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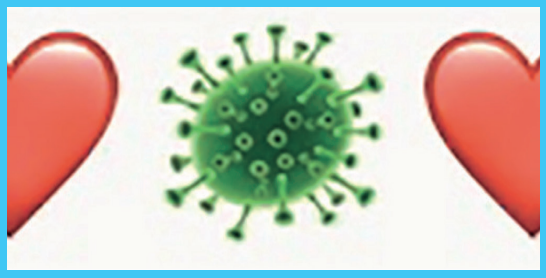
hiv treatment bulletin (e)



AIDS 2020; HIV and COVID-19 supp. 6 (22 July 2020)

CONTENTS

Contents continued inside...

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Contents continued

EDITORIAL

This edition of HTB includes reports from the virtual AIDS 2020 conference and linked satellite meetings on COVID-19.

The main heading news from AIDS 2020 included continued reductions in the signal concerning dolutegravir and neural tube defects, further results on weight gain from the ADVANCE study, cabotegravir as PrEP in HPTN 083, and an early report of HIV remission.

As the introduction to these reports shows, interacting with the virtual conference was not always easy. Although we include links to the site in our reports, the site will only be open access (without registration) after 27 July 2020.

The difficult website was reflected in overall attendance. Even when watching live events (and many were missed due to technical problems with the site), more than 2000 delegates were rarely online (when more than 20,000 people usually attend).

Many of the satellite workshops are easier to find and watch, and we include reports from the COVID-19 workshop on HCV drugs to treat COVID-19 and an update on remdesivir. As with the AIDS 2020 website, many of the webcasts and posters are now offline.

The rest of this extended issue includes both HIV reports and a continued focus on COVID-19.

For all the hope that coverage of COVID-19 might be less needed, this issue contains another 12 pages about coronavirus. Many important developments come from UK research – including new treatments, immune response, race and ethnicity and vaccines.

This supplement will also be formatted online as a separate PDF online.

i-Base 2020 appeal

Please support i-Base with £5 or £10 a month...

This year we are continuing a funding appeal to help i-Base continue to provide free publications and services during 2020.

i-Base now recieve more than 12,000 questions each year and the website has more than 500,000 view each month. We also distribute more than 80,000 booklets and leaflets free to UK clinics every year.

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

Plus a BIG thank you all all supporters over the years including in the recent Solidarity2020 campaign.

More than 70 people bought one or more posters curated by Wolfgang Tillmans and the Between Bridges Foundation, to who we are also really grateful :)

CONFERENCE REPORTS

IAS COVID-19 Conference

10-11 July 2020, virtual meeting

Introduction

Simon Collins, HIV i-Base

The two-day IAS workshop on COVID-19 at the end of the main AIDS 2020 meeting included excellent overview summaries with and oral abstract driven programme and additional posters.

COVID-19 has preoccupied global health for most of this year and it is right that IAS prioritised this with a special meeting. More than 11,000,000 people have been infected and more than 530,000 deaths.

Many HIV doctors and researchers - grounded in infection diseases - and related health workers including community activists have diverted time and resources into the response to COVID-19.

Access and free login

All presentations are available as webcasts and PDF files. Although access is still through the AIDS 2020 website, it is marginally easier to navigate.

https://cattendee.abstractsonline.com/meeting/9307 (direct URL to the meeting)

Registration is automatic for AIDS 2020 delegates. Otherwise, make a free login at this link:

Https://iasociety.us6.list-manage.com/track/click?u=3746d12bbc6932846a58d505c&id=e74f351668&e=506013d5a9

Reports in this HTB are:

- Conference opening: global approaches to prevention
- Making sense of the science
- HepC drugs works against COVID-19: faster recovery and reduced mortality from generic sofosbuvir and daclatasvir
- Predictors of response to remdesivir in GS-5773 COVID-19 study

Conference opening and making sense of the science

Simon Collins, HIV i-Base

Introduction and background

This conference was opened by Dr Anton Pozniak, IAS head and co-chair of AIDS2020 and Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO) set the background for the workshop. This included parallels between HIV and COVID-19 and acknowledging the talk from Nkosi Johnson 20 years ago at the IAS conference in Durban.

https://www.youtube.com/watch?v=rh9KIo4MWps (webcast)

The notes below summarise the next three talks from leading experts in global health provided overviews of different aspects of COVID-19 under the heading ‘making sense of the science’.

A common theme included the importance of community engagement in campaigns to reduce further incidence.

https://www.youtube.com/watch?v=yMuZVyURYxg (webcast)

Global summary of COVID-19

Anthony Fauci, NIAID

Dr Anthony Fauci provided an overview of the rapid development of COVID-19 into a global pandemic that is continuing to get worse.

SARS-CoV-2 transmission – largely via droplets, but airborne risk is likely to have some role – occurs in perhaps 40-45% of cases from people likely to be asymptomatic, with an incubation period of 4-5 days but out to 14 days.

Early flu-like symptoms include fever, cough, fatigue, shortness of breath, myalgia but also loss of smell/taste etc that can proceed onset. The range of responses from the same virus ranges from asymptomatic to mild/moderate, severe (80%) (14%) and critical (5%) with fatal outcomes in 1%). Older age is a predominant risk, with underlying medical conditions strongly associated with outcomes - complicated by race/ethnicity and higher risk employment.

In covering the range of therapeutic approaches, remdesivir was referred to as "a significant but modest impact on recovery", whereas dexamethasone reduces mortality in advanced disease requiring oxygen and ventilation with no supportive data for earlier stages of infection.

The strategic approach to vaccines includes supporting research into multiple lead compounds with the need and hope that several different approaches will all be effective. Several phase 3 studies have either started or are imminent - and the importance of planning for massive scale-up to meet the global need.

Origin of COVID-19 and response in South Africa

Salim Abdool Karim, CAPRISA

SARS2-CoV-2 is distinguished from related infections – SARS-1 and MERS are similar bat coronaviruses spread through intermediate animal hosts – by the high affinity ACE2 receptor binding capability of the spike protein.

This difference enabled SARS-CoV-2 to spread so rapidly and extensively from human to human, with more than 10 million infections globally, within a few months.

- **Person to person spread** is due to many cells in the nose and back of throat having ACE-2 receptors - making transmission easily spread. One example of the risk from prolonged close contact at work comes from 79/137 (58%) employees at a call centre catching SAR-CoV-2 - from one initial source infection.
- **Transmission via infectious surfaces** – for example, with virus on stainless steel and plastics remaining infectious for 3-4 days, In a hospital setting this will include bed rails, light switches, medical equipment etc. The risk then comes from self-inoculation when individuals touch their face.
- **Airborne risk**- aerosols 5 microns or less that survive in air play an uncertain but definite role. An example showing this risk included diners at a restaurant becoming infected based on direction of air from air conditioning.

Based on current data, the large close-crowded Black Lives Matter demonstrations did not lead to more infections, with protection linked to these being outside vs confined spaces.

While the prevention toolbox includes social distancing, hand hygiene and cloth masks as main stays, with environmental cleaning, testing and isolation.

Using data to drive the US response

Deborah Birx, US Ambassador

This talk emphasised the importance of engaging community responses - including testing by people without symptoms - and was informed by data from the significant and serious continued US epidemic.

The US is a high income setting, with high mortality, linked to an older population and higher comorbidities. US data is tracked by state and country, following new infections and changes in percentage of positive results with tailored prevention responses based on local incidence. Some states have counties with upwards of 20% positivity and others still report zero cases.

In the US, as with many other countries, the most vulnerable populations include the poorest (income <$25 pa), race (native American's, Latin and African American) and those with comorbidities.

As with HIV, reducing new infections depends on community responses that brings testing to asymptomatic people from communities at higher risk. Daily data summaries identify highest risk areas to prioritise prevention interventions including pooled testing in households, schools and other community settings.

Ref: All talks are webcast at: https://www.youtube.com/watch?v=yMuZVyURYxg (webcast)

HepC drugs works against COVID-19: faster recovery and reduced mortality from generic sofosbuvir and daclatasvir

Simon Collins, HIV i-Base

Tentative results from a small Iranian study using a combination of direct acting antivirals (DAAs) used to treat hepatitis C – sofosbuvir and daclatasvir (SOF/DCV) – led to faster recovery from COVID-19. In a meta-analysis with two other small studies the combination also reduced mortality.

The results were presented by Andrew Hill from Liverpool University at a press conference for the IAS COVID-19 workshop that will run after AIDS 2020. The study will be presented in full by Anahita Sadeghi from Tehran University. [1]

Both drugs have shown some evidence of in-vitro or in-silico activity against SARS-CoV-2, at equivalent to standard dosing. [2, 3, 4]

The main study was an open-label multicentre trial in Tehran that randomised 66 adults hospitalised with severe PCR-confirmed COVID-19 to either SOF/DCV or standard of care, which included lopinavir/r for both arms. Other entry criteria included fever (≥37.8°C) plus at least one of: respiratory rate >24/min, O2Sat<94% or Pa02/Fi02 ratio <300mgHg. [5]

The primary outcome was clinical recovery within 14 days (defined as normalised temperature, respiratory rate or oxygen saturation) with secondary outcomes that includes all-cause mortality.

Baseline characteristics were reported as similar and included approximate median age 60 (IQR: 25 to 70), 61% vs 42% men, enrolment within 1 day of admission. Although comorbidities were also not reported as significantly different, diabetes was reported more in the active arm (52% vs 33%, p=0.213), and chronic lung disease reported less (18% vs 27%, p=0.558). Median O2 saturation was 91% vs 90%, p=0.225, also in active vs control arm respectively.

Although the percentage of participants with <14 day recovery favoured the active arm: 88% vs 67% (n=29 vs 22), this was not statistically significant (p=0.076). However, in a multivariate analysis using logistic regression (for some reason not presented) the effect was significant after adjustment for baseline characteristics (supplementary data, in press).

Time to clinical recovery, a secondary endpoint, was significantly faster in the active vs SoC arm: median 6 days (IQR: 4 to 10) vs 11 days (IQR: 6 to 17), p=0.041.

When combined in a meta-analysis (n=176) with results from two other similar size studies (the Abadan and Sari studies, n=62 and 48, respectively) time to clinical recovery significantly favoured SOF/DCV: subhazard ratio 2.03 (95% CI: 1.33 to 3.08); SHR p-value <0.001. However, these studies, both also small, had different designs and also included ribavirin (one in a control arm and one with SOF/DCV).

Mortality in the meta-analysis was significant less with SOF/DCV: 5.4 % (5/92) vs 20% (17/84), p=0.005.

C O M M E N T

These are very small studies and design differences also caution the interpretation of results from the meta-analysis. The tentative results clearly also need to be supported by larger randomised clinical studies, but one of which (n=600) is already underway. [6]

Although both drugs are still in-patent high-cost medicines (approx. list price $18,000 and $7,000 for a 14-day treatment in the US and UK respectively), generic versions of a combined dual formulation are available for $7 or less. [7]

However, the study has also been selected as one of five clinical highlights selected by Anthony Fauci from the IAS virtual COVID-19 workshop that will take place directly after AIDS 2020. [8]

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Predictors of response to remdesivir in GS-5773 COVID-19 study

Simon Collins, HIV i-Base

Kristen Marks, from Weill Cornell Medicine presented results on predictors of response from patients in a substudy of GS-5773, comparing 5 vs 10-days of remdesivir in severe COVID-19. In practice, participants used remdesivir for a range of days in each arm and because the 5-day arms was as effective as 10-days, results from both arms were combined in this analysis. [1]

The 5773 study enrolled 397 participants, at 55 sites in 8 countries, most from the US (n=229), Italy (n=77) and Spain (n=61).

Endpoints included time to clinical improvement and all-cause mortality, both at day 14.

