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hiv treatment bulletin (e)

EACS and HIV & Ageing (1 December 2023)

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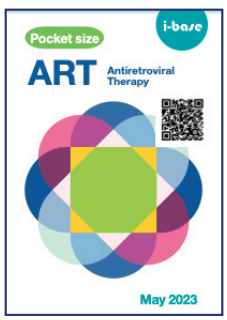

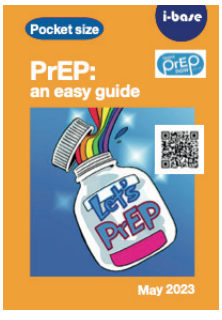

EDITORIAL

Welcome to the last edition of HTB for 2023.

We lead with a report on the latest HIV statistics in the UK that show a sustained drop in new infections, although with difference based on demographics, and a concern that late diagnoses still make up an overall large percentage of new cases.

This includes using the i-Base appeal to help an LGBTQI+ community in the Kakuma refugee camp in Kenya, many of whom fled Uganda earlier this year due to increased persecution after the Anti-Homosexual Act.

- We continue with reports from the recent ageing workshop with a focus on sarcopenia and news from EACS includes a major revision in European Guidelines.
- Global news includes the annual price of TLD (tenofovir/lamivudine/dolutegravir) dropping to US $45 in eligible low-income countries. This astonishing achievement shows the importance of having ambitious targets for universal health care. It shows that combining scientific advances with an activist determination from multiple stakeholders can achieve results that were never imagined when the early breakthrough of ART - then HAART - was reported more than 25 years ago.
- We report a potential for a nanoformulation of this combination as a once-monthly injection.
- But also include concerns about the sustainability of international funding in a report from CHAI and that the mortality risk for children under five remains much higher than for older children living with HIV.
- Other articles in this issue include reports on strategy studies for current ART and cautions about what to avoid, all-be-it with challenging data.
- BHIVA has published the first national guidelines on earlier use of statins based on the results of the REPRIEVE study. Notably, the latest US HIV guidelines still refer to REPRIEVE results as not being expected for several years.
- A drug interaction between NRTIs and bNAbs…
- Although mpox cases remained thankfully low throughout 2023, even with limited data on durability of vaccine responses, we include a brief review of recent papers, with the highest risks linked to advanced HIV infection.

- Finally, we review a new book by five leading African women, all proudly living with HIV, who document the African response to HIV in the UK in a compilation of more than 40 personal stories.

This will also be the last issue of HTB in this current format.

Since April 2000, HTB has compiled critical reviews of research that affects the clinical care of people living with HIV. We are proud to be one of the longest running HIV community publications, certainly with a focus on treatment. But change can also be good and we have done this before.

The forerunner of HTB was a fortnightly bulletin sent to doctors by fax and appropriately named DrFax. Multiple news sources now send out bite-size summaries of new data often before the research has even been presented. Both urgent and non-urgent news is now available instantly.

So it is also time for change - and change in a new year can be a good thing.

Thank you too all our readers and supporters and to the team at i-Base.

Best wishes for the seasonal holidays and the New Year ahead.

i-Base 2024 appeal: projects to support

This year the i-Base appeal includes options for readers to support community projects during 2024.

i-Base appeal 1: Help LGBTQI+ refugees in Kakuma

https://www.gofundme.com/f/help-lgbti-refugees-in-kenya

Although i-Base always needs help ourselves, this year we want to prioritise direct help to people affected by the Uganda Anti-Homosexuality Act.

This legislation attacked both LGBTQI+ individuals and anyone seen as providing support. It meant many people have lost their homes and jobs and the threat of physical assault or imprisonment meant many people left Uganda, including to claim asylum as refugees in neighbouring countries, when possible.

This has led to an expanding LGBTQI+ community in the UN refugee camp in Kakuma in north Kenya, which actually provides little security or safety.

The previous issue of HTB included a report that documented human rights abuses in Uganda due to the recent legislation and other links are included

for more information.

The following project below uses GoFundMe to support this community response.

This appeal is to help with basic needs including towards meals for LGBTQI+ refugees living in the Kakuma camp.

The current food allowance is 1 kg of rice, 1 kg of yellow peas and 1 litre of cooking oil per person per month.

This project will provide support for a stronger network of community support.

Any donation, however small, will make a difference for a community that still faces stigma and violence and that depends on support.

i-Base appeal 2: i-Base resources for NHS clinics

Individual donations from readers towards i-Base projects are also appreciated and always make a difference.

We use this support to fund leaflets and treatment guides that are used by sexual health clinics. We continue to provide all materials free to NHS clinics and to individuals.

During 2023, i-Base distributed more than 60,000 treatment guides to UK clinics.

i-Base only accepts independent funding to print these resources.

Reference

Uganda report: Increase in LGBTQI+ assaults and human rights violations need urgent activist responses. HTB October 2023.

https://i-base.info/htb/46384

SPECIAL REPORT

Latest figures published on HIV in the UK: 2023 report

Simon Collins, HIV i-Base

On 6 October 2023, UKHSA published the latest annual report on HIV, together with the supporting data tables. [1, 2]

This essential resource is always an impressive achievement that provides the evidence to plan services by highlighting recent trends as well as current needs.

It includes data from 2022 on HIV testing, new diagnoses and access to ART together with other key measures including use of PrEP. Breakdowns by age, sex, gender, ethnicity, sexuality, geographic region and other related factors are included (mainly based on data for England). Results from 2022 are also compared to previous years.

Data for Scotland were published by Public Health Scotland in September 2023. [3]

Summary points are included below.

HIV testing

More than 1,155,000 people had an HIV test at a sexual health services (SHSs) in England (rather than in other settings including pregnancy). This was 10% higher than in 2021 but still 16% lower than in 2019.

As in 2021, half of these were home tests ordered online.

Overall, approximately half the people who were eligible to need a test in a clinic took up this offer. Uptake

was higher by gay and bisexual men (74% tested, 23% not offered, 3% declined) compared to straight and bisexual women (38% tested, 40% not offered, 22% declined).

HIV PrEP

The proportion of clinic visits from people who could benefit from PrEP increased to 9.7% in 2022 to over 121,000.

Uptake varied by risk group: 59% of straight and bisexual women (n=2,695), 63%,of heterosexual men (n=2,607) and 84% of gay and bisexual men (n=83,223).

HIV diagnoses

Overall, HIV diagnoses in England rose by 22% from 3,118 in 2021 to 3,805 in 2022.

Of these, approximately one-third (1361/3805) were previously diagnosed outside the UK. Most were already on ART when they came to the UK, with an undetectable viral load (87%), and 96% were linked to UK care within three months.

New first-diagnoses in England increased by 6% from 2,313 in 2021 to 2,444 in 2022.

- 8% drop in gay and bisexual men to 724 in 2022, including a 3% drop in London (n=244),
- 14% increase in men and women in London identifying as straight to 325.
- 11% increase in men and women outside London identifying as straight to 651.
- 31% increase in women living outside London to 393. Of these, 77% (301) were born outside the UK.

Late and very late HIV diagnoses

The report notes that almost half (44%) the new diagnoses in England were late, based on having a CD4 count <350 cells/mm^3.

However, this 44% is based on a denominator of only 865 people diagnosed in England and who had not been previously diagnosed in another country. This is because a significant percentage of other people diagnosed for the first time in the UK were originally diagnosed outside the UK and most had undetectable viral load on ART.

The data tables report the combined figures. Table 1b shows 608/1997 men (35%) are listed as being diagnosed late and 387/1154 women (33%). This shows 1080/3151 people were diagnosed with a CD4 count <350 cells/mm^3 (roughly 34%),

The summary report also misses out information on very late diagnosis defined as having a CD4 <200 cells/mm^3.

Table 1a7 shows that 1081 people (34%) were diagnosed late with a CD4 <350 and a further 624 people (20%) were diagnosed very late with a CD4 <200 cells/mm^3. These figures show overall late diagnosis at 54% (1705/3155).

Although this figure for late diagnosis should ideally be adjusted to exclude people diagnosed in acute infection, before the expected rebound, it isn't clear whether this adjustment is included yet.

No data is provided for people with more serious immunosuppression, including those with a CD4 count <50 cells/mm^3. People in this category are at the highest risk for all opportunistic infections, including mpox where cases can be fatal, and including active CMV which requires urgent monitoring. They also have more difficulty normalising their CD4 count on ART and are likely to have more complex risk of future complications.

Table 1a7 also includes that 4% of diagnoses (n=155) had symptoms of opportunistic infection that made these advanced HIV disease (the new WHO recommended term for the historical diagnosis of AIDS)

HIV-related deaths during 2022

During 2022, there were 603 deaths in 473 men and 130 women: 22 aged <35, 120 aged 35 to 49, 338 aged 50-69, 123 aged >70.

Of these, 261/603 were gay men, 143 straight men and 100 straight women.

