% (95%CI: 59 to 68%) with the ring vs 59% (95%CI: 56% to 57%) with oral PrEP and are not significant.



Although the rapporteur referred barriers to harm reduction in a US study (not referenced) included fears about a particular drug intervention, lack of access to harm reduction and stigmatising language by service providers, it also included a comment that this was old news and that "after all these years we are still facing issues like these in providing effective prevention services".

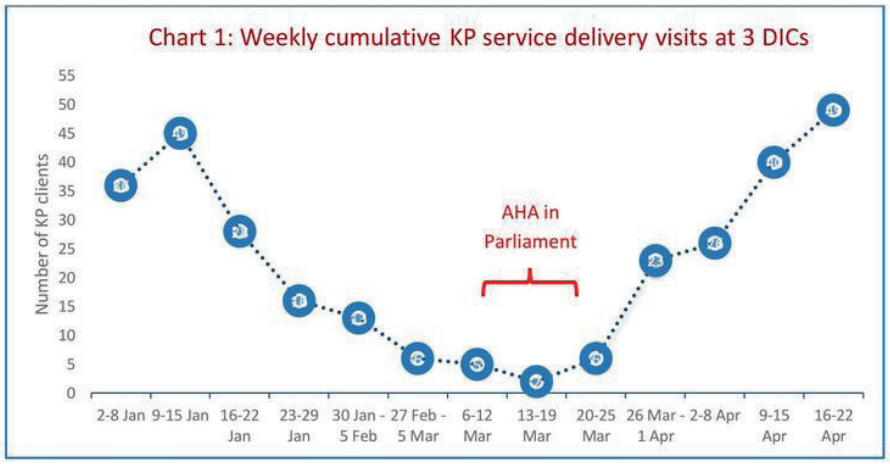
Editor's note: new data on barriers to harm reduction included aa late-breaking oral abstract about Kazakhstan prisons during COVID where prisoners discontinued HIV and TB meds to become hospitalised, thinking this might enable access to substitution therapy that was otherwise discontinue. [5]

And despite the relative ineffectiveness of doxy PrEP in Kenyan women, which we saw some further information about today, we now understand that the reason that doxy PrEP was not working in the Kenyan women's study was an adherence issue [6].

And again, this raises the question: what do we need to do? How do we need to change our approaches to assure that novel ways of addressing STIs are actually getting to the populations that need them? How do we change to actually incorporate lived social lives in the way that we provide HIV and STI prevention?

Social life of treatment: Uganda after the Anti Homosexuality Act

- Providing uninterrupted HIV treatment in Uganda following the Anti Homosexuality Act (26 May 2023).
- PEPFAR: 84 drop-in clinics for key populations; confidentiality and safety paramount.
- Telehealth; home delivery; enhanced legal and social protection; reporting innovations with enhanced security.



A late-breaking oral abstract described the impact of the horrific legal discrimination against LGBT people in Uganda with sentences from 10 years to the death penalty. This law also criminalises anyone who knowingly supports or helps LGBT people, that can be interpreted as providing health care and failing to report them. [7]

The reach of this law, hurriedly passed in May 2023 during a political corruption scandal, included high-profile media campaigns ('they are coming for our children") from the beginning of the year, scared many people from attending HIV services - with one clinic dropping from 40 weekly clients down to 2.

This meant that the implications ware also being discussed at IAS 2023 in terms of the impact on UNAIDS-defined key populations and the global PEPFAR programme. The political context, however, as noted in the presentations, is significantly more important than the impact on health.

This dual presentation included Natalie Brown, the US Embassy for Uganda, on the harm that is already being caused, including people being denied treatment and being reported to the police when they seek treatment with increased vulnerability from being fired from employment and evicted from housing and increased physical and sexual assaults.

PEPFAR currently supports 84 drop-in centres ("no questions asked") in Uganda for key populations, providing HIV treatment for more than 1.3 million people. In response to dwindling use over the first six months of 2023 these centres have increased training and structures about confidentiality with new safety protections, and introduced new ways of delivering services that include telehealth and home-based delivery

of ARVs. PEPFAR tracked the impact of the recent legislation with anonymised data and these measures have so far helped reconnect people to their services.

Changes in the way key populations are reported for safety reasons must also ensure that people are not erased from the data - particularly gay and bisexual cis men and people who are transgender.

Other late breakers included a survey of people who had mpox last year including on the positive and negative experiences of healthcare and a survey of workers providers providing HIV services in Mozambique, where educated and more knowledgeable people living with HIV were seen as difficult and more of a problem... [8, 9]

The rapporteur thought that this last point was interesting "given what we usually think about educated people actually having better access to treatment", This missing the point that the confidence to be able to question a health provider often implies a more privileged position and that this often results in being seen as a difficult patient. The survey was about health workers stress and non-questioning patients are no doubt easier to treat - but they don't necessarily get better health care.

