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Loneliness and HIV; further EACS reports

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HIV TREATMENT BULLETIN

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HTB is a not-for-profit community publication. It reviews the most important medical advances related to clinical management of HIV including access to treatment. We compile comments to articles from consultant, author and editorial responses.

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EDITORIAL

This final edition of HTB continues our reports from the 17th EACS conference recently held in Basel.

These include early data on a long acting (6-monthly) capsid inhibitor for MDR HIV, a review of dual therapy with dolutegravir/lamivudine, the lack of weight gain with doravirine, and an analysis on bone and renal changes in the ADVANCE study,

We also include a report on HIV loneliness from the recent workshop on HIV and Ageing.

ARV news includes: new UK access to doravirine, FDA submission for fostemsavir (but now on named patent access) and submission of a new paediatric formulation of dolutegravir.

Over the last few months i-Base has updated three treatment guides - see below - and we proudly distribute these free.

However, any loose change you have during the holiday season, could find a worse home that the i-Base appeal.

Thank you to all who have contributed so far....

SUPPLEMENTS

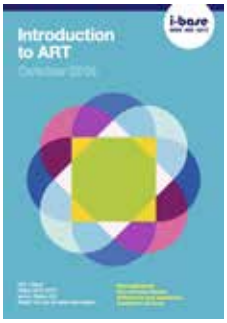
i-Base guide to HIV testing and sexual transmission (January 2020)

This updated booklet includes information on all aspects of HIV testing and sexual transmission.

The printed version has been reduced by 20 pages - signposting to information that is still online.

It is updated throughout to include both U=U and PrEP.

Introduction to ART - October 2019



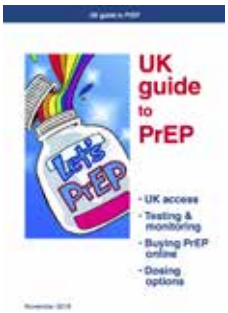
This widely used guide to HIV treatment (ART) has been updated. It is available a printed A5 booklet that is also available online.

Main changes to the 2018 edition are to update the choice of drugs, to include the most current treatment guidelines and add new information about recently approved drugs. So both the text and drug chart (the pull-out centre pages or separate PDF) includes bictegravir, Biktarvy, doravirine, Delstrigo, Dovato ad ibalizumab.

i-Base guides aim to help you understand your treatment choices, to encourage you to ask questions, and to have better health and better quality of life.

Thanks as always to the advisory group that have added comments each year, making this a collaboration between treatment advocates (many of who are living with HIV) and health workers.

UK Guide to PrEP - November 2019



The 5th edition of this UK guide to PrEP is now updated online and printed copies are free to order. [1]

Changes to this edition include:

- Latest information about how to access PrEP in the UK. This includes differences in how and where the NHS provides PrEP.
- It includes new information about the PrEPshop clinic in London and buying PrEP online.
- A new section on PrEP and sex work.
- Information about TAF/FTC for PrEP.
- Small changes to clarify the way PrEP dosing is described and new recommendation that heterosexual men can use event-based dosing.

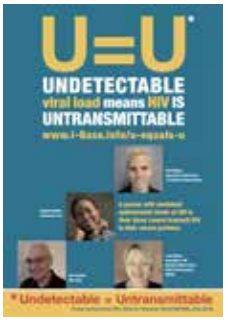
The guide is available in print and online.

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

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

Please continue to order these free resources.

Customise U=U posters for your clinic



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

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

i-Base 2019 appeal

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

Your help has been inspiring – and we hope this support will continue during 2019. If 1000 people support us with £5 a month we will be on course to meet our funding shortfall. All help is appreciated.

http://i-base.info/i-base-appeal-we-need-your-help

Subscriptions

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

http://i-base.info/htb/about/subscribe

CONFERENCE REPORTS

17th European AIDS Conference (EACS 2019)

6 – 9 November 2019, Basel

The 17th biennial European AIDS Conference was held in Basel from 6 to 9 November 2019.

This issue of HTB continues our coverage.

The programme, with links to abstracts is online:

http://www.professionalabstracts.com/eacs2019/iplanner/#/grid

and also

https://onlinelibrary.wiley.com/doi/10.1111/hiv.12814

https://onlinelibrary.wiley.com/doi/epdf/10.1111/hiv.12814

Slides and webcasts are already available as open access on the EACS library website, after the conference, although only for three months for non-EACS members.

http://resourcelibrary.eacs.cyim.com

Articles from the conference included in HTB are:

- Capsid inhibitor GS-6207: potential for 6 monthly dosing for MDR HIV
- Dolutegravir/lamivudine as dual ART
- Weight changes with doravirine-based first line therapy
- Bone and renal changes in the ADVANCE trial

Capsid inhibitor GS-6207: potential for 6 monthly dosing for MDR HIV

Simon Collins, HIV i-Base

Two studies at EACS 2019 included new information about the capsid inhibitor GS-6207.

This pipeline compound in early stages of development is important for having activity against HIV that is resistant to existing HIV drugs, high potency (with picomolar activity), being active at multiple stages of the viral lifecycle and having the potential for long-acting formulations for both treatment and prevention.

