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hiv treatment bulletin (e)

BHIVA and CROI, weight gain on ART (1 June 2023)

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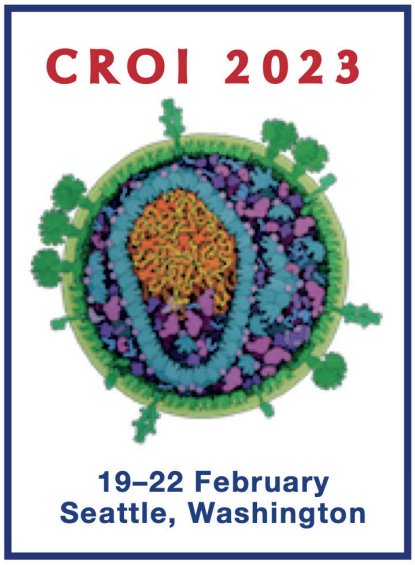

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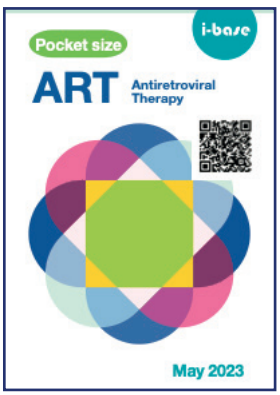
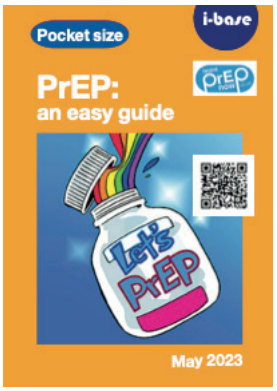
New i-Base pocket leaflets





Four new pocket leaflets have been updated and reprinted this month.

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

HIV and implementation science

Simon Collins, HIV i-Base

A recent editorial comment in JAMA focused on the time taken – a 'chasm' – between advances in evidence-based medicine and their implementation into clinical practice. [1]

The article quotes this as being an average of 17 years (without noting the irony that this time is quoted from a 2011 paper published 12 years ago) and uses examples from cardiovascular care and COVID, noting that only 1 in 5 evidence-based interventions make it to routine clinical practice. [2, 3]

And although the review positively references HIV research, it would be interesting to know how HIV compares to this average.

The hopefully faster timeline for advances in HIV to become clinical practice would likely be a marker of four factors.

- Continued research into HIV treatment; with public funded research such as the UK MRC, French ANRS, European NEAT and US ACTG networks including implementation studies.
- A high awareness of results presented at medical conference before peer-review publication.
- Access to regularly updated national and international guidelines (that also allow evidence from conference presentations).
- Incorporation of implementation research by international health organisations and funders, including WHO, IAS, PEPFAR etc - sometimes called operations or operational research. [4]

This extended timeline has also been often highlighted as a problem for data on people living with HIV who are routinely excluded from phase 3 regulatory studies or underrepresented in them including by age, ethnicity, gender and sex.

A plenary talk on ART-associated weight gain, given by Andrew Carr at the recent BHIVA conference, included a slide showing a delay of 2 to 18 years in the time taken to attribute drug toxicity after drug approval. This talk is also reported in detail in this issue of HTB together with summaries of other signposted presentations. [5, 6, 7]

We conclude our reports from CROI 2023 noting that plenary talks are now available as open access. These excellent presentations by leading researchers are often underreported in community reports, and yet, similar to talks at the pre-conference investigator workshops, summarise state-of-the-art research.

The talk on the HIV reservoir and cure-related research, by Janet Siliciano, included the recent awareness that long-term viral suppression on ART rather than steadily reducing the viral reservoir, actually leads to a slight increase. [8]

The increase however is driven by the clonal expansion of latently infected cells that are transcriptional deficient, and concludes that rather than indiscriminately targeting the entire viral reservoir, future cure-related studies could instead only selectively target cells that actively contribute to viral rebound when ART is stopped.

In a small way, compressing the timeline between integrating clinical advances into practice has always been an i-Base goal, including for HTB and it is sobering to note that the field of implementational science has developed during the 22 years that we have been publishing and reporting - especially during the last 16 or so years. [9, 10, 11, 12]

This double issue of HTB also brings news of NHS England approving selected use of F/TAF for PrEP, the first liver transplant from a living donor with HIV/HCV coinfection, data on CNS-penetrating ART, a review of idiopathic lymphocytopenia, suggested lower efficacy of mpox vaccines, and, yes, more.

Happy reading.

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CONFERENCE REPORTS

BHIVA Annual Conference 2023

24 – 26 April 2023, Gateshead, UK

Simon Collins, HIV i-Base

Introduction

This year the BHIVA conference was held in Newcastle at the Gateshead conference centre over three sunny spring days.

The conference included a strong programme of presentations about HIV care in the UK and included more that 150 posters.

BHIVA should be recognised (and thanked) for making webcasts online so promptly. This is a really important responsibility that comes with running and arranging medical conferences, especially given the financial challenges of organising face-to-face meetings.

Wider access to the data presented, should also be appreciated by sponsors who support these meetings. Community reports, including from i-Base, can only cover a fraction of the information that is presented, even from a single study. Our reports are primarily to flag research and to signpost to the presentations that include the full data.

Please use the links in our reports to see the webcasts and see the full posters. There is no substitute for going to the original presentations.

Conference programme and abstract book

https://www.bhiva.org/SpringConference2023

Conference presentations

https://www.bhiva.org/SpringConference2023Presentations

https://vimeo.com/britishhivassoc/videos

The following reports from BHIVA 2023 are included in this issue of HTB

- UK cascade data cautions UNAIDS 95:95:95 targets: re-engaging people with care
- Selected plenary talks at BHIVA 2023

UK cascade data cautions UNAIDS 95:95:95 targets: re-engaging people with care

Simon Collins, HIV i-Base

BHIVA 2023 included several talks in a symposium about the UK treatment cascade. Results show that UNAIDS targets can significantly overestimate the actual provision of HIV care and can inadvertently produce an overly optimistic view of current services. [1]

The presentations included strategies to retain people in care, up to 20% of whom might currently be excluded from 95:95:95 estimated targets. There are many complex reasons that prevent people from prioritising their own HIV health, often for many years. Bringing people back into care also makes economic sense and helps with achieving goals for HIV prevention.

Although the UK is one of the first countries to report that more than 95% of people living with HIV are diagnosed, on treatment and have an undetectable viral load, up to 18,000 people might be missing from this data.

This is because there are different denominators for each metric, because the cross-sectional snapshot only refers to data from the previous year (similar to an on-treatment analysis) and because of positive adjustments for missing data.

Why third target in the UK might only be 88%

The plenary talk by Dr Ann Sullivan from the Chelsea and Westminster Hospital, using data from England for 2021, reported top-line cascade results of 95.4% for testing, 98.7% for accessing care and 97.8% for achieving undetectable viral load. [2]

The talk also presented differences within the cascade linked to demographics, and highlighted different results by age, sex, sexuality, ethnicity and other factors.

But instead of 97.8, the third metric might only be 88% – also explained by Cuong Chau later in the session. The results are still impressive, but 88% shows how much still has to be done.

The first UNAIDS 95% target is the percentage of people living with HIV who have been diagnosed. In England, an estimated 95,930 people were living with HIV in 2021, of whom 95.4% were diagnosed. This left an estimated 4,400 people who were not yet diagnosed, with a 95%CI range of 3,500 to 6,100.

