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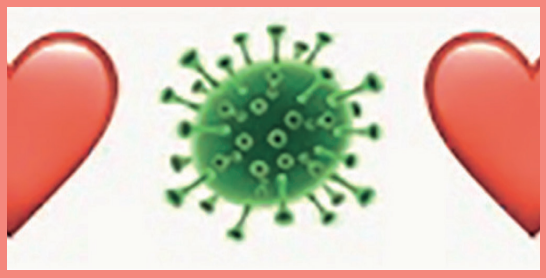
hiv treatment bulletin (e)



Second reports from CROI 2021 (1 April 2021)

CONTENTS

Contents continued inside...

Published by HIV i-Base

HTB no.4 (2021): HIV and COVID-19 supplement ISSUE 4

i-Base 2021 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.

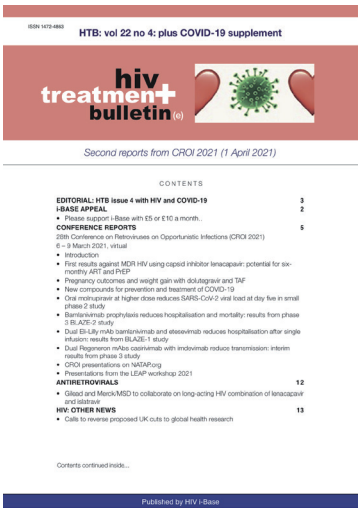
http://i-base.info/i-base-appeal-we-need-your-help

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 :)

EDITORIAL

This issue of HTB includes a second set of reports from CROI 2021, on new treatment for HIV and for COVID-19.



The COVID-19 supplement includes two new annoucnements from BHIVA:

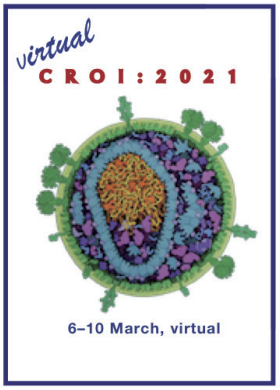
(i) COVID-19 vaccine guidelines are now online for comment.

(ii) An update on accessing vaccinations from UK HIV clinics.

Other HIV news includes the collaboration between Gilead and Merck/MSD that should enable quicker development of long-acting ART than has the potential for only needing six-monthly dosing.

We also link to the UK issues of cancelled funding for reasearch supporting global health.

Open access CROI - and the importance of supporting virtual meetings



Continued delegate registration is an important issue for virtual medical conferences in general. These events rely on registration fees, which for some meetings are now lower compared to in-person events.

Virtual meetings are also less expensive for us to attend (with no travel and accommodation costs), so supporting the events with registration is a community response that involves us all. Also in recognising that advances in HIV care have for many years been driven more by conference news than peer-review publications, or even guidelines.

Virtual meetings are not a way to by-pass registration to get free data. They are an evolving development from the COVID crisis and they need to be supported to ensure continued access to the latest developments in a trusted setting.

We strongly encourage readers to actively support these meetings, including for the upcoming BHIVA spring conference being held as a virtual meeting form 19 to 21 April 2021.

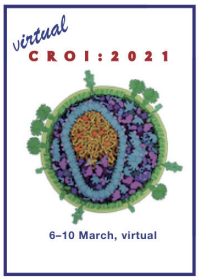
https://www.bhiva.org/AnnualConference2021

The recent virtual Best of CROI 2021 meeting organised by BHIVA focussed on the most important presentations related to clinical care. These will also be posted as open-access talk to the BHIVA website next week.

28th Conference on Retroviruses on Opportunistic Infections (CROI 2021)

6 – 9 March 2021, virtual

Introduction



This second HTB reports from virtual CROI 2021 include additional good news that from 15 April 2021 the conference will become open access.

i-Base would like to thank the organisers for this decision.

Initially, concerns about funding the conference meant the organisers were planning to keep most of the content behind a pay wall for six months. This would have included abstracts, webcasts and posters.

A community sign-on letter during the first days of the conference included wide support and was successful in having the abstract book posted online. The organising committee have now also reversed their initial plans and agreed that the rest of the rest of the programme, including webcasts, will also now become open access (from 15 April).

CROI 2021 conference materials

https://www.croiconference.org/access-to-croi-2021-conference-materials

The virtual conference was run on a separate website, contents are steadily being transferred to the standard CROI website. Abstracts from the 2021 meeting are already included in this main database.

https://www.croiconference.org

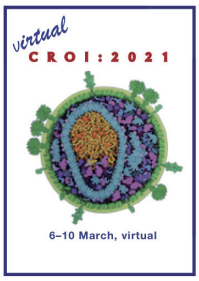
Report in this issue include:

- First results using capsid inhibitor lenacapavir against MDR HIV: potential for six-monthly ART and PrEP
- Pregnancy outcomes and weight gain with dolutegravir and TAF
- New compounds for prevention and treatment of COVID-19
- Oral molnupiravir at higher dose reduces SARS-CoV-2 viral load at day five in small phase 2 study
- Bamlanivimab prophylaxis reduces hospitalisation and mortality: results from phase 3 BLAZE-2 study
- Dual Eli-Lilly mAb bamlanivimab and etesevimab reduces hospitalisation after single infusion: results from BLAZE-1 study
- Dual Regeneron mAbs casirivimab with imdevimab reduce transmission: interim results from phase 3 study
- CROI presentations on NATAP.org
- Presentations from the LEAP workshop 2021

CROI 2021: ANTIRETROVIRALS

First results using capsid inhibitor lenacapavir against MDR HIV: potential for six-monthly ART and PrEP

Simon Collins, HIV i-Base



Several studies at CROI 2021 expanded on the profile of the experimental long-acting capsid inhibitor lenacapavir that has an oral formulation for weekly dosing and a subcutaneous injection for 6-monthly dosing. This included the first clinical results in people with multidrug resistant HIV.