Breakdowns are provided by sex for ethnicity, age, probable route of infection, country of birth and broad

demographics of the epidemic in the UK.

Key points from Scotland (December 2022) include:

- An estimated 6,600 people were living with HIV in Scotland, of whom 6,150 (93%) had been diagnosed.
- Of those engaged with HIV services, 98% were on ART and 93% of those had undetectable viral load.
- A continued decline in recently acquired HIV (within the previous 3-4 months).
- In 2022, 24 of 108 (22%) first ever diagnoses were made at a late stage of infection, 16 (67%) of which were very late stage, with advanced HIV disease.

C O M M E N T

These annual data sets and accompanying reports are always important and further analyses are still ongoing, including on mortality.

The impact of COVID, and to a lesser extent mpox, on social behaviour, testing and access to services still affects these figures, limiting the interpretation of trends.

A further report, not yet released will report on progress towards the 2025 target goals. [4]

This includes the commitment to achieving zero new HIV infections, zero cases of advanced HIV and HIV-related deaths in England by 2030.

Late diagnosis still accounts for a significant proportion of new diagnoses.

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CONFERENCE REPORTS

International Workshop on HIV & Ageing 2023

26 to 27 October 2023, Washington DC and virtual

Introduction

Simon Collins, HIV i-Base

This year the annual workshop on HIV and Ageing was held in Washington DC and included virtual participation. It was the first face-to-face meeting since COVID.

The programme included excellent plenary lectures, some of which are reported below, with roughly 20 oral abstracts and 40 posters.

https://academicmedicaleducation.com/meeting/international-workshop-hiv-aging-2023

Themes included the multifactorial nature of most age-related medical complications.

- Defining and measuring frailty.
- Muscle, bone and fat metabolism as components of a changing body composition.
- Risk of cardiovascular disease and stroke.
- Planning services to meet the needs of older people living with HIV.
- Whether subclinical neurocognitive changes can be identified - and whether or not this is helpful, in the absence of treatment options.

This issue of HTB includes the following reports from the workshop.

- Sarcopenia and mitochondrial dysfunction in people living with HIV: the impact of ageing
- Measuring sarcopenia in people living with HIV

Sarcopenia and mitochondrial dysfunction in people living with HIV: the impact of ageing

Kirk Taylor, HIV i-Base

The 2023 14th International Workshop on HIV and Ageing included many excellent plenary talks and discussions.

This included the opening session on sarcopenia, with oral presentations on age-related changes of muscle physiology, hallmarks of ageing and mitochondrial dysfunction, and defining sarcopenia. [1, 2, 3]

HIV is associated with more rapid declines in mitochondrial function but can be improved with exercise. [2]

Mitochondrial copy number can be used to identify ART-associated mitochondrial dysfunction.

Although there is no current consensus on the definition of sarcopenia, different research groups generally agree that this should include weakness (low grip strength for men <35.5 kg and women <20 kg) and slowness (low walking speed <0.8 m/s). [3]

Muscle structure and changes with ageing

Dr Gustavo Duque of McGill University Health Centre gave an overview of sarcopenia and changes in muscle tone and physiology that occur with ageing. [1]

Skeletal muscle is a complex tissue that directly interacts with the bone to facilitate movement. At its core, muscle is a collection of myofibrils that respond to myofilament contraction and relaxation in an ATP-dependent manner. These myofibrils are organised into muscle fibres, which form larger bundles that respond in a coordinated manner to nervous innervation.

Muscle accounts for up to 40% of body mass and regulates movement and metabolism. However, different muscle fibre types have specific properties and are adapted to either slow (type I) or fast (type II) responses.

Several muscle properties also directly influence health and disease.

- Neuromuscular junctions coordinate desired movement.
- Blood vessels deliver nutrients of oxygen and collect and distribute messenger molecules (myokines).
- Resident FAP (fibrotic/adipogenic progenitor) and stem cells coordinate responses and remodel following injury and environmental cues.

Hallmarks of ageing are driven by epigenetics, stem cell changes, mitochondrial dysregulation and metabolic changes. These factors determine the rate of muscular ageing and are the focus of current research.

Crucially, as part of the ageing process, fast fibres are steadily replaced by slow fibres, fat levels increase, and neuromuscular junctions begin to uncouple. The term inflammageing is used to refer to the chronic accumulation of inflammatory mediators that negatively impact muscle homeostasis and drive the

accumulation of intramuscular fat in most people.

The large Australian Body Study in the general population used DEXA scans to show age-related muscle loss in people aged 18 to 88 (n=15,479). Muscle mass declined with similar trends for male and female participants with atrophy of 0.5% to 1% per year.

Sarcopenia is associated with ageing but can be triggered by a range of factors including obesity, inflammation, low levels of physical activity and chronic health conditions including HIV. Sarcopenic muscles have very few fibres and a high fat content.

This means that bone health and muscle health are critically interdependent. Osteoporosis and sarcopenia have common risk factors and the increased risk of falls after muscle loss increases the risk of fractures which is also linked to age-related reductions in bone mineral density.

The AMBERS study of post-menopausal women aged 75 to 80 years (n=312) reported a link between fat levels in the bone marrow and muscle, with increased osteosarcopenia risk. The two major risk factors were ageing and poor nutrition.

Mitochondrial (dys)function and ageing

Dr Jing Sun of John's Hopkins University discussed mitochondria (dys)function and its links with sarcopenia for people living with HIV. [2]

Inflammageing in people living with HIV is a complex process driven by both viral factors (related to ART use and reservoir size) and lifestyle factors (including diet and exercise). This leads to mitochondrial damage, epigenetic changes, stem cell exhaustion and immunosenescence.

Mitochondria (mT) synthesis of ATP is essential for muscular contraction.

Mitochondrial DNA (mtDNA) haplogroups can be used to assess ageing characteristics for different geographical populations. For example, European men living with HIV (aged ≥50 years, n=455) within haplogroup J have a more rapid decline of walking speed as they get older. Meanwhile, Black women living with HIV haplogroup L2 were associated with lower incidence of diabetes compared to those in haplogroup L3 who had increased risk.

Analysis of mtDNA and copy number from the UK Biobank has also been performed to assess disease risk related to inherited or environmental factors.

Accrual of environmental-associated mtDNA mutations increases the risk of negative health outcomes and is associated with mortality risk. For example, significant associations were reported between environmental mtDNA mutations and all-cause mortality (HR 1.28; 95% CI: 1.20 to 1.37), digestive disorders (HR 1.47; 95% CI: 1.05 to 2.05) and neoplasms (HR 1.37; 95% CI: 1.25 to 1.50).

This talk explained that mT copy number is a surrogate marker of the quantity and function of mT and was used to highlight mT dysfunction with early generation NRTIs.

In the ALIVE cohort of people who injected drugs, mT copy number was derived from peripheral blood samples. Participants were living with HIV (n=543, 59%) and median age was 48 years. Copy number was lower for people living with HIV although significant declines were not observed for people who were taking ART, had CD4 counts >500 cells/mm^3 or had undetectable viral load. Participants that had <200 CD4 cells/mm^3, detectable viraemia, or were not taking their ART had the greatest decline of mT copy number.

Mitochondrial copy number also declines more rapidly during ageing for people living with HIV than for HIV negative individuals. The lowest quartile of copy number is associated with the greatest mortality risk and people within this group are more susceptible to kidney disease and kidney function decline.

Ongoing studies are evaluating the potential to improve mT function through increased exercise. Mitochondrial function was evaluated before and after six months of exercise. Participants were aged between 50 to 75 years and 12/30 participants were living with HIV. Exercise improved mT function, but the magnitude of change was smaller for people living with HIV.

The HEALTH study is currently enrolling people living with HIV to evaluate the best type of exercise to improve mT function and promote healthy ageing. The impact of continuous moderate exercise will be compared to high intensity interval training (HIIT).

Standardising sarcopenia definitions

Dr Peggy Cawthon of the California Pacific Medical Centre Research Institute discussed methods for monitoring sarcopenia and standardisation of sarcopenia definitions. [3]

Although DEXA scans are widely used to measure lean muscle mass, this approach is subject to measurement error and there is no gold standard alternative.

There are also differences between different sarcopenia consensus statements, although all agree that it is a multicomponent syndrome defined by muscle size and other factors. However, each statement has different thresholds and uses different measures for each component.

The European working group has three components: (1) low muscle strength, (2) low muscle quantity or quality and (3) low physical performance.

Depending on the consensus method used, sarcopenia prevalence in the elderly ranges from 10% to 40%.

Although sarcopenia definitions predict outcomes, it is unclear which components are most informative. The Sarcopenia Outcomes and Definitions Consortium (SDOC) are now reviewing and refining definitions and highlighting controversies within this field.

This group evaluated grip strength, lean mass and walking speed to produce the following summary:

"Low grip strength and low usual walking speed independently predict adverse health-related outcomes such as mobility limitation, falls, disability and mortality in community-dwelling older adults".