Rebecca Begley from Gilead Sciences reported the unblinded data from the first phase 1 PK and safety study in HIV negative participants. [1]

Although the virological results from this study were first presented at CROI 2019, the new analysis included additional safety data and modelied pharmacokinetics to predict likely dosing. [2, 3]

The most common side effects were injections site reactions (ISRs), reported in 19 (59%) participants receiving GS-6207 compared to in 2/8 (25%) of participants receiving placebo. These were all mild and mainly erythema (47%) or pain (38%) and resolved within a few days.

PK results showed that at the 100 mg, 300 mg and 450 mg doses, drug levels remained above the protein adjusted EC90 (3.89 ng/mL) at week 12, and was sustained out to week 24 in the two highest doses.

The second poster was from a similar randomised, placebo-controlled, dose-ranging phase 1b study in HIV positive participants. [4]

All participants receiving GS-6207 had at least 1 log copies/mL reduction (range: 1.16 to 2.86). Mean viral load reductions after 10 days monotherapy of –1.75, –1.76 and –2.20 in the 50 mg, 150 mg and 450 mg groups. At day 10 all participants started ART using bictegravir/FTC/TAF.

Although safety results from this study are still blinded, tolerability was good, with mild ISR's reported by 63% (15/24) of participants. There were no serious grade 3/4 laboratory abnormalities. Some of these results were previously presented as a late-breaker poster at IAS 2019. [5, 6]

The PK results have led to a phase 2 study in treatment-experienced participants that will use a modified formulation to enable 6-monthly injections. [7]

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Dolutegravir/lamivudine as dual ART

Simon Collins, HIV i-Base

The option to use dolutegravir/lamivudine (DTG/3TC) for both first-line ART and as switch option was a common topic at EACS, especially when compared to use of three-drug ART.

Numerous oral presentations and posters covered various clinical aspects of this dual ART that now included as a preferred combination for starting ART in the 2019 EACS guidelines

DTG/3TC has the potential to limit drug toxicity and also involve less expensive treatment but as with every combination it is important to define the best population who can benefit. This was also the basis of commercial rivalry between companies in the exhibition hall and related advertising throughout the conference.

Low level viraemia on DTG/3TC

Several studies presented new data on low-level viraemia on DTG/3TC, where any signal of suboptimal efficacy would be expected to be seen, but these studies continued to show no difference compared to triple-drug ART.

An oral presentation from the combined GEMINI 1 and 2 phase 3 studies analysed undetectable level viral load based on whether target was detected (TD) or not detected (TND) when less than 40 copies/mL. The 48-week analysis was presented as a poster at CROI in March 2019, showing no differences between groups. [2, 3]

The study at EACS 2019 included additional sub group analyses by baseline viral load (above and below 100,000 copies/mL) and CD4 count (above and below 200 cells/mm^3).

Regardless of baseline viral load or CD4 count, similar proportions or participants in each group had TND results overall at week 96, although this was slightly lower in both groups for those starting >100,000 copies/mL (approximately 52% vs 70% for those <100.000).

In a poster presentation, Wang and colleagues presented an updated analysis from the phase 3 TANGO study, that randomised 741 participants on stable ART to either switch to DTG/3TC or continue on their current ART. [4] This poster was an update of week 48 results that were previously reported at IAS 2019. [5, 6]

This analysis looked at various categories of low-level viraemia overall and in a subset of people with archived NRTI drug resistance (M184I/V and K65R) at baseline.

Again, there were no significant differences in patterns of blips between the two groups, though there were numerically more cases of low level viraemia in the triple therapy group. See Table 1.

Retrospective analysis of baseline samples only detected Mi84I/V in 1% (7/626) and K65R in <1% (1/626) of samples that could be amplified. Irrespective of treatment group, none of these people experienced viral load > 50 copies/mL.

Table 1: Low level viraemia in TANGO study

	DTG/3TC (n=369)	Triple ART (n=372)
1. VL 50–200 c/mL (but always < 200)	11 (3%)	22 (6%)
1a. VL blips - single result 50 -200 c/mL	9 (2%)	18 (5%)
1b. >2 VL 50-200 c/mL	2 (<1%)	4 (1%)
2. VL >200 c/mL	3 (<1%)	3 (<1%)
2a. Single >200 c/mL without 50-200	3 (<1%)	1 (<1%)
2b. 2 x > 50 c/mL and at least 1 x >200 c/mL	0	2 (<1%)
Total	14 (4%)	25 (7%)

Dual ART using dolutegravir + emtricitabine (FTC)

Results from a small open-label, multicentre Swiss study were presented by Delphine Sculier that randomimised 188 people on stable ART to either DTG + FTC or continuing triple therapy. [7]

Unlike phase 3 studies using DTG/3TC, there were no CD4, viral load or M184I/V exclusion criteria and the study additionally looked at reduced monitoring - with viral load monitored annually compared to every three months. Integrase inhibitor resistance was an exclusion criteria.

Baseline demographics included 17% women, 80% Caucasian and 9% HCV coinfection. Although median CD4 counts was about 660 cells/mm^3 (IQR: 500 to 900), many participants had a history of advanced HIV with approximate median CD4 nadir 250 cells/mm3 (IQR: 103 to 367) and viral load 100,000 c/mL (IQR: 30,000 to 326,000).