Thomas Cihlar presented an overview of capsid inhibition and the potential benefits as a drug target, covering the mechanism of action, pharmacokinetics (PK) and drug resistance. [1]

This included the history of this class and the 15-year development, with discovery of lenacapavir (previously GS-6207) from more than 3000 potential compounds, and with –2.3 log reductions in viral load in treatment-naïve participants in a phase 2b study presented at CROI last year.

Lenacapavir is active at multiple stages of the viral life cycle, including early uncoating (where it is most potent) but also later during core assembly and maturation phases. It has higher potency than other small molecule HIV drugs with activity in a picomolar range (mean EC50 0.05 nM: range 0.02 to 0.15) and in many cell types. As a drug in a new class, it remains sensitive to drug resistant HIV from all other classes. The binding site is conserved across all HIV-1 sub-types and slow metabolic clearance with single subcutaneous injection at doses of 30 mg to 450 mg produces systemic exposure for >6 months.

Significant drug resistant mutations during in vitro passaging include M66I, N74D (after 20 days) with Q67H mutation after 80 days. Further details on the drug resistant profile were presented in two other presentations at the meeting. [2, 3]

Importantly, CROI 2021 included clinical results were from a phase 2/3 study (CAPELLA) in 36 participants with multidrug resistant (to at least three classes) who had detectable viral load (>400 copies/mL) on their current ART. [4]

Participants were randomised (2:1) to add lenacapavir or placebo to current ART for 14 days before switching to an optimised background regimen (OBR) for a further 52 weeks. Entry criteria included having two or fewer sensitive drugs for the OBR.

A second cohort of 36 participants were enrolled in a non-randomised arm using open-label lenacapavir with OBR from day 1.

Baseline characteristics included median age 52 years (range 23 to 78), 25% were female at birth, and race included 38% black. Median CD4 was 150 cells/mm^3 (range 3 to 1300) with 64% <200 cells/mm^3. Median baseline viral load was 4.5 copies/mL (range 1.3 to 5.7) with 28% >75,000 copies/mL. Participants had considerable drug experience with median of 11 previous ARVs and median 24 years since HIV diagnosis.

At day 15, the primary endpoint of >0.5 log reduction in viral load was reported in 88% vs 17% of the active vs placebo groups respectively (difference: 71%, 95% CI 35 to 90%, p<0.0001). The median (range) change in viral load was –2.0 log copies/mL (range: –3.29 to –0.29) vs –0.08 (–1.93 to +0.31) in the active vs placebo groups. At week 4 (2 weeks after OBR), 58% (21/36) were undetectable (<50 copies/mL).

During median duration of follow up on lenacapavir of 26 weeks (range: 7 to 46), capsid mutations were detected in 2/72 participants. One reported M66I and N74D at week 10 when viral load was approximately 3000 copies/mL. This person had no fully active drugs in the OBR (maraviroc, T-20, DTG twice daily, DRV/COBI and 3TC) but resuppressed after changing the OBR. A second case detected M66I at 26 weeks when viral load was around 500 copies/mL. In this case viral load resuppressed without change to the OBR (F/TAF; with DRV/COBI and DTG twice daily).

There were no serious adverse events related to study drug, related discontinuations, or deaths. The most frequent side effects (any grade) were injection site swelling (28%) and nodule (25%). Injection site reactions (50%) were all mild or moderate.

These are impressive preliminary results and further follow-up will be reported later.

Several other studies looked at drug interactions and dosing.

Jordan Lutz et al. reported results from a PK drug interaction study on potential interaction between lenacapavir and strong inducers/inhibitors of P-gp, CYP3A and UGT1A1 or on sensitive P-gp, BCRP, OATP and CYP3A substrates. [5]

Consistent with in vitro studies, significant interactions were reported with strong UGT1A1 inhibitors and potent inducers of P-gp/UGT which should be avoided. Lenacapavir is a moderate inhibitor of CYP3A, and a weak inhibitor of P-gp and BCRP.

Results from a PK study in 10 participants with moderate hepatic impairment reported lenacapavir AUC and Cmax that were 1.5 and 2.6 fold higher than HIV negative controls. This was not judged clinically significant or needing a dose adjustment. [6]

Finally, results from a macaque study using lenacpavir as PrEP were also presented in at CROI 2021. Following a single long-acting injection and escalating weekly rectal challenge, breakthrough infections were detected in 3/8 animals after week 15, when all placebo animals had become infected (p=0.0002). Although drug levels at this timepoint dropped below the EC95 these were 6-fold lower than seen with equivalent human formulation, suggesting that in vivo protection could be higher and for longer. [7]

Two large international phase 3 PrEP studies are planned to enroll later in 2021, using six-monthly lenacapavir injections and using either TDF/FTC or TAF/FTC as active controls.