Both weakness (low grip strength for men <35.5 kg and women <20kg) and slowness (low walking speed <0.8 m/s) are easy to measure and should be included in the definition of sarcopenia.

In contrast, DEXA measures have a high degree of uncertainty and should not be used, either to predict sarcopenia risk or in the definition of sarcopenia.

The session concluded with a lively audience discussion.

Dr Duque commented that it is difficult to disaggregate biological and environmental factors that contribute to muscular ageing. Genetic factors also influence the ageing process. Some DEXA data shows that age-related muscle decline occurs irrespective of demographics.

Exercise improves muscle tone, and it is likely that HIIT will prove more beneficial than continuous moderate exercise. However, there is a decreased ability to respond to the same input over time. LIFE study data show that age-related complicating factors reduce adherence to exercise regimes (e.g. falls, fractures and illness).

Dr Duque discussed fat infiltration into muscles and that some sites are preferentially targeted (e.g. quadriceps). Infiltration of fat influences muscle structure and tone and could therefore be a measure of sarcopenia. Ongoing work is using advanced computer learning to evaluate fat infiltration from DEXA data.

Biopsies of muscle with fat infiltrates from people living with HIV look similar to older people with sarcopenia, but it is unclear whether it is caused by the same mechanisms or due, for example, to lipodystrophy as a side effect of ART. Observational data from the WIHS cohort show increased fat infiltration into muscle and impaired physical function for people living with HIV.

Luckily, osteoporosis drugs can improve muscle mass and function and reducing osteoporosis in studies lead to fewer falls, suggesting clinical benefits from improved muscle mass and function.

Links between mitochondrial copy number and ART classes were also discussed.

Self-reported data did not show a sizeable effect based on length of exposure to drugs, but there was a limited effect of drug class on copy number. Some studies report changes of mitochondrial copy number with ART use, but some studies do not normalise copy number relative to cell counts (e.g. platelets and leukocytes).

Dr Cawthon also discussed ways of measuring muscle mass that is included in a separate report in this issue of HTB. [4]

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Unless stated otherwise, all references are to the 14th International Workshop on HIV and Ageing, 26 to 27 October 2023, Washington, USA.

https://academicmedicaleducation.com/meeting/international-workshop-hiv-aging-2023

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Measuring sarcopenia in people living with HIV

Kirk Taylor, HIV i-Base

The 14th International Workshop on HIV and Ageing included an oral presentation by Dr Peggy Cawthon that discussed methods for measuring sarcopenia. [1]

Sarcopenia is loss of muscle mass and a hallmark of ageing that occurs even with regular exercise. Also, although sarcopenia is associated with important reductions in muscle size, strength and function, there is no consensus definition based on target levels of these factors.

Methods to measure muscle mass include DEXA (dual x-ray absorptiometry) scans, bioimpedance analysis (BIA), CT scans and D3-creatinine dilution. Muscle function or strength is assessed using grip strength, walking speed and self-reported disability or limitations. As a marker, grip strength is usually preferred due to low cost and quick test time, whereas lower extremity tests tend to be more subjective and have limitations in older people.

DEXA scans measure bone mineral density (BMD) and fat mass and can be used to indirectly approximate muscle mass. Dividing DEXA values of appendicular (legs and arms only) by height can be used as way to predict the risk of sarcopenia. Sarcopenia is defined as any result below 7.26 kg/m^2 for men or 5.45 kg/m^2 for women.

Reviews using meta-analyses have not shown a strong predictive link between DEXA-derived muscle mass and functional outcomes. Furthermore, interventional studies show maintenance of strength despite weight loss in participants with osteoarthritis or diabetes. DEXA is a highly subjective measure and prone to measurement errors.

Direct measurements of muscle mass can be calculated by measuring urine creatinine as 98% of creatine is stored in muscle tissue and levels are stable. Creatine levels are therefore proportional to muscle mass.

The D3-creatine dilution test is used to ascertain total muscle mass. Briefly, a 30 mg oral dose of labelled creatine is given, which is processed to creatinine and reaches steady state within three to six days. Urine D3-creatinine:creatinine ratio is used to calculate muscle mass. Higher D3-creatinine ratios correspond to lower muscle mass.

In the MrOS implementation study of 1400 men, measurement of muscle mass by DEXA or D3-creatinine correlated (r=0.66), but DEXA overestimated muscle mass. People with lower grip strength and walking speed had lower muscle mass calculated by the D3-creatine method. Similar outcomes were observed for women in the SOMMA study of 875 people aged >75 years.

There is similarly no standardised measure of sarcopenia in people living with HIV, including those who are older. Current approaches recommend collecting multiple components to cover muscle function, size, physical performance, self-reported disability and fitness.

Reference

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CONFERENCE REPORTS

19th European AIDS Conference (EACS)

18 to 21 October 2023

Introduction

Simon Collins, HIV i-Base

This year, the EACS conference, held every two years, returned to Warsaw which was also the host 20 years ago.

Abstracts from the conference are available by searching this link:

https://eacs2023.abstractserver.com/program/#/program/1/horizontal

They are also published in HIV Medicine, available as a PDF file.

https://onlinelibrary.wiley.com/toc/14681293/2023/24/S5

Reports in this issue of HTB are listed below.

EACS 2023: HIV cure-related research

Kirk Taylor, HIV i-Base

EACS 2023 included a lively oral symposium on HIV cure-related research with two comprehensive summary reviews and four oral abstracts. [1-6]

Data included updates on broadly neutralising antibody (bNAb) research, with some cases of ART-free virologic control for up to 24 weeks. [1]

The second update covered promising results on cellular therapies, similar to those used to target cancers, and how these may be adapted to combat HIV. [2]

New data from the INACTION cohort showed that earlier ART is linked to a smaller reservoir and reduced inflammation. [4]

Finally, early data on the use of PD-1 inhibitors to perhaps enable ART-free viral suppression. [5]

Treatment interruption studies

Professor Sarah Fidler from Imperial College London presented an update on treatment interruption studies. [1]

This included a survey of attitudes to participation in treatment interruption studies which showed that 39% of respondents were keen to join, citing altruism as a primary reason (89%). However, 9/10 people were concerned about HIV transmission when off ART and weekly viral load testing was preferred by 35%. [3]

A useful meta-analysis has also reported viral re-suppression rates for people restarting ART following a treatment interruption. Within three months of re-starting ART, 96% of participants achieved virologic control. Viral re-suppression rates were higher for people who had first started ART during the early vs chronic phase of HIV (13% vs 4%).

Recent bNAb data has reported cases of viral suppression out to 24 weeks. The ongoing UK RIO study using the same bNAbs is using a single infusion of 3BNC-117-LS plus 10-1074-LS to aim for viral suppression for up to 20 weeks.

Romidepsin has also been combined with bNAbs to target the viral reservoir. This approach decreased proviral RNA, enhanced T-cell responses, and delayed time to viral rebound. Similar data have been reported with an alternative strategy using TLR9 agonists plus bNAbs in the phase 2a TITAN study. The AMFAR study combining bNAbs, TLR9 agonist and a DNA/MVA vaccine reported a median time to viral rebound of 15 weeks.

Novel approaches to HIV cure-related research

Dr Asier Sáez-Cirión of the Pasteur Institute discussed progress of cure studies and approaches in the pipeline. [2]

Successful cure strategies will require combined approaches to reduce viral reservoir and reinforce immune barriers. Treatment interruption studies show that greater success is achieved if ART was initiated soon after HIV transmission. Currently, 82 cure-related trials have been registered that involve bNAbs (n=18), gene editing (n=14), vaccines (n=13) and ART-based (n=11) approaches.

The reservoir is being targeted through multiple strategies that include latency reversal agents, HIV replication-induced death, targeting specific cellular characteristics, repressing proviral replication with transcription inhibitors and removal of proviral DNA through gene editing.

Approaches to boost immune defences include the induction of intrinsic resistance, therapeutic vaccines, use of immune modulators and adoptive therapies using cells from elite controllers. Research into mechanisms to eliminate HIV-containing reservoir cells is ongoing.

Cell therapies are being developed with the aim to replicate the immune responses seen in elite controllers who retain high CD4 counts and very low viral load without using ART. This is being studied using vaccines to induce immune responses against HIV and reprogramming of CD8 T-cells. This approach can also be adapted to utilise natural killer cell responses against HIV. This has shown promise in the arena of cancer research, raising hopes for development of IV cure strategies.

Early ART reduces inflammatory response and viral reservoir

Dr Valeria Bono of the University of Milan presented results from the INACTION cohort study on the effect of early initiation of ART on inflammation markers and reservoir size. [4]

Responses were compared between participants with primary HIV (PH; n=55) or chronic HIV (CH; n=18). Both groups were predominantly male (96% for PH and 89% for CH) and median (IQR) age was 34 years (27 to 45) and 31 years (26 to 46) for the PH and CH groups, respectively. Higher baseline viral load and lower CD4 count was reported for the PH group.