Baseline ART included integrase inhibitors in approximately 60% with 41 participants newly starting DTG in the dual therapy arm.

At week 48, by the standard endpoint of viral suppression <50 copies/mL by snapshot analysis, 90.3% vs 91.5% in the dual vs triple arms respectively (difference –1.1%; 95%CI: –9.3 to +7.1%).

However, the primary endpoint defined for this study used a higher cut-off of <100 copies/mL with viral failure defined as two consecutive viral load results >100 copies/mL. Results in this analysis were 93.5% vs 94.7% in the dual vs triple arms respectively (difference: –1.2%; 95% CI: –7.8 to +5.6%).

Although this met criteria for non-inferiority using predefined margin –12.0%, non-inferiority wouldn't be met by the more stringent –4% margin now recommended for HIV switch studies. This is a factor of the small size of this study.

In either analysis, there were very few cases of virological failure, with the single confirmed viral rebound to >100 copies/mL occurring in the triple arm.

However, there were also no significant differences in side effects between the two groups, other than reduced creatinine clearance in the dual therapy arm (–2.4 vs +1.1: difference: 4.3, p=0.006).

Dolutegravir/lamivudine with historical M184I/V or K65R/E/N mutations

The question of whether historical/archived drug resistance to lamivudine (M184I/V mutation) could limit the option to use dolutegriavr/lamivudine as a switch option is important.

Although preexisting drug resistance has been an exclusion criterion for most studies, this has been based on limitations of population-based genotype results that can miss minority variants.

A small Spanish pilot study reported cases of successful viral suppression on dual therapy despite retrospectively discovered presence of either M184IV or K65R/E/N at low levels by single probe next generation sequencing (NGS). [8]

This study include 41 INSTI-naive adults who were switched to DTG/3TC after having been <50 copies/mL on current combination for at least a year. Presence of M184IV or K65R/E/N at baseline by routine genotype testing was an exclusion criteria. However, retrospective NGS testing later identified low levels of M184IV or K65R/E/N in 21 participants including >5% 3TC mutations (combined M184V/I and K65R/E/N) in 15/21.

At week 48, 92.7% of participants (38/41) remained with VL <50 copies/mL. There were no cases of virological failure however. The three premature discussions (all with historical 3TC resistance) included tow protocol violations (who discontinued with VL < 50 copies/mL) and one discontinuation due to insomnia (at week 8).

One participant with historical M184I rebounded to 1120 copies/mL at week 36 but resuppressed without changing treatment, and without developing 3TC or integrase resistance,

The conclusion noted that fully powered and long term studies were needed to confirm these results and the current study will run for 144 weeks.

Retrospective reviews of dual DTG/3TC in clinical practical

Several studies also reported on retrospective analysis of dual vs triple therapy.

Santoro and colleagues presented interim result of a 96-week superiority study that randomised 50 participants to either remain on their stable dolutegravir/lamivudine therapy or switch to elvitegravir/cobicistat/FTC/TAF (E/C/F/TAF). [9]

This was another way to look at whether low levels of viral activity that would not be picked up by routine viral load monitoring, could be detected between the 2-drug and 3-drug groups.

In 40/50 participants with results out to week-48 the study found no differences in levels of total HIV-DNA or in a panel of immune responses between the two groups, either at baseline or at week 48.

HIV DNA did increase in some participants, but this was similar between groups: 8/19 for DTG//3TC and 7/21 for E/C/F/TAF, p=0.745). Although the abstract commented on included two individuals in the dual therapy arm with a >4-fold increase in HIV DNA, these results were all well within the overall variability of the study overall.

However, a retrospective analysis of the large Spanish VACH cohort, was more controversial for reported shorter time to treatment failure with dual therapy (DTG/3TC or DTG/rilpivirine - roughly 2:1) compared to using an integrase inhibitor plus two NRTIs (roughly 50% E/C/F/TAF 40% DTG/ABC/3TC). [10]

The study, also funded by Gilead, included 5664 participants who either switched to dual (n=617) or triple (n=5047) integrase inhibitor-based ART between May 2016 (when TAF FDCs became available) to May 2019.

Importantly, baseline characteristics were significantly different for some important factors including that people in the two-drug were more likely to be older, women, people who injected drugs, to have had a longer treatment history, using more combinations and having more treatment failures (mostly p< 0.001) although also better viral control (90% vs 80%).

Over 756 and 8617 patient years of follow-up (in dual and triple groups respectively), discontinuations due to side effects were low and overlapping throughout the three years.

However, after controlling for baseline characteristics, participants using dual therapy had a higher risk of treatment failure in Kaplan-Meyer analysis (aHR 2.3. 95% CI: 1.3 to 4.1, p=0.003). Although this difference seemed to develop after two years, there were very few participants with data at these endpoints (n=130 at 24 months, 62 at 30 months and only 10 at 36 months on dual therapy). These results were similar in a subanalyses in participants who had undetectable viral load at the time of the switch and in those who just had viral failure.

