ISSN 1472-4863

hiv treatment bulletin (e)

HTB: 2019 vol 20 no 13

15 November 2019: no 13

HIV and Ageing Workshop; First EACS Reports

CONTENTS

Published by HIV i-Base

EDITORIAL

This edition of HTB leads with two reports from EACS 2019: the launch of the major update to the EACS guidelines and a detailed reveiw of weight gain in the randomised ADVANCE study, especially in women using both dolutetegravir and TAF.

We also include reports on frailty, cannabis and vaping (separate articles) from the 10th International Workshop on HIV and Ageing.

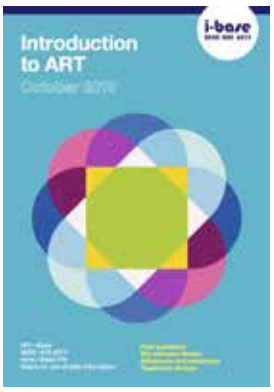
Futher reports from both meetings will also be included in the next issue of HTB.

The monoclonal antibody ibalizumab now has EU approval, and we include a comment that fostemsavir is also available on named patient access: people failing ART on their last combination are likely to need both drugs.

Richard Jefferys contributes two articles on HIV persistance and stem cell editing in cure research. And, almost fake news – but real – the US government is pursuing patent rights for use of TDF and TAF as PrEP.

SUPPLEMENTS

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.

This is the 24th edition of this guide. i-Base set out to make information clear, easy to understand and direct. We update this guide every 12-18 because treatment and the way it us used still changes - though not as quickly as for early editions.

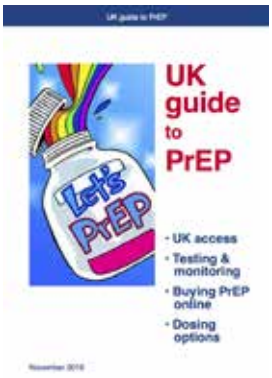
UK guidelines have for many years recommended that treatment should be reviewed annually and we think that information for people living with HIV should match this too.

Also, all i-Base resources (booklets, leaflets, U=U posters and cards, questions to the information service and UK-CAB membership) remain free to UK clinics. This follows the model of NHS care based on universal healthcare as a right.

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

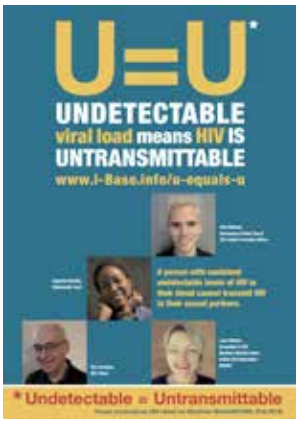
U=U resources for UK clinics: free posters, postcards and factsheets

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 conference always covers important European research but also focuses on key themes. This year included the question of weight gain with integrase inhibitors and the relative advantages of using two-drug vs three-drug ART. Social issues included treatment for migrant communities and differences between western and eastern Europe - and many sessions included simultaneous translation into Russian.

The conference was not without a few problems, including some rooms not being large enough and a move to electronic posters that were only viewable on interactive monitors. This made the sessions and posters difficult to either view or report and limited the chance to talk to researchers.

However, the posters are now already online and they have been formatted in a way that is easier to enlarge and view different sections. Each poster is also available to download and view as complete PDF files (from a link under the comments section underneath).

The programme, with links to abstracts is online:

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

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.

By the end of the conference, many webcasts have been posted online, which are searchable from the link below (though not hyperlinked from the conference planner).

http://resourcelibrary.eacs.cyim.com

The community talk given by Alex Schneider in the opening session was notable the focus on eliminating stigma, which was another theme throughout the meeting, including for the community march though Basel on Friday afternoon.

Articles from the conference included in HTB are:

- EACS launch major update to European Treatment Guidelines (November 2019)
- Weight gain and metabolic syndrome with dolutegravir and TAF: results from the ADVANCE trial

EACS launch major update to European Treatment Guidelines (November 2019)

Simon Collins, HIV i-Base

Every two years EACS publish a major update to their clinical guidelines, with minor revisions on alternate years. This is an international collaboration by over 60 leading European HIV doctors with additional input from experts in other fields.

This year the major update includes many new sections, taking the print edition up to 260 pages, with additional information online including video links to EACS management lectures.

https://eacs.sanfordguide.com

The guidelines are also available on a free app for Apple and Android devices.

There are six main sections: a general section of all major issues, recommendations for ART, drug-drug interactions, co-morbidities, hepatitis coinfection and opportunistic diseases.

In addition to the most widely applied sections, for example, on preferred drugs for first-line ART, or for managing virological rebound, there are new reference sections for use in specific populations. This edition includes new tables for managing drug interactions for transgender people, for older people and for those with reduced kidney function.

The guidelines are therefore developed as reference resource to cover the broad diversity of adults living with HIV - with different ages, genders and complex treatment histories.

They are both a reference for the minimum standards of care that HIV positive people can use with their doctors and they set a goal for optimum standards of care for activists when national guidelines, for example, still use older and less effective treatments.

The whole guidelines have been updated to include new ARVs with notes for different combinations and patient circumstances and removal of older drugs (including older PIs, ddI and d4T).

Other selected changes to this edition are listed below.

A full list of changes at this link:

https://eacs.sanfordguide.com/contents/changes-v9-1-to-v10-0

Translations into Chinese, French, German, Japanese, Portuguese, Russian and Spanish are currently being updated and will be available for the new edition shortly.

