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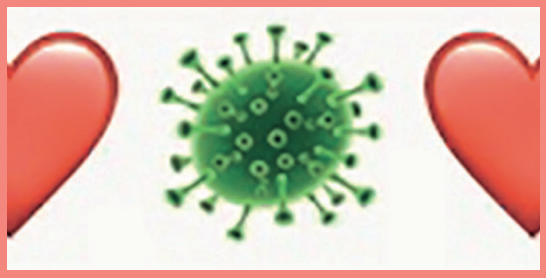
hiv treatment bulletin (e)



Injectable ART and COVID-19 vaccines (22 January 2021)

CONTENTS

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Published by HIV i-Base

HTB no.1 (2021): HIV and COVID-19 supplement ISSUE 1

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.

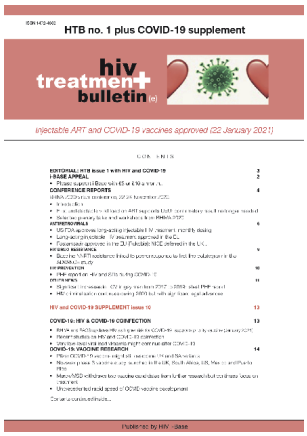
http://i-base.info/i-base-appeal-we-need-your-help

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 first issue of HTB for 2021 includes latest reports on both HIV and COVID-19.



HIV news includes approval of long-acting injectable ART in the EU and the US. US pricing is complicated - and this is set at just under $50,000 a year for the combination. Access and use in the UK will depend which of the current combinations it is pegged to - and in many EU countries too. Fostemsavir was also importantly just approved in the EU to treat MDR HIV, but the limited expected demand means approval in the UK will be able to sidestep NICE.

UK reports from PHE cover the increase in LGV among gay men and the impact of COVID-19 on rates of HIV and STIs.

And the South African ADVANCE study, used to provide data on dolutegravir use globally, also reports unexpected results linked to baseline drug resistance.

The last month also brought the most important news about vaccines against COVID-19 as three are now approved in the UK, and other are still in studies. And hopefully, as coverage is extended, this COVID section of HTB can steadily become smaller. But not for this issue…

Consensus is now growing - supported by BHIVA and EACS - that HIV might be associated with an increased risk of serious outcomes, based on several recent, large, well-powered studies. Even though none of these studies is perfect, they can justify HIV being included as a priority group in national vaccination programmes. In the UK this will routinely be priority group 6 (out of 9) but in complex cases this can be higher (group 4). HIV doctors are likely to need to work with GPs for their most at-risk patients.

We report that the Pfizer vaccine might retain sensitivity to recent SARS-CoV-2 variants - as least as we go to press. But by next week, more sophisticated analyses could easily become more informed.

And the news on treatment - covered in seven reports - includes more positive results than negative ones. A large phase 3 RCT reported that oral colchicine - a cheap anti-inflammaotry - reduced hospitalisations and deaths in outpatients. There is other positive news for IL-6 agonists tocilizumab and sarilumab, and two different dual combinations of monoclonal antibodies: one from Eli Lilly and one from Regeneron. Plus a small study tentatively reporting benefits from IV methylprednisolone in hospitlaised adults.

As a caution, negative results are reported for a monotherpy antibody, and azithromycin had zero benefit in the UK RECOVERY study -which many people expected. Also confirming no role for hydroxychloroquine and lopinavir/r, new WHO guidelines recommend that neither drugs has any benefit in any stage of infection, including within research.

We include several reports related to Long COVID - increasingly important - including recent NICE guidelines. Plus we report on other updated guidelines covering treatment and vaccines.

Last year was difficult and problems will continue long into 2021. So again, we hope all readers will be careful to reduce risks to yourselves and to others, and we continue to thank and appreciate the dedication of all who work to keep the rest of us safe.

Finally, if you have read this far, please could to take a minute for feedback. Is this expanded coverage of COVID in HTB still useful? Even a yes/no answer would help, thank you.

https://i-base.info/feedback

CONFERENCE REPORTS

BHIVA 2020 virtual conference now online

22-24 November 2020.

Introduction

Simon Collins, HIV i-Base

This year the BHIVA conference was held as a virtual meeting.

The programme and the abstract book are already online and webcasts from oral presentations became open access on the BHIVA website, four weeks after the meeting.