Analysis of preexisting drug resistance in those with virological failure was not yet available, nor were clinical data on their management after viral failure.

The presentation included a lively discussion after the talk, that also pointed out that while relative risk was significant the absolute risk in this study was small, only affecting a few patients.

Dolutegravir/lamivudine in transplant recipients

The potential to use dolutegravir/lamivudine in people who have undergone solid organ transplant was included in a poster presented by Castelli et al from University of Barcelona. [11]

Results from a retrospective case note review of six HIV positive recipients of solid organ transplants (five men, one women; three kidney, two liver and one heart) who were limited from using tenofovir or abacavir due to chronic renal and/or liver toxicity and who all switched to dolutegravir/lamivudine. Five people were receiving TDF/xTC plus either raltegravir (n=4) or rilpiviriine (n=1) and one was already taking dolutegravir/lamivudine before the transplant.

Exclusion criteria included previous ART failure, resistance to lamivudine or raltegravir and HBV infection.

Viral load remained undetectable (<50 copies/mL) during available follow-up (four to 36 months, one to 24 months and one to 6 months). Renal function (creatinine, glomerular filtration) stabilised or improved in all cases. Doses of immune suppressants (n=5 tacrolimus, 1 = cyclosporin) were not significantly changes and there were no cases of organ rejection.

However, one case with positive anti-core HBV antibodies (indicating previous infection) but negative HBsAg, HBeAg and plasma DNA-HBV, developed acute HBV two years after simplification. This person reestablished after restarting TDF, and HBsAg and DNA returned to undetectable.

COMMENT

These studies continue to broadly support the safety of dolutegravir/lamivudine dual therapy in many settings.

The Spanish cohort study reporting higher relative risk of treatment failure by Teira and colleagues will keep a focus on long-term outcomes.

Randomised data will become available from large phase 3 TANGO study that continues both arms until 148 weeks, with further follow-up to week 200. [12]

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Weight changes with doravirine-based first line therapy

Simon Collins, HIV i-Base

Given the concerns about weight gain with integrase inhibitors and NRTIs, especially dolutegravir and TAF, changes in weight and BMI should now be reported for other recently approved HIV drugs.

This is complicated because both starting ART and ageing are associated with weight gain and several studies have reported differences by gender, race and baseline HIV demographics.

This analysis for the NNRTI doravirine (DOR), presented by Chloe Orkin from Barts Health NHS Trust, London, used several ways to analyse changes including median and mean absolute changes, rates of people with more than 10% changes and changes in weight banding (ie change from underweight/normal to overweight/obese or from overweight to obese, etc).

The results generally showed no significant changes in treatment-naive adults for doravirine based ART, compared to DRV/r or EFV, with approximately 70% of people staying in the same weight category over 96 weeks. An important caution is that this was a post hoc analysis comparing different studies.

Doravirine data (at approved 100 mg dose) was compiled from three phase 2/3 studies in treatment naive adults.

- P007: DOR vs efavirenz (EFV) plus FTC/TDF
- DRIVE FORWARD: DOR vs darunavir/r (DRV/r) plus either FTC/TDF or abacavir/3TC
- DRIVE AHEAD: DOR/3TC/TDF vs EFV/FTC/TDF

The pooled groups included n=855 (DOR), 383 (DRV/r) and 472 (EFV) with results at 96 weeks. At baseline, median age was approximately 35 years old (+/– 10), 12–15% of participants were women and 18–23% were black. Mean weight and BMI were 76 (+/–15) kg and 25 (+/– 5.0).

At 96 weeks, mean and median weight increases were 2.4, 1.8 and 1.6 kg and 1.5, 0.7 and 1.0 kg, in the DOR, DRV/r and EFV groups respectively. This is similar to expected weight gains over time in the general population.

Percentage increases from baseline were similar for all three groups: approximately 68%, 17% and 15% had increases of <5%, 5 to 10% and >10% respectively.

Low baseline CD4 and high viral load correlated with a higher risk of >10% weight gain in all three groups.

Heat mapping graphs, excluding participants who were obese at baselines showed that 7%, 6% and 5% of participants became obese over 96 weeks, in the DOR, DRV/r and EFV groups respectively.

Sankey diagrams (showing direction of movement between categories) showed approximately 7% of participants with normal BMI at baseline became overweight but only 1% became obese. Slightly higher percentages of people who were overweight at baseline become obese on DOR (19% vs 13% vs 13%) - but with 10-15% returning to normal weight. Most people who were obese at baseline remained obese, although a higher percentage of people using DRV/r went back to just being overweight (though these were small absolute numbers).

The study concluded that weight gains in these studies were similar to those expected in an ageing population, with most people staying in the same weight category. However, there were relatively small percentages of women and black people, and objective measures including waist circumference and DEXA scan were not available.

COMMENT

Allowing for the important cautions for comparative post-hoc analyses, including baseline differences of some demographics between studies, the data are useful for not showing a signal of increased weight.

These results are helpful given the unexpected weight gain linked to dolutegravir and TAF in the ADVANCE study.