Baseline characteristics included 168 (42%) ≥65 years old, 144 (36%) female, 276 (70%) white, 45 (11%) Asian, and 44 (11%) Black. Overall, 122 patients (31%) were on high-grade oxygen support (including invasive mechanical ventilation (3%) and non-invasive positive pressure ventilation or high-flow nasal cannula (27%), with 220 (55%) on low-grade oxygen support. Comorbidities were reported as common (50% hypertension, 22% diabetes) and median BMI was 28.7 kg/m^2 (range: 16 to 63).

After median follow-up of 10 days (range: 1 to 33 days), 256/397 patients had ≥2-point improvement in the 7-point ordinal scale (from 1=death to 7= not hospitalised) and 44 died.

In a multivariable analysis, baseline factors significantly positively associated with ≥2-point clinical improvement or mortality are included in Table 1. Treatment duration (5 vs 10 days) was not significant for either endpoint.

Racial differences were also included in a poster at the conference. [2]

Table 1: Baseline characteristics associated with clinical outcomes

Baseline factors in multivariate analysis	HR (95%CI)	p-value
Factors with >2 point improvement		
Lower grade respiratory support (low-flow oxygen or room air)	2.16 (1.50 to 3.10)	p<0.0001
Age <65	HR: 1.91 (1.46 to 2.55)	p<0.0001
Black race vs Asian	3.80.16 (2.28 to 6.35)	p<0.0001
White vs Asian	2.45 (1.60 to 3.76)	p<0.0001
Outside Italy (likely linked to time period of enrolment)	1.59 (1.07 to 2.37)	p<0.0225
No concomitant biologic medication use (ie IL-6, IFN etc)	2.70 (1.49 to 4.88)	p<0.0010
Factors associated with increased risk all-cause mortality		
High-grade oxygen support	5.47 (2.74 to 10.90)	p<0.0001
history of COPD	3.41 (1.30 to 8.94)	p<0.0125
Age ≥65y	2.30 (1.18 to 4.47)	p<0.0139

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https://goodluckfindingthis/this_is_important_science

CONFERENCE REPORTS

23rd International AIDS Conference (AIDS 2020)

6 – 10 July 2020, virtual meeting (was San Francisco and Santa Barbara)

Introduction: AIDS 2020 online

Simon Collins, HIV i-Base

This year the largest HIV conference had the challenge to turn an international conference, usually attended by 20,000 delegates, into a meeting that would be entirely accessed online.

The meetings are organised every two years by the International AIDS Society and if done successfully, the virtual conference could involve and reach far more people globally than could ever attend in person.

Although the scientific programme is already online, access is restricted to delegates until the conference ends on 10 July 2020. After this, all material should then become open access.

Free access is already available to some sections, for example the virtual exhibitions linked to the Global Village, although this still requires one-time free registration. Some of these projects adapt to a virtual format but they certainly don't compare to direct interactions with real people.

Based on the experience from AIDS 2020, face-to-face conferences are not likely to be replaced by virtual ones, but they will have to develop into better models, as COVID-19 is likely to continue to limit travel, at least for the rest of this year.

Whether due to teething problems or lack of testing, the AIDS 2020 website was difficult to access and the programme was and is still difficult to follow.

The serious loss will be the scientific advances that are not yet reported and for the lack of critical scrutiny given to the studies that are reported.

However, now that the conference and related meetings have finished, there might be the potential for better online access afterwards. Technically, if all presentations were presented virtually, a larger percentage than usually will remain available online, and these will now be open access.

The articles below in this issue of HTB cover the main breaking news, but we will continue to report other studies in future issues.

- Navigating the website: PDF programme and abstract book...
- Neural tube defects in two of 1000 conception exposures with dolutegravir: reassuring update from Tsepamo study
- Dolutegravir associated with weight gain in African ART programmes: findings from AFRICOS
- ADVANCE 96-week results: dolutegravir weight gain continues, especially in women and when used with TAF - no evidence of a plateau
- Obesity linked to dolutegravir, especially with TAF, could increase risk of adverse pregnancy outcomes
- Pregnancy meta-analysis: dolutegravir- versus efavirenz-based ART
- Long-acting cabotegravir injections effective as HIV PrEP in gay men and transgender women: results from HPTN 083
- Case report of short-term HIV remission from adding oral nicotinamide to intensified ART
- New HIV remission case report at AIDS 2020: full report

Navigating the website: PDF programme and abstract book...

Simon Collins, HIV i-Base

Even for people used to attending the regular meetings, where the numbers of delegates, presentations and thousands of abstracts is always daunting, navigating the website is more difficult still.

There isn't a printable PDF version of the programme, or of the abstract book or even just of the oral presentations.

There isn't a URL for searching the whole programme.

Although the website includes various search engines, none of these cover the whole site, requiring instead a search within a specific track or for only oral or abstract title. Searches don't include the option to search abstract text. Various searches of what always looked like the whole programme returned 1, 4, 9, 11, 33 and 67 hits, all for the single generic drug name 'dolutegravir'.

With websites, simple is always best, especially as access to the internet is still limited and/or expensive for many people globally. Simple graphics, simple navigation, a fast and comprehensive search engine and easy hyperlinks to the results. Unfortunately the conference website has none of these.

Currently, searching the programme for presentations and abstracts doesn't then directly link to the webcast or PDF poster, which also makes it difficult to quickly share the conference material in reports from the meeting. Sharing a poster from the App will send an email with the title but again with no link to the actual presentation.

Since the conference ended, many talks, posters and abstracts have disappeared or have dead links. The organisers are working to fix this.

Key URLs

Wishing you luck, the following URLs will open the world of AIDS 2020.

They require a login (until 27 July) to enter (including free login for Global Village).

Not all content works with all web browsers. Firefox and Chrome are recommended.

Online programme.

https://www.aids2020.org/online-programme

Main auditorium

https://events.ugovirtual.com/event/AIDS2020/en-us#!/Auditorium

This link includes four main portals: Prime sessions, on-demand sessions, satellite sessions and on-demand abstracts (posters).

Global Village (access via lobby)

https://events.ugovirtual.com/event/AIDS2020/en-us#!
Don't be distracted by the graphics representing delegates, this is your gateway to community-based on-demand and live content including workshops, films, art exhibitions and campaigns.
Film screenings for example, are listed at this URL:

https://events.ugovirtual.com/event/AIDS2020/en-us#!/FilmScreenings

or maybe this one:

https://events.ugovirtual.com/event/AIDS2020/en-us#!/FilmScreenings/n480012

Links to five oral webcasts

Within the conference programme, the following URLs link to four oral sessions for clinical science (track B). These were navigated to from 'On Demand' and 'Prime Sessions'.

Antiretroviral oral abstracts: part 1 (OAB03)

https://cattendee.abstractsonline.com/meeting/9289/Session/158

Antiretroviral oral abstracts: part 2 (OAB04)

https://cattendee.abstractsonline.com/meeting/9289/Session/157

ARV, testing and cure strategies (OAB02)

https://cattendee.abstractsonline.com/meeting/9289/Session/33

Weight, metabolic changes and ART (OAB06)

https://cattendee.abstractsonline.com/meeting/9289/Session/35

Late-breaker orals: Track B

https://cattendee.abstractsonline.com/meeting/9289/session/42

Case report of short-term HIV remission from adding oral Neural tube defects in two of 1000 conception exposures with dolutegravir: reassuring update from Tsepamo study

Polly Clayden, HIV i-Base

After a decline since the original safety signal, the prevalence of neural tube defects (NTD) among infants born to women receiving dolutegravir (DTG) at conception seems to be stabilising at approximately 0.2%. This update from the Tsepamo study was presented at AIDS 2020. [1]

If there is anyone interested in ART for low- and middle-income countries (or indeed for women with HIV of reproductive potential everywhere) who missed this, the Tsepamo study has performed birth outcomes surveillance at government maternity facilities in Botswana, since August 2014.

It was originally set up to look at NTDs and other birth outcomes with efavirenz (EFV) exposure. Botswana began the rollout of DTG in 2016 allowing for its inclusion in the comparative analyses.

In April 2018 the study investigators were asked to provide any preliminary data to WHO for its upcoming ART guideline meeting. This interim analysis showed NTDs among 0.94% infants with periconception DTG exposure. This was much higher than the (as expected) prevalence in the other exposure groups of 0.12% with any ART exposure and 0.05% with EFV exposure.

Our previous reports describe the Tsepamo methodology, these findings in detail and the associated impact on guidelines and programmes. [2]

Tsepamo last reported NTD data up until the end of March 2019. [3] This report showed 0.3% prevalence following DTG at conception exposure compared with 0.1% following exposure to non-DTG antiretrovirals at conception. Although this prevalence was reassuringly lower it was statistically significantly higher than other exposure groups – but the absolute difference of 0.2% was very small.

The study is ongoing and the most recent update included a further 13 months of data collected to the end of April 2020.

Between 1 April 2019 and 30 April 2020, the study (which currently covers about 70% of all births in Botswana) documented 39,200 additional births, including 1908 DTG conception exposures. See table 1.

Table 1: Tsepamo study – new NTDs and exposures 1 April 2019 to 30 April 2020

	NTDs	Exposures
Total	28	39,200
DTG at conception	2	1908
Non DTG at conception	6	4569
EFV at conception	5	2999
DTG started in pregnancy	1	741
HIV negative	17	30,258

There were two new NTD cases with DTG conception exposure: one lumbosacral myelomeningocele (spina bifida) and one encephalocele.

This gave a total of 7 NTDs with 3591 DTG at conception exposures documented in this reporting period. Prevalence of NTDs with DTG at conception exposure, 1 April 2019 to 30 April 2020 has decreased to: 0.19% (95% CI 0.09 to 0.4).

Prevalence of NTDs in the comparator exposure group of non-DTG ART at conception was: 0.11% (95% CI 0.07 to 0.17). Prevalence for other exposure groups was: 0.07% EFV at conception; 0.04% DTG started in pregnancy; and 0.07% HIV negative. These groups have not changed substantially since the last Tsepamo report.

Prevalence difference between DTG at conception and non-DTG antiretrovirals at conception: 0.09% (95% CI -0.03% to 0.30%). This has also decreased since the last report as has the difference across all other exposure groups.

These prevalence estimates now suggest about one excess NTD per 1000 births with exposure to DTG at conception, with the lower bound of the 95% confidence interval just below or just about zero.

C O M M E N T

Good news that we can finally "lay this to rest" (as remarked at the AIDS 2020 press conference).

The very small, non-significant difference in risk of NTDs with DTG at conception exposure compared with other ART is outweighed by its advantages. Although we still need to consider the issue of DTG-associated weight gain – for which data continues to emerge, including that presented at AIDS 2020.

It shouldn't have to be said again, but, women are not a niche ("special", "sub", "key", whatever) population and pregnant women need safety data.

And quick glance at the new antiretroviral presentations shows the same-old-same-old inadequate proportion of women in most clinical trials investigating new agents.

Presenting author Rebecca Zash stressed that safety data for women and pregnant women will also be critical for treating and preventing COVID-19 so the same call for inclusion in trials applies.

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https://i-base.info/htb/36478

Dolutegravir associated with weight gain in African ART programmes: findings from AFRICOS

Polly Clayden, HIV i-Base

People with HIV receiving TLD (tenofovir disoproxil fumarate/lamivudine/dolutegravir) in sites across four African countries had increased rates of developing high BMI compared to those taking non-TLD ART. [1]

Clinical trials conducted in African countries, notably ADVANCE and NAMSAL, have shown dolutegravir (DTG)-associated weight gain and reports of hyperglycaemia have emerged during the rollout of TLD. [2, 3]

The African Cohort Study (AFRICOS) enrolled participants at twelve PEPFAR-supported clinics in Kenya, Nigeria, Tanzania and Uganda to look at the risk of developing high BMI and hyperglycaemia in this cohort.