Nine short webcasts (3-5 minutes each) with each panel chair talking through the changes are online at this link:

http://resourcelibrary.eacs.cyim.com/mediatheque/media.aspx?mediaId=78087&playlistId=78091&channel=28172

ART section

- New recommendation preferring unboosted integrase inhibitors (INSTI) with high genetic barrier (dolutegravir or bictegravir) as third drug for first-line ART.
- Doravirine + 2 NRTIs included in recommended regimens.
- When indicated, TDF/3TC has been added as a backbone.
- Dual therapy with dolutegravir (DTG) + lamivudine (3TC) has been upgraded to recommended regimen.
- High genetic barrier INSTI or boosted PI is recommended for initial therapy if results from resistance testing are not available.

- Switch strategies for virologically suppressed persons include DTG + 3TC has been included in dual therapies supported by large clinical trials and darunavir/b + rilpivirine has been included as dual therapy option supported by small trials.
- Whole section related to pregnancy and conception has been updated with treatment guidance regarding different scenarios.
- ART in TB/HIV co-infection updated for new drug interactions.
- Drugs for use in PEP has been expanded to include recently approved drugs.
- F/TAF is included as alternative for PrEP in MSM and transgender women.

Drug interactions - new tables

- All tables have been updated for bictegravir and doravirine and removal of older ARVs
- Hormone therapy and gender transitioning.
- Dose adjustments for non-HIV meds and kidney function.
- Drugs classes to avoid in older people.

Comorbidities

- This section included the greatest number of changes and new additions, covering a wide range of complications, many linked to lifestyle differences and changes.
- These included use of e-cigarettes, closer cardiovascular monitoring (based on 10% rather than 20% risk), blood pressure and hypertension, renal monitoring and liver monitoring etc.
- Sexual health changes include new statement on U=U, conception and screening for menopause.
- The section on depression, include the impact on overall well-being.
- The cognitive guidelines include either CSF resistance testing or on likely ART toxicity for modification of ART.

Viral hepatitis coinfection

Reorganised into general management, HBV and HCV with updates for:

- Recommendations for screening for HCC.
- Diagnosing fibrosis.
- HBV reactivation.
- Retreatment after treatment failure with DAAs.
- Preferred and alternative DAA combinations.
- Management of acute HCV.
- Management of hepatitis D and E (HDV and HEV).

Opportunistic infections (OIs)

- Updated information of timing of ART with different OIs
- New table on clinical presentation of IRIS.
- Updated information on treatment of CMV, HSV, VZV, histoplasmosis and cryptococcosis.
- New information on treatment for talaromycosis.
- Details on management of MDR-TB have been added to the TB section as well as a table detailing doses for all TB drugs.

Simon Collins is a community representative on the comorbidities panel for these guidelines.

C O M M E N T

These guidelines are an essential reference for the minimum standards of care that HIV positive people can use with their doctors.

They set a goal for optimum standards of care for activists when national guidelines, for example, still use older and less effective treatments.

They also provide up-to-date guidelines for many settings when national guidelines for whatever reason are either difficult to produce or update.

Reference

European AIDS Clinical Society (EACS). Guidelines version 10.0, November 2019.

https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

Weight gain and metabolic syndrome with dolutegravir and TAF: results from the ADVANCE trial

Polly Clayden, HIV i-Base

Dolutegravir (DTG) in combination with tenofovir alafenamide (TAF) is linked to increases in weight and clinical obesity – according to data from the ADVANCE trial presented at EACS 2019. [1]

The ADVANCE trial, conducted in South Africa, randomised 1053 treatment-naive participants to three first-line regimens: TAF/emtricitabine (FTC)/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].

The investigators also presented a pooled analysis with data from the NAMSAL trial comparing changes in body weight across the regimens at IAS 2019. [5]

The presentation at EACS provided additional detail on weight gain in ADVANCE.

Body weight, body mass index (BMI), lipids, fat mass, and lean mass were measured and differences between treatment arms were tested. DEXAs were performed at 48 and 96 weeks. At the time of analysis, 531 participants had reached week 96. The evaluation will be updated when everyone reaches this time point – around April/May 2020.

At baseline, participants were about 33 years old, 99.5% were black, CD4 was approximately 330 cells/mm3, about 20% had viral load between 100,000 and 500,000 copies/mL and only about 3% had viral load above 500,000 copies/mL. About 60% were women, with baseline BMI of 26 kg/m2; for men baseline BMI was 22 kg/m2. Approximately 25% of participants were overweight and 12% obese before starting ART.

In men, the mean change in weight at 96 weeks was: 5.9 kg, 3.5 kg and 1.2 kg in the TAF/FTC/DTG, TDF/FTC/DTG TDF/FTC/EFV arms respectively.

Body composition, measured by DEXA, was 59% fat (distributed fairly evenly across trunk and limb) and the remainder lean mass in the TAF/FTC/DTG arm. Participants in the TDF/FTC/DTG arm experienced weight gain with 74% fat. And for those in the TDF/FTC/EFV arm weight gain was 100% fat.

In women, the mean change in weight at 96 weeks was: 8.3 kg, 5.3 kg and 3.4 kg in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

In the TAF/FTC/DTG and TDF/FTC/DTG arms weight gain was 74% fat with most of the lean mass gained in the limbs. For women in the TDF/FTC/EFV arm, weight gain was 91% fat.

The investigators adjusted competing risk regression models for: socio-demographics; baseline weight or BMI, treatment arm, CD4 count or viral load; disease history and adverse events; and concomitant medications.

After multivariate analysis, associated factors for treatment-emergent obesity were: TAF/FTC/DTG, baseline CD4, baseline viral load and baseline BMI.

Excluding baseline BMI, other associated factors were female sex, South African nationality and employment.

Factors associated with 10% or more increase in body weight were: TAF/FTC/DTG, baseline CD4, baseline viral load, female sex, age, and baseline weight.