Baseline levels of HIV DNA were similar for both groups, however the relative decrease following initiation of ART was greater for those in the PH group at week 48. Inflammatory markers reduced in both groups but there was no difference between PH and CH. People with primary HIV infection had lower levels of plasma CD14 and E-cadherin. The authors suggest that treatment during the primary phase reduces the size of the reservoir and inflammatory markers.

Phase 1b studies of budigalimab, a PD-1 inhibitor, for HIV viral control off-ART

Dr Routy of McGill University Health Centre discussed ongoing trials on the use of a PD-1 inhibitor budigalimab for HIV cure. [5]

PD-1-expressing CD4 cells that have a high content of proviral HIV DNA and are a key target for HIV cure strategies. Randomised double-blind phase 1b studies (M19-939 and M19-972) are using low-dose (≤20 mg) budgialimab for people living with HIV and an international phase 2 study in 140 participants is due to enrol shortly.

The drug was well-tolerated with no serious treatment-related adverse events reported.

PD-1 receptor saturation was achieved for 10 weeks post treatment interruption. Biweekly budigalimab administration delayed viral rebound and/or enabled ART-free viral suppression for 6/9 participants but only by about a week, with only two participants having a response out to week 24.

PD-1 CAR T cells in a macaque model: caution for lymphoma

Dr Eichholz of the Fred Hutchinson Cancer Centre discussed their development of a CAR T cell approach to eradicate the HIV reservoir. [6]

Transfusion of PD-1 CAR T cells led to successful replication within macaques and destruction of HIV-containing follicular helper cells in lymph nodes.

However, this approach also resulted in serious complications, with two cases of immunodeficiency-related B cell lymphoma.

Further safety and specificity measures are being explored to enable further development of this model.

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EACS 2023: European guidelines fully revised (October 2023)

Simon Collins, HIV i-Base

The conference launched version 12 of the European guidelines developed by the European AIDS Clinical Society (EACS) which includes a major update to all sections.

The guidelines are available online as a pdf and web-based version and as a free App for iOS and Android devices. The pdf version continues to be translated into several different languages.

The guidelines also cover a large and diverse area geographically, with different national levels of access to care. The recommendations are often therefore broader than many national guidelines.

The 2023 version of the Guidelines includes updates of all existing sections.

The most essential changes are listed below and a more detaile summary of changes is listed online. [2]

ART

- Preference for second-generation INSTIs for initial ART, with boosted-PIs as an alternative.
- Sustaining viral load <200 copies/mL without ART is included as an exception to the universal use of ART in chronic infection. (Elite viral controllers).
- ART in primary HIV infection should be with a 30-drug rather than 2-drug combination.
- Injectable cabotegravir/rilpivirine as a switch option with undetectable viral load.
- Lenacapavir is included as a new option for people with viral failure.
- Pregnancy guidelines include removing the caution about using dolutegravir and TAF and downgrade the use of abacavir. Language about breastfeeding still emphasises a low risk with undetectable viral load. Supported breastfeeding should include frequent viral load monitoring of the mother and infant. Formula milk can be used when needed. However, introducing solid food earlier that six months increases the risk of transmission.
- TAF can be included in ART when treating TB.

HIV prevention

- Reduced need for PEP if the risk is only oral sex.
- Need to use 4th generation HIV testing and HBV serology before PrEP.
- PrEP should be changed to ART if HIV infection is suspected.
- PrEP users should be offered vaccines against HAV, HBV, HPV and mpox.
- DoxyPrEP is included for prevention of STIs.
- F/TAF and cabotegravir injections are included as alternative PrEP formulations when appropriate in some populations.

Drug-drug interactions (DDIs)

- All DDI tables have been updated to include changes implemented in the HIV drug interaction website (University of Liverpool) in the past year.
- A novel resource has been added for drug classes to deprescribe in older person with HIV in presence of certain conditions.
- Long-acting cabotegravir and rilpivirine incudes interactions that can change drug release and dosing recommendations after missed injections.
- Lenacapavir has been added to all DDI tables.
- A new table added for DDI between antiretrovirals and anti-infective drugs for OIs and STIs.

Co-morbidities

- A new section on Patient Reported Outcome Measures (PROMs).
- A new section on alcohol.
- Updated guidance on the management of cognitive and central nervous system symptoms, travel, sexual and reproductive health, type 2 diabetes mellitus, cancer screening including anal cancer, chronic lung disease and deprescribing.

Viral hepatitis

- Updates on screening for complications, including HCC and HBV vaccinations.
- Caution when switching HBV-active meds.
- Removing the algorithm for acute HCV treatment.

Opportunistic Infections (OIs)

- A new section on mpox.
- COVID-19 section extensively updated.

- TMP-SMX is an additional "preferred" treatment in toxoplasmic encephalitis. New discussion on diagnostic value of toxoplasma PCR in CSF and corticosteroids use in the context of large lesions with mass effect.
- WHO-recommended single-dose liposomal amphotericin B+fluconazole is now an additional "preferred" regimen in resource limited settings for the treatment of cryptococcal meningitis. Recommendations on primary prophylaxis have been reformulated.
- Liposomal amphotericin B+miltefosine has been added as an alterative regimen for the treatment of visceral leishmaniasis
- Updated recommendations on the ART initiation in the context of TB and cryptococcal meningitis.
- Hyperlinks to the DDI table between selected anti-infective agents and ART.
- A new comment on desensitization in the context of non-severe TMP-SMX allergy.
- Minor stylistic changes and rephrasing throughout.

Paediatric care

- Updated Table 1 on ART options for children.
- Deleted Table 2 on alternative dosing as no longer relevant.
- New section on "General principles of postnatal prophylaxis and infant feeding".
- Minor edits in the other sections.

C O M M E N T

These updated guidelines are always welcomed.

Please refer to the full version for full details.

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1. EACS. EACS guidelines v12.0 (October 2023).
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Doravirine drug resistance in large treatment-naive and -experienced cohort in British Columbia

Kirk Taylor, HIV i-Base

EACS 2023 included an oral presentation on the prevalence of mutations associated with resistance to doravirine in a large observational cohort in British Columbia.

A database reviewed almost 39,000 sequences collected since 1996 from more than 10,000 people living with HIV at the BC Centre for Excellence in HIV/AIDS. Approximately 5400 samples were NNRTI-naive, 15,400 were NNRTI-experienced and 18,000 with an unknown NNRTI history were assumed to have started with PI- or INSTI-based ART.

Doravirine resistance was categorised based on having one or more primary or secondary major mutations or having at least 5 minor mutations (based on Stanford).

Primary major	Y106A, Y188L, F227C/V, M230I/L, L234I, Y318F
Secondary major	A98G, V106M, V108L, G190E, H221Y, P225H, F227L, P236L
Minor mutations	V90I, K101E/H/P, K103N/R/, V106L, I135T, Y181C/I/V, E138A/G/K/Q/R, V179D/F/T, G109A/Q/S, Y188C/H, F2271, V245E, K311R

Overall, 20% genotypes (7995/38,808) included any NNRTI resistance (including 30% of those who were NNRTI-experienced). Only 835 samples (2.2%) showed resistance to doravirine (roughly 5% of those who were NNRTI-experienced).

Of the 230 people prescribed doravirine, 32% (75/230) had previous NNRTI resistance but most switched when already undetectable and used either triple-class or four-drug combinations, with only 10/75 starting on doravirine plus two NRTIs.

The three people with virological failure had single mutations at (i) V106M, (ii) M230L and (iii) with multiple mutations at V106I/M+V108I+F227C+M230L+L234I.

Reference:

Brumme C. Prevalence and clinical impact of doravirine-associated resistance mutations in a real-world population of NNRTI-naïve and NNRTI-experienced individuals. EACS 2023. Warsaw, Poland. Oral Presentation PS 1.05.

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Switching to daily fixed-dose doravirine/islatravir: 96-week results

Simon Collins, HIV i-Base

EACS 2023 included 96-week results from a phase 3 study that randomised 641 participants with undetectable viral load on current ART to either switch to daily DOR/ISL (100 mg / 0.76 mg) or continue on B/F/TAF (Biktarvy).

This was a double-blind placebo-controlled study for the first 96 weeks and continues for a further 48 weeks using open-label fixed dose combinations.

Baseline characteristics included mean age 47.8 years (SD: ±12.2), 72% male, 75% white.

At week 96, viral load was <50 copies/mL in 84.8% vs 90.9% in people taking DOR/ISL vs B/F/TAF (difference –6.1% [95% CI –11.3 to –1.1]). However, when excluding 13 participants from the DOR/ISL arm due to protocol-defined CD4 decreases >30% (introduced at week 72), results were 88.3% vs 90.9% respectively (difference –2.6% [95% CI: –7.5 to +2.2]).

Two participants taking DOR/ISL had viral failure (confirmed >200 copies/mL) at roughly 800 and 14,000 copies/mL, both with no detectable islatravir levels suggesting non-adherence. A single blip to 70 copies/mL in the B/F/TSF arm resuppressed without any changes.