The study defined high BMI as ≥25 kg/m^2: overweight 25–29 and obese 30+ kg/m^2. Hyperglycaemia was defined as fasting glucose >99, any glucose >199 or taking medication for this condition. Participants with either high BMI or hypoglycaemia at baseline were excluded.

Of 742 participants receiving TLD, 529 (71.3%) were men and 213 (28.7%) women. Older participants were also more likely to receive TLD than younger ones. Both comparisons <0.001. These differences were probably associated with caution about DTG use in women of child-bearing potential during transition to TLD. Depression was documented in 16.3% of participants receiving TLD compared with 12.8% receiving other ART, p=0.03.

Median time on TLD was 225 days (IQR 127 to 297); 451 participants developed high BMI during follow up. The authors noted that incidence of high BMI increased with any ART exposure.

After adjusting for study site, gender, age and depression, the adjusted hazard ratio (aHR) for developing high BMI for participants receiving TLD was 1.85 (95% CI 1.24 to 2.76). ART naive participants had a 55% lower rate compared to those on non-TLD ART: aHR 0.45 (95% CI 0.28 to 0.74).

Hyperglycaemia in AFRICOS was usually mild and the authors reported no severe cases. Although participants receiving TLD had an increased risk of hyperglycaemia compared with those on non-TLD ART in the unadjusted model, after

adjustment this difference was not statistically significant: aHR 1.27 (95% CI 0.02 to 1.97). ART-naive participants had a 78% lower rate of becoming overweight or obese compared to those receiving a non-DTG regimen: aHR 0.22 (95% CI 0.12 to 0.43).

The authors noted independent effects for male sex, older age and geographic location on high BMI. The same effects were also demonstrated for hyperglycaemia, as was high BMI. They added that these findings have implications for comprehensive care models.

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ADVANCE 96-week results: dolutegravir weight gain continues, especially in women and when used with TAF - no evidence of a plateau

Polly Clayden, HIV i-Base

Dolutegravir (DTG)-based regimens non-inferior to efavirenz (EFV)-based ART at week 96 in South African study but weight increase in the DTG arms continues, especially among women also receiving tenofovir alafenamide (TAF). These findings from ADVANCE were shown at AIDS 2020. [1]

ADVANCE is an ongoing three arm, 192 week, phase 3, study comparing first-line ART with: TAF/emtricitabine (FTC) + DTG, tenofovir disoproxil fumarate (TDF)/FTC + DTG or TDF/FTC/EFV.

Week 48 results were presented at IAS 2019 and published simultaneously in the NEJM. [2]

Participants were treatment naive and aged at least 12 years at baseline. Pregnant women and people coinfected with TB were excluded. There was no baseline genotyping, in accordance with South African ART guidelines.

A total of 1053 participants were randomised between February 2017 and May 2018: 99% black, 59% female, median age 32 years and CD4 count approximately 340 cells/mm^3.

At week 96, the percentage of participants with viral load <50 copies/mL was 79% for TAF/FTC + DTG, 78% for TDF/FTC + DTG and 74% for TDF/FTC/EFV.

In men the mean change in weight at week 96 was +5.2 kg for TAF/FTC + DTG, +3.6 kg for TDF/FTC + DTG and +1.4 kg for TDF/FTC/EFV. Although there was incomplete data at this timepoint, at week 144, weight change was +7.2 kg, +5.5 kg and + 2.6 kg in the respective treatment arms.

In women the mean change in weight at week 96 was +8.2 kg for TAF/FTC + DTG, +4.6 kg for TDF/FTC + DTG and +3.4 kg for TDF/FTC/EFV. Again the data were incomplete but at week 144, weight change for women was +12.3 kg, +7.4 kg and + 5.5 kg in the respective treatment arms.

Mass increases were largely fat over lean gain and were distributed between trunk and limbs in all arms. The gain in fat mass was significantly higher in women versus men, p<0.001.

At week 96, there was a statistically significant difference in treatment emergent metabolic syndrome between the TAF/FTC + DTG and TDF/FTC/EFV arms across all participants: 8.4% vs 3.9%, p=0.03. Almost 11% of women in the TAF/FTC + DTG arm experienced treatment emergent metabolic syndrome.

C O M M E N T S

Presenting author Simiso Sokhela suggested that these results from ADVANCE support current WHO ART guidelines, which reserve TAF/FTC + DTG only for people with osteoporosis or impaired renal function

It is concerning that weight continues to rise among people receiving DTG, particularly among women and those also receiving TAF, with no suggestion of a plateau. The study is now continuing until week 192, which will provide more information on this phenomenon.

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Obesity linked to dolutegravir, especially with TAF, could increase risk of adverse pregnancy outcomes

Polly Clayden, HIV i-Base

Treatment-emergent obesity with tenofovir alafenamide (TAF)/ emtricitabine(FTC)/ dolutegravir (DTG) and to a lesser extent, tenofovir disoproxil fumarate (TDF)/FTC/DTG, could increase the risk of adverse pregnancy outcomes in black women. This is according to modelled predictions that were presented at AIDS 2020 by the ADVANCE study investigators. [1]

DTG and other integrase inhibitors are associated with significant weight gain. This is higher when DTG is used with TAF. Increases in body weight are also associated with female sex and black ethnicity.

Pregnant women who are clinically obese have a higher risk of adverse outcomes – both for the mother and the infant. Short term results from studies of TAF/FTC/DTG in pregnancy have not shown significant increases in adverse birth outcomes.

The aim of the study was to look at whether there is an increased risk of adverse birth outcomes if women become obese after long-term ART.

The ADVANCE study found significant treatment-emergent obesity after 96 weeks of treatment, most notably among black women receiving TAF/FTC/DTG (these results were also presented at AIDS 2020). [2, 3] Fourteen per cent of women receiving TAF/FTC/DTG, 8% receiving TDF/FTC/DTG and 2% TDF/FTC/EFV, with normal BMI at baseline, developed treatment emergent obesity at week 96 in ADVANCE.

The authors ran a systematic review evaluating the association between pre-pregnancy obesity and adverse pregnancy outcomes. They calculated the relative risk (RR) for each adverse outcome in women with obese (30 kg/m2 and above) compared with normal BMI (18.5–24.9 kg/m2). BMI was measured at or before 16 weeks of gestation. Adverse pregnancy outcomes were those most frequently occurring in standard clinical practice.

To model the risk prediction, 1000 pregnant women with normal baseline BMI were allocated to each treatment arm of ADVANCE: TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV.

The ADVANCE treatment-emergent obesity rates were applied to the model to calculate the number of obese and normal BMI women at 96 weeks. For each adverse birth outcome, treatment emergent obesity at week 96 were combined with RR for obese versus normal weight pregnant women. The resulting predications for maternal and infant adverse pregnancy outcomes are shown in Table1.

Table 1: ADVANCE trial: predicted increased risks of adverse pregnancy outcomes (per 1000)

	Baseline	TAF/FTC/DTG 96 wks	TDF/FTC/DTG 96 wks	TDF/FTC/EFV 96 wks
Adverse maternal outcomes				
Preterm delivery	70	73 (+3)	71 (+1)	70 (0)
Gestational hypertension	28	39 (+11)	34 (+6)	29 (+1)
Gestational diabetes	16	23 (+7)	19 (+3)	16 (0)
Pre-eclampsia	25	35 (+10)	30 (+5)	26 (+1)
Postpartum haemorrhage	112	115 (+3)	114 (+2)	112 (0)
Caesarean section	213	232 (+19)	224 (+11)	215 (+2)
Total effect		+53	+28	+4

Adverse infant outcomes				
Small for gestational age	89	87 (-2)	88 (-1)	89 (0)
Large for gestational age	134	154 (+20)	145 (+11)	137 (+3)
Macrosomia	31	37 (+6)	34 (+3)	31 (0)
Stillbirth	4	4 (0)	4 (0)	4 (0)
Neonatal death	2	2 (0)	2 (0)	2 (0)
Neural tube defect	0	0 (0)	0 (0)	0 (0)
Total effect		+24	+13	+3

The model predicted a higher risk of adverse pregnancy outcomes with DTG regimens compared to TDF/FTC/EFV. This was most notable with TAF/FTC/DTG.

The authors noted that the increase in adverse pregnancy outcomes at week 96 with TAF/FTC/DTG was almost double that of TDF/FTC/DTG.

They added that these risks could increase further for women treated longer-term – the risk of clinical obesity continues to rise after week 96 in ADVANCE.

C O M M E N T

Although results from the VESTED trial – presented earlier this year at CROI – found TAF/FTC/DTG to be associated with significantly fewer adverse pregnancy outcomes than TDF/FTC/DTG or TDF/FTC/EFV (driven by lower rates of preterm delivery and small for gestational age) and fewer neonatal deaths than TDF/FTC/EFV, women in this study started ART in pregnancy so were taking it for a comparatively short time before delivery. [4, 5]

The model suggests that risks and benefits might be less clear for pregnant women who have received TAF/FTC/DTG longer-term.

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Pregnancy meta-analysis: dolutegravir- versus efavirenz-based ART

Polly Clayden, HIV i-Base

A meta-analysis of dolutegravir (DTG)- versus efavirenz (EFV)-based ART in pregnancy did not find a significant difference between rates of vertical transmission between treatments – according to data presented at AIDS 2020.

Preterm births and viral suppression rates were the only endpoints with a significant difference.

The analysis included the following five trials: DolPHIN-1, DolPHIN-2, IMPAACT 2010, ADVANCE and NAMSAL. These provided a sample of 1074 pregnant women.

Timing of ART varied across the studies, from late presenters in DolPHIN 1 and 2 to women already receiving treatment at conception in NAMSAL and ADVANCE. Women in VESTED, that provided the largest number of cases in this analysis, were enrolled in the second and third trimesters. See Table 1.

Table 1: Meta-analysis of five clinical trials in 1074 pregnant women

Study	Regimens	ART	Countries	DTG arm	EFV arm
DolPHIN-1	TDF/XTC/DTG vs TDF/XTC/EFV	3rd trimester	South Africa, Uganda	29	31
DolPHIN-2	TDF/XTC/DTG vs TDF/XTC/EFV	3rd trimester	South Africa, Uganda	137	131
NAMSAL	TDF/3TC/DTG vs TDF/3TC/EFV	From conception	Cameroon	13	12
ADVANCE	TAF/FTC/DTG vs TDF/FTC/DTG vs TDF/FTC/EFV	From conception	South Africa	26 (+ TAF) 25 (+ TDF)	30
VESTED (IMPAACT 2010)	TAF/FTC/DTG vs TDF/FTC/DTG vs TDF/FTC/EFV	2nd/3rd trimester	Botswana, Brazil, India, South Africa, Tanzania, Thailand, USA, Zimbabwe	216 (+TAF) 213 (+TDF)	211

DolPHIN 1 and 2 and ADVANCE defined viral suppression as less than 50 copies/mL and in VESTED this was defined as less than 200 copies/mL. NAMSAL did not provide viral load results for pregnant women.

Overall DTG was associated with significantly higher rates of viral suppression compared with EFV: OR: 2.90 (95% CI 1.54 to 5.46), p=0.001.

This difference was particularly notable in the studies with shorter duration of treatment: DolPHIN-1 69% vs 39%, p=0.02; DolPHIN-2 74% vs 43%, p<0.00001 and VESTED 98% vs 91%, p=0.0008, for the DTG and EFV arms respectively.

In ADVANCE, where women had been taking ART for as much as two years before conception, this difference was non-significant.

Although there was no significant difference between arms, the three cases of vertical transmission in DolPHIN-1 and two in VESTED occurred in the DTG arms.

The risk of preterm births was 4% higher in women receiving EFV: 8% vs 12%, p=0.04.