As it has been suggested that better tolerability of newer antiretrovirals might contribute to greater weight gain the investigators performed an analysis excluding participants with GI adverse events. But the differences remained similar with mean weight change from baseline of 7.8 kg, 4.3 kg and 2.7 kg for the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV respectively.

At week 96, 27% 17% and 11% of women in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively developed treatment-emergent obesity. For men the respective proportions were: 7%, 3% and 2%.

And 51%, 32% and 23% of women in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively experienced a 10% or more increase in body weight, compared to 42%, 27% and 18% of men.

When the investigators looked at treatment-emergent metabolic syndrome (using the International Diabetes Federation definition), at week 96 they found 9%, 5% and 3% of participants in the in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV (difference TAF/FTC/DTG vs TDF/FTC/EFV, p=0.025).

When questioned whether there was a threshold for switching people with large weight gain (as some of the participants have gained 30 or 40 kg with one as much as 50 kg), presenting author Michelle Moorhouse from Ezintsha, Wits RHI explained that although they have raised this, "…most point blank refused to switch from DTG and are not happy about EFV".

C O M M E N T

Sixty per cent of the study participants have data available at week 96 in this new analysis, so the findings here are more robust than those presented at IAS 2019.

There is significantly more treatment-emergent metabolic syndrome in the TAF/FTC/DTG arm (9%), compared with the TDF/FTC/EFV arm (3%). Metabolic syndrome is a predictor of diabetes and atherosclerosis.

The sensitivity analysis, removing anyone with GI adverse events, is important as it has been claimed that weight rises faster on TAF because it is so well tolerated, so people feel better. But this did not change the results. The investigators do not yet have a good explanation for the greater rises in body weight on TAF.

Twenty seven per cent of women in ADVANCE developed clinical obesity by week 96 and there is no sign of a plateau in weight gain. The investigators are now calculating the potential effects of this weight gain on increased risks of NCDs. These results will be submitted to CROI.

In the QDIABETES algorithm, if weight rises by 10 kg, the risk of diabetes rises by 3 cases per 1000 people treated. Although this does not sound much, in countries like South Africa where millions of people need ART, the absolute numbers could be substantial and create a huge extra burden on health services.

One of the ADVANCE investigators, Andrew Hill, gave an excellent overview of weight gain and clinical obesity with new treatments looking at these issues in more detail. [6] This is a recommended webcast (and will be summarised in the next issue of HTB).

The study team are actively seeking resources to continue follow up for another two years after week 96 to properly evaluate consequences of weight gain/clinical obesity.

Polly Clayden is on the scientific committee of ADVANCE and 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.

This is largely thanks, in addition the meeting organisers, to the work of long-term US community activist Jules Levin from NATAP who raised the urgency for greater funding for both research into HIV and ageing and better services for older HIV positive people long before the first ageing workshop – and who still continues with this primary drive.

As people living with HIV get older, we risk becoming less visible in all areas of our lives. In common with many other conditions that affect older people, our medical needs attract fewer resources, until at certain age thresholds – whether this is at 65, 75 or 85 – we fall off the priority to even access referral services for research studies, health screening or even treatment.

An easy example, raised in open discussions at the workshop, is that most, perhaps all, phase 3 studies for new antiretroviral drugs, have upper age limits (above 65 years) as an exclusion criteria. This is also the case in many cure-related studies. And yet in the US, where much of this research is funded, the majority of HIV positive people are now older than 50 years old.

As older people living with HIV, our lives become more difficult with new health complications: diabetes, cancer, osteoporosis, pancreatitis, heart attacks and stroke, frailty, failing memory and neurological changes that are difficult to report and manage.

ART still remains transformational – especially if started early – with most long-term HIV-related complications likely to be linked to the years before diagnosis and treatment. For example, the long-term impact of HIV on neurological changes were highlighted in a recent paper from the Poppy study. Age-related changes shown in CT brain imaging scans were similar for HIV positive people on ART and well-matched HIV negative controls. Differences that did occur for HIV positive people were explained by duration of untreated HIV.

Despite our accumulating experience of healthcare, our ageing HIV positive voices are heard less often. We ask reasonable and important questions about our future only to learn that there is very limited data to inform the answers.

So this workshop is vitally important and each year the programme adds to research, often in areas that are not included in other medical meetings.

Highlights this year including many studies referencing the importance of frailty as a syndrome that is clinically more important than its individual symptoms, the important differences between loneliness and social isolation in HIV care, the safety of smoking and/or vaping and reviews on medical use of marijuana.

This year the workshop had its highest attendance and number of submitted abstracts, helped by moving the venue three years ago to New York.

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

Highlights of the 2019 meeting are included in several short reports.

HTB reports in this issue include:

- Frailty in HIV care and the importance of lifestyle changes
- Research into use of medicinal cannabis in HIV management
- Vaping can help HIV positive people who are not motivated to quit cigarettes

Frailty in HIV care and the importance of lifestyle changes

Simon Collins, HIV i-Base

In the first plenary talk at the workshop, Linda Fried from the Mailman School of Public Health, Columbia University, presented an overview of approaches to frailty over the last three decades which has developed as a new discipline. [1]