Stigma and decolonisation

Stigma was another common theme of this conference, including an oral abstract session looking at Insights and interventions to tackle stigma (OAD02) and a symposium looking at a history of HIV-related social science and going forward into the next decade (SY02).

Conceptual critiques of stigma are sometimes limited too much to the interpersonal (or microlevel) and not extended out to the structural level, which has a very important impact. Symposium 2i, Kane Race from the University of Sydney talked about the importance of recognising stigma as macro and as impacting on populations when planning for the next ten years. [10]

The session also included a talk by Catherine Dodds from the University of Bristol about the individualised and apolitical conception of stigma that sometimes dominates international HIV research and targets. [11]

The absolute critical importance of locality in understanding what stigma is how it actually impacts on affected people was emphasised again and again.

Oral abstract session 2, also included research on measurement of and responses to internalised and interpersonal stigma and CBT as a psychological intervention. [12, 13]

Decolonisation was another critically important overarching theme in the conversations at the conference.

- Who gets to attend conferences?
- Who gets to speak and shape the conversation?
- Whose knowledges are valued and influential?
- How do we think about and 'centre' the local in global HIV and health?

James Ward from the University Of Queensland Poche Centre For Indigenous Health, gave a plenary talk about the excruciatingly bad influence of colonial history in shaping Aboriginal and Torres Strait Islander people's experience of STIs, including the devastating example of Lock Hospitals with people effectively being incarcerated. He also demonstrated how community engagement can reframe health promotion and identify pathways to overcoming entrenched stigma. [14]

Deevia Bhana gave a symposium talk about how the history of HIV interventions has been shaped by colonial paradigms, by power imbalances and Western-centric perspectives, limiting our progress to actually understanding HIV where it is occurring in the world today and addressing the complex challenges of the epidemic. She advocated for the centring of the experience of communities in their specificity and in the locality. [15]

Sex cultures, sex-positivity and chemsex

In a marvellously sex-positive symposium we heard trans people and other members of key populations discussing chemsex, with one qualitative study talking about it operating as a coping mechanism that can reduce inhibition and allow non-judgemental exploration of sexuality. [16]

Other discussions however did include about the negative role that chemsex might play in ongoing epidemics.

Symposium SY18 also discussed emerging sexual cultures and social contexts that pose unforeseen challenges to ongoing efforts to meet the 2030 targets. [17]

The rapporteur also commented on the changing toles of social science, including a quote from the talk by Gary Dowsett. [18]

"Social science was indispensable in moving beyond quantifying HIV, introducing ideas about structural drivers and social determinants to public health, and revealing how the epidemic is deeply shaped by knowledge systems, cultures, politics, economics, history."

This was in a talk about 40 years of responses from social science to HIV. Whilst he was talking about the historical context, the points that he makes about the epidemic being deeply shaped by knowledge systems, cultures, politics, economics and history, remain critically important for us to understand today, when we have the best tools that we have ever had, and yet we still have competing theories about the best way to use these tools most effectively.

In conclusion, as the tools of biomedicine become more refined, we need to understand how the social world determines how and why people can really use the available interventions (effectiveness, not ***just*** efficacy).

We need to understand the legacies of colonial injustice and how they endure today and shape programmes. Addressing these legacies requires genuine partnership and power-sharing with specific local communities and key populations.

And finally, we need to consider the looming crises and problems, such as climate change, the impact of authoritarian regimes and panics about LGBTIQ+ people. These problems, facing us now and into the future, make critical social research more important than ever for the ongoing response to HIV and to achieve these goals, that are so deeply-held by all of us here today.

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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.

Hopefully showing a continued unmet need, we can keep proper funding and commissioning support to make sure services are stable for the future.

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.

DRUG INTERACTIONS

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 use) 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.

Reference:

Fisher MC et al. Association of marijuana, tobacco and alcohol use with estimated glomerular filtration rate in women living with HIV and women without HIV. AIDS 37(10), 1555-1564. DOI: 10.1097/QAD.0000000000003625 (09 June 2023).

COMPLICATIONS: MPOX

Tecovirimat resistance in a person with advanced HIV and delayed ART

Simon Collins, HIV i-Base

Although tecovirimat is currently being used to treat mpox it has a low genetic barrier to drug resistance. The Annals of Internal Medicine published a very difficult case report of a 53-year-old man diagnosed with advanced HIV and who on autopsy also showed tecovirimat resistant mpox.

He presented in November 2022 with symptoms of advanced HIV infection including weight loss, weight loss; a longstanding large, painful anal ulcer; and proctitis, but without skin lesions. His CD4 and viral load were 20 cells/mm^3 and 523,000 copies/mL, respectively. He also had chronic HBV, latent syphilis, *Cryptococcus neoformans* antigenemia, anal *Chlamydia trachomatis* infection, and suspected CMV colitis.