Reference

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Bone and renal changes in the ADVANCE trial

Polly Clayden, HIV i-Base

Smaller decreases in bone mineral density (BMD) in the TAF-containing versus TDF-containing arms of the ADVANCE trial, according to findings presented at EACS 2019. [1]

The 96-week ADVANCE trial, conducted in South Africa, randomised 1053 treatment-naive participants to three first-line regimens: tenofovir alafenamide (TAF)/emtricitabine (FTC)/dolutegravir (DTG) vs tenofovir disoproxil fumarate (TDF)/FTC/DTG vs TDF/FTC/efavirenz (EFV).

Week 48 results, showing DTG-based regimens to be non-inferior to EFV-based ones (but associated with substantial weight gain) were presented at IAS 2019 and published in the NEJM in July. [2, 3, 4]

One of the aims of the ADVANCE study was to compare bone and renal changes over 96 weeks in participants receiving TDF-containing regimens versus those receiving TAF-containing regimens. At the time of analysis, all participants had completed 48 weeks and approximately half had reached 96 weeks.

In this sub study, the investigators used DEXA scan to measure BMD for whole body, spine and hip and baseline, week 48 and week 96.

T-scores for BMD results were calculated using WHO categories to diagnose treatment emergent osteopenia and osteoporosis.

The FRAX (Fracture Risk Assessment) tool was used to assess fracture risk in all participants aged 40 and above. This method calculates the overall 10-year probability of fracture with BMD based on: age and sex; height and weight; previous history of fractures; presence of glucocorticoids and/or rheumatoid arthritis; presence of secondary osteoporosis; alcohol and smoking and femoral neck BMD. Of note, FRAX is based on population-based cohorts from Europe and South America and is not validated in African patients.

Renal tests included uric acid, phosphate, B2 microglobulin, urine retinol-binding protein, serum creatinine clearance and urine albumin-to-creatinine ratio. Changes from baseline were measured every study visit.

At baseline, participants were about 33 years old, 99.5% were black and about 60% were women. Mean BMD scores were: 1.20 g/cm2, 1.03 g/cm2 and 1.00 g/cm2 for whole body, hip and spine respectively. These were similar across the three treatment arms and <1% had a history of bone fractures.

Mean renal markers were also balanced across the treatment arms and approximately 8% had a history of renal and urinary disorders.

All participants showed similar decline (approximately -7%) in whole body BMD to week 48, which levelled out to week 96. There were no significant differences in changes in whole body BMD across the three study arms at either time point.

There was a decrease across all three arms in spinal BMD, which at weeks 48 and 96 was greater in the two TDF-containing arms compared to the TAF-containing one (mean per cent change: -6% vs -4%). The difference was statistically significant at week 96 ($p<0.001$).

There was also a decrease in hip BMD across all three arms at weeks 48 and 96, which was greater in the two TDF-containing arms than the TAF-containing arm (mean per cent change: -4.5% and -6% vs -3%). Notably the greatest decrease was seen in the EFV arm. All comparisons are statistically significant at week 96, including the difference between the TDF/FTC/DTG arm compared to the EFV/FTC/TDF arm ($p<0.001$).

The percentage of participants developing treatment-emergent whole body osteopenia at weeks 48 and 96 was small across all three arms: 1.8%, 2.3% and 0% for TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/ EFV, at week 96 respectively. (All comparisons NS except TDF/FTC/DTG vs TDF/FTC/ EFV, $p=0.05$).

The percentage of participants developing treatment-emergent spinal osteopenia at weeks 48 and 96 was higher than seen with whole body across all three arms: 21%, 23% and 30% for TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/ EFV, at week 96, respectively. There were no significant differences between the three arms. And 1% of participants in the TDF/FTC+DTG arm developed osteoporosis at week 96.

A higher percentage of participants had treatment-emergent hip osteopenia in the EFV arm at both weeks 48 and 96 than in the other two study arms: 6.3%, 11.1% and 30% for TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV, at week 96, respectively.

At week 48, only the difference between the TAF/FTC/DTG and TDF/FTC/EFV arms is significant ($p=0.005$). At week 96 the differences between the EFV arm and the other two study arms are both statistically significant (both $p<0.001$).

As with the whole body data, no participants in this paired analysis developed treatment emergent osteoporosis at week 48 or week 96 in any treatment arm.

Seven fractures were reported during the study and were balanced across the arms and none were related to study drugs.

Using FRAX, the predicted 10-year risk of major fractures was 0.2% lower in the TAF/FTC/DTG arm compared with the TDF/FTC/DTG arm. There was no difference between TAF/FTC/DTG and TDF/FTC/EFV.

There were very few grade 3 or 4 renal adverse events (<1%) seen in the study. Grade 3 or 4 abnormalities in creatinine clearance were infrequent with no statistical differences by treatment arm. No consistent difference between TAF and TDF arms in elevations of renal markers above the normal range. But there was an apparent difference in B2M and RBP with in the EFV arm.

The investigators concluded that longer-term follow-up is needed to continue to balance the risks of clinical obesity observed with DTG and TAF and follow up changes in bone and renal markers for these first-line regimens.

Polly Clayden is on the scientific committee of ADVANCE and a co-author of the NEJM paper.