The second target is not based on percentage of people diagnosed, but only those who connected to care in the previous year and who are on ART. This is based on HARS data (HIV and AIDS Reporting System) from people who were registered at and attended an HIV clinic in the previous year. These records need to also have either a treatment status update or an undetectable viral load (assuming continued use of ART).

The third target relating to treatment efficacy is the percentage of people who have an undetectable viral load, but the denominator is also the subset of people on ART who have a viral load test result recorded during the last year. Rather than being the number of people in care or the number diagnosed, this factor depends on engagement with viral load testing and tends to enter missing data as a positive response.

The definitions for each of these stages don't account for the significant minority of people who disconnect from care, or that they might often remain out of care for many years.

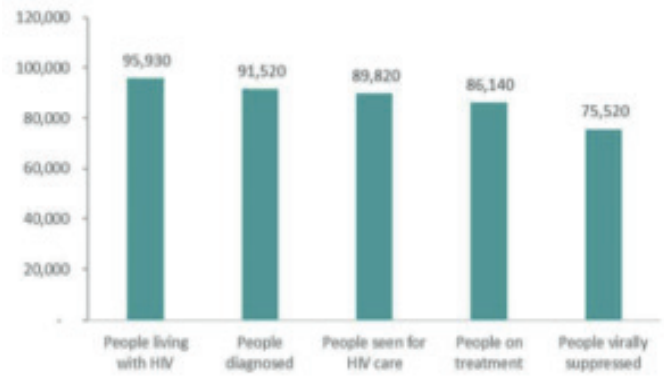
Taken together, a significant number of people are not counted when calculating the UNAIDS targets, and between 12,000 and 28,000 people in England might have detectable viral load, see Table 1.

Table 1: Estimates of people in England with detectable viral load (2021)

	lower estimate	upper estimate
Not diagnosed.	4,400	6,100
Diagnosed but not linked to care.	147	147
In care but not on ART.	1195	1500
On ART but not suppressed.	1799	1799
On ART, suppressed but no recent VL.	_	2621
Not retained in care.	4118 (previous 15 mo).	13,963 (previous 5 yrs).
Total	11,659	28,130

- Using the upper 95%CI for people undiagnosed drops the first column from 95.4% to 93.7% and counting missing viral load data as detectable drops viral suppression in the third column from 97.5% to 90.5%.
- Assuming missing data is a negative outcome, the percentage linked to care drops from 98% to 94% and drops viral suppression from 97% to 82% (or only 77% using the upper estimate of those undiagnosed).

Table 1: Continuum of care in England (2021)



Successful examples to re-engage in care

The second talk in this session by Kate Childs from Kings College Hospital, continued the theme of missing data by showing how the cascade can reverse, for example if viral load rebounds on ART, and if people discontinue ART or fall out of care completely. [3]

It also included new data from a project first presented at BHIVA last year, that tries to contact people once they have become lost to care for more than a year.

This included 7092 people living with HIV who were registered for treatment in Lambeth, Lewisham and Southwark in South London. Of these, 2275 had not been seen in the previous 12 months, 521 of whom were identified by UKHSA as still in care and another 930 of whom were identified as in care or confirmed to have either died or left the country.

Of the remaining 824 people who are potentially disconnected from care, intense tracing efforts were able to re-engage with 153 (18%).

The characteristics of these 153 people included a median CD4 of 305 cells/mm^3, with 48/153 <200 cells/mm^3. The median age was 46, just over half (57%) were women and 71% Black African/Caribbean. Just under half (45%) came from the lowest 20% of defined bands of social deprivation, showing significant health inequalities related to ethnicity, sex and poverty.

Reconnecting to care was successful with durable outcomes reported this year for many. Of the 153 people who re-engaged between July 2020 and December 2021, 117/153 (76%) were still in care a year later, most at the same clinic. Of the 97 with recent viral load data, 63/97 (65%) had undetectable viral load <50 copies/mL and 74% were <200 copies/mL.

Common issues linked to being lost to care helped explain some of the reasons that prevented people from prioritising their own health.

In the short-term, missing an HIV appointment or even disconnecting from care doesn't usually directly affect how well someone feels. They might even feel better if not having to take meds is seen as one less thing to worry about, but it will increase the risk of much more serious and debilitating outcomes later. And this talk included devastating real-life examples.

These competing needs include financial poverty, having a difficult housing and immigration status, living with a fear of disclosure, and having sole responsibility for looking after children. Some people reported being in a relationship that undermined the importance of HIV and care. These factors also overlapped with issues of mental health, complications from drug and alcohol use, and perhaps never having HIV-related illness.

Overcoming barriers to engaging in care

The presentation highlighted several ways that tried to overcome barriers to attending HIV clinics.

- Enabling appointments at venues outside the traditional clinic setting and at a wider range of times.
- Having a dedicated smartphone for the clinic to enable easier communication, including by Whatsapp messaging, emails and calls that don't involve going through a switchboard, which can help with continuity of care.

- Working closely with services providing mental health, social work and drug and alcohol support and ensuring access to peer support.
- Using a case management approach that could include supermarket and travel vouchers.
- Helping people register at new clinics and GP surgeries, especially if they move to live in a different region.
- The potential role of positive public health campaigns to 'welcome back' people who are currently disengaged. Also, outreach to communities where HIV stigma is still a significant issue.

In one case, the repeated contact and messaging by the clinic eventually convinced someone that HIV care was important and that their health mattered.

This highly intensive and individualised approach is not currently funded, even though the numbers of people lost to care are already likely to be significantly higher than those who are not yet diagnosed.

However, UKHSA now actively works to identify people who have been lost to care and these cases are reported back to every individual clinic to check as part of the annual dashboard. To be effective, individual clinics need to engage with this process and also report back to UKHSA.

Finally, Cuong Chau from UKHSA presented a talk on the agency's responses that included extending the window from 12 months to 15 months to allow for retention in care, including new data fields for people who leave the UK or who are no longer seen at the clinic, and data tracing for people being seen at alternative clinics. [4]

This also expanded on considerable work involved in reporting lost cases back to all clinics as part of the HIV dashboard mentioned above and on how to interact with UKHSA. So far this has led to updating CD4 baseline data for 261 people, adding viral load results for almost 5000 people (80% of whom were undetectable) and identifying 721 people as still being in care.

However, only 63% of clinics responded to dashboard follow-up and the talk gently encouraged all clinics to actively engage.

C O M M E N T

This focus on helping people to re-engage with care is likely to affect all clinics.

One recommendation is to include a named contact person responsible for overseeing people out of care at each site. Another includes the urgency of appropriate funding.

Misconceptions about the way UNAIDS metrics are calculated will also affect global reporting of the 95:95:95 targets as they steadily approach 100%.

Although reaching these goals is a considerable achievement, significantly underestimating the actual levels of care risks undermining this success.

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Selected webcasts from BHIVA 2023

Simon Collins, HIV i-Base

As always, BHIVA 2023 included a diverse range of plenary talks that covered important aspects of care in the UK.

All talks are now easy to view as webcasts using the links included below.

Navigating new pandemics: what have we learnt

In the opening talk at BHIVA 2023, Susan Hopkins from UKHSA compared responses to three global pandemics – 1918 flu, HIV and COVID-19. This included the importance of working as part of international and global networks to understand and the appropriate responses to reduce transmission - and that these will be different for each new health threat.

The talk also covered the range of recent issues that UKSHA responded to including H1N1, Ebola, MERS, zika, STI outbreaks (MDR gonorrhoea, LGV, mpox).

Looking to the future, G7 countries have launched a 100-day challenge for the timeline to identify, test and treat any new pathogen and that population-based responses are political rather than medical.