Mean CD4 counts were lower with DOR/ISL vs B/F/TAF (+6 vs +60 cells/mm^3).

Adverse events, including infections, were comparable in each arm. More discontinuations on DOR/ISL were linked to the decline in CD4 counts.

Reference

Paredes R et al. Switch to fixed-dose doravirine/islatravir (100/0.75 mg) once daily in adults with HIV-1 virologically suppressed on bictegravir/emtricitabine/tenofovir alafenamide: week 96 results of a phase 3, randomized, double-blind, non-inferiority trial. 19th EACS, 18–21 October 2023, Warsaw, Poland. Oral presentation PS 1.01.

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EACS 2023: TDF/FTC dual-nuke ART: not supported by ALTAR study

Kirk Taylor, HIV i-Base

EACS 2023 included an unexpected oral presentation on use of TDF/FTC as dual-NRTI combination, a combination that is not recommended in guidelines and that would risk viral breakthrough due to reduced potency compared to triple combinations.

However, the results from a small number of participants collected before the study was ended early, are much too limited to support dual-NRTI ART.

Several integrase inhibitor-based (INSTI) dual-ART regimens are included in clinical guidelines (DTG/3TC, DTG/RPV and CAB/RPV), but tenofovir does not have the same potency and pharmacokinetic properties as integrase inhibitors.

The randomised open-label ALTAR study aimed to assess non-inferiority for viral suppression at week 48 for participants receiving either DTG/3TC or TDF/FTC. For the TDF/FTC arm, there was a 12-week oral lead-in with triple therapy (TDF/XTC/INSTI) before switch to dual therapy.

The study was approved in 2016 and aimed to enrol 180 participants per arm. However, the trial was halted to await results from GEMINI and then was beset by issues arising from the unfolding COVID-19 pandemic in France. The regulator stopped the trial in 2021 and data out to week 24 were collected for 45 participants only. Participants were female (16%), median age was 32 years (IQR: 26 to 47) and 78% were heterosexual.

Viral suppression rates at week 24 were comparable between groups, with 87% achieving <50 copies/mL. There were comparable improvements in virologic parameters for both arms. Viral load decreased by 0.57 (SE: 0.1) vs 0.32 (SE: 0.11) log copies/mL for the TDF/FTC vs DTG/3TC arms, respectively. Participants on TDF/FTC gained +0.9 kg (SE: 3.9 kg), vs +1.4 kg (SE: 2.7 kg) with DTG/3TC.

One case of virologic failure was reported in each arm. For TDF/FTC, a participant had a viral load increase to 139 copies/mL but resistance mutations were not detected. Following re-introduction of DTG they achieved viral suppression. The case in the DTG/3TC arm was linked to missed clinic visits and likely low adherence. They discontinued from the study and PI- and INSTI-associated resistance mutations were identified. With improved adherence to DTG/3TC they achieved an undetectable viral load.

Comparable virologic success was observed for both dual-ART regimens in this small sample size. Further investigation may lead to identification of alternative dual-ART regimens to reduce drug burden of lifelong ART, and provide alternatives for people with INSTI resistance.

C O M M E N T

The rationale for using TDF/FTC in this study was the short- to long-term side effects reported in a minority of people using INSTIs. However, as alternative third drugs are available, participants in the study risked developing NRTI drug resistance.

Although comparable levels of virologic control were observed at week 24 in the DTG/3TC (87%) and TDF/FTC (86.4%), the risk of viral rebound with TDF/FTC would be expected at later timepoints. The low participant numbers mean all results are underpowered to interpret either way.

Historical data using dual nukes showed viral load rebound with dual AZT/3TC took a little longer. Even if tenofovir has a slightly higher genetic barrier to drug resistance compared to AZT, resistance can still develop later with suboptimal combinations, and mutations can be cross-resistant to other NRTIs.

Reference

Katlama C et al. Can we drug reduce antiretroviral regimen with dual NRTI regimen in naïve patients with viral load <50,000 copies/mL and CD4>300 cells/µL?: results from a randomized non-inferiority ANRS 173 ALTAR trial. EACS 2023, Warsaw, Poland. Oral Presentation PS 1.03.

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EACS 2023: EATG video campaign against HIV stigma

Simon Collins, HIV i-Base

The European AIDS Treatment Group (EATG) is a long-standing activist organisation that has focused on HIV treatment and related issues for over three decades.

For World AIDS Day this year the group released a new 38-minute video, recorded at EACS 2023, as part of a campaign to reduce HIV stigma.

The video stresses the importance of ending stigma and discrimination to reduce the impact on the mental health and wellness of communities affected by HIV.

The group aimed to represent the voices and concerns of people living with HIV and community, HIV and mental health community workers and HIV clinicians.

Reference

Stigma-Free: For the Mental Health and Wellness of People Living with and Affected by HIV/

https://www.youtube.com/watch?v=oP_5pQ7BCZs

ANTIRETROVIRALS

Price of first-line ART drops below US $45 a year for low-income countries

Polly Clayden, HIV i-Base

The Global Fund recently announced a 25% price reduction for tenofovir disoproxil fumarate, lamivudine and dolutegravir (TLD) – now below US $45 per person, per year for eligible governments and other implementers.

The World Health Organisation (WHO) has recommended TLD as the preferred first-line ART since 2018 for adults and adolescents. It is also used second-line for people who used efavirenz-based ART first-line.

This price reduction builds on work done in 2017, when Indian generic manufacturers, with support from UNAIDS, Unitaid, PEPFAR, the Bill & Melinda Gates Foundation, the Global Fund and other partners, made TLD available for low-income countries at a ceiling price of around US $75 per person, per year.

According to the Clinton Health Access Initiative (CHAI) about 19 million people living with HIV in low-income countries are now receiving TLD.

The Global Fund uses its Pooled Procurement Mechanism to order volumes on behalf of participating grant implementers and to negotiate prices and delivery conditions with manufacturers. Antiretrovirals make up about 40% of the mechanism's annual spend.

Reference

Global Fund press release. Global Fund agreements substantially reduce the price of first-line HIV treatment to below US$45 a year. 30 August 2023,

https://www.theglobalfund.org/en/news/2023/2023-08-30-global-fund-agreements-substantially-reduce-price-first-line-hiv-treatment-below-usd45-a-year

Potential for monthly injectable: nanoformulated tenofovir/3TC/dolutegravir

Polly Clayden, HIV i-Base

A novel long-acting injectable formulation of tenofovir, lamivudine and dolutegravir (TLD) sustained effective concentrations over four weeks in a macaque study. These findings were published ahead of print in AIDS, 23 August 2023. [1]

Researchers from the University of Washington TLC-ART (Targeted, Long-acting and Combination Anti-Retroviral Therapy), are developing a long-acting TLD drug-combination. [2]

The group have previously successfully formulated water insoluble-and-soluble antiretrovirals with biocompatible lipid-excipient to form drug-combination-nanoparticles (DcNP).

This pre-clinical pharmacokinetic study looked at whether short-acting TLD can be transformed into a single long-acting formulation.

The investigators used oral ARVs from generic manufacturers to formulate TLD-in-DcNP.

Five macaques were dosed 6.2, 5.1 10 mg/kg TLD-in-DcNP suspension and two (control) were dosed with free-soluble mixture TLD (dissolved in liquid but not using DcNP) – both by subcutaneous injection.

Blood samples for the TLD-in-DcNP were collected at 0, 0.25, 0.5, 1, 3, 5, 8, 24, 48, 120, 168, 192, 336, 50, 672 hours (4 weeks) for drug analysis – the free TLD samples were collected at the same time points up to 120 hours.

In four animals dosed with TLD-in-DcNP, peripheral blood mononuclear cells (PBMC) were isolated, in the 48– and 168–hour blood samples, and also analysed for drug content.

Tenofovir, 3TC and dolutegravir were detectable in plasma throughout a four-week period. By contrast, plasma drug levels in the animals receiving TLD-free dosage fell below detectable levels within three days.

TLD-in-DcNP AUC were 7.0–, 2.1–, and 20–fold higher, for tenofovir, 3TC, and dolutegravir, respectively. The effects of DcNP on TLD half-life extension were 10–, 8.3–, and 5.9–fold over the free-soluble combination.

All drug concentrations were above the estimated IC90 for the four-week study: 0.3, 0.2, and 0.25 ng/mL for tenofovir, 3TC and dolutegravir, respectively.

The intracellular tenofovir concentration in PBMCs was 2.2– and 3.1–fold higher than plasma, at 48 and 168 hours, respectively; 3TC in PBMC was 3– and 15–fold higher than in plasma; and dolutegravir in PBMC was 29– and 4.1–fold higher than in plasma.

The investigators concluded that these data show water-soluble tenofovir, 3TC, and water-insoluble dolutegravir combined into the single TLD-in-DcNP injectable provided four weeks plasma exposure in monkeys above detectable, measurable, and IC90-predicted levels.