As part of the treatment programme, a phase 2 study in HIV naïve participants (CALIBRATE) is fully enrolled with results expected later this year. [8]

C O M M E N T

These results highlight a remarkable drug profile and shortly after CROI 2021. Gilead announced in a joint statement with Merck/MSD that lenacapavir will be developed in combination with islatravir. [9]

Reducing ART to a six-monthly treatment without needing daily pills but maintaining undetectable viral load might for many people "feel" like a significant step to a cure.

Also, of interest for the role of capsid in the viral life cycle, a plenary lecture at CROI 2021 included electromicroscopy videos showing that rather than early uncoating early after entry into the CD4 cell, the capsid instead enters the cell nucleus intact and that reverse transcriptase converts viral RNA to DNA as a late stage in the nucleus. [10]

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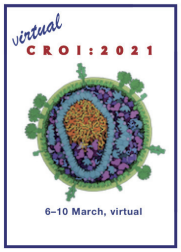
Pregnancy outcomes and weight gain with dolutegravir and TAF

Polly Clayden, HIV i-Base



Dolutegravir (DTG) and tenofovir alafenamide (TAF) have been linked to excessive weight gain. Both low and high weight gain during pregnancy have been associated with adverse outcomes. Three studies, presented at CROI 2021 looked at these associations.

- A secondary analysis from VESTED found low (but not high) antepartum weight gain was associated with adverse pregnancy outcomes. Women starting DTG + emtricitabine (FTC)/TAF in pregnancy gained more weight than women starting DTG + FTC/tenofovir disoproxil fumarate (TDF) or efavirenz (EFV)/FTC/TDF. Women starting EFV/FTC/TDF had the lowest weight gain. [1]
- Data from the Tsepamo birth outcomes surveillance study showed gestational weight gain to have weaker associations with adverse outcomes than baseline weight among women on ART at conception. Time on pre-pregnancy ART was associated with higher baseline pregnancy weight for DTG but not for EFV. The risk of maternal hypertension by baseline weight was higher for DTG than EFV. [2]
- Using data from ADVANCE, modelling predicted 18 additional adverse outcomes for every 100 women becoming pregnant after three years of TAF/FTC + DTG. [3]

VESTED study

VESTED (IMPAACT 2010) evaluated three ART regimens started in pregnancy. (Primary results were presented last year at CROI 2020 and 50 week postpartum results were also presented at CROI 2021). [4, 5]

Women with HIV in nine countries were randomised 1:1:1 at 14–28 weeks gestational age (GA) to start DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF. All women were followed up for 12–26 weeks antepartum and 50 weeks postpartum. There was significantly lower rate of adverse pregnancy outcomes in the DTG + FTC/TAF arm at 14 days follow up postpartum.

This secondary analysis focused on antepartum weight gain and evaluated associations between weight and adverse pregnancy outcomes. Low weight gain was defined as less than 0.18 kg/week and high weight gain as at least 0.59 kg/week.

Six hundred and forty three women were randomised: 217 to DTG + FTC/TAF, 215 to DTG + FTC/TDF and 211 to EFV/FTC/TDF arms. At baseline, maternal medians were: age 26. 6 years; GA 21.9 weeks; viral load 903 copies/mL; and CD4 count 466 cells/mm3. Mean enrollment weight was 66.2 kg.

Antepartum weight data were available for 632 (98.3%) women and median duration of antepartum follow up was 17.4 weeks.

Weekly average weight gain was highest with DTG + FTC/TAF (0.378 kg) vs DTG + FTC/TDF (0.319 kg, p=0.011) vs EFV/FTC/TDF (0.291 kg, p<0.001). Notably the recommended maternal weight gain for second/third trimesters is 0.42 kg/week – so none of the arms reached this.

Low weight gain was least common with DTG + FTC/TAF (15.0%) vs DTG + FTC/TDF (23.6%) vs EFV/FTC/TDF (30.0%). The opposite was true for high weight gain: DTG + FTC/TAF (12.7%) vs DTG + FTC/TDF (9.9%) vs EFV/FTC/TDF (6.3%).

Low weight gain was associated with higher risk of any adverse pregnancy outcome and slightly higher but not significant risk of SGA: HR 1.4 (95% CI 1.02 to 1.96), p=0.037 and HR 1.5 (95% CI 0.99 to 2.22), p=0.054, respectively. There was no interaction by treatment arm.

Across all treatment arms there was a significant association between higher average weekly weight gain and a lower risk of any adverse pregnancy outcome: HR 0.5 (95% CI 0.25 to 0.97), p=0.04.

And overall low weight gain appeared to be associated with higher risk of stillbirth and preterm delivery compared with normal weight gain. The investigators noted that these data should be interpreted with caution as the numbers in the subgroups are quite small.

Tsepamo study

Tsepamo is a birth outcomes surveillance study in Botswana – it is the largest dataset of DTG exposure in pregnancy. [6]

The purpose of this analysis was to better understand the implications of ART-associated weight gain using Tsepamo data to define the associations between baseline maternal weight and weight gain on adverse pregnancy outcomes (very preterm, very small for gestational age, perinatal death, macrosomia and maternal hypertension) among women receiving ART from conception.

Of 22,828 women on ART at conception with singleton deliveries between August 2014 and April 2020, 16,300 (71%) had a documented weight measured at <24 weeks gestation (baseline weight) and 4437 (19%) had documented weight measured both at 12 (+/-2) weeks and 24 (+/-2) weeks.