C O M M E N T

Although the study authors explain it was an unexpected finding that faster virological suppression with DTG did not translate to lower vertical transmission, in DolPHIN 2 the three transmissions in the DTG arm were considered likely to be in utero as ART was started very late and the women had low viral loads at delivery.

The authors rightly point out that longer term safety considerations, especially the impact of weight gain on women's health and pregnancy outcomes, need continual assessment. People with HIV are likely to take ART for many years and more and more women will conceive in pregnancy after several years on ART.

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Long-acting cabotegravir injections effective as HIV PrEP in gay men and transgender women: results from HPTN 083

Simon Collins, HIV i-Base

Two oral presentations at AIDS 2020 provided headline news from the HPTN 083 study about a new formulation of PrEP that uses two-monthly injections compared to a daily oral pill. [1, 2]

Although top-line results from the HPTN 083 had been released a month earlier [3, 4] the new results included more details on incident infections and also showed how effectively important populations were successfully enrolled in the research.

HPTN 083 is an international, double-blind, active control study that randomised 4566 gay men and transgender women who have sex with men to either cabotegravir injections (CAB-LA) or daily oral TDF/FTC PrEP plus matching placebo. Cabotegravir was given by intramuscular injection every eight weeks, after an initial five-weeks using placebo-controlled oral formulations of both drugs.

Pre-specified minimum demographics included that overall 50% of participants would be younger than 30 years old, 10% would be transgender women (TGW) and more than 50% of US participants would be black/African-American. The study included 43 sites in the US, Latin America (Argentina, Brazil, Peru), South-East Asia (Thailand, Vietnam) and South Africa.

Overall baseline characteristics included: median age: 26 years (IQR: 22 to 32); 12%TGW (n=567); and that 50% of US participants were black (n=844). Retention was high with 91%, 87%, and 74% at 6, 12, and 24 months, respectively.

For the primary endpoint, 52 participants became HIV positive over 6389 person-years: 13 in the CAB-LA arm vs 39 randomised to oral TDF/FTC. This produced an overall incidence rate of 0.81% (95%CI 0.61 to 1.07); with 0.41% (95% CI: 0.22% to 0.69%) vs 1.22% (95% CI: 0.87% to 1.67%) in the cabotegravir vs TDF/FTC groups respectively in favour of CAB-LA.

This showed CAB-LA to be superior to TDF/FTC based on the primary endpoint of reducing new infections (HR: 0.34; 95%CI: 0.18 to 0.62, p=0.0005). However, both arms were highly effective given background incidence before the study was estimated at approximately 4.5%.

The most important new information was on the incident infections in the CAB-LA arm. This is because the greater adherence assumed with CAB-LA was expected to drive the differences compared to TDF/FTC. However, given the TDF/FTC in the context of good adherence generates 100% efficacy, any infections on CAB-LA (when adherent) might technically favour oral PrEP.

Of the 13 HIV infections on CAB-LA, two were now known to already be HIV positive at baseline, three who became positive during the oral phase, and five who become HIV positive after an extended time without having an injection (two who never returned after the oral dosing phase, two who already switched to oral TDF/FTC and one who had missed an injection visit for 31 weeks).

This left 5/13 participants who became positive despite continuous cover on CAB-LA (effectively during confirmed 100% adherence). However, further essential details on these cases are not yet available due to complications in sampling and testing linked to COVID-19. These analyses might show, for example, whether these cases can be explained by infection with drug-resistant HIV or low drugs levels (linked to either low individual absorption or faster clearance, for example at the end of the dosing cycle).

Of the 39 infections in the TDF/FTC group, 3 became positive during the lead-in phase, 6 after not returning for prescriptions and 30 who were still routinely in the study. Further information on drugs levels, adherence and drug resistance are still needed to explain these cases.

Tolerability was good in both arms, but injection site reactions (ISRs) were significantly more common in CAB participants – as was fever (5.6% vs 2.4%, p<0.001) and increased glucose (9.0 vs 5.1, p<0.001). Nausea was significantly more common in TDF/FTC participants. Injection intolerance led to discontinuation in 46 (2.2%) active CAB-LA recipients and was associated with the severity of the intolerance/reaction.

In the second presentation, Beatriz Grinsztejn, from The Oswald Cruz Foundation (FIOCRUZ), Brazil, presented more detail on the populations enrolled in HPTN 083, including breakdowns for key demographics and results by region and age.

This included that median age in the four regions varied from 23 to 27 with 61 to 80% being <30 years and 7% to 30% were TGW.

By the same categorisation, of the 52 incident HIV infections, 44 were <30 years old (11 vs 33; HR: 0.32; 95%CI: 0.16 to 0.63), 9 were TGW (2 vs 7; HR 0.29; 95% CI: 0.06 to 1.41) and 19 were black (4 vs 15; HR 0.28, 95%CI: 0.10 to 0.83), all CAB-LA vs TDF/FTC respectively.

Across regions, the HR ranged from 0.19 (95% CI: 0.07 to 0.56) in the US to 0.54 (95% CI: 0.20 to 1.46) in Latin America for CAB-LA vs TDF/FTC respectively.

CAB-LA was also significantly more effective than TDF/FTC in gay men (HR 0.34; 95%CI: 0.17 t0.67) and US region (HR: 0.19; 95%CI: 0.07 to 0.56).

The presentation also reported by sub-populations on retention at 12 months (overall 86%, similar across groups), side effects (generally injection site reactions, slightly higher in African-Americans) and new sexually transmitted infections (generally slightly higher in younger participants). For more details please see webcast and slides.

Further information is available form the HPTN website, including a community webinar with 30-minute Q&A sessions. [5, 6]

COMMENT

These results are important in providing clear data to support a new option for PrEP in gay men and that included 12% transgender women.

They show high acceptability within a research setting to include and retain people from groups who are at high risk of HIV but often underrepresented in studies, including a high proportion who were younger and black.

Overall, CAB-LA was superior to oral TDF/FTC, with the better results likely due to suboptimal adherence to oral TDF/FTC. However, in the context of perfect adherence, TDF/FTC is already effectively 100%, so further analyses are needed on drug resistance and drug levels to understand the cause of the five infections linked to CAB-LA. Either way, these are tiny numbers in a study this size.

Results from the related HPTN 084 study are expected within a year. This study with a similar design is being run in women at 20 sites in 7 high-incidence countries: South Africa, Botswana, Uganda, Kenya, Malawi, Eswatini, and Zimbabwe. Although it started a year later, the results are needed for regulatory submission to include women. [7]

A late-breaker poster at AIDS 2020 from ViiV looked at implementation barriers among health workers for injectable ART. [8]

Results from a macaque study reporting on penile protection from cabotegravir were also just published in JID (1 August 2020). [9]

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Case report of short-term HIV remission from adding oral nicotinamide to intensified ART

Simon Collins, HIV i-Base

An HIV cure study from Brazil presented early news from the AIDS 2020 virtual conference.

This included an HIV positive man who has stayed off HIV treatment for more than a year without viral rebound after using oral drugs that added nicotinamide to intensified antiretroviral treatment (ART). The same response was not seen in four other people using this intervention. [1]

Overall, the study included 30 participants randomised to one of five different interventions, or to a control group that only used ART. Results were presented by Ricardo Diaz from University of Sao Paulo.

The case involved a 35 year old man who was diagnosed HIV positive in 2012 with a CD4 count of 372 cells/mm^{3}and viral load of 20,000 copies/mL. He started ART with efavirenz/AZT/3TC and maintained undetectable viral load, switching NRTIs to TDF/FTC after two years.

In 2015 after joining this study (when CD4 count was 720), nicotinamide was added and ART was intensified by adding dolutegravir and also maraviroc (which might also induce HIV transcription and cell activation). Nicotinamide is an HDAC inhibitor that has multiple mechanism of action that might to induce HIV transcription, cell activation and latency reversal. [2]

ART was given at standard doses and nicotinamide at 500 mg twice-daily, all for 48 weeks. Routine ART was then continued for another three years before an analytic treatment interruption (ATI) in March 2019. Of note, total HIV DNA was not detectable in PBMCs just before the treatment interruption.

His viral load has remained undetectable for 64 weeks. However, HIV antibody titres declined during the intervention and on regular ART afterwards and were not detected during the ATI.

The results were presented as extremely preliminary, requiring further follow-up to determine how long they might continue and also that the single case could not show that any of the interventions were directly responsible for the outcomes.

Other interventions in the study include a dendritic cell vaccine using autologous HIV and auranofin (to decrease the ratio of long-lived central memory/transitional memory CD4+ T-cells). One arm includes all four interventions (ie also including ART intensification and nicotinamide). [3]

The presentation is due to be live on Wednesday 8 July at 14.24 (PDT) as a prime channel live session.

C O M M E N T

This report is still tentative, with many of the expected investigations (testing lymph samples etc) being delayed due to restricted research during COVID-19.

As with most things that seem to good to be true, this might prove to be the case here. Even if this individual remains in remission, this might be more due to an individual Visconti-like response this strategy producing a cure. This is especially as a similar response was not seen in the other four participants in this arm and that treatment intensification and the use of HDAC inhibitors have not been particularly effective interventions in other studies.

The full study was presented the following day and a more detailed analysis from Richard Jefferys is included in the next article. [4]

It is a shame that IAS continues to release important scientific news by press release rather than giving researchers an appropriate time to first present their results in full. As a result, the headline news in both mainstream and community media have already reported the conclusions, before the detailed results have been presented.

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New HIV remission case report at AIDS 2020: full report

Richard Jefferys, TAG

On 7 July 2020, a presentation by Ricardo Diaz at the ongoing virtual International AIDS Conference (AIDS 2020) caused a major splash in the media by reporting that one out of 30 participants in a clinical trial conducted in Brazil has experienced a lack of viral load rebound for a little over a year (64.7 weeks) after interrupting antiretroviral therapy (ART). [1, 2]

The trial was launched in 2015 and involved a complex design in which 30 participants with HIV were divided into six groups of five people each. One group continued on a standard ART regimen and served as controls, while the other five groups received the following additional interventions:

- Group 2: Dolutegravir and the CCR5 inhibitor maraviroc (which has been to reported to also exert HIV latency-reversing effects). [3]
- Group 3: Dolutegravir, maraviroc and nicotinamide (a water-soluble form of vitamin B3 that may have HIV latency-reversing activity [4]).

- Group 4: Dolutegravir, maraviroc and auranofin (an antiproliferative drug).
- Group 5: Dolutegravir and a dendritic cell therapeutic vaccine.
- Group 6: Dolutegravir, a dendritic cell therapeutic vaccine, auranofin and nicotinamide.

Results from the trial have been presented on a number of previous occasions, including at AIDS 2018, CROI 2019, and the 2019 HIV Persistence Workshop (see abstract OP 8.6 in the abstract book and the report from NATAP). [5, 6, 7, 8]

Results from participants who received auranofin were also the subject of a published paper last year. Overall, declines in HIV DNA levels (a surrogate measure of the HIV reservoir) were found to be greatest among recipients of the multiple interventions in group six. [9]

The original study design did not include an analytical treatment interruption (ATI), but the protocol was later revised and 25 of the participants underwent an ATI approximately 2.5 years after the end of the 48-week study period (during which the interventions were administered).

The presentation at last year's HIV Persistence Workshop reported that two participants in group six and one in group three displayed undetectable HIV viral loads after the ATI. However, after around 16 weeks the two people from group six showed evidence of viral load rebound and restarted ART.

The remaining participant from group three was the subject of today's AIDS 2020 presentation. The individual was diagnosed with HIV infection in October 2012 and started ART two months later. According to an article by Jon Cohen in ***Science***, they estimate the date of HIV acquisition to be around June 2012 (the last previous HIV negative test result was in 2010). [10]

Viral load at ART initiation was relatively low: 20,221 copies/mL.