The rest of the conference is also now online:

https://www.bhiva.org/Autumn2020Presentations

PDF files for posters however that were all available on the conference site have been taken down and/or not been transferred to the new site.

The programme included both clinical and community presentations.

Reports in this issue are:

- Single undetectable viral load is sufficient for U=U in the context of good adherence
- Selected plenary talks and workshops from BHIVA 2020

Single undetectable viral load is sufficient for U=U in the context of good adherence

Simon Collins, HIV i-Base

The widespread adoption of U=U (undetectable=untransmittable) as a foundation for public health campaigns to eliminate HIV transmission is successfully challenging decades of HIV-related stigma.

While many UK doctors use the first undetectable viral load as the time to recommend U=U, some guidelines still recommended waiting for a confirmatory viral load result. Waiting for a second undetectable result is especially complicated during restrictions during COVID-19 and also delays this aspect of normalising life.

Given that the risk of viral load rebound is low after first becoming undetectable but is also possible after the second confirmatory test, comparing rates in these two situations might provide an evidence base to relax the recommendation for the confirmatory test.

Researchers with the UK-CHIC observational cohort analysed patterns of viral rebound in 1574 gay men starting ART during 2015 and 2016 with CD4 counts >350 cells/mm^3 and more than one viral load <50 copies/mL.

The first undetectable viral load was reported after a median 2.5 months (IQR: 1.1 to 4.3) after ART initiation, with a second viral load 2.8 months later (IQR: 0.9 to 4.5). Over 4,707 person-months of follow-up, 69 men (4.3%) had subsequent rebound: rate = 1.47/100 person months (95%CI: 1.16 to 1.86).

This compared to 176/1552 men (11.3%) with viral rebound after two initial consecutive undetectable results: rate = 0.82/100 (95%CI: 0.71 to 0.95) over 21,420 months of follow-up.

Although the rebound rate was slightly higher in the initial group, rates of rebound were low in both groups.

The differences between the two groups were even closer when using a <200 copies/mL rather than <50 copies/mL viral load threshold (0.62 vs 0.64).

This study noted that this approach is also likely to overestimate risk of viral rebound in the context of U=U as it will include all cause viral rebound, including low adherence. This is an important consideration given that U=U is dependent on good adherence.

C O M M E N T

Although the international U=U campaign is based on a single undetectable viral load, this UK dataset provides evidence to support this recommendation.

The context of good adherence remains essential.

The study noted that as this was in gay men, the results might not be generalizable to other groups.

References
1. Okhai H et al. P54 Understanding patterns of early viral rebound in the current ART era: the UK CHIC study. BHIVA 2020 virtual conference, 22-24 November 2020. Poster abstract P54.
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Simon Collins is a co-author of this study.

Selected plenary talks and workshops from BHIVA 2020

Simon Collins, HIV i-Base

Links to selected talks are included below

Patient standards of care and new HIV-2 guidelines

https://vimeo.com/490647622

Talks by Ben Cromarty from the UK-CAB and Clare Van Halsema.

Lest we forget: two talks on early years of HIV in the UK

Ed Wilkins gives a moving hisotrical perspective on clinical care and Simon Collins talks about the early UK community responses to HIV.

https://vimeo.com/490666913

UK-CAB community programme

https://vimeo.com/491101577

Three UK-CAB members - Jo Josh, Memory Sachikonye and Robert James - present some of the positive outcomes that HIV activists have been able to bring to HIV are in the UK. This includes working with research groups and on guidelines panels.

Professor Caroline Sabin talks about community involvement from the perspective of a researcher.

Workshop on late HIV diagnosis

https://vimeo.com/491553977

Public health and clinical issues involved with late HIV diagnosis,

Stigma of HIV

https://vimeo.com/491613310

Talk by Dr Iain Reeves on approaches to tackle HIV stigma amongst health workers,

“how to distinguish clumsy lack of knowledge from true stigma…”

Lunchtime workshop on recently acquired HIV

These talks looks at UK surveillance data on recent infections, including HIV positive and doctor responses to Surveillance of HIV Acquired Recently: Enhanced (SHARE) questionnaires. The session reported that indicator risks were common (for example recent STI) but that this was not matched but knowledge and access to PrEP.