Of 16,300 women, median baseline weight was 60.3 kg: 13% with low weight (<50 kg) and 7% high weight. Among the 4437 women, median gestational weight gain was 0.33 kg/week: 21% had low weight gain (<0.15 kg/week) and 15% high weight gain (>0.55 kg/week).

There were no substantial differences between low, high and average gestational weight gain categories and adverse pregnancy outcomes except for high weight gain and increased risk of macrosomia (birthweight >4000 g): aRR 2.01 (95% CI 1.8 to 2.32).

In contrast, compared to women with baseline weight 60–70 kg, low baseline weight was associated with any severe birth outcomes: aRR 1.63 (95% CI 1.45 to 1.83). Specifically low baseline weight was associated with increased risk of very preterm delivery and very small for gestational age: aRR 1.30 (95% CI 1.03 to 1.65) and aRR 1.96 (95% CI 1.69 to 2.28), respectively.

High baseline weight was associated with increased risk of macrosomia and maternal hypertension: aRR 3.24 (95% CI 2.36 to 4.44) and aRR 1.79 (95% CI 1.62,1.97), respectively. Baseline weight was not associated with perinatal death.

Baseline weight was similar for women on DTG vs EFV: 62.9 kg vs 62.3 kg, respectively. This differed by length of time on ART before conception for DTG (62.5 kg <1 year, 63.3 kg 1–2 years and 64.4 kg 2–3 years, p=0.11) but not EFV.

The investigators noted that maternal hypertension was higher among women on DTG compared with EFV across all baseline weight categories and in adjusted analyses, ART regimen was a significant effect modifier (p<0.001) for the relationship between baseline weight and this outcome.

ADVANCE stucy

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 96 results, as well as an earlier version of this pregnancy outcomes analysis, were presented at AIDS 2020. [7, 8].

This study predicted long-term risks of adverse outcomes in pregnancy and child health from treatment-associated clinical obesity among pregnant women, using data from the ADVANCE trial.

After 144 weeks of treatment in the ADVANCE trial, the percentage of women with normal baseline BMI becoming clinically obese was 19% for TAF/ FTC + DTG, 5% for TDF/FTC + DTG, and 0% for TDF/FTC/EFV.

From baseline to week 144, the predicted increase of adverse maternal outcomes was 15% with TAF/ FTC + DTG vs 4% with TDF/FTC + DTG. Risk predictions for adverse infant outcomes were 12% and 3% in these two groups, respectively.

The predicted risk of adverse outcomes in child health was 28% and 7% for TAF/FTC + DTG and TDF/FTC + DTG, respectively. No additional adverse events were predicted for pregnant women treated with TDF/FTC/EFV.

This model predicted that for every 100 women becoming pregnant after three years of TAF/FTC + DTG treatment, there would be 18 additional adverse outcomes.

The authors suggested that new stopping rules may be required to switch women off TAF/FTC + DTG and similar combination treatments, to lessen these risks.

C O M M E N T

Tsepamo investigators noted that ART-associated weight gain with newer antiretrovirals may have both a positive and negative impact on maternal and child health depending on the mother's weight at the start of pregnancy.

Tsepamo only looked at DTG-based ART with TDF so the greater weight gain in ADVANCE and VESTED with TAF and DTG-based ART was not evaluated.

In VESTED all women started ART in pre-pregnancy and the data did not include pre-pregnancy weight.

ADVANCE pregnancy outcomes were modelled compared with clinical data in VESTED and Tsepamo.

All groups plan further analyses – for VESTED this will include postpartum weight through 50 weeks.

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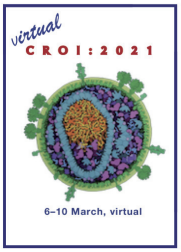
CROI 2021: COVID-19

New compounds for prevention and treatment of COVID-19

Simon Collins, HIV i-Base



CROI 2021 included important results from experimental treatments that reported positive results from early interventions, especially using monoclonal antibodies.

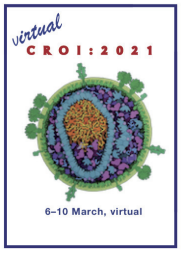
It is significant that the first presentations of much of this data was at an HIV conference.

Four short reports are included below.

- Molnupiravir significantly reduced SARS-CoV-2 viral load after five days in early infection
- Bamlanivimab works as prophylaxis in high risk populations
- Bamlanivimab and etesevimab (Eli-Lilly) reduced hospitalisation and mortality in mild/moderate infection
- Casirivimab and imdevimab (Regeneron) dual mAbs reduce risk of symptomatic transmission

Oral molnupiravir at higher dose reduces SARS-CoV-2 viral load at day five in small phase 2 study

Simon Collins, HIV i-Base



Results from a double-blind, randomised, placebo-controlled, phase 2 dose-range finding study reported faster viral load clearance after five days using oral molnupiravir at the highest dose. [1]

Entry criteria included symptoms of COVID-19 confirmed by PCR and molnupivavir was dosed at 200, 400, or 800 mg twice-daily for five days.

Of 78 participants with positive PCR at baseline (n=52 active, n=26 placebo), 20% vs 28% (p=0.56) and 24% vs 0% (p=-.001) remained positive at day 3 and day 5 respectively.

Several larger phase 2/3 studies are already ongoing.

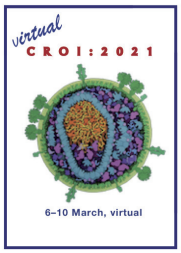
Two questions in the online chat (from Jean-Michel Molina) ask about why the difference is only seen by day 5, and whether the company are also planning to study use as prophylaxis. Neither have been answered yet.