At the time of entry into the trial in September 2015, viral load was undetectable and the CD4 count 720. Two very low level transient viral load blips occurred while receiving the study interventions but otherwise undetectable levels have been maintained while on ART.

HIV DNA was detectable in rectal tissue and blood samples at the end of the 48-week intervention period. Measurements of blood HIV DNA levels subsequently showed a decline during treatment with regular ART regimens, eventually becoming undetectable immediately prior to the ATI which was initiated in March 2019.

After the ATI, viral load did not rebound and has remained undetectable ever since (the last available measurement at the time of the presentation was from June 22, 2020). Slides showing CD4 count and CD4:CD8 ratio over time indicated a notable decline shortly after the ATI, which is surprising given the apparent lack of viral load rebound in the blood, but no further longitudinal data on these measures was reported.

HIV antibody levels evaluated by the Abbott ARCHITECT antigen/antibody combination assay have declined throughout follow up, with the exception of one possible slight increase immediately after the ATI. Results of a rapid HIV antibody test are now negative (in some media reports this has been mistakenly represented as indicating that no HIV antibodies are detectable, which is not accurate).

The case appears encouraging for HIV cure research, with the caveat that late rebounds in viral load have occurred in some previous examples of HIV remission. Importantly, it's unclear as yet whether the interventions received during the trial contributed to the outcome; the person may have started ART fairly soon after HIV acquisition and there have been other case reports of early-treated individuals containing viral load for variable periods after ART interruptions.

Notably, of the other 30 study participants, nine received nicotinamide and 14 received dolutegravir and maraviroc. Although it's unclear whether all of these other participants were among those that underwent ATI, no additional examples of similarly prolonged absence of viral load rebound were observed. This appears to argue against a strong effect of these interventions. Additionally, HIV DNA levels continued to decline long after the cessation of the interventions in the participant who has not rebounded.

Emphasizing the uncertainty about the role of the study drugs is important given that nicotinamide is available over-the-counter as a supplement. At the current time, there is no evidence to suggest that adding dolutegravir, maraviroc and nicotinamide to ART regimens would lead to similar outcomes in other people with HIV.

Further analyses will hopefully shed light on how viral load rebound has so far been prevented, and whether the interventions contributed in some way. Information on HIV-specific T cell responses and the individual's HLA type could be particularly helpful. The Associated Press article on the research includes the welcome news that Diaz will receive support to conduct a larger 60-person trial, so more robust results should be forthcoming. [11]

Source
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HIV: ANTIRETROVIRALS

FDA approves fostemsavir for multidrug resistant HIV in the US

Simon Collins, HIV i-Base

On 2 July 2020, the US FDA approved fostemsavir as an HIV treatment for people with extensive drug resistance and few choices for antiretroviral treatment (ART). [1, 2]

Fostemsavir is a gp120 attachment inhibitor, the first drug in this new class, that works at an early stage of the HIV lifecycle to block the virus from infecting CD4 cells.

The indication also covers people who are failing their current ART due to resistance, intolerance or safety considerations.

Approval was primarily based on results from the international phase 3 BRIGHTE study, which has reported 96-week follow-up, but longer term results are available from some participants out to week 192. [3, 4]

Fostemsavir (previously BMS-663068) has had a long development history, and was acquired by ViiV Healthcare from Bristol-Myers Squibb with other investigational compounds in 2015.

Fostemsavir is dosed at 600 mg twice-daily.

Potential drug-drug interactions are possible with strong cytochrome P450 (CYP)3A inducers, would significantly reduce temsavir (the active moiety of fostemsavir) plasma concentrations. These drugs include, but are not limited:

- Androgen receptor inhibitor: enzalutamide
- Anticonvulsants: carbamazepine, phenytoin
- Antimycobacterial: rifampin
- Antineoplastic: mitotane
- Herbal product: St John's wort (Hypericum perforatum)

Fostemsavir is marketed by ViiV Healthcare under the trade name Rukobia.

It is marketed by ViiV Healthcare under the trade name Rukobia.

For more details please see the full prescribing information. [5]

C O M M E N T

Although the pool of people on failing ART with multiple drug resistance is luckily small, fostemsavir In combination with other active drugs, is likely to be a life-saving option.

Fostemsavir was submitted to the EMA for approval in the EU in January 2020, with a decision expected shortly.

A limited named patient access programme is available, including in the UK, for people who are urgently need access to fostemsavir. For details, doctors should directly contact ViiV Healthcare.

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HIV: PREVENTION

UK government cuts HIV PrEP budget in England by a third

Simon Collins, HIV i-Base

On 3 July 2020, the UK government cut the budget for HIV PrEP in England by £5 million to £11 million, projected to cover three years.

This was three months after PrEP was finally approved by NHS England with a (limited) budget of £16 million. [1, 2]

Although several community groups have further protested this cut the government response has not yet been publicised. [3]

C O M M E N T

PrEP is one of the most effective ways to prevent continued HIV transmission.

Even though generic PrEP is widely used by people buying PrEP themselves, continued further obstructions will effect the most vulnerable people in the UK who are unable to do this.

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HIV: ON THE WEB

BHIVA virtual conference: Best of CROI and COVID-19 update

Simon Collins, HIV i-Base

BHIVA have produced important educational webcasts, including the feedback meeting from CROI 2020 that was suspended due to COVID-19.

Although the full content is currently only available to BHIVA members and people from the community who were awarded free registration to the April conference (hopefully this might be reviewed at some point), the "Best of CROI" update is open access.

The COVID-19 sessions will also be made available to the HIV community.

Best of CROI

https://fsmevents.com/bhivavc20/bhiva_best_of_croi_roundup_1 (webcast)

Access and procurement to ARVs in the Russian federation

ITPCru report

ITPCru have published their annual report on ARV procurement monitoring in Russia in 2019.

The summary points are very important for a broader awareness of how ART differs compared to current treatment in western Europe.

The report contains the following:

- Volume and structure of procurements of ARV drugs in 2019.
- Procurement structure of ARV drugs by expenses.
- Cost of ARV drugs in 2019.
- Cost of the most common treatment regimens.
- Number of patients on ART, treatment coverage.
- Conclusions and recommendations.

The main findings in the Russian Federation in 2019 include:

1. The estimated number of annual courses of ART in 2019 was 464,318. This covers about 60% of the total number of people under regular medical care, and about 43% of all registered people living with HIV.
2. Overall, 64% of the budget was spent on five drugs. All of them are under patent in the Russian Federation: lopinavir/ritonavir (18%), raltegravir (14%), dolutegravir (14%), etravirine (9%), rilpivirine/tenofovir/emtricitabine (9%).
3. Atazanavir is no longer in the top five drugs in terms of cost. This is due to an approximate 80% reduction in prices procurements of the Ministry of Health of the Russian Federation.
4. Dolutegravir for the first time entered the top five drugs. Although its price decreased at the end of 2019, at the time of procurement it was the same as in 2018. Dolutegravir budget almost doubled - from 7% to 13%.
5. ART combinations are still mainly purchased as separate drugs rather than combination pills: (a) tenofovir + lamivudine + efavirenz and (b) tenofovir + lamivudine + lopinavir/ritonavir.
6. The weighted average cost of an annual treatment course with efavirenz in the centralised procurements in 2019 was approximately $180 USD. This was 9% lower than in 2018.
7. The cost of an annual treatment course with lopinavir/ritonavir was ~930 USD (similar to 2018).
8. Only 1.6% of patients use fixed dose combinations; Only 3.3% use dual 2-in-1 drugs.
9. Most drugs are generics, including almost 100% of NRTIs. As with other countries this was linked to expired patents.
10. The website pereboi.ru recorded 455 reports of interruptions in the provision of ARV therapy. This doubled compared to 2018. In 37% of cases reported substituting drugs without a medical indications due to the lack of drugs (in 2018 - 31%), 26% of reports were related to the refusal to provide ARV drugs (in 2018 - 27%).

The report is available in English and Russian.

Community-driven procurement monitoring was successfully replicated by Armenia, Belarus, Kazakhstan, Kyrgyzstan and other EECA countries. The reports are available on our web-site in Russian.

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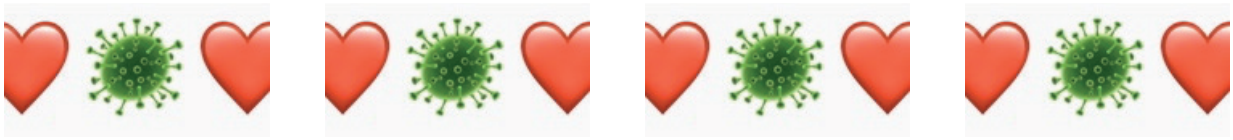
HTB SUPPLEMENT ON COVID-19: Issue 6



COVID-19: HIV and COVID-19 COINFECTION

Pneumocystis Jirovecii Pneumonia (PJP) mistaken for COVID-19 in late stage undiagnosed: urgency of including HIV testing on admission

Simon Collins, HIV i-Base

On 1 July 2020, a letter to CID reported a case of missed diagnosis of HIV-related Pneumocystis Jirovecii Pneumonia in a person hospitalised with COVID-19. [1]

This case was a 52 year old gay man with a fever of 40°C, cough and shortness of breath who was hospitalised at Saarland University Medical Centre, Germany, and positively diagnosed with SARS-CoV-2 and bacterial infections that were treated with a broad antibiotic regimen containing meropenem and linezolid.

However, symptoms continued, leading to admission to ICU and ventilation. Differential cytology included a CD4 count of 12 cells/mm^3, CD4% 2 and CD4:CD8 ratio of 0.08 then led to testing for HIV, which was positive with viral load of 360,000 copies/mL. Further details of diagnosis and management are included in the letter.

Oral ART was started immediately with twice-daily darunavir/ritonavir plus TDF/FTC. Trimethoprim-sulfamethoxazole was added to antibiotics and on the basis of CMV coinfection (170,000 U/mL blood), ganciclovir (5 mg/kg) was also added.

The patient recovered well, was able to discontinue ventilation and was later discharged from hospital.

The paper highlights the risk of COVID-19 masking symptoms of HIV infection but also that ART was safely starting in a patient on ICU and that in this case the extremely low CD4 count did not result in IRIS.

C O M M E N T

This case further highlights the importance of including routine HIV testing in hospitalised cases of COVID-19. This should not just be based on risk factors for HIV, for example, because the case described above was a gay man.

Several other COVID-19 cohorts have also reported previously undiagnosed HIV, and even if this is at a higher CD4 count, it will enable referral to local HIV services.

Although these cases include very low CD4 counts and the late-stage HIV is important, COVID-19 might also directly contribute to worse absolute results. In this case, it is unclear why ganciclovir was included given the potential toxicity, and whether this was used to directly treat CMV or was being used as prophylaxis due to the low CD4 count.

On 7 April 2020, a letter to the BMJ raised an early concern for HIV/COVID-19 coinfection in HIV positive people in the UK who are undiagnosed or not on ART. This was also to ensure the best management of COVID-19 management in all HIV positive people, including to avoid interruption of HIV treatment. [1]

Unfortunately, an early missed UK case of HIV-related Pneumocystis Jirovecii Pneumonia being assumed to be COVID-19 has been anecdotally reported where, even after HIV was diagnosed, the patient died.

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NYC cohort reports similar outcomes from COVID-19 in HIV positive vs HIV negative adults

Simon Collins, HIV i-Base

A retrospective case-control analysis of outcomes from COVID-19 reports similar outcomes for 88 HIV positive adults in New York compared to HIV negative people. [1]

Of the 4,402 adults hospitalised at five clinics between 12 March and 23 April 2020, 88 were HIV positive (2%). Median age of HIV positive group was 61 years (IQR: 54 to 67) and most were black (40%) or Hispanic/Latino (30%). Cases were then matched to controls (1:5) by age, sex or race/ethnicity.