Ref: Hopkins S. Navigating new pandemics: what have we learnt. BHIVA 2023. Plenary talk.

https://vimeo.com/822934793 (webcast)

Overview of the UK cascade

Three talks were included in a symposium on the UK HIV Care Cascade. Although impressive, a repeated theme included how the actual levels are significantly lower the that 95:95:95 targets suggest. This relates to the methodology used to estimate these goals, especially in the way that people who fall out of care are also missing from the data.

I-Base also covered this symposium in detail in a separate report.

Links

Overview of the cascade: where should we focus next? BHIVA 2023. Symposium with three plenary talks.

https://vimeo.com/822989830 (webcast)

HTB. UK cascade data cautions UNAIDS 95:95:95 targets: re-engaging people with care.

https://i-base.info/htb/45425 (i-Base detailed report)

Impact of COVID and Ukraine war on HIV care in Europe and central Asia

Sanjay Bhagani from the Royal Free Hospital, London, talked about the impact of COVID, Ukraine and mpox on the HIV care cascade across Europe and central Asia regions.

For all the difficulties, some new health innovations included new models for care including telemedicine and new way to provide care (including home testing and longer prescriptions. However, not all these developments were universally acceptable or accessed by all demographic groups.

The Russian war against Ukraine disrupted services in a country with more than 270,000 people living with HIV and a low cascade targets, and huge displacement of refugees.

The talk covered numerous initiatives for new partnerships across the region to reestablish and then maintain HIV and other care.

Ref: Bhagani S. Of pandemics and wars. BHIVA 2023. Plenary talk.

https://vimeo.com/822938232 (webcast)

Public health approach to HIV treatment and the impact of drug resistance

Nick Paton, from National University of Singapore, presented the evidence for changes in the approach to ART in countries who deliver HIV care based on population-based model. This included how evidence from several randomised studies including DAWNING, ERNEST and NADIA showed continued antiviral activity of nucleoside analogues, even with evidence of genotypic drug resistance to this class.

This supports the importance of retaining tenofovir from first-line ART in second-line combinations without the need to use AZT or resistance testing. The studies also support using dolutegravir and darunavir/r interchangeably as the third component of either first- or second-line ART.

Ref: Paton N. Public health approach to HIV treatment and the impact of drug resistance. BHIVA 2023. Plenary talk.

https://vimeo.com/822955414 (webcast)

Best management for people with drug resistance: UK access to latest drugs

Laura Waters from the Mortimer Market Centre, London, talked about the definition, management and treatment of people with extensive drug experience. This included the importance of access programmes to ensure that people who need these options are able to use them, even if they might not meet strict prescribing criteria in the drug license. The talk included information on fostemsavir, ibalizumab and lenacapavir.

Ref: Waters L. Highly Treatment Experienced: what it means & best management. BHIVA 2023. Plenary talk.

https://vimeo.com/822955414 (webcast, from 30 minutes)

Community programme: myths, misconceptions and other patient questions

https://vimeo.com/823030343

A symposium programmed by the UK-CAB included direct experiences of community advocates talking about the range issues that are still important in HIV care.

This symposium covered a wide range of practical questions asked by members of the UK-CAB and included examples of adherence that still cause problems, even with modern meds that involve much fewer pills. It also covered new drug interactions that can be missed by non-HIV doctors including GPs and for supplements not included on the Liverpool drug interaction website, side effects, including weight gain and travelling.

Ref: Tablet tales - myths, misconceptions and other patient questions. BHIVA 2023. Community symposium.

https://vimeo.com/823030343 (webcast)

Providing mental health care and wellbeing in HIV

This symposium included two linked presentations relating to providing mental health care and psychological support as part of HIV care.

In the first, Sarah Rutter from Manchester University NHS Foundation Trust, talked about updating the standards of care with results from a consultation with people living with HIV. Hajra Okhai from University College London also provided an important update in the approach to addiction treatment.

In the second talk, Andrea Hearn from Newcastle Upon Tyne Hospitals NHS Foundation Trust provided an important overview on addiction treatment.

Links

Providing mental health care and wellbeing in HIV: Learnings from the field. BHIVA 2023. Symposium.

https://vimeo.com/823068713 (webcast)

Rutter S and Okhai H. Updating the Standards for Psychological Support for Adults Living with HIV: Results of the stakeholder pre-consultation. BHIVA 2023.

https://www.bhiva.org/file/645ba46c3cd2f/Sarah-Rutter-Hajra-Okhai.pdf (slides)

Hearn A et al. Recent updates in the provision of addiction treatment. BHIVA 2023.

https://www.bhiva.org/file/645ba46c54e5c/Andrea-Hearn.pdf (slides)

Weight gain and cardiovascular disease and integrase inhibitors

In an important invited lecture, Andrew Carr from St Vincent's Hospital, Sydney, provided a detail review of the data on weight changes and cardiovascular risk with ART and the recent associations to integrase inhibitors.

This included the historical timeline for linking individual HIV drugs to side effects that were not initially reported in phase three studies. It also included understanding the role of other HIV drugs that have recently been associated with weight loss.

Ref: Carr A. Longer-term safety of integrase inhibitors. BHIVA 2023. Invited lecture.

https://vimeo.com/823052252 (webcast)

Overview of weight gain, integrase inhibitors and ART

Kirk Taylor, HIV i-Base

BHIVA 2023 included a detailed overview of the association between weight gain and antiretrovirals by Professor Andrew Carr from St Vincent's Hospital Sydney. [1]

Both tenofovir disoproxil (TD) and efavirenz (EFV) have been linked to weight loss, whilst tenofovir alafenamide (TAF), dolutegravir (DTG) and bictegravir (BIC) are linked to weight gain.

In addition to the effect on quality of life, the clinical impact from each 5 kg/m^2 increase in BMI is a 30% increase in mortality. This effect is independent of age, sex or geographic region. For an average Australian man this would require a 15 kg increase in weight. ART-associated weight gain is between 2 kg to 10 kg.

WHO statistics show a tripling of the global prevalence of obesity (BMI >30 kg/m^2) between 1975 to 2016, then standing at 13%. Seven countries have a prevalence >30%, including the UK, led by America where 40% of adults are now estimated to be obese. Based on limited data, obesity is estimated between 15 to 39% in people living with HIV, showing a need for better research. Being overweight increases risk of comorbidities (e.g. cardiovascular disease (CVD), hypertension, type-2 diabetes, multiple cancers, sleep apnea and fatty liver disease).

Professor Carr emphasised the historical lag time (taking from 4 to 18 years) for establishing links between ART and comorbidities and that initial attribution has not always been correct. For example, the signal between myocardial infarction and abacavir (ABC) use took 10 years. Meanwhile, TDF-associated weight loss took 18 years and DTG-related weight gain has taken 6 years to establish. Although lipoatrophy was initially linked to PIs, it took five years to show that this was caused by the thymidine analogues AZT and d4T.

ART and weight gain: evidence from research studies

The talk reviewed several studies that reported weight changes.