Reference

1. Painter WP et al. Reduction in infectious SARS-CoV-2 in treatment study of COVID-19 with molnupiravir. Poster abstract 777.
https://ww2.aievolution.com/cro2101/index.cfm?do=abs.viewAbs&abs=2667 (abstract)
https://www.vcroi2021.org/sessions/19764945/subsession/25654928/REDUCTION-IN-INFECTIOUS-SARS-CoV-2-IN-TREATMENT-STUDY-OF-COVID-19-WITH-MOLNUPIRAVIR (webcast)

Bamlanivimab prophylaxis reduces hospitalisation and mortality: results from phase 3 BLAZE-2 study

Simon Collins, HIV i-Base



The BLAZE-2 study randomised 1175 residents or staff who were at high risk of COVID-19 through living or working in residential care homes to either bamlanivimab or placebo. [1]

Of these, 966/1175 were PCR negative, using bamlanivimab as prophylaxis and 209/1175 were PCR positive, using the intervention as treatment.

Participants in the prevention group needed to be PCR negative at baseline with a primary endpoint of incidence of COVID-19 symptoms and secondary endpoint of PCR-positive transmission, both at day 57.

Full results presented at CROI 2021 showed an 80% reduced risk of symptoms: OR 0.20 (95%CI: 0.08 to 0.49), p<0.001.

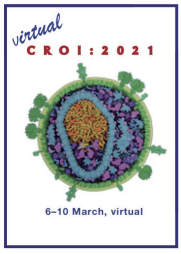
Preliminary results had been released in a company press statement in January. [2]

References

1. Cohen M et al. Bamlanivimab prevents COVID-19 morbidity and mortality in nursing-home setting. Oral abstract 121.
https://ww2.aievolution.com/cro2101/index.cfm?do=abs.viewAbs&abs=2538 (abstract)
https://www.vcroi2021.org/live-stream/19762744/NEW-WEAPONS-AGAINST-SARS-CoV-2-AND-HIV (webcast)
2. Bamlanivimab (LY-CoV555) prophylaxis prevents COVID-19 in care homes: results of BLAZE-2 study. HTB (24 February 2021).
https://i-base.info/htb/39886

Dual Eli-Lilly mAb bamlanivimab and etesevimab reduces hospitalisation after single infusion: results from BLAZE-1 study

Simon Collins, HIV i-Base



Results from the phase 3 stage of the BLAZE-1 study in 1053 participants with confirmed mild/moderate COVID-19 reported a 70% reduction in hospitalisation or death by day 29 (n=11 vs 36) in those randomised to the active monoclonal antibodies (mAbs) vs placebo (p=0.0004). [1]

The two neutralising mAbs in development by Eli-Lilly (2800mg bamlanivimab+2800mg etesevimab) were given together as a single infusion within three days of diagnosis.

Deaths were significantly reduced (n=0 vs 10) and symptoms resolved faster in the active arm. Median drop in viral load at day 7: difference –1.20 log (95%CI: –1.46 to –0.94), p<0.00000001).

Similar rates of adverse events were reported for the combined treatment vs placebo groups (13.3 % vs 11.6%).

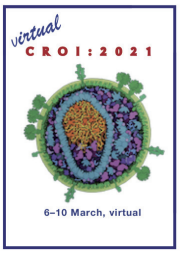
Results from the phase 2 dose-finding stage of this study were reported in the NEJM in October. [2]

References

1. Dougan M et al. Bamlanivimab+etesevimab for treatment of COVID-19 in high-risk ambulatory patients. Late breaking oral abstract 122.
https://ww2.aievolution.com/cro2101/index.cfm?do=abs.viewAbs&abs=2585 (abstract)
https://www.vcroi2021.org/live-stream/19762744/NEW-WEAPONS-AGAINST-SARS-CoV-2-AND-HIV (webcast)
2. Two different dual antibody treatments each reduce SARS-CoV-2 viral load by >0.5 log. HTB (22 January 2021).
https://i-base.info/htb/39718

Dual Regeneron mAbs casirivimab with imdevimab reduce transmission: interim results from phase 3 study

Simon Collins, HIV i-Base



Another combination of dual nAbs - this time from Regeneron - also reported positive results compared to placebo in reducing the chance of SARS-CoV-2 infection from an interim analysis of a phase 3 study. [1]

This randomised, double-blind, placebo controlled study primarily looked at prophylaxis in household contacts at high risk of SARS-CoV-2, but also included a smaller treatment study in participants who were diagnosed positive at baseline.

Participants were randomised to either 1200 mg casirivimab/imdevimab (600 mg of each antibody administered subcutaneously) or to placebo, with interim results presented from the prevention data.

Significantly fewer participants in the active arm were diagnosed with symptomatic infection: 0/186 (0%) vs 8/223 (3.6%); OR: 0.00 (95% CI: 0.00 to 0.69). There were also significantly fewer infections with SARS-CoV-2 PCR levels >1000 copies/mL: OR: 0.00 (95% CI: 0.00 to 0.37).

Although the overall rate of SARS-CoV-2 positive infections was reduced, this was not statistically significant: 10/186 vs 23/223; OR 0.49 (95% CI: 0.20 to 1.12).

Placebo recipients having 100-fold greater peak viral load and SARS-CoV-2 became undetectable within a week in the active arm but persisted in 40% of placebo recipients at 3-4 weeks. Statistical significance of both these differences was not reported.