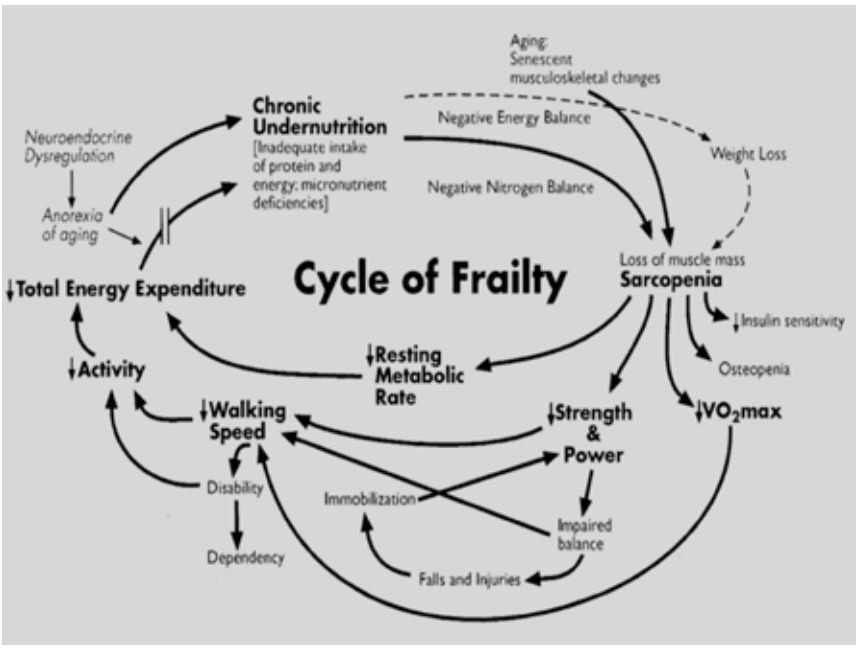
Fried is a leading researcher in this field who helped define frailty as a syndrome that is independently predictive for serious comorbidities and mortality than just the factors that contribute to its definition.

Starting in the 1980s, Fried outlined that the initial idea of frailty was used interchangeably with disability in connection with comorbidity and ageing. However, within a decade, six component parts were better defined by geriatricians.

- Declines in lean body mass, strength.
- Weight loss.
- Loss of endurance.
- Slow walking.
- Relative inactivity.
- Decreased balance and morbidity.

Many of these factors were related in a cycle of frailty involving poor nutrition, loss of muscle mass, reduced physical activity, metabolic rate and walking speed. See Figure 1.

Figure 1. Cycle of frailty, Fried et al, 1998.



Each stage of the cycle was related and an point could start or accelerate progression to a frail state. For example, sarcopenia predicted lower strength, which would be further weakened by reduced exercise (affecting the resting metabolic rate,) which in turn slowed walking, which then limits further exercise. Often, a subset of adults with low activity who were not regulating their diet, become chronically undernourished, which then worsened sarcopenia and led to further weight loss etc.

The next decade saw the links between frailty factors become recognised as a geriatric syndrome, although there was still little explanation for how and why these component factors were related or for explaining differences between other patients who were ageing without frailty.

More recently, perhaps since 2015, frailty has been characterised as a medical syndrome linked to a distinct underlying pathology that is underpinned by other diseases with shared biologic pathways driven by ageing.

So frailty is now commonly contrasted as the inverse of resilience.

The new model developed by Fried and colleagues is focused on this cycle of dysregulation which can start at any point. Working with Russ Tracey and colleagues in a cardiovascular and frailty study helped define a frailty phenotype made up of shrinking, weakness, slowness, poor endurance and low activity, see Table 1. [2]

Table 1: Phenotype of frailty in CHS study, 2001 [2]

Characteristic	Definition
Shrinking	Unintentional weight loss >10 lbs, past year; F/U: ≥ 5% weight loss over 1 year
Weakness	Grip strength: lowest 20%
Slowness	Walking time: lowest 20%
Poor endurance	Exhaustion (self report)
Low activity	Kcal/week : lowest 20%

The presence of three or more of these factors were used to define frailty, with one or two factors defining an intermediate stage of prefrailty and no factors being non-frail.

Using this definition, a 2015 study of people in the US older than 65 years categorised 15% as being frail and 45% pre-frail. Importantly, not everyone who was frail had one or multiple chronic diseases and not everyone who was frail was disabled – but there was a significant overlap. The prevalence of frailty also increased geometrically with age, from 9% in those aged 65-69 to 38% in those aged 90 or above. [3]

Studies on cardiovascular disease and women's ageing were used to validate frailty phenotype by showing the association with very high risk of serious outcomes. [2, 4]

For example, only 81% of participants diagnosed as frail at baseline were alive three years later in unadjusted analysis - but adjusting for 78 related factors still showed independent high risk of serious outcomes including mortality, disability, falls, hospitalisation, poor post-surgery outcomes and slow recovery from illness.

In an earlier study, 20/78 of these factors were independently and jointly predictive of frailty. [5]

This meant that ten years ago, researchers had validated a clinical presentation that increased with age and that had demographic differences: in the US, there are higher risks for women compared to men and for African Americans compared to Caucasian race. These data also supported a natural history where frailty had a very high risk for 6-month mortality and pre-frailty had a very high risk of becoming frail.

Over the last ten years specific biomarkers including dysregulation of inflammatory, endocrine and immune activation pathways have broadened the molecular and genetic factors of frailty.

Many of these studies showed similar characteristics between fail and non-frail participants at baseline, but then showed significantly different responses after exposure to stress tests.

For example, glucose and insulin dynamics were significantly increased (approximately twice as high and with at least three times as long for recovery) in a study of non-diabetic women (age 84 to 93) in response to glucose tolerance test. [6]

In a similar population, after a 30 second calf exercise, frail women had 41% slower and prefrail women 15% slower phosphocreatinine recovery, compared to non-frail participants. [7]

The implications of these dysregulations of energy homeostasis and longer recovery time sets up a biological vulnerability that can affect any component in the frailty phenotype. After adjusting for age, race, education, and number of chronic diseases, the risk of frailty is increased in a greater than linear way as an increasing number of physiologic systems dysregulated, see Table 2. [8]

Table 2: Odds Ratio (OR) for frailty based on number of dysregulated body systems

Number of dysregulated systems	OR for frail vs non-frail	p-value
0	1	
1-2	4.8	<0.05
3-4	11.0	<0.01
5+	26.0	<0.01

Treatment of frailty

The compelling picture, where frailty drives a difference between ageing well and ageing with a higher risk of mortality, and importantly, highlight the importance of lifestyle changes - given that no direct treatments are available for frailty itself.