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CONFERENCE REPORTS

10th International Workshop on HIV and Ageing

10–11 October, 2019

Introduction

Simon Collins, HIV i-Base

The 10th International Workshop on HIV and Ageing, now held annually in New York, continues to raise this increasingly important subject.

The programme for the conference is online.

https://www.virology-education.com/event/previous/10th-hiv-aging-workshop-2019/

Abstracts, PowerPoint slides and posters will be posted online shortly after the workshop.

http://www.infectiousdiseasesonline.com/presentations

Reports in the last issue of HTB focused on frailty, vaping and medical use of cannabis.

HTB reports in this issue include:

- Impact of isolation and loneliness on older people living with HIV

Impact of isolation and loneliness on older people living with HIV

Simon Collins, HIV i-Base

Maille Karris from the University of California, San Diego presented a talk on loneliness and social isolation as factors in ageing that included a review linking the pathogenesis of loneliness to poorer clinical outcomes. [1]

While social isolation is easy to define by the degree an individual connects with society, loneliness is a more complex outcome of the difference between someone's preferred and actual relationship with other people. Being alone is not the same as feeling alone and many people enjoy being on their own without feeling lonely. But while solitude can be positive, loneliness, even though very common, is significantly linked to poorer health.

Large national surveys have defined epidemic levels of loneliness in the US. Longitudinal surveys over decades have reported that almost half of Americans either sometimes or always felt alone or left out and that a quarter rarely or never feel that there are people who really understand them. Social networks have also become smaller with increasing numbers of people (from 10% in 1985 to 18% in 2018) having no significant person that they discuss important matters with. [2]

In the context of ageing, loneliness also differs by whether this is occurring during adolescence, middle age or in older age, with other differences by demographics including race and gender. Numerous studies have included having closer social networks and not living alone as reducing the risks of being lonely.

Being HIV positive can compound issues of loneliness in many long-term survivors through a history of losing friends and partners – and HIV positive people at all stages can be affected by the social effects of stigma and discrimination limiting the size of their social networks and increasing the risk of social isolation.

A large meta-analysis of studies in the general population reported strong associations between social isolation and higher rates of mortality that were consistent across gender, length of follow-up, and geographical region. It reported that social isolation, loneliness and living alone were associated with 29%, 26%, and 32% increased likelihood of mortality, respectively. [3] Some of the same research group, again in large meta-analysis, reported that people with larger social networks have higher survival outcomes. [4]

Smaller surveys have reported higher levels of loneliness (~60%) in people living with HIV, and more negative health outcomes, including a greater likelihood of smoking, at-risk drinking or substance use, higher rates or depression and lower quality of life. [5] Higher rates of isolation are especially linked to higher rates of depression.

From a public health perspective, people who are socially isolated have higher medical costs: with a US study reporting higher Medicaid costs of $134/month ($6.7 billion annually), driven by cardiovascular disease and stroke. [6]

The pathogenesis of clinical symptoms of loneliness was shown to be moderating health through stress-induced cortisol dysregulation, higher rates of inflammation, higher levels of viral activity (EBV and HHV8) and poorer immune responses (including to influenza vaccine). Induced stress tests were also reported to increase some proinflammatory cytokines, including IL-6. [7]

Other factors associated with loneliness in a study of almost 1000 HIV positive people, included not being in a relationship, lower financial income, poorer adherence, living alone, higher risk of smoking and comorbidities (including frailty, cognitive decline and depression) and lower quality of life. [8]

Practical ways for managing loneliness include psychosocial therapy, befriending interventions and supporting leisure skill and activities. In the US this has included a novel village model of community living where networks of friends contribute membership costs towards shared resources to support needs as they age as a group. The needs of communal villages enable people to live independently as they age but are likely to be easier when people are well (and by definition likely wealthy). A current example that hopes to overcome some of the challenges of sustainability has linked an initiative for older HIV positive people in San Diego to the local LGBT centre.

This project, currently being evaluated, includes a local social media app and network to identify and meet needs for the group that includes quality of life as a primary outcome.

C O M M E N T

Poor medical outcomes associated with higher levels of social isolation that someone would ideally like, are easily impacted by HIV, but also they provide the chance for lifestyle interventions that could theoretically reverse these risks.

Very few people deliberately set out to become lonely or isolated but for many people the social challenges of living with HIV make this easier to say than do, both on individual and population levels.

This talk produced many comments from community participants who confirmed this importance of the subject in people's real lives and asked for further research into this complex aspect of living with HIV.

An easy suggestion for doctors is just to ask their patients if they are lonely.

References

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ANTIRETROVIRALS

Doravirine approved by NHS England as single NNRTI and as part of FDC with 3TC/TDF

Simon Collins, HIV i-Base

On 29 November 2019, NHS England published prescribing guidelines for the access to the NNRTI doravirine. [1]

These guidelines report that there is sufficient evidence to support a policy for the routine commissioning of this treatment in line with cost-based, regional prescribing guidelines for the treatment of adults with HIV-1 who have no past or present evidence of resistance to the NNRTI class.

Where doravirine is used with a two NRTI backbone, those backbone components should be fully active.