- START reported weight loss for those with viral load <3000 copies/mL who started TDF-efavirenz (EFV) immediately. There were no differences in weight gain with higher baseline viral load when there would have been a return-to-health increase in weight.
- NA-ACCORD reported weight gain over six years for people receiving INSTIs (+5.9 kg, n=4093), protease inhibitors (+5.5 kg, n=7063) and NNRTIs (+3.7 kg, n=1071). The majority of the weight gain occurred within two years and then continued in line with the USA average (+0.5 to 1.0 kg/year).
- Gilead reviewed weight gain in their studies and reported odds ratios (OR) for weight gain with use of BIC or DTG vs EFV (OR: 1.82), rilpivirine (RPV) vs EFV (OR: 1.57), TAF vs ABC (OR: 1.90) or TAF vs TDF (OR: 1.47). Baseline CD4 count <200 cells/mm^3 (OR: 4.36), RNA >100,000 copies/mL (OR: 4.98), baseline BMI >25 kg/m^2 (OR 1.54), being a women (OR: 1.54) and Black ethnicity (OR: 1.32) all increased chance of weight gain (OR: ≥1.66).
- ADVANCE reported greater weight gain for women compared to men. This was higher in people using TAF vs TDF. It was also greater in people who received DTG vs EFV, although this effect was only seen in slow metabolisers of EFV. It is still unclear whether weight gain will continue or whether it reaches a plateau after about three years. Given the importance of ADVANCE in identifying weight increases, Carr showed two large South African datasets showing that after three years, the average weight in ADVANCE only returned

to the average weight. These population studies also report BMI as approximately 5 kg/m2 higher for women compared to men.

- IMPAACT/VESTED was largely run in Uganda, South Africa and Zimbabwe, and reported weight gain during pregnancy for DTG/TAF (+0.38 kg/week) that was close to the expected level (+0.42 kg/week) but this was significantly lower with EFV/TDF (+0.29 kg/week). Lower weight gain is linked to more adverse pregnancy outcomes and smaller babies.
- OPERA reported an approximate 2 kg increase over the first nine months after switching from TDF to TAF, before returning to a steady weight gain over five years similar to pre-switch. Weight gain at nine months for those also switching to an INSTI, NNRTI or PI was 2.64 kg, 2.25 kg or 1.98 kg, respectively. Subsequent weight gain was steady, suggesting it is not a sustained phenomenon.
- STEAL reported an approximate +1 kg difference in people switching NRTIs to include abacavir compared to TDF.
- TANGO reported no change in weight gain for people switching from TAF to DTG after three years, showing potentially a similar impact.
- NEAT022 reported greater weight gain at one year (+0.56 kg) for people who switched immediately from a PI to DTG. However, there is great variation in these data showing some people gain significantly more weight than others. During the second year, a similar increase was seen in the deferred switch group.

When considering the effect of ART on weight gain, we learn more from individual trials where single components are switched. At this level, data suggests that switching from elvitegravir (EVG) to BIC, from EFV to rilpivirine (RPV) or from ABC/TDF to TAF leads to a small increase in weight. No differences in weight occur when switching from DTG to BIC.

Data from PrEP in people who were HIV negative

PrEP studies provide opportunities to study direct effect of ART on weight gain without HIV-associated factors. Weight increases across one year for cabotegravir (CAB) were greater than for TDF-FTC at +1.3 kg and +0.3 kg, respectively ($p<0.001$). There were no differences when cabotegravir was compared to placebo, suggesting that weight loss caused by TDF was more likely than increases from cabotegravir.

Participants that received TDF in the iPrEX study experienced initial weight loss of 0.8 kg, which recovered to normal levels by year two. Conversely, participants on TAF or TDF in the DISCOVER study gained 1.7 kg or 0.5 kg across two years, respectively.

Comorbidities and INSTIs

RESPOND data show a prevalence rate for hypertension of 12.6% per 100 person years. Hypertension was more common on INSTIs than NNRTIs, but risk was similar for PIs and INSTIs.

Incidence of NAFLD (non-alcoholic fatty liver disease) is greater for people living with HIV who have diabetes (OR: 4.7), increased BMI (OR: 2.1) and women (OR: 7.3) but is not due to INSTI use (OR: 0.8). The risk of progression to fibrosis is greater for women (OR: 7.3). Excessive weight gain increases the incidence of diabetes and is more common in people who receive DTG or EVG.

Although the risk of CVD rises in the first three years of INSTI in unadjusted data, in adjusted analyses the signal peaks in the first six months and it is likely that people starting INSTI-based therapy have greater baseline CVD risk. The Swiss cohort study reported that the risk of myocardial infarction was 34.3% for people receiving an INSTI, compared to 65.7% for those on other ART regimens. Since 2013, this large cohort (n=5362) includes a third of people starting with INSTI-based regimen due to updated EACS guidelines.

The ATHENA cohort reported that CVD risk in the era of PIs was driven largely by traditional factors (e.g. smoking and hypertension). Carr believes that as INSTIs don't have similar metabolic effects to PIs, traditional factors will primarily drive CVD risk for people receiving INSTIs.

Approaches to reducing weight

In primary care settings, the single most effective weight loss strategy is to combine calorie restriction with increased physical activity.

People living with HIV who are already overweight or obese people can also consider: (i) switching away from an INSTI or TAF, (ii) weight loss medication (e.g. GLP-1 agonists), or (iii) bariatric surgery (currently only supported for HIV in limited case reports). Reviewing medications for comorbid conditions may also help (e.g.

antipsychotics and steroids). Although GLP-1 agonists report significant weight reductions (12% after a year) this commonly returns to baseline if therapy stopped.

A randomised placebo-controlled trial of switching from B/F/TAF to doravirine/islatravir (DOR/ISL) reported no significant increase in weight at year one (+0.3 kg, p=0.39). SOLAR reported no significant weight gain at one year after switching from B/F/TAF to long-acting injections of CAB+RPV. Notably, SOLAR participants were neither overweight at baseline nor did they experience weight gain on B/F/TAF.

In a placebo-controlled study, weekly dosing of a GLP-1 agonist (e.g. semaglutide) induced a 12% decrease in weight across a year, whilst reducing incidence of diabetes and CVD. Semaglutide is currently being investigated for use in people living with HIV who are obese.

What does this mean?

This data was then interpreted using the example of an average Australian man weighing 86 kg with a BMI of 27.8 kg/m^2 to model ART-related weight gain.

For each 15 kg of weight gain, their BMI increases by 5 kg/m^2 and their mortality risk rises by 30%. Expected weight gain on INSTIs or TAF is between 2 kg to 10 kg and may increase morbidity, which is linked to smaller BMI increments. However, Australian men are not an adequate marker for people living with HIV globally, especially as the ADVANCE study reported that weight gain disproportionately affected African women.

Whilst weight gain might not generally be severe, there are outliers and sub-groups where increased weight is likely to drive comorbidities and deaths, even without obesity. Weight gain associated with initiating INSTI-based therapy is greater than switching ART or taking PrEP, which may reflect the return to health phenomenon.

TDF and EFV have been linked to weight loss but TAF, DTG and BIC can increase weight. Other INSTIs (i.e. CAB) have not been linked to weight gain but dolutegravir was often used in the control groups.

It remains unclear why high levels of plasma tenofovir (TDF) induce fat loss but low levels (TAF) lead to weight gain. Traditional interventions to prevent and treat CVD and weight gain remain more beneficial than switching from an INSTI or TAF, but doing both might have additive results.

Less optimistically, the talk included the possibility that weight changes induced by ART might not be reversible, similar to weight gain experiences reported with steroids, antipsychotics and after pregnancy.

The Q&A to the talk included a discussion of whether TAF-associated weight gain is more related to the drugs that people have switched from (e.g. TDF or EFV). Although data to inform this question could come from a study that added either an INSTI or TAF to non-TDF containing ART, very few people use such combinations. There would be ethical issues in this approach and also for placebo-controlled studies in this area.

There is currently no mechanism to explain weight gain, although as 5% of people in PrEP studies withdraw due to nausea, there may be an effect on mitochondria and metabolism changes with INSTIs. However, there are limited mechanistic studies and we still don't know the root cause(s).