Significant differences that still remained however including a higher proportion of smokers in the HIV positive group (55% vs 23%, p<0.001) and more comorbidities (compared to matched controls). These included COPD (10% vs 3%, p<0.001), cirrhosis (6% vs 2%, p=0.02) and a history of cancer (17% vs 6%, p=0.001).

All HIV positive people were on ART (78% INSTI-based) with 81% having recent undetectable viral load. However, only 58% had a CD4 count >200 cells/mm^3 and CD4% was generally reduced compared to most recent pre-admission test (median decline –4% (IQR: 0 to 9%).

Compared to controls, the study reported no differences by HIV status in key outcomes. Severity of COVID-19 on admission (measured by need for oxygen) was similar (p=0.15). Although poor outcomes after hospitalisation were frequent, they were also similar in each group. Overall, 18% vs 23% required mechanical ventilation and 21% vs 20% died, in the positive vs negative groups respectively.

The study reported a similar cumulative incidence of death over time by HIV status (p=0.94).

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Spanish study reports associations between COVID-19 and HIV treatment including NRTIs

Simon Collins, HIV i-Base

A large observational Spanish study looking at the incidence and severity of COVID-19 in HIV positive people on ART diagnosed with COVID-19 has reported a potential benefit from TDF/FTC. [1]

However, as with all observational data, these results, published in Annals of Internal Medicine, need to be interpreted with caution and haven't been seen in other cohort studies. Most importantly, the study doesn't appear to report or adjust for comorbidities, which are critical for COVID-19 outcomes.

This national cohort included 77,590 HIV positive adults at 60 HIV clinics in Spain whose records were included from 1 February to 15 April 2020.

Of these, 236 people were diagnosed with PCR-confirmed COVID-19, 151 were hospitalised and 15 were admitted to the ICU. There were 20 deaths: 5 in ICU, 12 in hospital (but not in ICU) and 3 who were not hospitalised.

The risk per 10,000 for HIV-positive vs general population (standardised for age and sex and excluding health workers) was 30.0 vs 33.0 for COVID-19 diagnosis and 3.7 vs 2.1 for death.

The analysis of ART use focused on the NRTI component due to modelling data supporting potential activity against SARS-CoV-2 from tenofovir disoproxil (TD), tenofovir alafenamide (TAF), abacavir (ABC), emtricitabine (FTC) and lamivudine (3TC).

The main results reported lower risk for diagnosis and hospitalisation associated with ART containing TDF/FTC, with no related ICU admissions or deaths. However, the multivariate models adjusting for ART don't appear to have adjusted for other clinical factors associated with COVID-19 outcomes. See Table 1.

Table 1: COVID-19 outcomes by NRTI (note: not adjusted for COVID-19 factors)

NRTI component	n	Risk for C-19 diagnosis	Risk for hospitalisation
TAF/FTC	100	39.1 (95%CI: 31.8 to 47.6)	20.3 (95%CI: 15.2 to 26.7)
TDF/FTC	21	16.9 (95%CI:10.5 to 25.9)	10.5 (95%CI:5.6 to 17.9)
ABC/3TC	57	28.3 (95%CI:21.5 to 36.7)	23.4 (95%CI:17.2 to 31.1)
Other	8	29.7 (95%CI:22.6 to 38.4)	20.0 (95%CI:14.2 to 27.3)

Note: Table includes 186 people on 3-drug ART. 50 participants were on 2-drug ART.

COMMENT

We reported this study because of the high profile generated from the top-line conclusion. However, it is surprising the paper was published given the important cautions, where associations could easily be from confounding factors related to COVID-19.

Although this is a larger cohort, including one of the largest groups of people with HIV/COVID-19, the numbers are small when looking at the impact of ART components.

Also, while the paper reports on HIV treatment, it includes no information are reported on other risk factors for COVID-19 (other than age and gender) including prevalence and severity of comorbidities. The lack of information on kidney disease at baseline and as an outcome is especially important given the focus on tenofovir and TAF.

It is also not clear from the paper whether this was a prospective or retrospective study.

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Review on COVID-19 in people with immune suppression

Simon Collins, HIV i-Base

A recent review in CID looks at the increasing literature on COVID-19 in a range of different health conditions associated with immune suppression. [1]

These populations includes cancer, hematologic malignancy, solid organ transplant, patients taking biologics and targeted disease modifying anti-rheumatic drugs, primary immunodeficiency, and HIV infection.

The review concludes that with malignancy and solid organ transplant recipients, there might be at increased risk of severe COVID-19 disease and including higher mortality.

Evidence for other types of immunosuppression is less clear however, with further research, ideally prospective studies to determine the attributable risk of immunocompromising conditions and therapies on COVID-19 disease prognosis.

C O M M E N T

This paper was mainly included to highlight the impact of COVID-19 on related health conditiona. The HIV review is useful, but HTB has reported on additional recent HIV coinfection studies. [2, 3]

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COVID-19: TREATMENT ACCESS

EMA recommends approval for remdesivir in the EU to treat COVID-19

Simon Collins, HIV i-Base

On 25 June 2020, the European Medicines Agency (EMA) announced that the CHMP had recommended conditional approval in the EU for remdesivir as a treatment for COVID-19. [1]

Conditional approval will allow immediate access to remdesivir, but also requires supplementary efficacy and safety results to be submitted by August and December 2020.

Although the submission for approval was only made on 5 June, the EMA has been evaluating accumulating results from remdesivir studies since late April. The indication is for adults and children (>12 years old) with pneumonia who require supplemental oxygen.

Approval is largely based on results from the US NIH randomised placebo-controlled ACTT study that reported an overall average 5-day shorter recovery time (approximately 9 vs 15 days) with remdesivir (dosed for 10 days) compared to placebo. [2]

However, differences were reported depending on severity of COVID-19 at baseline. No differences were reported for participants with mild-moderate disease (at 5 days in both active and placebo arms) or in people who started mechanical ventilation while already taking remdesivir. The difference was driven by the 90% of participants with severe disease (12 vs 18 days).

Remdesivir is manufactured by Gilead Sciences with the trade name Veklury.

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Drug price announced for remdesivir - as US buys up world stock

Simon Collins, HIV i-Base

On 29 June 2020, within a week of the first articles speculating on the likely price of remdesivir, Gilead announced a base price. [1]

This will be $520 USD per vial ($3,120 per course) for the US patients with health insurance and high-income countries and $390 per vial ($2,340 per course) for low-income countries.

The immediate implications for wider access in the UK and many other high-income countries is likely to be limited though. On 30 June 2020, it was announced that the majority of future production for at least the next three months had already been secured for the US home market, thanks to a bulk contract negotiated by the US government. [2]

C O M M E N T

Strangely, most mainstream media did not mention that the medical urgency for access to life-saving medicines during a health crisis would enable compulsory license. This allows countries to set aside patents in to order to access generic versions of these drugs.

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COVID-19: INVESTIGATIONAL TREATMENTS

UK study reports inhaled interferon-Beta reduces time to recovery from COVID-19

Simon Collins, HIV i-Base

On 20 July 2020, a UK study reported that an inhaled formulation of interferon-B was associated with some better outcomes against COVID-19, including the overall chance of recovery. [1]

Although not all outcomes were significantly improved, the study was important for including people who were not hospitalised, and for using a treatment that was easy to take at home.

This was in a double-blind, placebo-controlled phase 2 study that randomised 220 adults with confirmed COVID-19 (100 hospitalised, 120 still at home) to either inhaled interferon-Beta-1a (IFN-β1a) or a matching placebo. The primary endpoint was a change in symptoms measured over two weeks, measured on a standerd scale used to categorise COVID-19. [2]

So far, only limited top-line results are currently available from a company press release until the study is peer-reviewed and published in detail.

These include:

- A 79% reduction in chance of developing severe COVID-19 (defined as needing ventilation or death) over 16 days. This was significant with odds ratio (OR) 0.21 (95% CI: 0.04-0.97); p=0.046.
- Being more than twice as likely to recover (defined as having no symptoms affecting daily life or evidence of viral infection). This was also significant with hazard radio (HR) 2.19 (95% CI: 1.03 to 4.69); p=0.043).
- Significantly reduced breathlessness, p=007.
- Three deaths were reported in the placebo group compared to none receiving IFN-β1a. This outcomes was not reported as being significant or not.
- People with more severe COVID-19 who already needed oxygen at the start of the study (numbers not provided) returned home on average three days earlier (after six vs nine days). This difference was not statistically significant: HR 1.72 (95%CI: 0.91 to 3.25), p=0.096.

- IFN-β1a was associated with a significantly higher chance of recovery by day 28: HR 2.60 (95%CI: 0.95 to 7.07), p=0.062.

Time with symptoms before entering the study was not limited to chance of recovery with IFN-β1a treatment.

The research was run in Southampton by Synairgen Research and the formulation of interferon-Beta has a development name SNG001.

C O M M E N T

Reporting from a press release is limited but these results are important for showing important benefits compared to placebo.

In addition to anti-inflammatory effect from interferon, IFN-β1a has shown in-vitro activity against MERS CoV, SARS-CoV-1 and SARS-CoV-2 with earlier phase 2 studies against asthma and that studies in COPD are also ongoing. [1, 3]

Two small earlier studies, both using different version of interferon (IFN-α-2b and IFN-α-1b) have also reported benefits in early stages of COVID-19. [4]

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RECOVERY study reports that lopinavir/r fails to show benefit against COVID-19

Simon Collins, HIV i-Base

On 29 June 2020, that the UK RECOVERY study announced by press release that lopinavir/r was not effective as a treatment for people hospitalised with COVID-19. [1]

RECOVERY is a large ongoing randomised study with multiple open-label experimental treatment arms and a shared control group receiving standard of care. The primary endpoint is all-cause mortality at day 28 with multiple secondary endpoints.

So far more than 11,800 participants have been enrolled from 176 hospitals across the UK.

The numbers of participants in this analysis included 1596 in the lopinavir/r arm and 3376 in the control arm. Although other baseline characteristics have not been released, on entry, most participants (70%) required oxygen alone and 26% did not need any respiratory intervention. The low percentage on mechanical ventilation (4%) was explained by the difficulty of administering lopinavir/r in this state.

The top-line results report no significant difference in 28-day mortality between arms, with 22.1% vs. 21.3% in investigational vs control group, respectively. The relative risk of mortality was 1.04 (95%CI: 0.91 to 1.18), p=0.58. The results were consistent in different subgroups of patients, but low use on mechanical ventilation technically prevented the study concluding on effect in this group.

The press statement summarises the results by saying the data "convincingly rule out any meaningful mortality benefit of lopinavir-ritonavir in the hospitalised COVID-19 patients we studied".

C O M M E N T

RECOVERY was planned using an adaptive design to identify and continue effective treatments similarly identify those that had no effect, enabling new strategies to then be added to the study.

This is same study that reported positive results for dexamethasone two weeks ago. [3]

However, this is the second time that the RECOVERY study has reported negative results from experimental treatment for COVID-19. [2]

The current lopinavir/r analysis, and decision to close the lopinavir/r arm, was based on a routine review of the DSMB on 25 June 2020 that recommended unblinding this arm of the study.

Although a different statistical analysis and DSMB review plan might have identified the lack of signal for potential benefit earlier, so far, the statistical analysis plan has not yet been posted online. [4]

It is unclear whether data from earlier studies reporting a lack of benefit with lopinavir/r were used to define likely expectations in this arm. [5, 6]

The three remaining active arms in RECOVERY use azithromycin, tocilizumab and convalescent plasma. Other papers have included more hopeful (though still uncertain) results with tocizumab and convalescent plasma.