All patients for whom doravirine is considered a treatment option must be considered in an HIV specialist treatment multidisciplinary (MDT) meeting and the decision of the MDT recorded.

Doravirine is contraindicated with drugs that are strong cytochrome P450 CYP3A enzyme inducers, because of the potential to reduce doravirine levels.

These drugs include, but are not limited to, the following:

- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin.
- Androgen receptor inhibitor: enzalutamide.
- Antimycobacterials: rifampin, rifapentine.
- Mitotane.
- St. John's wort (*Hypericum perforatum).*

Doravirine can be taken with or without food and it is available as a single pill (100 mg) and in a fixed dose combination with lamivudine and TDF.

Doravirine is marketed with the trade name Pifeltro and the doravirine/TDF/3TC FDC is marketed as Delstrigo.

C O M M E N T

It is good news that doravirine is now available in England.

NICE have taken a year to review the three phase 3 studies (two in naive and one switch) that formed the basis for the European Medicines Agency in November 2018. [2]

This NHS process has therefore successfully delayed access to these new medicines by only a year.

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Fostemsavir submitted to US FDA for multidrug resistant HIV

Simon Collins, HIV i-Base

On 5 December 2019, ViiV Healthcare announced that the company had submitted a new drug application for fostemsavir to the US FDA. [1]

Fostemsavir is a gp120 attachment inhibitor, the first drug in this new class, that was developed as a treatment for people with multi-drug resistance to other HIV drugs.

The submission is based on 96-week results from the phase 3 BRIGHTE study. [2]

Submission to the EMA for access in the EU is expected in early 2020.

C O M M E N T

A limited named patient access programme is for people who are urgently need access to fostemsavir before it will be approved.

For details, doctors should directly contact ViiV Healthcare.

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Paediatric dispersible formulation of dolutegravir submitted to EMA and FDA

Polly Clayden, HIV i-Base

On 13 December 2019, ViiV Healthcare submitted new drug applications to both the FDA in the US and to the EMA in the EU, for a new paediatric formulation of the integrase inhibitor dolutegravir. [1]

The new formulation uses film-coated dispersible 5 mg tablets, including in children from 4 weeks to 18 years old.

These submissions to the EMA and FDA are based on data from the ongoing phase 3 P1093-and ODYSSEY (PENTA20) studies. [2, 3, 4, 5]

If approved this will enable children globally to be able to use comparable treatments to adult care.

COMMENT

Through a partnership with CHAI and Unitaid, ViiV are providing support and technical transfer to generic manufacturers (Mylan and Macleods) to develop dispersible scored 10 mg DTG tablets to accommodate WHO paediatric weight bands with fewer tablets/formulations.

This process will include submission to the FDA for Tentative approval as well and support expediated roll out once the products are available.

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SIDE EFFECTS & COMPLICATIONS

Tesamorelin for NAFLD in positive living with HIV

Simon Collins, HIV i-Base

A potential new use for tesamorelin as a treatment for Non Alcoholic Fatty Liver Disease (NAFLD) in HIV positive people was reported based on results from a US study recently published in Lancet HIV. [1]

Tesamorelin is currently licensed in the US as a treatment to reduce visceral fat in people central fat accummulation (lipodystrophy).

This was a randomised. double-blind. placebo controlled study in 61 HIV positive participants with a hepatic fat fraction (HFF) greater >5%. Participants were randomised to receive tesamorelin (2 mg sub-cutaneous injection once-daily) or matched placebo for 12 months.

Baseline characteristics included mean age 53 (+/– 8) years, 80% male, 30% black race, 16 years HIV infection. Alcohol use was low (<1 drink a week), 13% with diabetes, 45% currently on a lipid-lowering drug. Histological NASH was present in about one-third, with approximately 52%, having no fibrosis and 10-20% having fibrosis stage 1, 2 or 3,

Based on the primary endpoints of change in HFF, tesamorelin significantly reduced HFF compared with placebo (effect size –4·1%, 95% CI –7·6 to –0·7, p=0·018), with no differences after adjusting for baseline measures of race, antiretroviral use, statin use, or smoking.

This was a –37% (95% CI –67 to –7) relative change in HFF, with 35% of participants in the active group having a reduction that brought HFF to <5% compared to 4% on the placebo arm (p=0.0069),

Tesamorelin also prevented progression of fibrosis, with 2 vs 9 participants progressing in the active vs placebo groups respectively (p=0.044).

Tesamoreliin did not affect overall ALT, lipids, or fasting glucose, although ALT was significantly reduced in people with elevated levels at baseline. CRP was also significantly reduced (effect size –4·7 mg/L; 95% CI: –9·2 to –0·2) but with no effect on adiponectin.

The study also included an additional six month open label continuation phase where tesamorelin was provided for all participants.

An accompanying editorial commentary in the same journal notes the importance of these results, given the lack of current treatment, but raises similar concerns to the indication for reducing visceral fat: what happens when tesamorelin is stopped? It also notes that the impact on fibrosis relies on early diagnosis.

COMMENT

Even though NAFLD is common (>30% in the general population), there are no currently approved treatments for

NAFLD, in HIV positive people or otherwise. Management involved lifestyle changes that generally need 5-10% weight loss for a significant effect.