COMMENT

This excellent review highlighted the complexity of interpreting results from different study designs in different populations. Nevertheless, a common consideration was that the clinical implications are more significant for those with greatest increases in weight, including outliers and that these participants are often overlooked when average changes are reported.

For example, in ADVANCE some drugs are associated with weight gain and others with weight loss and these changes will cancel each effect when comparing average outcomes to expected weight in the South African general population datasets. The changes seen in ADVANCE linked to different components of ART are supported by the randomised study design.

Diet and exercise (ideally combining both) are currently first-line management for reducing weight, but this needs to be based on achievable goals and supported by professional advice. [2]

However, behaviour change can be difficult to sustain in the long-term, and these are not always easy to achieve in all settings. A WHO analysis from 121 studies looking at dietary interventions in over 20,000 participants only reported an average weight loss of –3 kg over 12 months. Adding exercise can have much more significant results.

Clarity about the impact of antiretrovirals is therefore critical to be able to individualise options for people who are most affected.

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2. Collins S. Weight changes on ART and how to lose weight successfully. HTB (1 June 2021). https://i-base.info/htb/40717

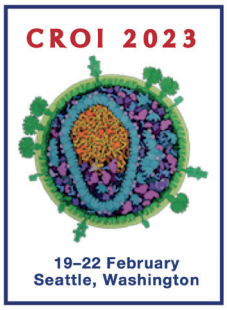
CONFERENCE REPORTS

30th Conference on Retroviruses and Opportunistic Infection (CROI 2023)

19–23 February 2022, Seattle and virtual

Simon Collins, HIV i-Base

Introduction



This year the annual Conference on Retroviruses and Opportunistic Infections (CROI) was held in Seattle and as a virtual meeting.

The programme was dynamic and exciting with much to report.

Open access to all other material including most webcasts is now available online.

https://www.croiconference.org/search-abstracts

New reports included in this issue of HTB are:

- Viral reservoir increases on long-term ART: new strategies for a cure
- Microbiota biomarkers might predict risk of HSIL progression: succinyl-CoA and cobalamin
- CROI overviews by BHIVA and IAS-USA

Viral reservoir increases on long-term ART: new strategies for a cure

Simon Collins, HIV i-Base

An excellent plenary talk by Janet Siliciano from Johns Hopkins University School of Medicine, Baltimore, reviewed how our understanding of the viral reservoir has developed over the last 25 years.

This residual pool of latently infected long-lived resting cells was discovered during the early years of ART. It prevents HIV treatment from eradicating the virus and is a significant barrier to an HIV cure.

These cells can proliferate by clonal expansion without being activated and are not affected by ART. They will however, rapidly activate and cause viral rebound if ART is stopped. The reservoir is established within weeks of initial HIV infection.

Until recently, researchers measuring the size of the reservoir using quantitative viral outgrowth assays (QVOA), showed that on suppressive ART the reservoir continues to steadily decline over many years, with a cellular half-life of 3.7 years. New data in 2023 show that this decline does not continue indefinitely but actually slightly increases due to cellular proliferation. [2]

The reservoir is therefore in a dynamic state of change. Over time, an increasing proportion of clonally identical cells harbouring defective HIV (due to large sections of internal deletion and hypermutation) become the majority in the reservoir. These single or multiple clones can also proliferate in response to antigen, to cause viral load to become detectable at low levels. In this case, changing or intensifying ART will not suppress viral load.

But even after 20 years on suppressive ART, a minority of cells carrying replication competent virus still persist in people on very long-term ART. And it is this minority of phylogenetically distinct minor variants, representing less than 1% of the viral reservoir, that cause rapid and substantial viral rebound if ART is stopped. These variants are not detected in viral outgrowth tests.

One optimistic implication from this new data is that rather than needing to activate the total viral reservoir, this component of curing HIV might only need to selectively target the subset of cells responsible for viral rebound.

In order to significantly delay viral rebound without ART, or to reduce it to a level that immune-based strategies might be able to control any rebound, the reservoir – estimated at 10 x 10(9) log cells – would need to be reduced by >5 to 6 logs. Modest reductions by only 1 to 2 logs only delay rebound by a couple of weeks. [3]

References

Unless stated otherwise, references are to the Programme and Abstracts of the 30th Conference on Retroviruses and Opportunistic Infections, 19 – 22 February 2023, Seattle and hybrid.

www.croiconference.org/search-abstracts

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2. McMyn MF et al. Persistence of inducible replication-competent HIV-1 after long-term ART. CROI 2023. Poster396. https://www.croiconference.org/abstract/persistance-of-inducible-replication-competent-hiv-1-after-long-term-art/
3. Peluso MJ et al. rebound dynamics following immunotherapy with an HIV vaccine, TLR9 agonist, and bNAbs. CROI 2023. Poster 435. https://www.croiconference.org/abstract/rebound-dynamics-following-immunotherapy-with-an-hiv-vaccine-tlr9-agonist-and-bnabs/

Microbiota biomarkers might predict risk of HSIL progression: succinyl-CoA and cobalamin

Simon Collins, HIV i-Base

An oral presentation by Sergio Serrano-Villar from Hospital Ramón y Cajal, Madrid looked at whether certain microbiota could predict the risk of progression from HSIL to anal cancer.

The group developed two cohorts of largely MSM being screened for HSIL with high-resolution anoscopy and anal biopsies to confirm HSIL One cohort (n=167, with 70 confirmed HSIL) was to identify potential biomarkers from the bacterial DNA, proteins, and metabolites from anal cytology samples and the second (n=46, with 25 confirmed HSIL) was used to validate any findings.

HSIL was associated with higher levels of Prevotella copri (over-expressing proteins to produce succinyl-CoA and cobalamin) and lower levels of Sneathia sanguinegens.

The combination of succinyl-CoA and cobalamin improving sensitivity from 91.2% to 96.6%, specificity from 34.1% (from anal cytology), to 81.8%. This increased the positive predictive value from 48.1% to 77.8%, and negative predictive value from 85.3% to 97.3%.

The combination of both metabolites improved the classification to 87.7% compared to only 59.9% with anal cytology and the study concluded that these two biomarkers could improve the current strategy for anal cancer screening.

C O M M E N T

These preliminary results are interesting and other research groups are investigating changes in metabolic pathways (metabonomics) in cancer detection and diagnosis, so this might become a useful tool in the future.

However, what works in one specialist centre's research lab does not often translate to universal applicability. Non-standardised tests need to be validated and will come with additional costs that may outweigh the cost efficiency advantage of improved accuracy of screening.

Reference

Serrano-Villar S et al. Microbiota-derived metabolites are powerful biomarkers for anal cancer prevention. CROI 2023. 19 – 22 February 2023. Oral abstract 148.
https://www.croiconference.org/abstract/microbiota-derived-metabolites-are-powerful-biomarkers-for-anal-cancer-prevention

CROI overviews by BHIVA and IAS-USA

Simon Collins, HIV i-Base

Several other medical organisations have produced excellent overviews on research topics that i-Base hasn't covered.

BHIVA Best of CROI

Every year BHIVA hold several feedback meetings based on studies selected by BHIVA members who were able to attend the conference. Each meeting in now online as webcasts and includes five short 10-minutes talks from BHIVA experts followed by an audience Q&A.

These talks cover prevention strategies, antiretroviral studies, comorbidities & ageing, hepatitis. TB and COVID, and women & vulnerable populations.