COMMENT

Oral TLD is a currently recommended by WHO and national guidelines as first-line (and increasingly subsequent) HIV treatment.

Through its competitive tenders, the Global Fund, with its partners and generic manufacturers, recently announced further price reductions for eligible countries, making this one-pill-once-a-day available for less than US $45 a year. [3]

The TLC-ART group suggest that a long-acting TLD may overcome daily pill fatigue – for people who find this a problem (and if it can be manufactured for an acceptable price).

They also note that as the TLD-in-DcNP can be given by subcutaneous injection it may mean people can self-administrate this formulation, unlike intramuscular injection needed for long-acting cabotegravir and rilpivirine, that requires a health worker (and cold chain for RPV-LA).

Another advantage could be that an oral lead-in may not be necessary due this LA formulation's short time to peak.

And because the combination includes tenofovir it provides coverage for people with HIV and HBV (unlike cabotegravir and rilpivirine).

Most importantly, if this formulation becomes available, there is already a wealth of experience with oral TLD – including in populations where data can be scarce for new drugs and strategies notably pregnant women.

On the downside, monthly administration is less desirable than longer dosing intervals.

A monthly injectable formulation could be very useful for paediatric populations – where there is still a huge need for effective ART. This would need to include abacavir instead of tenofovir. But the monthly dosing interval might be more acceptable in infants and children as dosing is weight-based and this changes as they grow.

Phase 1 human data will be presented in early 2024.

References

1. Perazzolo S et al. A novel formulation enabled transformation of 3 HIV drugs tenofovir-lamivudine-dolutegravir (TLD) from short-Acting to long-acting all-in-one injectable. AIDS ():10.1097/QAD.0000000000003706, August 25, 2023. | DOI: 10.1097/QAD.0000000000003706.
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TREATMENT STRATEGIES

CD4:CD8 ratio recovery reduces with higher age when starting ART

Kirk Taylor, HIV i-Base

A longitudinal cohort study published in the 28 November issue of AIDS reports decreased CD4:CD8 recovery levels relative to age at time of ART initiation. [1]

A lower CD4:CD8 ratio is a marker of reduced immune function and immune activation and values >1.0 are considered normal. Across all participants, median (IQR) ratios increased significantly from 0.24 (0.24 to 0.38) to 0.88 (0.64 to 1.17) after 10 years on ART. However, there was no age group in which the majority of people had CD4:CD8 ratio >1 after 10 years.

The cohort enrolled 1859 people age 20 to 78 who were living with HIV and who accessed HIV care at the Royal Free Hospital in London between 2001 and 2015. Within the study period there were two major HIV epidemics: one for gay and bisexual men and a second amongst Black heterosexual men and women.

Study participants were female (25%), Black (29%) and Asian (6%). Baseline age was split into the following deciles: 20 to 29 (n=235), 30 to 39 (n=748), 40 to 49 (n=597), 50 to 59 (n=221), 60 to 69 (n=49) and 70 to 79 (n=9). Data were adjusted for baseline CD4 count, year of ART initiation, ethnicity and gender.

Overall, median (IQR) CD4 counts increased from a baseline of 256 cells/mm3 (132 to 375) to 668 cells/mm3 (511 to 837) at year 10. Median (IQR) CD4:CD8 ratios followed a similar trend with a net increase from 0.24 (0.24 to 0.38) to 0.88 (0.64 to 1.17) across the 10-year period.

Median (IQR) ratios at 10 years by age decile were as follows: 0.95 (0.75 to 1.29: 20 to 29 years), 0.92 (0.71 to 1.2: 30 to 39 years), 0.84 (0.61 to 1.09: 40 to 49 years), 0.80 (0.56 to 1.24: 50 to 59 years), 0.57 (0.46 to 0.86: 60 to 69 years) and 0.57 (0.52 to 0.60: 70 to 79 years).

There was a positive correlation between age at ART initiation and 10-year mortality. Total mortality was 1.7% for those aged under 60 and rose to 8.2% for those over 60, and 22% (2/9 participants) for the over 70s.

Older age was associated with slower ratio recovery and lower ratios at years 5 and 10 of follow-up. It should also be noted that the study only included people who achieved viral suppression within six months of ART initiation, and the group sizes for the oldest deciles were small.

COMMENT

These results are important for quantifying the impact associated with the later use of ART and the importance of earlier diagnosis.

At least part of the explanation for lower numbers of people reaching a CD4:CD8 ratio >1.0 will be linked to years when ART was only recommended at a lower absolute CD4 count.

Since 2015, earlier use of ART has been recommended at any CD4 count thanks to results from the START study. [2]

References

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2. Collins S. Starting HIV treatment at high CD4 counts protects against both AIDS and non-AIDS events: overall and in subgroup analyses of START study. HTB (1 August 2015). https://i-base.info/htb/28606

Dolutegravir monotherapy still not recommended: 4-year follow up in early-treated durably suppressed participants

Simon Collins, HIV i-Base

Several years ago, early switch studies of dolutegravir monotherapy were quickly stoppedm due to viral rebound with INSTI class resistance in some participants. [1]

Treatment guidelines also specifically excluded dolutegravir monotherapy as an option in any circumstances.

The Early-Simplified study however, using dolutegravir monotherapy in early infection, continued, and has reported follow-up to four years. [2]

This study included 101 participants who had started ART within six months of infection and who had been suppressed on ART for a median of 3.5 years. Participants were randomised (2:1) to either switch to dolutegravir monotherapy or continue their current ART.

Surprisingly - and luckily - no cases of viral rebound occurred over this extended time. These results still do not suggest that dolutegravir monotherapy should be repeated or used, but they add to our knowledge about the complexity of treatment.

The researchers rightly conclude that the high efficacy and safety of dual therapy using dolutegravir and lamivudine make the current data of historical value only. Also, that monotherapy should not be used in any setting.

An editorial comment in the same publication notes the intriguing results linked to participants having started ART soon after infection when the CD4 count was still high and the viral reservoir remained relatively small. [3]

Participants had also maintained undetectable viral load for a median of 3.6 years before switching to monotherapy.

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TREATMENT ACCESS

CHAI 2023 market report: decline in HIV funding threatens 20 years of progress

Polly Clayden, HIV i-Base

CHAI recently released the fourteenth issue of its annual HIV market report. This excellent publication provides a detailed overview of "the complex, ever-changing HIV landscape in low- and middle-income countries based on aggregated market intelligence from our work in over 20 countries".

CHAI warns that with just two years left to meet the UNAIDS 95-95-95 targets, declining and uncertain funding threaten to erode the advances made in the HIV response over the last 20 years. And stresses that in order to make continued progress towards ending HIV, global initiatives must prioritise key populations and their partners, bridge treatment gaps between adults and children, and ensure sufficient and sustainable funding, among others.

Key highlights include:

- Thirty-nine million people living with HIV (37.5 million adults and 1.5 million children). Of which 77% adults (15 plus) and 57% children are on ART.
- 91% of adults in generic-accessible low- and middle-income countries (LMICs) use dolutegravir (DTG)-based ART, the WHO-recommended treatment, which costs less than US $45 per person per year.
- Over 160,000 of children are on paediatric DTG, which had the shortest regulatory approval on record for a generic HIV product. And for the first time there is a generic triple fixed-dose combination containing DTG for children: ABC/3TC/DTG. Over 80 LMICs are procuring this product.
- HIV diagnosis is still the largest gap among the UNAIDS 95-95-95 targets and testing rates for children and adolescents are significantly below those of adults. But, diagnostic services are improving, with self-tests available for US $1, the introduction of affordable combination tests including a dual HIV/syphilis test, and the continued decentralisation of multiple point-of-care options for CD4, viral load, and early infant diagnosis.
- Despite improvements in ART coverage, 630,000 people died from AIDS-related causes in 2022. Tuberculosis, cryptococcal meningitis and bacterial infections remain among the major causes of death for both adults and children. There is an urgent need to prevent advanced HIV disease, particularly for children.
- Overcoming political and social barriers remains critical to sustaining and expanding the HIV response, especially among key populations.

Reference

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TREATMENT GUIDELINES

HIV guidelines recommend a statin for all people older than 40: new BHIVA document

Simon Collins, HIV i-Base

On 21 November 2023, BHIVA published rapid guidance relatiing to the use of statins for people living with HIV. [1]

The 8-page document is in response to results from the REPRIEVE study published earlier this year that were also presented at the IAS and EACS conferences. [2]

Other evidence is also reviewed.

REPRIEVE showed that people at low risk of major cardiovascular events (MACE) who were randomised to daily pitavastatin had a significant reduction in MACE compared to daily placebo.

The BHIVA document interprets the results from REPRIEVE in order to reduce overall lifetime risk of cardiovascular events, rather than just to reduce the 10-year risk.

Recommendations

The guideline includes four graded recommendations supported by evidence.