Pipeline compounds include elafibranor, obeticholic acid, selonsertib, simtuzimab and cenicriviroc and other studies in HIV positive people include using aramchol, maraviroc, metformin and raltegravir.

These results are therefore intriguing although both the need for daily injections (and the high US price) currently are likely to limit access. A newer formulation was recently developed that requires a smaller injection volume and storage at room temperature. [3]

i-Base has produced a free leaflet on NAFLD for use in clinics. [4]

Reference

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condemn all forms of violence and discrimination against LGBT people conduct a thorough and expedited investigation into these recent killings and aggressively prosecute all persons involved in inciting violence towards LGBT people. We urge the Government of Uganda to join Botswana, Lesotho, Mozambique and South Africa in unshackling our continent from discrimination by decriminalising same-sex activity.

Signed

IAS Governing Council Africa Regional Representatives

Serge Paul Eholié, Côte d'Ivoire

Keletso Makofane, Boston

James G. Hakim, Zimbabwe

Kenneth Ngure, Kenya

Reference

IAS Statement: Anti-homosexuality Bill poses severe threat to human rights of LGBT community in Uganda. (23 October 2019).

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CURE RESEARCH

5th Conference on Cell and Gene Therapy for HIV Cure 2019: webcasts

The edited videos from the 5th Conference on Cell and Gene Therapy for HIV Cure 2019 have been posted to the defeatHIV YouTube channel.

The presentations have been edited into stand-alone videos, and each of these have been placed into a playlist according to the day they were presented. Links to the two playlists are below.

CGT4 HIV Cure 2019 DAY ONE:

https://bit.ly/2P9akp5

Welcome and opening remarks

HSC Transplantation & Gene Editing

Keynote: Robert F. Siliciano

HIV Latency & Reservoirs

CAR T Cells & Other T Cell Therapies for HIV

Lessons from Cell & Gene Therapy for Other Conditions

CGT4 HIV Cure 2019 DAY TWO:

https://bit.ly/37TvJuL

Workshop on In Vivo Gene Therapy

Plenary: David Baker

Viral Delivery Vectors

Non-Viral Delivery Vectors

In Vivo Gene Therapy Panel Discussion & Closing remarks

FUTURE MEETINGS

Conference listing 2020

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

HIV and neurology 2020 - an update

30 January 2020, London

https://www.rsm.ac.uk

10th International Workshop of HIV & Women

6 – 7 March 2020

www.virology-education.com

Conference on Retroviruses and Opportunistic Infections (CROI 2020)

8–11 March 2020, Boston

www.croiconference.org

26th Annual BHIVA Conference (BHIVA 2020)

27 – 29 April 2020, Manchester

www.bhiva.org

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

13 – 15 May 2020 (TBC), New York

www.virology-education.com

International Workshop on HIV Paediatrics 2020

3 – 4 July, San Francisco tbc

www.virology-education.com

Community Reclaiming the Global Response (HIV 2020)

5 – 7 July 2020, Mexico City

https://www.hiv2020.org/registration

23rd International AIDS Conference (AIDS 2020)

6 – 10 July 2010, San Francisco and Santa Barbara

www.aids2020.org

HIV Glasgow Congress 2020

4 – 7 October 2020

www.hivglasgow.org

HIV Research for Prevention (HIV R4P 2020)

11 – 15 October 2020, Cape Town

https://www.hivr4p.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

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

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

- Introduction to ART (October 2019)
- PrEP in the UK (November 2019)
- HIV testing and risks of sexual transmission (November 2019)
- Guide to HIV, pregnancy & women's health (April 2019)
- Guide to changing treatment and drug resistance (Jan 2018)
- HIV & quality of life: side effects & long-term health (Sept 2016)

Pocket guides

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

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

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

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

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

This project was developed with the Kobler Centre in London.

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

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

email: subscriptions@i-base.org.uk

Fax: 0208 616 1250

Other i-Base resources can still be ordered online as usual.

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

Customise U=U posters for your clinic

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

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

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

roy.trevelion@i-Base.org.uk

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http://i-base.info/order

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- **Pocket leaflets** - *A7 small concertina-folded leaflets (2017)*

Pocket HCV coinfection	**quantity** _____	**Pocket PrEP**	**quantity** _____
Pocket ART	**quantity** _____	**Pocket pregnancy**	**quantity** _____
Pocket side effects	**quantity** _____	**PrEP for women**	**quantity** _____

- **Booklets about HIV treatment**

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

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

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

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

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

HIV and quality of life: guide to side effects and long-term health *(Sept 2016): 96-page A5* **quantity** _____

Guide to HIV testing and risks of sexual transmission *(Jan 2020): 32-page A5 booklet* **quantity** _____

Guide to hepatitis C coinfection *(April 2017): 52-page A5 booklet* **quantity** _____

- **Other resources**

U=U resources:

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

HIV Treatment 'Passports' - Booklets for patients to record their own medical history **quantity** _____

Phoneline *posters (A4)* **quantity** _____

Please post to the above address, or email a request to HIV i-Base:

subscriptions@i-Base.org.uk