The two virtual meetings this year were held on 7 and 13 March and webcasts are available online:

https://www.bhiva.org/BestofCROI2023

IAS-USA webinars

Eight e-publication articles produced by IAS-USA who organise the annual CROI conferences are now available online. They are published in the May and June issues of the IAS-USA journal *Topics in Antiviral Medicine*.

May 2023

https://www.iasusa.org/tam/may-2023/

- Epidemiology, diagnosis, and management of HIV
- Advances in antiviral therapy in HIV and viral hepatitis
- Epidemiologic trends and prevention for HIV and other sexually transmitted infections
- Acute and post-acute COVID-19

June 2023

https://www.iasusa.org/tam/june-2023

- Summary of basic science research in HIV
- Metabolic and other complications of HIV infection
- Tuberculosis and infectious complications in persons with HIV
- Neuropsychiatric complications in people with HIV

ANTIRETROVIRALS

ART increases life expectancy by 30 to 40 years: impact of CD4 count, sex and calendar year

Kirk Taylor, HIV i-Base

The Lancet HIV has published a large collaborative cohort study (n=206,981) that predicts life expectancy for people living with HIV on long-term ART. [1]

Two cohorts included data from people who started ART between 1996 and 2019 and who had been on ART for ≥1 year. Life expectancy was estimated from associations between mortality and clinical and demographic factors.

This was a retrospective analysis of the Antiretroviral Therapy Cohort Collaboration and the UK Collaborative HIV Cohort Study. Mortality risk ratios were calculated by Poisson regression models for women and men, based on starting ART before or after 2015, and reported as predicted life years remaining at age 40.

When ART was started before 2015, estimated life expectancy was 75.8 years (95% CI: 75.2 to 76.4 years) for women and 74.5 years (95% CI: 73.8 to 75.2 years) for men. Life expectancy increased for people who started ART after 2015 and is estimated at 79 years (95% CI: 78.5 to 79.5 years) for women and 77.0 years (95% CI: 76.5 to 77.6 years) for men. Life expectancy estimates correlated with CD4 count at start of follow-up. Table 1 summarises estimated life expectancy by sex, CD4 count and year of ART initiation.

These data suggest that life expectancy has increased by 4.6 years for women and 1.8 years for men relative to predictions made in 2016 by the Kaiser Permanente analyses. [2]

Overall, life expectancy remains lower than for HIV negative individuals.

The largest influence on life expectancy was CD4 count at start of follow-up. These data highlight the efficacy of ART and the importance of early diagnosis and sustained ART. Starting ART after 2015 increased life expectancy by about three years.

Table 1: Predicted life expectancy in years (95% CI) stratified by sex, year of ART initiation and CD4 count at start of follow-up.

	Women		Men	
Baseline CD4 (cells/mm^3)	**1996 to 2014**	**2015 to 2019**	**1996 to 2014**	**2015 to 2019**
0 to 49	69.4 (58.2 to 60.5)	64.9 (63.9 to 65.9)	58.2 (57.1 to 59.4)	63.7 (62.7 to 64.8)
50 to 99	63.2 (62.2 to 64.3)	68.9 (67.9 to 69.8)	61.3 (60.2 to 62.4)	66.9 (65.9 to 67.9)
100 to 199	67.8 (66.8 to 68.7)	73.0 (72.2 to 73.7)	66.2 (65.2 to 67.2)	71.7 (70.9 to 72.5)
200 to 349	73.6 (72.8 to 74.3)	78.0 (77.4 to 78.5)	72.1 (71.3 to 72.9)	76.5 (75.9 to 77.1)
350 to 499	77.6 (77 to 78.1)	80.8 (80.4 to 81.2)	76.2 (75.6 to 76.9)	78.4 (77.9 to 78.9)
≥500 CD4	80.2 (79.7 to 80.6)	82.0 (81.7 to 82.3	78.0 (77.5 to 78.5)	79.2 (78.7 to 79.7)

COMMENT

These results are encouraging and are welcomed. They provide confidence for people to make long-term life plans and they challenge the continued stigma associated with HIV.

However, there are also significant differences within the average estimates.

An editorial comment on this study noted that life expectancy still remains lower than the general population. Also, that comorbidities occur approximately ten years earlier for people living with HIV and that this would likely impact on differences in quality of life. [3]

Although there were few differences in life expectancy between women and men in this study, in relative terms this shows a reduced benefit for women, who generally live an additional 4 to 8 years compared to men. No data was presented for transgender individuals.

Injecting drug use was also linked to shorter life expectancy.

The US cohort also reported that life expectancy was approximately a decade shorter for Black compared to white gay and bisexual men and a similar impact from injecting drug use.

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   https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(23)00060-7/fulltext

TREATMENT GUIDELINES

BHIVA guidelines modify assessment of cardiovascular risk (2023)

Simon Collins, HIV i-Base

On 28 May 2023, BHIVA added a short note on cardiovascular assessment to the 2022 guidelines and published this as an interim update.

The new text was added to section 8.3.1 on page 157 and is included below.

New text in 2023 interim update:

The previous advice to adjust estimated CVD risk by a factor of 1.6 for people living with HIV has been removed based on limited evidence. CVD risk assessment will be included in the next update of the BHIVA monitoring guidelines. It is important to acknowledge that standard tools, such as QRISK, may underestimate CVD risk for some populations, including people living with HIV, as acknowledged by the NICE guidelines for estimating CVD risk [68].

We suggest assessing individuals on a case-by-case basis, considering HIV-specific CVD risk tools, and that clinical judgement should be applied when interpreting risk assessment scores [68,81].

68. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline [CG181]. 2014. Available at: https://www.nice.org.uk/guidance/cg181 (accessed July 2021).

81. Healthcare Improvement Scotland. Risk estimation and the prevention of cardiovascular disease (SIGN 149). 2017. Available at: https://www.sign.ac.uk/media/1085/sign149.pdf (accessed May 2023).

Reference

BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022 (2023 interim update). 28 May 2023.

https://www.bhiva.org/HIV-1-treatment-guidelines (download page)

https://www.bhiva.org/file/63513a1745ea9/BHIVA-guidelines-on-antiretroviral-treatment-for-adults-living-with-HIV-1-2022.pdf (direct PDF)

BHIVA guidelines on non-TB mycobacteria (NTM)

BHIVA.org

The section of the BHIVA OI guidelines on non-tuberculous mycobacteria (NTM) is now posted online and is available for comment.

A wide spectrum of non-tuberculous mycobacteria (NTM) has been reported as isolates from or causes of disease in people living with HIV.

This is typically in the context of very advanced immunosuppression in the absence of virological suppression with ART and most people have presented with disseminated disease.

NTM are environmental organisms. Therefore it is important to determine, prior to treatment initiation, whether the organism is the cause of the disease process rather than a reflection of subsequent colonisation.

With the exception of Mycobacterium avium complex (MAC), there is limited evidence to guide the choice or duration of treatment and expert opinion should be sought from a clinician experienced in managing mycobacterial disease in the context of HIV.

Also, with the exception of MAC, most of the recommendations for the treatment of NTM have been extrapolated from trials of treatment for NTM pulmonary disease in individuals without HIV, although some evidence from early trials in populations with advanced HIV has added to this guidance.

The consultation will be open until 5.00pm on Wednesday 17 May 2023.

Ref: British HIV Association guidelines on the management of opportunistic infection in people living with HIV: The clinical management of non-tuberculous mycobacteria 2023.