- That all people living with HIV aged 40 years or older should be offered a statin for primary prevention of CVD irrespective of lipid profile or estimated CVD risk (Grade 1B).
- First-line choice for primary prevention should be pitavastatin 4 mg daily when it becomes available in the UK (Grade 2A).

- That atorvastatin 20 mg daily can be used as an alternative (Grade 2B).
- That a family history of high cholesterol should be excluded when assessing all people with total cholesterol > 7.5 mmol/L without clear cause or a personal/immediate family history of coronary artery disease below the age of 60 years (Grade 1C).
- To optimise ART in people at high risk of CVD in line with BHIVA treatment guidelines (Grade 1C).

Seven additional recommendations are graded as a Good Practice Point (GPP).

- That CVD risk assessment and discussion about pharmacological primary prevention is combined with a holistic approach to lifestyle modifications including smoking cessation and dietary advice. People needing further support should be signposted to or referred for appropriate multidisciplinary support (GPP).
- That CVD risk is assessed using tools recommended by BHIVA monitoring and national guidelines (GPP).
- All people living with HIV should have a baseline lipid assessment (GPP).
- That people living with HIV aged 40 years or older with an estimated 10-year CVD risk of 5% or greater are prioritised for primary prevention with a statin (GPP).
- That people currently on a low-intensity statin should switch to one of moderate intensity if clinically appropriate and tolerated (GPP).
- To offer an alternative lipid-lowering drug in line with national guidelines for people unable to tolerate a statin (GPP).
- That best practice for primary prevention is for statins to be prescribed and monitored in primary care (GPP).

Please see the full document for detailed discussion of the issues and evidence that supports these recommendations.

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WOMEN'S HEALTH

Modest increase in rate of cardiovascular disease progression during perimenopause for women living with HIV

Kirk Taylor, HIV i-Base

Declining oestrogen levels during menopause are associated with increased cardiovascular risk. A longitudinal cohort study evaluated early markers of atherosclerosis (e.g. carotid artery stiffness) at two to three year intervals.

Increased arterial thickening was observed for perimenopausal women living with HIV compared to premenopause (difference in slope: 1.64 μm/year, p = 0.002).

Use of hormone replacement therapy (HRT) may reduce cardiovascular risk for menopausal women living with HIV.

This longitudinal cohort study between 2004 and 2019 included regular monitoring of carotid artery stiffness and plaque development. Participants (n=979) were Black (62%), Hispanic (28%) or white (7%), median age at enrolment was 40 years (IQR: 34 to 46) and median BMI was 28.3 kg/m2(IQR: 24.3 to 33.6). Women living with HIV (n=703) were receiving ART (69%) and median baseline viral load and CD4 counts were 210 copies/mL (IQR: 80 to 8450) and 445 cells/mm3 (IQR: 281 to 661), respectively.

Progression of carotid artery thickening was greatest for perimenopausal women living with HIV. Across the study, the rate of arterial stiffening was not dependent on HIV status.

Increased arterial thickness may lead to greater risk of cardiovascular disease for women living with HIV. Use of HRT may be beneficial for menopausal women living with HIV.

C O M M E N T

Some of the limitations of this study include the imbalance of women with and without HIV, the lack of effect on plaque progression, low level of ART use and related high viral load.

Additionally, menopause data was self-reported for the final menstrual period.

Reference

Peters BA, et al. Subclinical atherosclerosis across the menopausal transition in women with and without HIV. The Journal of infectious Diseases. 08 November 2023. DOI: 10.1093/infdis/jiad488.

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COMPLICATIONS: MPOX

Mpox vaccines still available and recommended in the UK and US

Simon Collins, HIV i-Base

The mpox vaccine should still available from sexual health clinics in England, and hopefully other countries in the UK. It is important to increase awareness of this.

This follows a reversal of the earlier decision to end the vaccine programme in July, though continued access was not announced publicly. [1]

It is therefore an ideal time for people to access the vaccine and/or to complete the recommended two-dose course if they previously only received one dose.

Although cases in the UK are still low,

The US CDC recently publicised the importance of broader and routine access to the vaccine in the US for people in the following groups who are at higher risk of mpox. [2]

- Gay, bisexual, and other men who have sex with men, transgender, or nonbinary people who in the past 6 months have had one of the following:
- Being diagnosed with a new sexually transmitted disease.
- More than one sex partner.
- Sex at a commercial sex venue.
- Sex in association with a large public event in a geographic area where mpox transmission is occurring.
- Sexual partners of persons with the risks described in above.
- Persons who anticipate experiencing any of the above.

C O M M E N T

A summary of mpox in Europe continue to be published as a joint ECDC and WHO regional report.

This included 175 cases during the four weeks up to 6 September 2023, from 13 countries and areas. **This included 46 in Spain, 41 in Portugal and 28 in the UK. [3]**

The highest risk of severe mpox complications is associated with a very low CD4 count in people who are either not yet diagnosed with HIV or who have disconnected from care and who are no longer on ART.

This is a good reason to routinely link HIV testing to the mpox vaccine.

People whose HIV test is negative or who are diagnosed HIV with a CD4 count >200 cells/mm^3 could receive mpox vaccine at the same time. Those diagnosed HIV positive with a lower CD4 count are likely to get a better vaccine response after they have started ART.

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Mpox update: recent publications

Simon Collins, HIV i-Base

Luckily, throughout 2023, mpox remained at low levels in the UK. Less than a handful of cases were reported for most weeks, generally at London clinics and often linked to recent international travel.

Hopefully this trend will optimistically continue next year, although it is difficult to predict future risks as the durability of vaccine protection is not yet understood.

The following papers were recently published and may be of interest.

Low CD4 vs detectable viral load as predictors of severe mpox

A review from Brazil of approximately 400 cases reported at a single clinic from June to December 2022, half who were living with HIV, highlighted very low CD4 count as the predominant risk for more severe symptoms. Both deaths were in people with a CD4 count <50 cells/mm^3. [1]

Although low CD4 count was a significant predictor of worse mpox, a similar size cohort from the US reported that only detectable viral load >200 copies/mL was significant in multivariate analysis with twice the odds compared to those who were undetectable (2.10 [95% CI: 1.00 to 4.39]). [2]

Another paper in JID reported severe and prolonged mpox in three people with advanced HIV and CD4 counts of 127, 7 and <20. All cases report multiple detailed complications with mpox persisting for many months, even with tecovirimat. The person with the CD4 count of 7 cells/mm^3 died on day 202 still showing mpox antigen in lung and skin tissue. [3]

Complications of mpox

A case report of inguinal lymphadenitis several weeks after mpox had resolved emphasised the potential for sexually transmitted co-infections and bacterial superinfections to complicate mpox, and that viral DNA continued to persist in affected sites after initial symptoms had resolved. [4]

Complicated mpox cases that were unresponsive to tecovirimat were reported in a US cohort from Los Angeles. The cohort included more than 1580 cases, of which approximately half were HIV positive and 60 had a CD4 count >200 cells/mm^3. Overall, 134 were complicated (8.5%), including 8 cases that were not responsive to tecovirimat, all with a CD4 count >200 cells/mm^3. At the time of reporting, only three people had fully resolved mpox and the single death was in a 30-year-old transgender women who presented with a CD4 count <35 cells/mm3 and a viral load >130,000 copies/mL. [5]

Another study from Atlanta reported mpox viral dynamics in different body sites (from throat, skin and anogenital tissue) in ten HIV positive people with mpox infection, also looking at markers of infectivity. [6]

Vaccine non-responders: breakthrough infection

This is a case report of a breakthrough mpox infection in someone who was a non-responder to the mpox vaccine.

The 39-year-old gay man was on PrEP, and also on high-dose prednisolone for four months with other drugs to manage severe asthma following SARS-CoV-2 infection.

He was one of ten other participants in a small mpox vaccine study (12% n=10/85) who did not show detectable antibodies six months after the vaccine (antibody titre <1/10) and who was categorised as a non-responder. The steroid treatment at the time of vaccination was suggested as a possible explanation of the non-response.

The authors report that antibody responses generally remain higher in people who previously experienced mpox compared to vaccination, but that breakthrough infections have been reported in individuals from both groups.

They also suggest that antibody response testing might be clinically useful to identify individual risk for mpox in the future.

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PAEDIATRIC CARE

Review of US PEPFAR programme highlights continued higher infant mortality

Simon Collins, HIV i-Base

On 1 December 2023, the US MMWR included an important review of the positive impact the PEPFAR programme has had globally on the health of children living with HIV.

This included highlighting the disproportionately higher mortality experienced by children younger than five compared to those older.

Across all US PEPFAR sites from October 2020 to September 2022, almost 5% of babies younger than a year old and nearly 3% of children aged 1-4 years on antiretroviral treatment died each year.

We include below the abstract from the report but please see the full online report for full details.

Abstract

Globally, children aged <5 years, including those living with HIV who are not receiving antiretroviral treatment (ART), experience disproportionately high mortality. Global mortality among children living with HIV aged <5 years receiving ART is not well described.