The benefit of lifestyle interventions (diet, exercise, mobility etc) can help many of the individual factors in the frailty syndrome. The discussion of the evidence of each intervention showed the potential to reverse frailty. For example, even in older age, moving from a sedentary to more active lifestyle has been shown to reverse frailty factors and reduced frailty incidence. [9]

C O M M E N T

As the HIV population steadily ages, a focus on frailty should help direct services to support HIV positive people at greatest risk of associated complications.

In the same month (and as further reading) the Lancet published two excellent overview articles on frailty including on the implications for clinical practice. [10, 11]

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Medicinal cannabis in HIV management

Simon Collins, HIV i-Base

Two talks at the workshop provided different perspectives on use of cannabis and derivatives in the US as medicines.

The first, by Thomas Marcotte from the University of California, San Diego, provided a historical review of the legal changes in the US, including a note that this was a legal medicine for many years..

As of January 2018 there are 30 states with some form of legalised medical marijuana law and 9 states including DC, Guam and Puerto Rico having legalised recreational use. Only 4 states have no form of marijuana legislation. Approximately 60% of the US population live in states with some form of legalised marijuana. showing the importance of the need for research into the effects of cannabis.

The interest in research was taken up again in the 1990s (after the Regan "war on drugs") and by 2010 US public opinion reached a cross over with a majority supporting legalisation.

The history of legal changes included the Compassionate Use Act in 1996 in California and the Medical Marijuana Research Act in 1999. The Center for Medicinal Cannabis Research (CMCR) was established in 2000 to support high quality research, with funding extended in 2016 by the Adult Use of Marijuana Act.

The CMCR team is notable for including the oncologist Donald Abrams, one of the first HIV specialist doctors, who helped establish the Ward 86 clinic at San Francisco General Hospital in 1983 and who saw the benefits from marijuana for pain relief and as an appetite stimulant to counteract HIV wasting.

However, regulation is complicated as there are more than 100 cannabinoids (including THC as the psychoactive compound) and CBD (a non-intoxicating cannabinoid). Terpenoids modulate how cannabinoids interact with receptor, may act on serotonin, dopamine, etc and are responsible for the distinctive aroma. Flavonoids determine the colour of the plants and are being researched for potential anti-oxidant and anti-inflammatory properties.

A national academies report in 2017 comprehensively reviewed the evidence of medicinal benefits of cannabis although not all claims have good quality evidence. [2]

This included:

- Substantial/conclusive evidence for chronic pain, spasticity of multiple sclerosis and control of nausea.
- Moderate evidence for improving sleep in those with chronic medical conditions (ie chronic pain, fibromyalgia, etc)
- Limited evidence for certain anxiety disorders and PTSD, and promoting appetite and weight gain.
- No or insufficient evidence for treatment of cancers, irritable bowel syndrome, epilepsy, movement disorders due to Huntington Disease or Parkinson Disease and schizophrenia.

Details of these studies were included in the talk, including the recent studies showing a more than 50% reduction in frequency of seizures compared to placebo. [3]

But the therapeutic window for an effective dose can also important. Some studies reported no effect at a very low dose, benefits with a moderate dose but worsened symptoms with a higher doses, for example both for pain relief and for neurocognitive impairment. [4, 5]

Also, in an HIV study, the factors positively associated with “superageing” included higher lifetime cannabis use disorder. Superageing is a recently invented term for people older than 50 have been protected from the normal expected age-related neurological changes, retaining neurocognitive scores of someone younger than 25, after adjusting for demographics (se, race, education etc). A proposed mechanism for the neuroprotective effect is though activation of the cannabinoid receptors (CB1 and CB2) in the central nervous system. [6]

This study reported 17% of 734 HIV positive compared to 35% of 123 HIV negative people aged 50 to 64 were superagers. These results can be taken positively - ie that ageing well with HIV is possible, even though the rate was half that of an HIV negative control group.

Other research challenges were also discussed, included the harmful effect of smoking with tobacco. Practical difficulties include the US Drug Enforcement Agency (DEA) treating different formulations of cannabis differently: the plant has the highest restrictions (schedule I, siimilar to heroin) based on potential harm, whereas some synthetic formulations (nabilone and dronabinol (Syndros) are schedule II and dronabinal (Marinol) is schedule III. However the plant-based Epidox to treat seizures is schedule V (lowest abuse risk) and access to regulated supplies for research, although more than 20 ongoing studies listed on clinicaltrials.gov.

This limits the ability to research any of the many formulations of marijuana that are already widely available including vape, ointments, lotions, oils, drinks, foods and capsules etc. Even comparing smoking compared to ingesting marijuana produces very different pharmacokinetic dynamics for the active ingredient of THC.

Even though there are potential anti-inflammatory and neuroprotective qualities from cannabis use that might could provide cognitive benefit to HIV positive people, larger scale longer-term clinical trials assessing benefits and possible toxicities are still needed,

The second talk was given by Linda Chang from the University of Hawaii looking at the cannabis use from a basic science persepctivee. The review covered at least a dozen studies, including in vitro, animal and human studies, including in HIV positive people, with a focus on evidence for both potential benefits and harms. [7]

As background, marijuana is apparently the most used drug worldwide including 43 million people in US in last year and 8 million people reporting daily use. Doubling of use over the large decade makes this one of the fasted growing US industries involving multi-billion dollars. Wider access to legal marijuana in the US was reported as being used for medical reasons over the previous year by 26% of HIV positive people compared to 17% of the general population. [8] These data show the importance of getting accurate results from well-designed studies on potential risks and benefits.