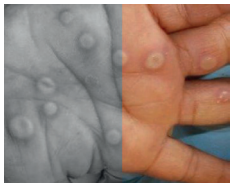
https://www.bhiva.org/OI-guidelines-NTM

MPOX (MONKEYPOX)

US studies report mpox vaccine efficacy from single- vs double-dose might only be 36% vs 66%

Simon Collins, HIV i-Base

There is limited direct data available to estimate the efficacy of the mpox vaccine used last year (Imvanex, Imvamune, Jynneos, MVA) – and, for ethical reasons, none from prospective randomised controlled studies.



In addition, recent estimates from observational studies are flawed by not adjusting for demographic and other factors associated with both risk and likely access to vaccines.

A large case-control study published in the NEJM is therefore important for having a closer match between participants in the case and control groups, including for markers associated with health-seeking behaviour and for calendar time. [1]

The study used data from a large electronic database (>170 million records) to identify 2266 cases (diagnosed with mpox) who were matched (at least 1:4) to two control groups: (i) 4033 people recently diagnosed with HIV, and (ii) 20,570 HIV negative men actively receiving PrEP. All criteria related to a three-month period from mid-August to mid-November 2022.

Most importantly, the study adjusted for vaccination status, age group, ethnicity, social vulnerability index and presence or absence of HIV-related complications. It also reported results that showed significantly lower efficacy rates compared to previous studies and significantly lower levels of protection after only one dose of the vaccine.

Overall 25/2193 cases and 335/8319 controls received two doses (full vaccination). This produced an adjusted vaccine efficacy of 66.0% (95%CI: 47.4 to 78.1). In the 146 cases and 1000 controls who received only one vaccine dose, estimated efficacy dropped to 35.8% (95% CI: 22.1 to 47.1).

COMMENT

Although several observational studies have reported high levels of protection (>85%), including from the US, UK and Israel, these results have not been adjusted for the demographic and behavioural differences between groups who received the vaccine vs those who didn't, even though these differences have been widely acknowledged. [2, 3]

Vaccinations were disproportionally accessed by largely white cis gay men who were already connected to social media networks used to publicise vaccine programmes. These people were often at lower or even negligible risk from mpox, and in whom mpox cases would be expected to be significantly lower.

Other challenges in estimating mpox vaccine efficacy include:

- **Case numbers of mpox were already dropping before vaccines were widely available, certainly in the UK.**
- **Uncertainty over the time needed between having a vaccine shot and developing an immune response (likely at least two weeks).**
- **Continued behaviour changes to reduce risk, so that people actively seeking vaccines might also continue to cautiously avoid risk until at least two weeks after the second dose (if available) and possibly for much longer.**

The results from the current paper by Deputy et al are therefore welcomed as a more reliable base to estimate population risk from future outbreaks of mpox.

Recent modelling by the US CDC calculated that at least 33% of the at-risk population need to have full vaccine cover in order to prevent an outbreak similar to that in 2022. [4]

Currently, only around 26,000 gay and bisexual men in the UK at highest risk have received two vaccines. [5]

As this report was published, a second US case-control study was published by MMWR reporting higher levels of vaccine efficacy. [6]

This study used conditional logistic regression models that adjusted for week of diagnosis, region, age, race and ethnicity. Among 252 eligible mpox cases and 255 controls, the vaccine efficacy of one dose (received ≥14 days earlier) was 68.1% (95% CI: 24.9% to 86.5%) and for two doses was 88.5% (95% CI: 44.1% to 97.6%).

Both studies emphasise the importance of completing the two-dose course of injections.

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COMPLICATIONS

No benefit on HIV-associated neurocognitive impairment from CNS-penetrating ART

Kirk Taylor, HIV i-Base

A randomised-controlled trial (ACTG5324) of ART intensification for people with HIV-associated neurocognitive impairment (NCI) was published in Clinical Infectious Diseases. [1]

Dolutegravir (DTG) or maraviroc (MVC) were added to existing ART regimens because they achieve therapeutic levels in cerebrospinal fluid.

Adding DTG+MVC to ART did not lead to global improvement of NCI overall although verbal learning and memory tests showed some benefit.

People living with HIV (n=191) were recruited into the double-blind placebo-controlled study across 24 sites, including the USA, Brazil and South Africa. Participants were randomised 1:1:1 to either dual placebo, DTG + placebo or DTG+MVC and followed over two years. The primary outcome was the change from baseline to week 48 based on the mean of the individual NC test z-scores.

Participant demographics included 21% women, 51% Black, 22% Hispanic and mean age was 54 (SD ±8) years. Baseline viral load was ≤50 copies/mL, mean CD4 count was 703 (±300) cells/mm^3 and 30% had a CD4 nadir <100 cell/mm^3. Gender identity was not collected. Exclusion criteria included a wide range of factors that could contribute to NCI, including previous depression and current substance use.

Multiple comorbidities included an average of ≥4 conditions (e.g. 39% hypertension, 12% asthma or 12% arthritis). All participants had NCI at baseline and two thirds met the criteria for HIV-associated dementia (HAND).

NCI was assessed at six-month intervals using a battery of neurocognitive tests across six domains and classified according to Frascati criteria. Tests were translated for non-English speaking regions and regular training was given to those administering the tests.

In all arms, total z-score, depressive symptoms, and daily functioning improved over time, with no significant differences between them at week 48 or later in adjusted analyses. This disproved the study hypothesis that NCI was linked to residual HIV replication.

The DTG+MVC arm showed greatest improvement relative to placebo (p=0.01) for verbal learning (z-score 0.53, 95% CI: 0.26 to 0.79) and memory domains (z-score 0.64, 95% CI: 0.24 to 1.04). For all other test domains, changes were similar across all arms and sub-analyses by HAND diagnosis or CD4 nadir were not significant.

CD4 and CD8 cell counts increased in the DTG+MVC arm compared to dual placebo. Over two years mean BMI increased by 0.32 kg/m^2 (95% CI: 0.11 to 0.74 kgm^2) across all study arms and was not due to DTG use.

Adverse events (n=15) were between grades 1 to 3 and included reduced creatine clearance (n=6) and gastrointestinal disorders (n=5). Virologic failures were reported for participants on the dual placebo (n=4) and DTG+MVC (n=1) arms.

C O M M E N T

The lack of benefit from adding HIV drugs that cross the blood-brain barrier to ART for people diagnosed with HIV-associated neurocognitive impairment is an unexpected finding that challenges current HIV treatment guidelines.

Even though this is the largest RCT on this issue, the discussion in the paper includes that the study was likely underpowered for some of the results that it reported, including the impact on people with higher scores of NCI impairment.

This study was sponsored by the US NIH.

Reference:

Letendre SL et al. Antiretroviral therapy intensification for neurocognitive impairment in HIV. 2023 Clinical infectious diseases, ciad265, DOI 10.1093/cid/ciad265. (15 May 2023).

https://pubmed.ncbi.nlm.nih.gov/37183889

First successful liver transplant from living donor with HIV/ HCV coinfection: surgical video online

Simon Collins, HIV i-Base

In March 2023, the journal AIDS included the first case report of a successful liver transplant where the donor was living with both HIV and HCV.

The donor was a mother in South Africa and the recipient was her child. Neither the donor nor the recipient experienced any complication.

This showed that people with well controlled HIV/HCV and without additional risk factors may be suitable to donate part of their healthy liver.

The case is presented in a remarkable short open access video that includes film of the surgery.