This report compares mortality and related clinical measures among infants aged <1 year and children aged 1–4 years living with HIV with those among older persons aged 5–14, 15–49, and ≥50 years living with HIV receiving ART services at all clinical sites supported by the U.S. President's Emergency Plan for AIDS Relief.

During October 2020–September 2022, an average of 11,980 infants aged <1 year and 105,510 children aged 1–4 years were receiving ART each quarter; among these infants and children receiving ART, 586 (4.9%) and 2,684 (2.5%) respectively, were reported to have died annually. These proportions of infants and children who died ranged from four to nine times higher in infants aged <1 year, and two to five times higher in children aged 1–4 years, than the proportions of older persons aged ≥5 years receiving ART.

Compared with persons aged ≥5 years living with HIV, the proportions of children aged <5 years living with HIV who experienced interruptions in treatment were also higher, and the proportions who had a documented HIV viral load result or a suppressed viral load were lower.

Prioritising and optimising HIV and general health services for children aged <5 years living with HIV receiving ART, including those recommended in the WHO STOP AIDS Package, might help address these disproportionately poorer outcomes.

Reference

Mortality Among Children Aged <5 Years Living with HIV Who Are Receiving Antiretroviral Treatment — U.S. President's Emergency Plan for AIDS Relief, 28 Supported Countries and Regions, October 2020–September 2022. MMWR, 72(48);1293–1299. 1 December 2023.

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DRUG INTERACTIONS

Oral tenofovir/FTC increases clearance of bNAb VRC01: implications for future research

Simon Collins, HIV i-Base

A paper published on 28 November 2023 in the journal Nature Communications reports a drug interaction between the drugs commonly used as PrEP and VRC01, a broadly neutralising antibody (bNAb) which was used in a large HIV prevention study. [1]

The results are from a post-hoc analysis of the VRC01 AMP study and reported that people using PrEP had 14% lower levels of the bNAb.

This subsidy included 48 participants in the VRC01 AMP study, half of whom were also using TD/FTC oral PrEP, and compared drug levels in each group.

Viral clearance of VRC01 was significantly faster (0.08 L/day, $p = 0.005$) in people using PrEP. Overall drug exposure was also significantly lower (dose-normalized area-under-the-curve of VRC01 serum concentration over time was 0.29 day/mL lower, $p < 0.001$).

The authors proposed a potential mechanism linked to oral PrEP increasing serum levels of intestinal Fatty Acid Binding protein (I-FABP), a marker of epithelial intestinal permeability.

VRC01 clearance is positively associated ($r = 0.33$, $p = 0.03$) with levels of serum I-FABP) which also increases when starting PrEP ($p = 0.04$) and after months of self-reported use ($p = 0.001$).

COMMENT

Although PrEP was not widely used in the Antibody Mediated Prevention (AMP) study, which only produced a minimal protection against HIV infection in a subset of participants, people who were also taking tenofovir disoproxil/emtricitabine would have had lower levels of the antibody.

While the PrEP would have protected these participants against HIV, it might have complicated the interpretation of the impact of the antibody.

As this is the first report of an interaction between HIV drugs and HIV bNAbs these results might have implications for other research using bNAbs.

Because of the delay associated with journal publications, most new and significant drug interactions are first presented at a medical conference, especially when the findings might have safety implications for other ongoing research.

The paper was submitted to the journal six months ago, so these results could easily have been a late-breaker at the IAS conference in July.

I should also apologise in advance if the study was presented at an earlier meeting and we just missed this.

Reference

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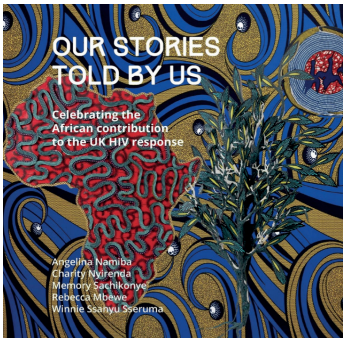
BOOK REVIEWS

Our stories told by us: Celebrating the African contribution to the UK HIV response

Review by Simon Collins, HIV i-Base

Launched in May with a limited first run, this celebration of the power of friendship and community is now available online in Kindle, paperback and limited hardback editions. [1]



More than 250 pages, illustrated in colour with uniquely designed African prints, the book compiles the experiences of more than 40 activists involved in the African response to HIV in the UK.

The five authors – from Kenya, Uganda, Zambia and Zimbabwe – are all Black African women who are proudly living with HIV. They are also some of the most prominent, respected and popular HIV advocates in the UK.

These women have known and supported each other for many years, including through a virtual reading group during COVID. Their decision to write about their own experiences, rather than just reading others, was inspired by their friendships, which also unites all the other contributions.

For more than two years, the group collected stories from the diverse communities of African people living with HIV and included allies. The contributions cover life before and after coming to the UK and before and after learning about their HIV status. One of the few criteria for inclusion involved being visible in your communities.

Many of the contributors claimed asylum in the UK because of persecution in their home countries, some were just joining family members here as part of their life plans. Most only learned about HIV later, often without realising that their HIV was already advanced.

A common response was to develop community networks that could provide support, to learn about HIV treatment and to become community educators to help others.

All contributors talk about having to overcome stigma both in the UK and in their home countries. They talk about the harm this continues to cause today and of the freedom from deciding to live openly, and the importance of everyone being able to now benefit from the medical breakthroughs in effective treatment.

If you get a chance, come to one of the talks being organised across the UK, with European dates planned. Or better still, get in touch via their website, to organise one yourself for your own organisation - you will not regret it.

The website also includes related news and podcasts and direct links to Amazon, Barnes & Noble and Waterstones. [2]

These stories will inspire you. They are direct and easy to read. Delight in their humour and learn from their wisdom. And any friends lucky enough to borrow or be gifted a copy of this beautiful book over the holidays will also thank you for making their winter a little warmer.

For transparency, Simon Collins was lucky to be included as a contributor, and is proud to be an ally of such inspiring activists.

References

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OTHER NEWS

Pricing new gene therapies for sickle-cell: implications for an HIV cure

Simon Collins, HIV i-Base

The recent UK and US approvals for gene therapy approaches to treat and potentially cure sickle-cell disease are remarkable scientific advances. [1, 2]

They also come with prices of upwards of $2 million for a single treatment.

The model supporting this cavalier approach to pricing is based on reducing the lifetime costs of treating sickle-cell disease.

A similar model for hepatitis C drugs, justified the $1000 a pill price by including the costs of a liver transplant. It is also disassociated from both the research and manufacturing costs. Generic formulations for these meds are now produced at a fraction of these prices.

The model is also based on the US only treating 2000 people per year, although more than 100,000 people in the US are likely to have sickle-cell disease, which predominently affects Black communities.

We include this news in HTB because gene therapy is one of the most active approaches to finding a cure for HIV. If this research is scientifically successful, we will have the same issues of cost in order to achieve access by those who need it most.

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Up to 3% of medical research papers are fake

Simon Collins, HIV i-Base

The seasonal bonus article, as we finish the issue this year, was highlighted in Nature as a caution for going into the New Year.

A review of papers published over the last two decades concluded that 400,000 show strong similarities to previously published work or that were clearly produced by research paper mills.

Of these, approximately 70,000 were published during the last year, with a rate of 3% among biology and medicine papers.

The analysis itself though is not yet published, and the report in Nature is behind a paywall, so the anarcho-skepticist editors at HTB bow out to leave you with unsatisfactory click-bait.

Reference

How big is science's fake-paper problem? Nature. (6 November 2023)

https://www.nature.com/articles/d41586-023-03464-x

MEETINGS & WORKSHOPS 2024

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)

2024

CROI 2024

3 – 6 Mach 2024, Denver, Colorado

https://www.croiconference.org

AIDS 2024

22 – 26 July 2024, Munich

https://www.iasociety.org/conferences/aids2024

5th HIV Research for Prevention Conference (R4P 2024)

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

www.iasociety.org/conferences/HIVR4P2024

HIV Drug Therapy Glasgow 2024

10 – 13 November 2024

https://hivglasgow.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

All i-Base publications are available online, including editions of the treatment guides.

http://www.i-Base.info

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

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

i-Base treatment guides

i-Base produces six booklets that comprehensively cover important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

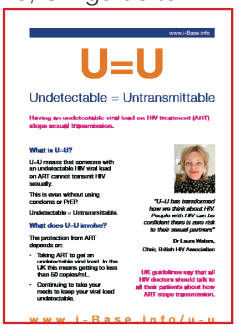
http://www.i-base.info/guides

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

Pocket guides

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

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



The leaflets use simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

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

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

This project was developed with the Kobler Centre in London.

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

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

email: subscriptions@i-base.org.uk

Customise U=U posters for your clinic

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

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

For further information please email: subscriptions@i-Base.org.uk

h-tb

HIV TREATMENT BULLETIN

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

http://www.i-Base.info

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

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- **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:

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