Potential neurprotective effects of cannabinoids linked to endogenous ligands for CB1 and CB1 have the potential to reduce inflammation. This has been supported by research in cell cultures and animal studies, where endocannabinoids directly or indirectly prevented HIV-mediated neuronal cell damage and showed anti-inflammatory effects in rodents and slowed SIV progression and neuroinflammation in macaques. [9]

However, a recent review of 45 studies looking at potential harm (memory deficits and impairment etc) reported varied results, but included the concern that both HIV and marijuana might independently negatively affect memory, especially with medium to high exposures. [10]

Research into long-term effects is complicated by duration of both marijuana use, especially if started at a young age and HIV history which might include a period before ART. However, some studies, including MRI and neuroimaging, have reported that HIV positive status isn't associated with higher risks compared to being HIV negative. [11]

Another study into chronic use, requiring weekly marijuana use for at least two years, reported that independent of marijuana use, HIV positive participants had slightly higher axonal damage and lesser myelination with radial diffusion, but that the link with inflammation needed further research and mixed effects could be seen. [12]

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Vaping can help HIV positive smokers who are not motivated to quit cigarettes

Simon Collins, HIV i-Base

A small US study reported that switching to vaping produced higher rates of stopping cigarettes than many other options to quit, even though follow-up was also relatively short.

The study included 19 HIV positive smokers who entered the study without a particular desire to stop smoking.

Cartridge-based E-cigarettes were provided weekly for eight weeks, followed by advice to stop smoking and smoking cessation resources. Benefits included reduced use of cigarettes and reduced CO exposure that were maintained to week 12 and an increased desire to quit.

Mean number of daily cigarettes dropped quickly (from mean 15/day at baseline to 1.7/day at week 8 and 2.2 at week 12. Mean exhaled CO dropped from 15.7 ppm at baseline to 6.68 at week 8 and 6.74 at week 12).

Seven participants (36%) reported a complete change to e-cigarettes at week 8.

Smoking associated symptoms of coughing, wheezing and shortness of breath improved although over this short period there were no changes in FEV1, pulse, BP or heart rate.

C O M M E N T

Quitting cigarettes is the single most important change that HIV positive people who still smoke can make to have the greatest impact on their long term health.

Although this was a small pilot study and follow up was limited, these results are encouraging, especially as it was in participants who didn't enter the study wanting to quit.

Longer follow-up is important to see whether the results are durable.

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ANTIRETROVIRALS

Ibalizumab approved in the EU

Simon Collins, HIV i-Base

On 26 September 2019, the European Medicines Agency (EMA) approved ibalizumab as a treatment for adults with HIV multidrug resistance. [1]

Ibalizumab is a monoclonal antibody that works by interfering with post-attachment steps for HIV to infect a CD4 cell. It is given by intravenous infusion every two weeks and needs to be used in combination with other active HIV drugs. Ibalizumab needs an initial loading dose of 2,000 mg followed by a maintenance dose of 800 mg every two weeks.

Approval is based on results from combined results in less than 300 people during the long clinical development phase, which has been ongoing for at least a decade.

For full details, please see the prescribing information and summary of product characteristics. [2]

Ibalizumab was approved by the US FDA in March 2018. [3]

Ibalizumab was developed by TaiMed Biologics with the trade name Trogarzo. It is marketed by Theratechnologies.

C O M M E N T

Ibalizumab can be a life-saving option for people with multidrug resistance, with the potential to contribute a >1 log drop in viral load (based on monotherapy data).

This is likely to be needed for a very small number of UK patients - and as a bridging therapy until new oral drugs become available.

Access in the UK will depend on NHS commissioning, but this might be expedited due to urgency of need. Doctors should also contact Theratechnologies to ask about compassionate or named patient access.

Although a UK price has not been released, US list price is US $118,000 (WAC/Wholesale Acquisition Cost).

An expanded access programme fostemsavir is also now available from ViiV Healthcare and using both compound might be essential for people using ibalizumab.

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PREVENTION

US government claims patent infringement by Gilead Sciences over use of F/TAF and FTC/TDF as PrEP

Simon Collins, HIV i-Base

On 6 November 2019, the US Department of Health and Human Services (HHS) website included a news release about filing action with US courts over patents for PrEP. [1]

The complaint alleges infringement on HHS patents by Gilead Sciences who manufacture and market the two FDA-approved formulations of TDF/FTC and F/TAF in the US. It also seeks damages for the millions of dollars of public funding for the CDC research that led to the development of PrEP and for the profits made by Gilead since.

Earlier this year, a coalition of community organisations (PrEP4all) filed a class action lawsuit over delayed access to generic versions of TDF/FTC. There were also open hearings by the US House Oversight and Reform Committee. [2]

Gilead have issued a statement claiming HHS improperly filed for the patents and that they want the court to stop the lawsuit to settle in an out-of-court inter parte review. [3]

A detailed analysis of the implications of these actions are reported in an open-access article in the journal Science. [4]

C O M M E N T

Although the HHS press release looked like an activist stunt to hi-jack the government website - similar convincing actions have been successful [5] – this story is indeed real news.

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CURE RESEARCH

Distinguishing potential mechanisms of HIV persistence

Richard Jefferys, TAG

For researchers attempting to develop a cure for HIV infection, it's important to understand the mechanisms by which the virus persists in the body despite suppression of viral load to undetectable levels by ART. Debate has centred around two possibilities that aren't necessarily exclusive:

- HIV continues to replicate at low levels in body tissues that ART drugs may not penetrate well (often referred to as sanctuary sites).
- Cells with HIV integrated into their genetic code – latently infected cells – persist and proliferate even though ART has shut down virus replication.