Reference

Sandro D et al. Successful living donor liver transplantation from an HIV and HCV positive donor: report from the first case in the world. Concise communication. AIDS doi: 10.1097/QAD.0000000000003533. (6 March 2023)

https://journals.lww.com/aidsonline/Abstract/9900/Successful_living_donor_liver_transplantation_from.220.aspx (web page)

https://cdn-links.lww.com/permalink/qad/c/qad_2023_02_26_disandro_aids-d-22-00707_sdc3.mp4 (video report)

Review of idiopathic lymphocytopenia

Simon Collins, HIV i-Base

A useful report in the NEJM reviews data on idiopathic lymphocytopenia (ICL) that might be useful for HIV doctors who periodically might be contacted for their experience in managing people with suppressed CD4 counts.

The lack of mechanism to explain reductions in CD4 counts not related to HIV or use of immunosuppressants is difficult.

This study reports the clinical, genetic, immunologic, and prognostic characteristics of 91 people with ICL who were enrolled during an 11-year period. Median follow-up was 3 years (IQR: 0 to 6).

Whole-exome and targeted gene sequencing were used to identify genetic causes of ICL and reported factors associated with clinical events, responses to Covid-19 vaccinations, and mortality.

The median CD4 and CD8 counts were 80 cells/mm^3 (IQR: 25 to 168) and 130 (IQR: 58 to 317), respectively. Median NK cells were 142 (IQR: 100 to 378) and B cells were 144 (IQR: 92 to 218).

The most common opportunistic infections overlapped with those reported in advanced HIV and included:

- Severe skin or anogenital human papillomavirus (HPV)-related diseases (n=27 patients)
- Cryptococcosis (n=22 patients), which presented as meningoencephalitis, pneumonia, and disseminated skin or musculoskeletal diseases.
- Molluscum contagiosum (n=8)
- Disseminated nontuberculous mycobacterial infection (n=2).
- Disseminated histoplasmosis (n=2) and pulmonary histoplasmosis (n=2).
- Progressive multifocal leukoencephalopathy (PML) (n=3).
- Cytomegalovirus diseases (colitis and retinitis in 1 patient each).
- Pneumocystis jirovecii pneumonia (PJP), oral candidiasis, pulmonary coccidioidomycosis, and pulmonary aspergillosis were observed in 1 patient each.

A total of 21 of 53 people (40%) had at least two different opportunistic infections.

C O M M E N T

Although idiopathic lymphocytopenia is by definition not related to HIV, the i-Base information service has also been contacted by people with significant and progressive immune suppression.

For some reason, these individuals have great difficulty getting access to prophylaxis medicines used in the management of advanced HIV.

Reference

Lisco A et al. Reappraisal of Idiopathic CD4 Lymphocytopenia at 30 Years. N Engl J Med 2023; 388:1680-1691. DOI: 10.1056/NEJMoa2202348. (4 May 2023).
http://www.nejm.org/doi/full/10.1056/NEJMoa2202348

COVID-19

Tenofovir reduces risk of COVID-19 in pre-vaccine studies

Simon Collins, HIV i-Base

Long after most people will be following this research, several studies have reported a protective impact of tenofovir (TD or TAF) on the risk of catching SARS-CoV-2 and/or on the severity of symptoms.

As a caution, including the latest study published in CID, this data is from the early COVID-19 epidemic, before vaccines became available. Results were seen both for people living with HIV taking ART and for HIV-negative people taking PrEP.

References

1. Lea AN et al. HIV status, tenofovir exposure and the risk of poorCOVID-19 outcomes: Real-world analysis from 6 United States cohorts before vaccine rollout. Clinical Infectious Diseases 76(10):1727–1734. (15 May 2023).
https://doi.org/10.1093/cid/ciad084
2. Julia del Amo. Question of whether tenofovir disoproxil fumarate/emtricitabine provides protection against clinical severity of coronavirus disease. 2019 Clinical Infectious Diseases, 76(10):1735–1737. (15 May 2023).
https://doi.org/10.1093/cid/ciad086

DRUG RESISTANCE

Tracking HIV A6 strain in Europe: implications for injectable CAB-LA for treatment or PrEP

Simon Collins, HIV i-Base

A phylogenetic and modeling study about the spread of the A6 strain of HIV in Europe has been published in CID together with an editorial looking at the clinical implications for using injectable cabotegravir as treatment or prevention.

Earlier research reported that A6 is associated with a lower barrier to developing cabotegravir resistance and a higher risk of treatment failure, even in the context of perfect adherence to two-monthly injections.

Other factors identified in the low number of treatment failures include baseline resistance to rilpivirine, low drug levels of rilpivirine, BMI >30 (perhaps linked to lower drug levels), and the L74I integrase mutation (when other factors are present).

A6 was previously reported as circulating in Russia and Ukraine but the migration due to the war against Ukraine has also been associated with new cases being identified in Poland, and likely other European countries.

The accompanying editorial notes that CAB-LA failure rates are low, but this risk increases when several of the above risk factors are present.

Having the A6 strain as the only risk doesn't prevent effective use of CAB-LA, so management can be individualised, perhaps with closer monitoring. Use would not be recommended though if A6 is present together with other factors associated with treatment failure.

References

1. Serwin K et al. Circulation of HIV-1 A6 variant in the eastern border of the European Union—dynamics of the virus transmissions between Poland and Ukraine. Clinical Infectious Diseases, 76(10):1716–1724. (15 May 2023)
   https://doi.org/10.1093/cid/ciad058
2. Schapiro JM. Dynamics of Human Immunodeficiency Virus Type 1 A6 Variant Transmissions Between Poland and Ukraine, Clinical Infectious Diseases, 76(10):1725–1726. (15 May 2023).
   https://doi.org/10.1093/cid/ciad062

HIV PREVENTION

NHS England approves use of F/TAF as alternative PrEP

Simon Collins, HIV i-Base

On 24 May 2023, NHS England updated guidelines on PrEP to include tenofovir alafenomide (TAF) as a component of PrEP.

Previously, PrEP was only reimbursed for generic formulations of tenofovir disoproxil (TD).

In both cases, TD or TAF need to be used in a combination tablet that also includes emtricitabine (FTC).

F/TAF is now approved for cases where preexisting bone or kidney disease limits the use of TD.

The paper estimates that this might affect from 400 to 700 people currently in need of this second-line PrEP. This estimate is based on 40,000 to 70,000 people currently using PrEP in the UK.

Reference

NHS England. Reimbursement for the use of generic drugs for pre exposure prophylaxis (PrEP) for the prevention of HIV. (24 May 2023).

https://www.england.nhs.uk/publication/reimbursement-for-the-use-of-generic-drugs-for-pre-exposure-prophylaxis-prep-for-the-prevention-of-hiv/

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

15th AIDS Impact Conference

12 – 14 June 2023, Stockholm, Sweden

www.aidsimpact2023.com

HIV Cure & Immunotherapy Forum

22 July 2023, Brisbane, Australia

www.iasociety.org/conferences/ias2023/take-part/pre-meetings

12th IAS Conference on HIV Science

23 – 26 July 2023, Brisbane, Australia

iasociety.org

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

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

8 – 10 November 2023, Cape Town, South Africa

www.sahcsconference.co.za

2024

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

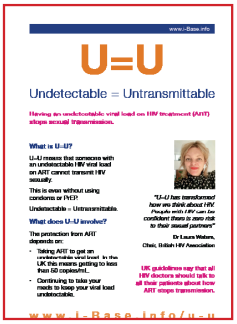
- Introduction to ART (May 2022)
- HIV & quality of life: side effects & long-term health (Sept 2016)
- Guide to PrEP in the UK (February 2022)
- HIV testing and risks of sexual transmission (June 2021)
- Guide to changing treatment and drug resistance (August 2021)
- Guide to HIV, pregnancy & women's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

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

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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- **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