However, he did not start ART for a further six weeks after worsening anal pain and lesions that were mpox positive. Treatments for HIV (Biktarvy), CMV (IV ganciclovir) and mpox (tecovirimat) were all started.

Tecovirimat was given 600 mg twice-daily and the majority of lesions resolved within two weeks. However, some anal lesions and viral shedding persisted, and further testing was run. Retrospective sequence analysis identified a F13L mutation, present from day 11, which confers tecovirimat resistance.

Although mpox DNA was no longer detectable in blood after day 25 it remained high up to day 48 (Ct, 21.58) and detectable up to the end of follow-up (Ct, 33.94 at day 88).

However, the retrospective analysis also showed protracted mpox shedding for at least 87 days before of tecovirimat, when a minor fraction of the resistant variant was already detectable.

This case highlights the rapid development of tecovirimat resistance in the context of multiple clinical complications and advanced HIV, despite recovery of CD4 count to approximately 100 cells/nm^3 by day 48.

Reference:

Mertes H et al. Tecovirimat resistance in an immunocompromised patient with Mpox and prolonged viral shedding. Annals of Internal Medicine. DOI:10.7326/L23-0131. (25 July 2023).

https://www.acpjournals.org/doi/10.7326/L23-0131

OPPORTUNISTIC INFECTIONS

Timing of ART with cryptococcus: Europe and the US cohort data challenged by African RCT data and editorial comment

Simon Collins, HIV i-Base

The clinical management of cryptococcus in people with advanced HIV and a low CD4 count usually involves deferring ART for 4-6 weeks while the OI is treated directly. This reduces higher risk of IRIS-associated mortality when both infections are treated at the same time.

Results from a large collaborative observational cohort study, published as a major article in Clinical Infectious Diseases suggested that these risks depended on the country and health setting. This paper found no increased risk of IRIS when starting both treatments at the same time, in Europe and the US.

These results are based on results from190, of whom 33 (17%) died within 6 months. Using this data to model; expected results from an RCT suggested 13 vs 20 deaths with early vs late ART. The crude and adjusted hazard ratios comparing late with early ART were 1.28 (95% CI: 0.64 to 2.56) and 1.40 (0.66 to 2.95), respectively.

A linked editorial in CID acknowledges that significant differences including milder infections and greater access to better antifungal treatment and lumber puncture characterise the cohort population, compared to management in African studies that were involved in the randomised clinical trials showing the benefits of deferring ART. [2]

However, the editorial also challenges the results due to the limitation of observational data where confounding by indications might have included early use of ART in low-risk clinically stable patients.

More importantly, it highlights the very high percentage of cases in the cohort study (256/630, 41%) with no outcome data and that a further exclusion of 176 cases (28%) due to missing CD4 or HIV viral load. This last group excluded 39 deaths from the overall analysis. The mortality in this last excluded group was significantly higher than the overall study: 22.1% (39/176), vs 13.2% (25/ 190) (p=0.028).

By comparison, loss to follow-up in three international African cryptococcal meningitis trials studies was only 0.2%.(4/1712). Modern clinical management with deferred ART has also reduced the risk of IRIS to 5%, although this rate is not reported in the cohort analysis.

The editorial suggested that RCTs in high-income countries would be important before guidelines recommend any change in current management.

COMMENT

It is notable that CID published a major article supporting a significant change of clinical management together with a editorial challenging the results based on significant issues that were not acknowledged as limitations in the peer-reviewed paper.

Current UK BHIVA guidelines (from 2011) note the lower incidence of cryptococcus since ART and recommend deferring HIV treatment for two weeks until after the induction treatment for cryptococcus. [3]

Current US guidelines, updated in 2021 and reviewed in 2023, recommend deferring ART for 4–6 weeks. [4]

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HIV PATHOGENESIS

Cannabis does not reduce T cells in people living with HIV

Kirk Taylor, HIV i-Base

A cross-sectional study published in the Journal of Infectious Diseases reports no link between cannabis use and altered T cell count or function in people living with HIV who reported modest use compared to matched non-users. [1]

Effects of occasional cannabis use upon T cell count immunological parameters for people living with HIV (n=75) were studied. Median time since diagnosis was 12 years (range: 2 to 34 years), and participants were female (20%), Black (69%) and median age was 43 years (range: 33 to 53 years).

Cannabis use was defined by positive urine test plus self-reported use for over 12 days in the past three months. Cannabis users (n=33) were compared with matched controls (n=42).