In recent years, evidence has accumulated indicating that, in most people who are adherent to ART, HIV replication is completely suppressed. A new report in the journal Science Advances adds to this evidence by analysing individuals in receipt of long-term ART. The results support the increasing research focus on the persistence and proliferation of HIV-infected cells as the major obstacle to a cure, a topic addressed by several other recently published papers.

The study by Giorgio Bozzi and colleagues described in Science Advances involved a total of six participants – three had initiated ART soon after HIV infection, while the remaining three had been diagnosed with AIDS prior to beginning

treatment (one individual in each group had died and autopsy samples were available). The individuals were all male with an average age of 40 at diagnosis, and median time on ART was 17.8 years (range: 8 to 22.7 years).

As was expected, levels of HIV DNA were higher in the group that initiated ART late, both in blood and tissues. HIV was also significantly more genetically diverse in these participants. Lymphoid tissues harboured the largest amounts of HIV DNA in both groups.

Analyses of HIV evolution (changes in the virus's genetic makeup that occur if it's replicating) revealed no evidence of ongoing virus replication in any participant during continuous ART. In two cases, antiretroviral monotherapy and dual therapy had been received prior to starting effective ART, and this allowed the researchers to demonstrate that their techniques could detect HIV evolution during these periods when viral load was not fully suppressed (likewise, short-term HIV evolution was seen in one participant as a result of a brief ART interruption).

Overall, when data from all participants were combined, no genetic changes indicative of HIV replication were observed during 60 person-years of suppressive ART.

The researchers did observe evidence of proliferation of some latently infected cells. Certain patterns of HIV hypermutation that are induced by cellular ABOPEC proteins are unique to individual infected CD4 T cells. If these CD4 T cells proliferate, the number of copies of HIV with the same pattern of hypermutation increases. One example cited by the researchers is a single hypermutated HIV sequence identified in one participant prior to ART. After 16 years of treatment, 42 copies of the identical hypermutated HIV were detected in both ileum- and colon-derived tissues. This represents evidence that the original CD4 T cell containing the hypermutated HIV proliferated, generating multiple new CD4 T cells containing duplicates of the same hypermutated virus.

Several other recent papers address the role of CD4 T cell proliferation in maintaining the HIV reservoir.

In the Journal of Clinical Investigation, William McManus and colleagues from Mary Kearney's laboratory at the National Cancer Institute present evidence that proliferation of latently infected CD4 T cells in lymph nodes underlies the persistence of HIV in people on ART. The researchers documented the phenomenon by identifying genetically identical copies of HIV that were integrated into the genetic code of the CD4 T cells at the same exact location. [2]

Marie-Angélique De Scheerder and colleagues from the HIV Cure Research Center at Ghent University Hospital have published results from the STAR study, an observational assessment of HIV sequences present before and after an analytical treatment interruption (ATI). The study was not able to pinpoint a consistent source of the HIV viral load that rebounded during ATI – either in terms of particular CD4 T cell types or anatomical location – but did find evidence that genetically identical viral expansions played an important role (consistent with the proliferation of latently infected CD4 T cells). The authors write: "Focusing on mechanisms that drive antigenic and homeostatic proliferation of immune cells will be crucial to achieve progress toward an HIV cure." [3]

A paper by Sarah Joseph and colleagues in Clinical Infectious Diseases describes three study participants on ART with detectable HIV RNA in cerebrospinal fluid (CSF). In two cases the researchers pinpointed trafficking and proliferation of latently infected cells as the likely source, whereas there was some evidence of persistent replication in the third individual. [4]

Lastly, a study published this week in mBio by Xiaomin Li and colleagues identifies CD4 T cells expressing the cell surface marker CD161 as particularly prone to proliferating while harbouring replication-competent latent HIV. The researchers suggest that developing anti-proliferative strategies that focus on CD161-expressing CD4 T cells may offer a means to reduce the HIV reservoir. [5]

Source

Jefferys R. TAG Basic Science Project. (11 October 2019).

https://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2019/10/distinguishing-potential-mechanisms-of-hiv-persistence.html

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Case report from the first clinical trial of CRISPR-edited stem cells in people with HIV and cancers

Richard Jefferys, TAG

One of the ways TAG keeps track of developments in HIV cure research is by maintaining an online listing of clinical research culled from trial registries (primarily clinicaltrials.gov). [1]

In May 2017, a research group in China registered the first human HIV trial involving the CRISPR/Cas9 gene editing system – a technology that has generated considerable excitement and attention due to promising results in small animal models. [2]

Last month in the New England Journal of Medicine, the researchers published a case report describing outcomes in a study participant (presumably the first individual enrolled). [3]

The design of the study is similar to several prior gene therapy trials for HIV positive people with cancer diagnoses that require stem cell transplantation as part of the treatment regimen (City of Hope in California has been a notable pioneer of this research). [4]

After appropriate stem cell donors are identified, some of the donated cells are subjected to genetic modification in the laboratory prior to being administered to study participants. Unmodified cells are also delivered to guard against any risk of the genetic modifications compromising the normal therapeutic efficacy of the stem cell transplantation.

The novel aspect is the use of CRISPR/Cas9 to edit the gene for the CCR5 receptor that most HIV strains use to infect cells. The researchers previously published laboratory results demonstrating the feasibility of the approach. The goal is for the gene-edited stem cells to generate a population of HIV-resistant CD4 T cells after transplantation. [5]

The participant described in the NEJM paper is a 27-year-old HIV positive man diagnosed with acute lymphoblastic leukemia, which was successfully driven into remission by chemotherapy regimens prior to the stem cell transplant. After transplantation, tests showed that the stem cells successfully generated a new donor-derived immune system by four weeks post-transplantation (referred to as full donor chimerism) and the cancer remained in remission with a very low predicted risk of relapse. ART was maintained throughout.