The Q&A discussion noted that although RITA testing is currently on-hold, samples are being stored for later testing and that the PrEP IMPACT study was quickly oversubscribed and access was capped.

https://vimeo.com/491553977

Lunchtime workshop on neurosyphilis

Clinical and epidemiological perspectives from Patrick French and Michael Marks.

https://vimeo.com/492026476

Two talks on community involvement in HIV research.

https://vimeo.com/492005964

Two excellent talks about community inclusion and collaboration from Longret Kwardem, London, and Francisco Ibáñez-Carrasco, Toronto.

ANTIRETROVIRALS

US FDA approves long-acting injectable HIV treatment: monthly dosing

Simon Collins, HIV i-Base

On 22 January 2021, ViiV Healthcare announced that the combination of long-acting injections of cabotegravir and rilpivirine had been approved by the US FDA. In the US, both injections are being distributed under a single trade name of Cabenuva. [1, 2]

The indication is as an HIV treatment for people who are stable on current ART with an undetectable viral load on current treatment. It also includes having no history of treatment failure, and no known or suspected drug resistance to either drugs.

The US indication is every month (12 treatments a year).

The company plans to submit an extension for two-monthly injections in the US within the first six months of 2021.

The US approval also included details on pricing:

- Oral drugs for the first four weeks are provided free.
- The initial loading dose will cost $5,940 (600 mg CAB-LA and 900 mg RPV-LA).
- Subsequent monthly continuation doses will cost $3,960 (400 mg CAB-LA plus 600 mg PRV-LA).

These prices are based on the wholesale list price and work out at $ 47,520 a year on stable ART. [3]

On 21 December 2020, the same drugs were approved by the EMA in the EU but with separate trade names: cabotegravir (Vocabria) and rilpivirine (Rekambys). EU approval included the option of two-monthly dosing, but using the higher 600/900 dose throughout. [4]

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

C O M M E N T

Approval is welcomed for this first combination that doesn't depend on oral pills. Alternative formulations have always been awaited for many years. This will also offer a completely different option for people who struggle with daily medication.

The EU option for injections every two months involves 6 treatments a year, using the higher 600/900 dose throughout.

References

1, FDA press notice. FDA approves first extended-release, injectable drug regimen for adults living with HIV. (21 January 2021). https://www.fda.gov/news-events/press-announcements/fda-approves-first-extended-release-injectable-drug-regimen-adults-living-hiv

2. ViiV Healthcare announces FDA approval of Cabenuva (cabotegravir, rilpivirine), the first and only complete long-acting regimen for HIV treatment. (21 January 2021). https://www.gsk.com/en-gb/media/press-releases/viiv-healthcare-announces-fda-approval-of-cabenuva-cabotegravir-rilpivirine-the-first-and-only-complete-long-acting-regimen-for-hiv-treatment

3. ViiV Healthcare. Personal communication. (22 January 2021).

4. Long-acting injectable HIV treatment approved in the EU: includes two-monthly dosing. HTB (21 December 2020). https://i-base.info/htb/39602

5. Cabenuva. Full prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf (PDF)

Long-acting injectable HIV treatment approved in the EU with option for two-monthly dosing

Simon Collins, HIV i-Base

On 21 December 2021, ViiV Healthcare announced that the combination of long-acting injections of cabotegravir (Vocabria) and rilpivirine (Rekambys) had been approved for HIV treatment. [1]

Both drugs are also available as oral tablets to be used for four weeks before switching to long-acting injections.

Cabotegravir is an integrase inhibitor and rilipivirine is an NNRTI, and long acting intramuscular injections are given concurrently, rather than in the same formulation. Rilpivirine LA requires cold-chain storage.

Although approval was largely based on results from three phase 3 studies using monthly injections, the EMA decision includes the option to use either monthly or two-monthly dosing schedules, although the two-monthly injections use a higher dose. A lead-in phase using oral versions of both drugs is also required. [2]

Contraindicated medications due to potential drug interactions include carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, systemic dexamethasone (>1 dose), and St John's wort.

This full approval comes two-months after the EMA issued a positive opinion on this new combination, although the original application was submitted in July 2019. [3]

C O M M E N T

This breakthrough treatment will be an especially important option for people who have difficulty with oral tablets or with adherence. This is especially important as these people do not have the loudest voices.

Access in England will depend on the outcomes of an ongoing review by NICE – the first time that it will be reviewing HIV medicines. The NICE decision is expected by 20 October 2021. [4]

Although information about price has not yet been provided, this will be a key factor for access in the UK. There might be reasons for optimism linked to the potential for cabotegravir to be used as PrEP.