Earlier results from this combination reported a 0.5 log reduction at day 11. [2]

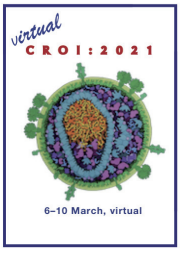
References

1. O'Brien MP et al. Casirivimab with imdevimab antibody cocktail for COVID-19 prevention: interim results. CROI 2021. Late breaker oral abstract 123. https://ww2.aievolution.com/cro2101/index.cfm?do=abs.viewAbs&abs=2542 (abstract) https://www.vcroi2021.org/live-stream/19762744/NEW-WEAPONS-AGAINST-SARS-CoV-2-AND-HIV (webcast)
2. Two different dual antibody treatments each reduce SARS-CoV-2 viral load by >0.5 log. HTB (22 January 2021). https://i-base.info/htb/39718

CROI 2021: ON THE WEB

Presentations from the LEAP workshop 2021

Simon Collins, HIV i-Base



One of the most useful workshops held just before CROI each year is organised by a collaboration of researchers focused on loon-acting drugs to treat HIV, TB, viral hepatitis and other infections (LEAP). [1]

This year the LEAP Workshop was a virtual meeting on 5 March 2021.

As with previous years, the resources from this meeting are now online. [2]

The programme includes at least 12 short presentations covering all the main long-acting pipeline compounds and main research approaches. It also includes feedback from four key working group sessions.

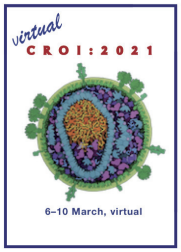
References

1. LEAP website. https://longactinghiv.org
2. Web casts and slides from LEAP workshop 2021. https://longactinghiv.org/content/long-actingextended-release-laer-antiretroviral-research-resource-program-leap-0

CROI presentations on NATAP.org

Simon Collins, HIV i-Base

The US-based activist organisation NATAP posted many of the CROI 2021 conference materials online.



In addition to original NATAP reports from Mark Mascolini and others, this community website also includes slide sets from oral presentations and posters, currently covering approximately 200 studies.

https://www.natap.org/2021/CROI/CROI.htm

Also, from 15 April 2021, the main CROI website will host all abstracts, posters and web casts from the 2021 conference. This will make the whole conference available as an open access resource.

https://www.croiconference.org

ANTIRETROVIRALS

Gilead and Merck/MSD to collaborate on long-acting HIV combination of lenacapavir and islatravir

Simon Collins, HIV i-Base

On 15 March 2021, in a joint press release, two leading research-based pharmaceutical companies – Merck/MSD and Gilead – announced they would be collaborating on long-acting HIV combinations. [1]

Each company has extremely promising compounds in development that need to be used in combination with similar long-acting drugs. Working in partnership should lead to much faster development than each company waiting to develop combinations independently.

From Merck/MSD, this includes islatravir, a highly potent NRTTI with the potential for daily, weekly and monthly oral formulations in phase 3 studies and an annual implant in phase 2.

From Gilead, this includes a long-acting capsid inhibitor being dosed as an infusion every six months that recently presented phase 2 results.

Both companies with be involved in development sharing costs and potential income 60:40 (Gilead:Merck/MSD). Gilead will lead in the US with Merck/MSD leading in the EU and rest of the world. Each company will have options to use other selected HIV drugs being developed by the partner company.

Both compounds are also being studied independently for use as PrEP, where the need to use combinations are currently not thought to be needed.

COMMENT

This is good news. Collaborating to use the most promising compounds from each company always seemed a more effective and faster way to develop new treatment options.

It also probably makes good commercial sense compared to the time needed for each company to develop a combination independently.

References

1. Joint press release. Gilead and Merck announce agreement to jointly develop and commercialize long-acting, investigational treatment combinations of lenacapavir and islatravir in HIV. (15 March 2021).
https://www.gilead.com/news-and-press/press-room/press-releases/2021/3/gilead-and-merck-announce-agreement-to-jointly-develop-and-commercialize-longacting-investigational-treatment-combinations-of-lenacapavir-and-islatr (Gilead)
https://www.merck.com/news/gilead-and-merck-announce-agreement-to-jointly-develop-and-commercialize-long-acting-investigational-treatment-combinations-of-lenacapavir-and-islatravir-in-hiv/ (Merck).

HIV: OTHER NEWS

Calls to reverse proposed UK cuts to global health research

Simon Collins, HIV i-Base

On 11 March 2021, severe cuts were announced to UK Research and Innovation (UKRI) Official Development Assistance (ODA) related spending. [1]

UKRI is UK's largest public funder of research and innovation, including many international projects related to global health.

The proposed cuts of £125m mean no new projects will start and existing projects will not be supported after July 2021.

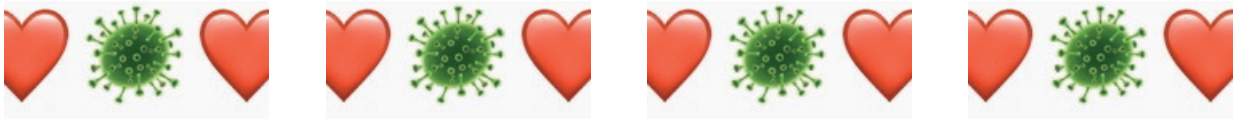
A BMJ includes more details, including the contrast between this relatively small amount and the £37 billions spent on track and trace.