Cannabis use did not alter the total number of CD4 or CD8 T cells, nor did it impact their immunological response. Cannabis use was linked to lower levels of exhausted and senescent T cells, without altering the response to HIV.

Longitudinal studies are needed to fully evaluate the impact on the viral reservoir.

C O M M E N T

It is important to note that the results noted by this study are a small aspect of safety.

Harms of smoke inhalation have also been reported by other studies.

A recent US study also reported higher levels of metals in smokers, though data are not available for other ways of using marijuana. [2]

The benefits reported from marijuana use individualises the benefit:risk decision.

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Defective HIV proviral particles linked to persistent inflammation and immune activation despite effective ART

Kirk Taylor, HIV i-Base

US researchers at NIAID report that defective HIV proviral HIV DNA, RNA and proteins were associated with consistent and continued inflammatory responses, despite viral suppression on ART for many years.

The study, published in the journal AIDS, describes expansion of defective HIV proviral particles in people living with HIV that are on suppressive ART. Whilst these particles are not replication competent they are transcriptionally active and may produce HIV-related proteins that trigger immune and inflammatory responses.

The combined cohort study included 23 participants who were split into cross-sectional (n=20) and longitudinal groups (n=3). In the cross-sectional group, five participants had detectable viral load and all others were on suppressive ART (range: 1 to 11 years). The longitudinal group were followed for up to 20 years with data collected at a minimum of five timepoints per person. Median age at enrolment was 47 years (IQR: 38 to 57) and participants were female (n=5), Black (n=5) and Hispanic (n=5).

Across both groups, levels of HIV DNA, RNA and protein were consistent despite prolonged viral suppression. A pool of PBMCs were identified that were capable of clonal expansion and producing defective provirus. In one particiapnt, 31 unique proviral clones were identified and proviral proteins generated immune responses.

The levels of inflammatory markers (e.g. TNF-α, IL-6 and CRP) correlated with expression of HIV DNA, RNA and associated proteins. D-Dimer positively correlated with levels of detected HIV RNA ($r= 0.53$, $p<0.01$) and protein ($r= 0.52$, $p=0.01$). CD8 counts correlated with HIV DNA ($r= 0.52$, $p=0.01$) and RNA ($r= 0.65$, $p<0.01$).

The authors concluded that long-term replication of defective HIV may provide a source of immunogenic material that promotes continued inflammatory responses in people living with HIV even when viral load is undetectable for many years.

Reference

Singh K et al. Long-term persistence of transcriptionally-active “defective” HIV-1 proviruses: Implications for persistent immune activation during antiretroviral therapy. AIDS. DOI: 10.1097/QAD.0000000000003667. (08 Aug 2023).

https://journals.lww.com/aidsonline/abstract/9900/long_term_persistence_of_transcriptionally_active.322.aspx

Peripheral inflammation linked to structural brain changes and reduced blood flow despite suppressive ART

Kirk Taylor, HIV i-Base

A cohort study published in the Journal of Infectious Diseases reported an association between increased inflammatory markers and declining cerebral blood flow (CBF) and brain volume for people with undetectable viral load.

A cohort of people living with HIV (n=173) with undetectable viral load (<50 copies/mL) were recruited to evaluate markers of inflammation and changes in brain structure and CBF.

Correlations were reported between reduced CD4/CD8 ratio and lower brain volume (total cortex and grey matter). These changes coincided with increased levels of inflammatory ($CD16^+$) monocytes. Reduced CBF in the parietal, temporal and occipital regions of the brain was associated with increased plasma levels of the inflammatory marker CD14. The underlying mechanism by which these changes occur remains unclear.

Reference

Burdo et al. Increased peripheral inflammation is associated with structural brain changes and reduced blood flow in virologically controlled people with HIV. Journal of Infectious Diseases. Jiad229 DOI:10.1093/infdis/jiad229. (23 June 2023).

https://doi.org/10.1093/infdis/jiad229

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

30th Intl Workshop on HIV Drug Resistance and Treatment Strategies

20–22 September 2023, Cape Town, South Africa

www.hivresistance.co.za

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

2024

CROI 2024

3 – 6 Mach 2024, Denver, Colorado

https://www.croiconference.org

5th HIV Research for Prevention Conference (R4P 2023)

6 – 10 October 2023, Lima, Peru, and virtual.

www.iasociety.org/conferences/HIVR4P2023

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.

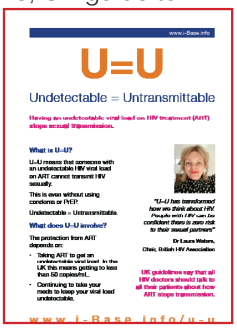
http://www.i-base.info/guides

- 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

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Editor: Simon Collins

Contributing Editor: Polly Clayden

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

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

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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** _____

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subscriptions@i-Base.org.uk