Results from two large phase 3 studies (HPTN 083 and 084) recently reported that cabotegravir injections are highly effective as HIV PrEP. In this context ViiV Healthcare included a commitment to wide access to cabotegravir PrEP in the sub-Saharan African countries where the study was run. [5] The results as PrEP also led to innovation status. [6]

This perhaps implies a flexibility for pricing in high-income countries that could be comparable to price of other commonly prescribed ART combinations.

There is always a narrow window for new drugs to recover development cost for new drugs - whether as treatment or PrEP. The most successful business model is for pricing to be affordable in all countries.

It is always better for these exciting advances become widely used with a more marginal profit rather than remain out of use with a higher (unused) price.

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https://viivhealthcare.com/en-gb/media/press-releases/2020/december/viiv-healthcare-announces-the-marketing-authorisation
2. EMA. Vocabria.
https://www.ema.europa.eu/en/medicines/human/EPAR/vocabria
3. EMA issues positive opinion to approve cabotegravir LA/rilpivirine LA injections (Vocabria/Rekambys) as new HIV treatment. HTB (November 2020).
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4. NICE. Cabotegravir and rilpivirine for treating HIV-1 [ID3766].
https://www.nice.org.uk/guidance/proposed/gid-ta10658
5. Two-monthly cabotegravir injections prevent HIV infection in African women: HPTN 084 study recommends early unblinding. HTB (11 November 2020).
https://i-base.info/htb/39327
6. Innovation benefits of cabotegravir LA injections for HIV PrEP will enable a closer FDA review. HTB (11 November 2020).
https://i-base.info/htb/39528

Fostemsavir approved in the EU (Rukobia): NICE deferred in the UK

Simon Collins, HIV i-Base

On 11 December 2020, ViiV Healthcare announced approval of fostemsavir in the EU. [1]

Fostemsavir is the first gp120 attachment inhibitor and was developed as a treatment for people with multi-drug resistance to other HIV classes.

Submission to the EU was made in December 2019 based on results from an international phase 3 BRIGHTE study in in 371 participants, 99 of who used open-label fostemsavir.

Given extensive drug resistance at baseline, fostemsavir was still associated with achieving undetectable viral load in roughly 40 - 60% of participants at week 96.

Notably, mean increase in CD4 counts was 205 cells/mm^3 with 56% of participants increasing from < 50 to >200 cells/mm^3.

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

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

C O M M E N T

Fostemsavir had a long development history and it is important that ViiV Healthcare followed this through to approval after acquiring the compound from BMS in 2015.

Currently, the demand for drugs to use in multidrug resistance in the UK is too limited for a full NICE evaluation. Access however, will be available based on NHS recommendations from specialist HIV commissioning.

The significant increase in CD4 count, might deserve further researcher, including in cases of discordant responses to ART, where viral load is suppressed but CD4 count remains low, especially if this continues to present a risk for opportunistic infections.

Cases of urgent need should contact ViiV directly until this access is in place.

Similar commissioning arrangements are also being organised for access to ibalizumab which was also recently approved.

For people with a history of multidrug resistance and detectable viral load on current ART, using both fostemsavir and ibalizumab together might provide life-saving holding treatment until the next pipeline drugs.

Even though each drug is likely to be priced close to £100,000 per year, they would only need to be used during a window period until the next drug approvals.

Reference

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2. ViiV Healthcare. Prescribing and patient information. https://viivhealthcare.com/en-gb/our-medicines/rukobia https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_GB/files/Final_Rukobia_Prescribing_Information_NDA_212950.pdf (PDF)

HIV DRUG RESISTANCE

Baseline NNRTI resistance linked to poorer response to first-line dolutegravir in the ADVANCE study

Polly Clayden, HIV i-Base

Participants with pretreatment NNRTI resistance, receiving dolutegravir (DTG) in ADVANCE, had lower rates of viral suppression at 96 weeks than those without – according to findings reported in the 1 December issue of Nature Communications. [1]

ADVANCE is an ongoing, three arm, 192-week, phase 3 study, comparing first-line ART with: tenofovir alafenamide (TAF)/emtricitabine (FTC) + DTG, tenofovir disoproxil fumarate (TDF)/FTC + DTG or TDF/FTC/efavirenz (EFV). Week 96 data were presented this year. [2]

The resistance analyses were conducted with the hypothesis that pre-treatment NNRTI resistance significantly affects efficacy of EFV-containing regimens but has a negligible effect on outcomes for those starting DTG-based therapy.