This includes links to a sign-on letter and petition to parliament, both asking to reverse the proposed cutes to global health research. [3, 4]

References

1. UKRI Official Development Assistance letter. (11 March 2021). https://www.ukri.org/our-work/ukri-oda-letter-11-march-2021
2. BMJ blog. The government must urgently reconsider UK Research and Innovation funding cuts. (17 March 2021). https://blogs.bmj.com/bmj/2021/03/17/the-government-must-urgently-reconsider-uk-research-and-innovation-funding-cuts/
3. Open letter - Revoke decision on UKRI funding cuts https://docs.google.com/forms/d/e/1FAIpQLSd_cn28DpU0A-wCfW39_hEq8aNRHdCkL8ySdOT_L9eZlkju-Q/viewform
4. Revoke Government cuts to global health research https://petition.parliament.uk/petitions/580046

HTB SUPPLEMENT ON COVID-19: Issue 9



HIV and COVID-19 COINFECTION

BHIVA guidelines on COVID-19 vaccines and people living with HIV: DRAFT online for comment

Simon Collins, HIV i-Base

On 24 March 2021, the British HIV Association (BHIVA) posted draft guidelines on COVID-19 vaccinations in people living with HIV. The guidelines are online for comment for a month until 24 April 2021. [1]

A plain-language community summary will be posted online in the next week or go, at the same link.

The 17-page document reviews current evidence on the efficacy and safety of the main vaccines. It includes the following key recommendations.

- The increased risk of severe COVID-19 associated with HIV means that routine COVID-19 vaccination is strongly recommended for ALL people living with HIV.
- There are no HIV-specific safety concerns for any of the mRNA, adenovirus or vector (protein) based vaccines. There are no concerns related to CD4 count or viral load.

- The few contraindications (serious allergy to ingredients) are the same for people who are HIV positive and HIV negative.
- The first vaccine offered is recommended: no vaccine is better than another.
- Vaccinations are especially important for anyone with higher risks for COVID-19.

This includes HIV factors (low CD4 or detectable viral load), non-HIV factors (other serious health issues) and pregnancy.

- It is important to complete the course (both vaccine). The second vaccine should routinely be the same make, unless there was a severe reaction to the first shot. It the same vaccine is not available for any reason, a different vaccine can be used.
- Limited data are available on the duration of protection. Even if this if affected HIV a high degree of cover is still expected from all vaccines.
- Further research will decide on whether future vaccine boosts are recommended. This includes in people living with HIV.
- Vaccine protection should not be assumed. Future symptoms should still involve SARS-CoV-2 testing and speaking to a doctor.
- Evaluating individual immune responses with antibody tests, either before or after vaccination, is not recommended, unless part of a research study.
- Vaccines are recommended even if you recently had coronavirus. If symptoms are very recent, it is best to wait about four weeks before having the vaccine.
- No recommendations are made for use of passive immunisation other that in a research setting.
- As with HIV negative people, taking part in research studies is supported and recommended when appropriate.

Reference
1. British HIV Association guidelines on immunisation for adults with HIV: SARS-CoV-2 (COVID-19) 2021 - consultation open. (24 March 2021). https://www.bhiva.org/COVID-19-immunisation-guidelines-consultation (webpage) https://www.bhiva.org/file/605b1447c8ffa/COVID-19-Immunisation-Guidelines-Consultation.pdf (PDF link)

BHIVA advice on access to COVID-19 vaccines and shielding in the UK

Simon Collins, HIV i-Base

On 16 March 2021, BHIVA issued updated information about how HIV positive people can access vaccines against COVID-19, and also on shielding in the UK.

The vaccine advice includes information on:

- How HIV clinics can directly refer HIV positive people to vaccine hubs. This covers the slightly differences between HIV clinics in Wales, Scotland, Northern Ireland and England.
- Although some HIV clinics are already providing vaccines, it is also taking time for this to be arranged.
- Ways to ensure access to vaccines for people without an NHS number.
- Reassurance that vaccine databases do not record any other medical information, other than the data and make of vaccine that is given.

New information on the UK shielding policy includes:

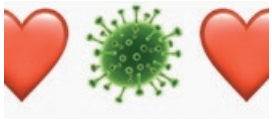
- Recognising that the QCovid risk predictor has been wrongly assessing risk – but that attempts to fix problems are already ongoing.
- That HIV positive people may have been wrongly added to the Shielded Patient list, or added for non-HIV reasons. GPs can currently make changes to the list and BHIVA is looking at whether HIV clinics can also do this.

References
BHIVA. Important COVID risk and vaccine updates, QCovid risk assessment & Shielding advice - update from BHIVA. (16 March 2021). https://www.bhiva.org/important-covid-risk-and-vaccine-updates-march-2021.

COVID-19: VACCINE RESEARCH

US study results enable FDA review of the Oxford/AstraZeneca vaccine

Simon Collins, HIV i-Base



After an unexpected series of announcements the Oxford/AstraZeneca vaccine looks ready for FDA regulatory review in the US, almost three months after approval in the UK.

This study provides an important data set with constant and consistent dosing. Earlier phase 3 studies had used half dosing and extended dosing periods in UK participants, although this did not prevent approval in the UK and EU.