References
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WHO discontinues hydroxychloroquine and lopinavir/r arms of SOLIDARITY study

Simon Collins, HIV i-Base

On 4 July, the WHO announced that two experimental arms of the international SOLIDARITY study – using hydroxychloroquine and lopinavir/r – were now stopped based on results from an interim analysis.

The decision was also based on results from other studies that was presented at the WHO Summit on COVID-19 research and innovation from 1-2 July 2020. This would have included similar results that were recently announced from the UK RECOVERY study.

The press release is not very clear on other aspects of the study and provides no further details of the results, other than that these will be published later.

As of 1 July 2020, nearly 5500 patients have been recruited in SOLIDARITY from 21 of the 39 countries that have approval to begin recruiting. [2]

The remaining two arms in SOLIDARITY are remdesivir and a dual combination of lopinavir/r plus interferon beta-1a. It is unclear whether lopinavir/r will also be discontinued in this second arm.

C O M M E N T

It is important that ongoing studies promptly respond to new evidence that becomes available on both the investigational interventions and the management of COVID-19 in general.

These negative results should also prompt closer review of studies where DSMB access to unblinded data is not showing any clear signal of efficacy.

Reference
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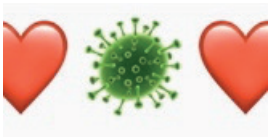
   https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19
2. WHO SOLIDARITY Study.
   https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

Individualising management of COVID-19 based on real-time inflammatory responses

Simon Collins, HIV i-Base



An open-access paper in CID proposing further individualise management of COVID-19 to include choice of treatment to reduce immune inflammation and anti-cytokine treatment in selected patients. Current studies, for example using the IL-6 blocker tocilizumab, are used as COVID-19 treatment without entry criteria that are specific baseline immune markers.

For example, the inflammatory response - the cytokine storm - in progressing COVID-19 has been compared to conditions that include classical acute respiratory distress syndrome (ARDS), macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH), but that is likely different to all of these.

The paper describes current understanding of immune responses to COVID-19 and highlights a range of therapeutic responses that might help, although with a caution that treating these symptoms might still not improve clinical responses. For example, prostaglandin E1, ketoconazole and GM-CSF have not been effective with ARDS (in studies that did not individualise immune profiles of participants).

The paper suggests that drugs like tocilizumab or anakinra might only be appropriate in a subset of patients with the most severe elevations in systemic pro-inflammatory cytokines (e.g. IL-6 levels > 1,000 pg/mL).

It also suggests that treatment should be guided by real-time changes in the immunophenotype and using short-acting drugs so that protocols can adapt to the dynamic nature of immune response over time.

The paper concludes that management of immune modulation in COVID-19 has wide inter-patient variability and should adapt to the dynamic nature of the individual pathogenesis and related immune response.

References

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Further positive reports using tocilizumab to treat COVID-19

Simon Collins, HIV i-Base

Two new publications provide additional reports of positive outcomes from using the anti-IL-6 monoclonal antibody tocilizumab to treat COVID-19.

The largest of these is a retrospective analysis of 544 patients hospitalised with severe COVID-19. Results were reported by Giovanni Guaraldi from University of Modena on 24 June in Lancet Rheumatology. [1]

Median age was 67 years (IQR: 56 to 77) and 359 (66%) men, with more severe baseline characteristics in participants who received tocilizumab.

Overall, 179/544 participants received open-label tocilizumab and 365/544 received standard of care. Of these, a similar percentage progressed to need mechanical ventilation: 57 (16%) vs 33 (18%), p=0.41, for the Soc and tocilizumab groups respectively. These results were similar for both intravenous (n=88) and subcutaneous (n=91) formulations of tocilizumab.

However, mortality was significantly higher in people just receiving SoC: 73 (20%) vs 13 (7%) in Soc vs tocilizumab, p<0·0001).

In multivariate analysis, adjusting for sex, age, recruiting centre, duration of symptoms, and SOFA score, tocilizumab was associated with a significantly reduced risk of invasive mechanical ventilation or death (adj. HR 0·61, 95% CI: 0.40 to 0.92; p=0·020).

Tocilizumab was also associated with significantly fewer new infections: 24/179 (13%) vs 14/365 (4%), p<0·0001).

The second report was from an observational US cohort of 27 people hospitalised with SARS-CoV-2 pneumonia who received tocilizumab. Median age was 63 years (IQR: 51 to 75 years) and 23/27 were men. Seventeen patients (63%) had a significant comorbidity, including hypertension in 12/17. [2]

Participants received a 400 mg intravenous dose of tocilizumab as part of a compassionate access programme at a single site in Los Angeles. Participants also received hydroxychloroquine and azithromycin, with 7/27 on blinded placebo-controlled remdesivir study.

At baseline, all participants were already receiving oxygen support with oxygen levels <90%, with most (21/27) on mechanical intubation. All showed IL-6 as the predominant cytokine.

Although tocilizumab was associated with significant rapid reductions in temperature and CRP, 4/27 showed no response, and 3/4 progressed with poorer outcomes. The paper discussed whether the non-responses might have been different with higher dosing.

Two deaths, at days 3 and 11, were not judged to be linked to tocilizumab.

The report concluded that these results were significantly better than historical reports with hypothetical mechanism for reducing elevated IL-6 that is associated with severe COVID-19 and poor prognosis.

C O M M E N T S

Although small retrospective analyses, these results add to the a growing number of studies that have reported potentially positive results with tocilizumab. Four earlier studies were reviewed in a recent earlier issue of HIV and COVID-19. [3]

Many other prospective studies are already ongoing, including the large UK RECOVERY study, using a randomised design. [4]

Based on limited success with all approaches based on monotherapy, combination approaches should be prioritised, with at least one study looking at tocilizumab plus remdesivir. [5]

References

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COVID-19: EPIDEMIOLOGY

Higher mortality from COVID-19 outcomes in London study in Asian or Black compared to white participants

Simon Collins, HIV i-Base

Research from five leading acute London hospitals in east London, part of the largest NHS Trust, reports significantly worse outcomes from COVID-19 in people from Black, Asian and minority ethnic (BAME) backgrounds.

The paper, by Vanessa Apea and colleagues reports from a prospective observational majority ethnic diverse (60%) cohort of almost 2000 admission records of confirmed SARS CoV-2 in adults (>16 years). The results are published online, but ahead of peer review. [1]

After excluding 259 records due to lack of ethnicity data, the study included 1737 participants from January to May 2020, 511 of whom had died by day 30 (29%). Overall, 538/1739 (31%) were from Asian, 340 (20%) Black, 156 (7·8%) other and 707 (40%) white backgrounds.

BAME participants were younger (median 64 years for Black and 59 for Asian vs 73 white, p<0.001)) and were less frail with different comorbidity profiles (available for 85%). Being Black or Asian was significantly associated with admission to intensive care and receiving invasive ventilation (OR 1.54; 95% CI: 1.06 to 2.23], p=0.023 and 1.80; 95%CI: 1.20

to 2.71], p=0.005, respectively). Admission to ICU occurred for 20%, 18% and 11% for Asian, Black and white participants, respectively (p<0.001) although there were no significant differences in use of mechanical ventilation or length of stay in ICU (median 8 to 9 days).

Although a larger proportion of white participants died (33%) overall, after adjusting for age and race, the primary endpoint of mortality by day 30 was significantly higher in Asian (hazard ratio: 1.49; 95%CI: 1.19 to 1.86, p<0.001) and Black (HR: 1.30; 95%CI: 1.02 to 1.63, p=0.036) participants.

After further adjusting for other factors associated with clinical outcomes (including comorbidities, BMI and smoking) the link with mortality persisted in Asian (HR 1.48, CI 1.09 to 2.01, p=0.011) but not in Black (HR 1.32; 95%CI: 0.96 to 1.84, p=0·090) participants. However, in sensitivity analyses, the associated with mortality remained for both these groups.

After admission to ICU, being Black and Asian was linked to short time before death compared to white participants: median 6 days (IQR: 3 to 12) and 5 (IQR: 3 to 11) vs 9 (IQR: 4 to 16) respectively, p<0.001.

Also important, acute kidney injury within seven days of admission was highest in Black (35%) participants (vs Asian (22%) and white (24%), p=0.003), who also had higher levels of inflammation (measured by CRP and D-dimer) compared to other ethnicities.

C O M M E N T

The significant links between race and increased mortality from COVID-19, even after adjusting for comorbidities and socioeconomic factors urgently need further research.

This is likely be a combination of medical, biological and other behavioural/social factors, which are also likely linked to structural ways that related to accessing healthcare in the UK.

The paper itself concludes that the relative contribution of different factors is currently unclear, but.

Although AIDS was reported as an infrequent comorbidity in five (1.7%) Black and one (0.2%) white participants, it is unclear whether this referred to HIV status or advanced HIV (ie CD4 <200 cells/mm^3).

A recent US study also highlighted the disproportionate impact of race in a cohort of 47 HIV positive people with confirmed (n=36) or probable (n=11) COVID-19. Comorbidities were common (85%) but 77% of the COVID-19 cohort were Black and Latinx compared to 40% of the HIV clinic overall. [2]

References
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COVID 19: PATHOGENESIS

UK study reports antibody responses linked to more severe COVID-19 in higher risk populations

Simon Collins, HIV i-Base

UK longitudinal study reports seroconversion dynamics by Ig ELISA from 845 samples from 177 adults previously diagnosed with SARS-CoV-2 by RT PCR.

Baseline characteristics included 34% white, 35% non-white, median (IQR) age 64 years (IQR: 52 to 77), 57% male, and 73% had one or more co-morbidities; 19% were defined as asymptomatic with no respiratory symptoms on admission.

Seroconversion was associated with older age, more comorbidities)especially hypertension and higher BMI), non-white race and higher inflammatory markers (CRP), but 8.5% of participants showed no evidence of seroconversion even weeks after infection.

Antibody responses were maintained for more than two months.

Overall, 25% (44/177) died after median (IQR) 19.1 days (14.8 to 24.8).

The paper concluded that longer studies are needed to find out the duration of humoral responses that contribute to protection against future SARS-CoV-2 exposures.

Reference

Staines HM et al. Dynamics of IgG seroconversion and pathophysiology of COVID-19 infections. MedRxiv. Pre-peer review paper. DOI: 10.1101/2020.06.07.20124636. (8 June 2020).

https://www.medrxiv.org/content/10.1101/2020.06.07.20124636v2

COVID-19: DIAGNOSTICS

Leading SARS-CoV-2 antibody tests meet specificity but fail current sensitivity guidelines

Simon Collins, HIV i-Base

A 30-page report from Public Health England (PHE) found that four leading SARS-CoV-2 antibody tests – from Abbott, DiaSorin, Roche, and Siemens – all met criteria for specificity, but that only the Siemens test also met requirements for sensitivity.

The study by independent researchers at the University of Oxford and Oxford University Hospitals NHS Foundation Trust was commissioned by the Department of Health and Social Care (DHSC).

Sensitivity was tested on 536 positive samples from adults with laboratory-confirmed SARS-CoV-2 infection at >20 days post-symptom onset. Specificity was tested on 994 pre-pandemic (2015-2018) specimens from unique, healthy adults.

Primary results are shown in Table 1.

In order for all four tests to meet sensitivity criteria, specificity thresholds needed to be optimized to >98% and the sample timeframe extended to >30 days post-symptom onset.