Over 19 months of follow up, the proportion of gene-edited cells detectable in bone marrow ranged from 5.20% to 8.28%. Seven months after transplantation, permission was obtained to conduct an analytical treatment interruption (ATI).

At the time of the ATI, the proportion of peripheral blood CD4 T cells showing evidence of CCR5 gene disruption was 2.96%. The proportion increased after treatment cessation, peaking at 4.39% during the ATI. ART was restarted after four weeks due to a very high viral load rebound to 30 million copies/mL; this is not atypical in stem cell transplant recipients because the new donor-derived immune system cells have not been exposed to HIV before, and therefore no virus-specific immunity is present (arguably it would have been prudent to restart ART sooner, if possible). After the ATI, the proportion of gene modified CD4 T cells stabilised at a little over 2.5%.

No adverse events related to the editing of the CCR5 gene were documented. The researchers conducted multiple searches for any evidence of off-target effects (gene edits in the wrong places) but found none. They note, however, that the relatively low efficiency of the gene editing in this study may have limited their ability to detect off-target activity.

The results offer encouragement for further pursuit of CRISPR/Cas9 as a gene editing tool in HIV, but the study authors state in their conclusion: "To further clarify the anti-HIV effect of CCR5-ablated HSPCs [hematopoietic stem and progenitor cells], it will be essential to increase the gene-editing efficiency of our CRISPR–Cas9 system and improve the transplantation protocol."

In an accompanying commentary, Carl June adds that "additional patients who undergo engraftment with higher frequencies of CRISPR Cas9-edited stem cells will have to be followed for longer periods of time in order to ensure the safety of this approach."

Both the paper and the commentary cite the recently published claim that homozygosity for the CCR5-delta 32 mutation is associated with a reduced lifespan as reason for caution regarding the editing of CCR5, however this concern no longer holds because the work was retracted due to a flaw in the analysis. [7]

Source

Jefferys R. TAG Basic Science Project. (24 October 2019).

https://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2019/10/case-report-from-the-first-clinical-trial-of-crispr-edited-stem-cells-in-people-with-hiv-and-cancers.html

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Where is cell and gene therapy in an HIV cure?

Simon Collins, HIV i-Base

Rowena Johnston, vice president and director of research at amfAR, opened the 2019 Conference on Cell and Gene Therapy for HIV Cure with a look at where cell and gene therapy is in HIV cure.

Starting with a network map of papers on HIV cure research between the Berlin and London patients - roughly from February 2009 to March 2019 - that looks at the history of gene research over the previous 20 years and how research groups have also becoming increasingly connected.

An interesting and rarely reported persepctive...

https://www.youtube.com/watch?v=NVyW_6iq9iY

TB COINFECTION

DR-TB drugs under the microscope: five urgent actions to improve DR-TB treatment (6th edition)

MSF report

This new MSF report provides an overview of the landscape of optimal treatment for drug-resistant TB (DR-TB), outlines the key barriers to accessing affordable effective treatment, and provides recommendations for action that can improve DR-TB care on a global scale.

There is much in need of improvement. According to WHO Global TB Report 2019, in 2018: Of the estimated half a million people fell ill with MDR/RR-TB, only 39% of people with MDR/RRTB were diagnosed, and only 1 in 3 people with MDR/RRTB were started on treatment. According to the latest global cohort data available, cure rates are still unacceptably low:: 56% and 39% of people treated for MDR/RR-TB and XDR-TB, respectively.

The five urgent actions to improve access and treatment outcomes are:

Countries to make a timely switch to the newly recommended all-oral drug regimens, discontinuing the use of harmful and difficult-to-use injectable agents, and prioritising the use of the newer drug bedaquiline.

Johnson and Johnson (J&J) to reduce the price of bedaquiline to no more than US$1 a day, especially given the fact that substantial public and philanthropic funding went into the development of bedaquiline. This public collective effort in drug R&D for bedaquiline needs to be reflected in its availability for people with DR-TB for whom access to this medicine is a matter of life or death. Since bedaquiline was recommended in WHO's August 2018 rapid guidance as a core drug to treat MDR-TB, less than 12,000 have received bedaquiline-containing regimens (according to DRTB STAT).

Countries to overcome restrictive patents and exclusive licensing of key TB drugs, including bedaquiline and delamanid, in order to facilitate generic competition to bring down prices and increase access.

Countries to adopt effective national drug procurement policies in order to reduce risk to quality, affordability, access to critical TB medicines, particularly as more country shift from the Global Fund -supported pooled procurement mechanisms to domestic national processes.

Governments to support public health-drive R&D and better governance of new medical tools to ensure affordable and sustainable access.

The report is available online:
https://www.msfaccess.org/sites/default/files/2019-10/IssueBrief_UTM_6th_Ed_FINAL_web.pdf (PDF)

FUTURE MEETINGS

Conference listing 2019/2020

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

Conference on Retroviruses and Opportunistic Infections (CROI 2020)

8–11 March 2020, Boston

www.croiconference.org

10th International Workshop of HIV & Women

6 – 7 March 2020

www.virology-education.com

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

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

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

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

Order publications and subscribe online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK. http://i-base.info/order

h-tb

HIV TREATMENT BULLETIN

HTB is published in electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered using the form on the back page or directly from the i-Base website:
http://www.i-Base.info
by sending an email to: subscriptions@i-Base.org.uk
Editor: Simon Collins
Contributing Editor: Polly Clayden

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

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

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http://www.i-Base.info

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HIV i-Base

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(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.
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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**

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: side effects and long-term health *(Sept 2016): 96-page A5* **quantity** _____

Guide to HIV testing and risks of sexual transmission *(July 2016): 52-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