First, on 22 March 2021, US NIH and AstraZeneca both issued press releases reported 79% efficacy against symptomatic COVID-19. This was from a planned interim analysis from a phase 3 study that was run in the US and South America. [1, 2]

However, this prompted a letter from the NIH Data and Safety Monitoring Board (DSMB) for the study suggesting efficacy rates of 69% and 74%. A second NHI press release reported that the DSMB claimed AstraZeneca had selected inappropriately positive results. [3] The company responded with a short statement that the interim results were planned but the full results would be available within two days. [4]

Then on 25 March, the updated results based on the full data set reported 76% efficacy (95%CI: 68% to 82%) against symptomatic COVID-19. [5]

Other results from the full analysis included 100% efficacy against severe and critical disease and hospitalisation (0 vs 8 cases in active vs placebo) and 85% efficacy (CI: 58% to 95%) against symptomatic COVID-19 in participants aged 65 and older.

These results included an additional 49 cases - now totaling 190 from almost 32,500 participants (randomised 2:1 for active:placebo). They are all broadly consistent with the interim analysis published a couple of days earlier.

Symptomatic cases were reported two weeks after the second vaccination, with doses given four weeks apart.

Baseline characteristics included 60% having higher risk health complications (diabetes, obesity etc). Approximately 80% were white and 8% African American and 4% Native American.

The vaccine was well tolerated, and no safety concerns including for blood clots.

C O M M E N T

The most important outcome is that this vaccine will now be submitted to the US FDA.

No-one has commented on the four-week dosing schedule in the US study. The complications of the earlier UK study that separated doses by 12 weeks was reported as a factor for 90% efficacy - and was used to supported this longer schedule currently used in the UK.

The motivation for the highly unusual action by the DSMB, and the difference between their efficacy claim and the final results are unclear.

References

1. NIH press release. Investigational AstraZeneca vaccine prevents COVID-19. (22 March 2021). https://www.nih.gov/news-events/news-releases/investigational-astrazeneca-vaccine-prevents-covid-19
2. AstraZeneca press release. AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. (22 March 2021). https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html
3. NIH second statement. NIAID Statement on AstraZeneca Vaccine (23 March 2021) https://www.nih.gov/news-events/news-releases/niaid-statement-astrazeneca-vaccine
4. AstraZeneca press release. Update following statement by NIAID on AZD1222 US Phase III trial data. (23 March 2021). https://www.astrazeneca.com/media-centre/press-releases/2021/update-following-statement-by-niaid-on-azd1222-us-phase-iii-trial-data.html
5. AstraZeneca press release. AZD1222 US Phase III primary analysis confirms safety and efficacy. (25 March 2021). https://www.astrazeneca.com/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html

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 will now be virtual, including those that were rescheduled in the hope that COVID-19 restrictions would be relaxed.

Virology Education meeting and workshops

Several VE workshops are highlighted below but 35 meetings are planned for 2021:

https://www.virology-education.com

5th Joint Conference of the British HIV Association (BHIVA)

& The British Association for Sexual Health & HIV (BASHH)

Virtual

19 – 21 April 2021

https://www.bhiva.org/AnnualConference2021

COVID-19 Clinical Forum (one of a series)

Virtual (to cover research presented at CROI)

20 April 2021 at 20:00 CET / 15:00 EDT

https://academicmedicaleducation.com/covid-19-clinical-forum-2021

11th International Workshop on HIV & Women

26 – 28 April 2021, virtual

https://www.virology-education.com

International Workshop on HIV and Transgender People 2021

17 July 2021. virtual.

https://www.virology-education.com

11th IAS Conference on HIV Science (IAS 2021)

18 – 21 July 2021, Hybrid - virtual and in Berlin

https://www.ias2021.org

12th International Workshop on HIV & Aging

23 – 24 September 2021, virtuaal

https://www.virology-education.com

18th European AIDS Conference (EACS 2021)

27 – 30 October 2021, Hybrid - virtual and in London

https://eacs-conference2021.com

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.

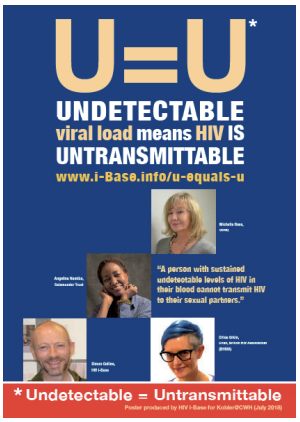
This project was developed with the Kobler Centre in London.

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

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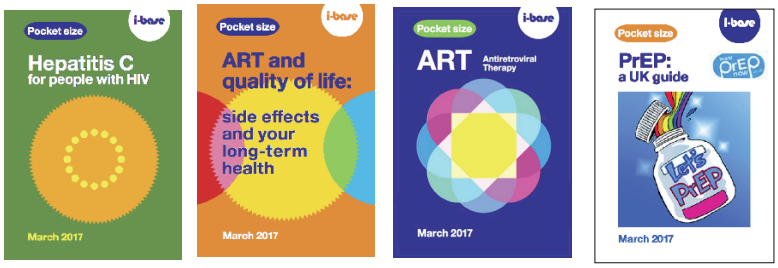

h-tb

HIV TREATMENT BULLETIN

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Editor: Simon Collins

Contributing Editor: Polly Clayden

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- **HIV Treatment Bulletin (HTB) every two months** ☐ **by e-mail**
- **Pocket leaflets** - *A7 small concertina-folded leaflets (2017)*

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

- **Booklets about HIV treatment**

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

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