Table 1: Sensitivity and specificity of four commercial SARS-CoV-2 antibody tests

Assay	Sensitivity [95% CI]	Specificity [95% CI]	Appraisal against MHRA target product profile (TPP)
Abbott	92.7 (90.2, 94.8)	99.9 (99.4, 100)	Meets specificity criterion
DiaSorin	95.0 (92.8, 96.7)	98.6 (97.6, 99.2)	Meets specificity criterion
Roche	97.2 (95.4, 98.4)	99.8 (99.3, 100)	Meets specificity criterion
Siemens	98.1 (96.6, 99.1)	99.9 (99.4, 100)	Meets sensitivity and specificity criteria

Reference

PHE. Evaluation of sensitivity and specificity of four commercially available SARS-CoV-2 antibody immunoassays. (July 2020).

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/898437/Evaluation__of_sensitivity_and_specificity_of_4_commercially_available_SARS-CoV-2_antibody_immunoassays.pdf (PDF)

COVID-19: TRANSMISSION

Infectious SARS-CoV-2 in air and on surfaces in London hospitals

Simon Collins, HIV i-Base

A prospective cross-sectional observational study collected both air samples and swabs from multiple hospital sites occupied by people hospitalised with COVID-19 as well as general areas of a London hospital.

The results were reported by Jie Zhoi and colleagues from Imperial College London and reported on 8 July 2020 in Clinical Infectious Diseases.

Surfaces included bed rails, clinical monitoring devices (blood pressure monitors), ward telephones, computer keyboards, clinical equipment (syringe pumps, urinary catheters), hand-cleaning facilities (hand washing basins and alcohol gel dispensers), with air sampled in immediate vicinity.

All areas were disinfected daily with an additional twice daily disinfection of high touch surfaces using a combined chlorine-based detergent/disinfectant.

Between 2 - 20 April 2020, during the peak of the epidemic, viral RNA was detected on 114/218 (52.3%) of surfaces and 14/31 (38.7%) air samples. However, no virus was cultured, likely due to lower concentrations (all corresponding to an E gene copy number of $<10^5$ per mL.

Samples were more likely to be positive in COVID-19 wards than other areas (67/105 (63.8%) vs. 29/64 (45.3%); OR 0.5, 95% CI: 0.2 to 0.9, p=0.025.

These results supported the need for effective use of PPE, physical distancing, and hand/surface hygiene.

Reference

Zhou J et al. Investigating SARS-CoV-2 surface and air contamination in an acute healthcare setting during the peak of the COVID-19 pandemic in London. Clinical Infectious Diseases, ciaa905, DOI: 10.1093/cid/ciaa905. (08 July 2020).

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US prisoners have higher mortality rates from COVID-19

Simon Collins, HIV i-Base

A research letter to JAMA has reported that US prisoners in federal and state prisons had higher adjusted risks of COVID-19-related mortality compared to the general US population.

By 6 June 2020, there had been 42,107 cases of COVID-19 and 510 deaths among 1,295,285 prisoners with a case rate of 3,251 per 100,000 prisoners.

Crude COVID-19 death rates were 39 vs 29 deaths per 100,000 in prisoners vs general population respectively.

After adjusting for lower age in prisoners, the death rate in the prison population was 3.0 times higher than the US general population.

Reference

Saloner B et al. COVID-19 Cases and Deaths in Federal and State Prisons. JAMA, research letter. DOI:10.1001/jama.2020.12528. (8 July 2020).

https://jamanetwork.com/journals/jama/fullarticle/2768249

US epidemic could see 100,000 cases per day: NIAID head Anthony Fauci to Senate hearing

Simon Collins, HIV i-Base

On 20 June 2020, mainstream news reported that NIAID director Anthony Fauci had given evidence to the US Senate hearing that daily cases in the US could reach 100,000 cases daily.

This is important for the leading scientific and medical advisor predicting significantly worse US outcomes than presidential statements.

Since then, daily cases have consistently continued to rise during the first two weeks of July.

Fauci guaranteed it would be very disturbing "because when you have an outbreak in one part of the country, even though in other parts of the country they're doing well, they are vulnerable."

Reference

Segers G. Fauci warns U.S. could see 100,000 new coronavirus cases per day. CBS news, (30 June 2020).

https://www.cbsnews.com/news/fauci-coronavirus-united-states-100000-new-cases-per-day

COVID-19: RESEARCH

Research issues and COVID-19

Simon Collins, HIV i-Base

As if you didn't already have enought to read.... The following four papers highlighting different issues related to research during COVID-19.

COVID-19 clinical trials: a teachable moment for improving our research infrastructure and relevance

A paper looking at issues related to trials design for compounds to treat COVID-19

Kimmel SE et al. Annals of Internal Medicine. DOI: 10.7326/M20-2959. (16 Jun 2020).
https://www.acpjournals.org/doi/10.7326/M20-2959

Proposing minimum requirements for announcing clinical trial results during the COVID-19 pandemic

This paper proposes minimal information that should be routinely included when researchers announce study results by press releases. This undemines the value of their research and restricts information needed to inform both standard of care and other ongoing research.

Siedner MJ et al. Clinical Infectious Diseases, ciaa945, DOI: 10.1093/cid/ciaa945. (8 July 2020).
https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa945/5868929

Paying participants in COVID-19 trials

A paper on ethical issues related to paying participants in COVID-19 studies.

Largent EA et al. Journal of Infectious Diseases, Volume 222, Issue 3, 1 August 2020, Pages 356–361, DOI:10.1093/infdis/jiaa284 (29 May 2020).
https://academic.oup.com/jid/article/222/3/356/5848446

Overcoming challenges in COVID-19 translational research

An paper on researcher collaborations on establishing a biobank and practical issues for obtimising use of future samples.

Li JZ et al. Journal of Infectious Diseases, jiaa397, DOI: 10.1093/infdis/jiaa397. (7 July 2020).
https://academic.oup.com/jid/article/doi/10.1093/infdis/jiaa397/5868463

COVID-19: VACCINE RESEARCH

Vaccine candidates report phase 3 studies after early safety and immune responses in phase 1/2 studies

Simon Collins, HIV i-Base

As this issue of HTB was being compiled, three research groups released data that will launch large phase 3 studies.

The first of these involved the Moderna mRNA-1273 vaccine, with phase 1 interim results published in the NEJM and first patients expected to enrol 30,000 participants in the US in a phase 3 study from 27 July 2020. [1, 2, 3]

The Lancet also published the first results on two other vaccine studies using an adenoviral vector. These studies reported good safety (fever, fatigue, and injection site pain) but no seriosus events. Both vaccines also generated both humoral responses to the spike glycoprotein receptor and cellular T-cell responses.

The phase 1/2 trial of the chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) being developed by the Jenner Institute at Oxford University and AstraZeneca (Oxford COVID Vaccine Trial Group) included 1077 volunteers. Neutralising antibodies were generated in more than 90% of participants that lasted out to 56 days. [4]

The phase 2 vaccine study developed by researchers in Wuhan, China with support from CanSino Biologics involved 508 participants. Seroconversion occurred in more than 96% of participants, and neutralising antibodies were generated in about 85%. More than 90% generated T-cell responses. [5]

The Lancet included a useful editorial commentary discussing short-term expectations for upcoming phase 3 research. [6]

A useful article in JAMA also summaries different approaches for five leading COVID-19 candiates. [7]

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FDA guidance on COVID-19 vaccine includes minimal target of 50% efficacy

Simon Collins, HIV i-Base

In June 2020 the US FDA published guidelines for manufactures working on producing a vaccine against COVID-19.

The 20-page document includes guidelines for investigating, testing and manufacturing, including appropriate populations for different stages of development. The document references the importance of racial diversity, use in children and during pregnancy.

Approval will need to be based on direct evidence of safety and efficacy in protection against SAR-CoV-2 and/or clinical disease.

Phase 3 placebo-controlled studies need to show at least 50% effective for the primary efficacy endpoint point of protection.

Safety data needs to be provided for at least 3000 participants but post-licensing pharmacovigilance data is also expected. Details on the duration of protection are not discussed.

Reference

US FDA. Development and Licensure of Vaccines to Prevent COVID-19. (June 2020).

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

https://www.fda.gov/media/139638/download

COVID-19: FUTURE MEETINGS

The following listing covers selected upcoming HIV-related meetings and workshops. Registration details, including for community and community press are included on the relevant websites.

Due to the new coronavirus health crisis, most meetings are either being cancelled or rescheduled (ie BHIVA, INTEREST, IAS AIDS 2020 and PK and paediatrics workshops).

New dates for workshops organised by Virology Education are at this link:

https://www.virology-education.com/covid0-19-update/

Community Reclaiming the Global Response (HIV 2020)

NOW VIRTUAL. (Was 5-7 July, Mexico City).

Now reprogrammed as a series of 2-hour zoom sessions between July and October 2020.

https://www.hiv2020.org/program (summary)

https://www.hiv2020.org/post/the-program-for-hiv2020-online-is-now-available

23rd International Workshop on Co-morbidities and Adverse Drug Reactions in HIV (2020)

NOW VIRTUAL.

12 – 13 September 2020, New York

https://www.intmedpress.com/comorbidities/default.cfm?itemtypeid=1&title=The%20Workshop

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

28 – 30 September, New York (rescheduled from May)

www.virology-education.com

11th International Workshop on HIV & Ageing (2020)

NOW VIRTUAL.

1 – 2 October 2020, NYC

https://www.virology-education.com

HIV Glasgow Congress 2020

NOW VIRTUAL

5 – 8 October 2020, Glasgow

www.hivglasgow.org

International Workshop on HIV Paediatrics 2020

16 – 17 November 2020, San Francisco, USA.

www.virology-education.com

26th Annual BHIVA Conference (BHIVA 2020)

22–24 November 2020, Harrogate (rescheduled from April)

www.bhiva.org

International Conference on HIV Treatment, Pathogenesis, and Prevention Research in Resource-Limited Settings (INTEREST) 2020

1 – 4 December, Windhoek, Namibia (rescheduled from May)

https://virology.eventsair.com/interest-2020/registration/Site/Register

HIV Research for Prevention (HIV R4P 2020)

17 – 21 January 2021, Cape Town (from October 2020)

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 (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)

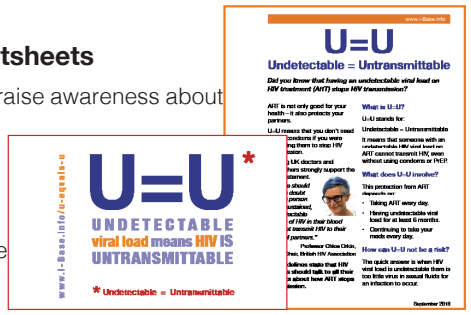
Pocket guides

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.

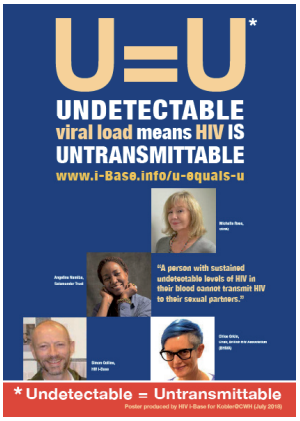
This project was developed with the Kobler Centre in London.

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.

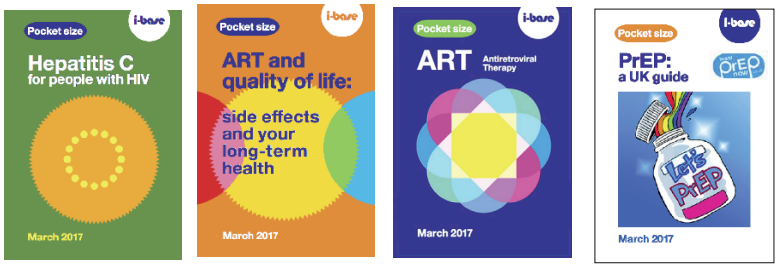
Personalising these for your clinic is cheap and easy and might be an especially nice way to highlight the good news.

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.

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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☐ I would like to make a donation to i-Base - *Please see inside back page*

- **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