Of 1053 participants enrolled in ADVANCE, 991 (94%) consented for specimen storage and had pretreatment plasma available; 874 (83%) had successful sequencing.

Among participants included in the resistance analyses, 289 (33%) were randomised to the EFV and 585 (67%) to the DTG arms. All had completed week 96 of the study at the time of the analyses. Participants starting DTG-based regimens had a higher prevalence of pretreatment drug resistance than those starting EFV-based regimens: 16.5 vs 7.4%, $p<0.001$. Otherwise, there were no clinical or demographic differences between the two groups.

The investigators found 14% (122/874) of participants with at least one WHO-defined pretreatment drug resistant mutation. Most of the resistance was to NNRTIs, with over 98% (120/122) of participants with pretreatment resistance having at least one NNRTI mutation.

K103N was the most common NNRTI mutation (9%, 81/874). Only 2% (20) of participants had a NRTI mutation. M184V was the most frequent (1%, 12 participants) followed by K65R (1%, 8 participants). Two per cent (18 participants) had at least one NRTI mutation and one NNRTI mutation.

Rates of virologic suppression were significantly lower overall in participants with pretreatment drug resistance than those without: respectively, 65% (73/112) vs 85% (605/713), $p<0.001$.

This was similar for those starting EFV- or DTG-based ART: respectively, 60% (12/20) vs 86% (214/248), $p=0.002$, and 66% (61/92) vs 84% (391/465), $p<0.001$.

In multivariate analysis, adjusted for demographics, clinical factors and adherence, pretreatment drug resistance was a strong predictor of virologic success: AOR 0.38 (95% CI 0.21 to 0.61).

Results were similar when the investigators assessed persistent virologic failure (defined as two consecutive viral loads >200 copies/mL): respectively, 85% (73/86) vs 94% (428/453), $p=0.001$ and 68% (13/19) vs 93% (217/233), $p<0.001$ for DTG and EFV-based ART.

By contrast, pretreatment drug resistance only had an effect on early virologic response for participants receiving EFV-based but not DTG-based ART. At week 12, the drop in viral load was greater for those without pretreatment drug resistance in the EFV arm but not in the DTG arms: respectively 1.89 vs 2.61 log10 copies/mL, $p<0.001$, and 2.76 vs 2.68 log10 copies/mL, $p<0.43$ ($p=0.001$ for interaction between arms).

The investigators wrote that "…the finding that NNRTI resistance appears to ultimately predict treatment failure among individuals initiating DTG-based ART in LMIC was unexpected, and to our knowledge not previously reported in the literature".

They noted that integrase resistance mutations were not assessed in this study but are generally believed to be rare (<1%) in this region.

They speculated that one explanation for the lack of long-term suppression in participants receiving DTG-based ART might be behavioral – pre-existing EFV mutations could be a linked to earlier undisclosed ART exposure. Previous ART exposure has been associated with treatment failure and predicts virologic failure, even after controlling for pretreatment drug resistance and adherence.

COMMENT

The finding that NNRTI resistance is associated with a reduction in efficacy of DTG-based ART has multiple public health implications.

It means that viral load monitoring remains a priority with DTG-based regimens.

Second- and third-line options will also still be needed and integrase inhibitor resistance testing should be considered.

However, the authors also recommend that these findings need to be validated. Future analyses also need to:

- **Assess the contribution of pretreatment integrase mutations to outcomes.**
- **Look at the impact of prior exposure to ART on treatment outcomes.**
- **Find out whether treatment failure observed on DTG-based ART is associated with emergence of integrase inhibitor mutations.**

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   https://i-base.info/htb/38493

HIV PREVENTION

PHE report on HIV and STIs during COVID-19

Public Health England

A provisional analysis from Public Health England (PHE) on the impact of the COVID-19 pandemic response on sexually transmitted infections (STIs), HIV and viral hepatitis service provision and epidemiology.

Main findings include that between March and May 2020, there were reductions in:

- Consultations undertaken by sexual health services (SHSs) and specialised HIV services.
- Testing for viral hepatitis in drug services, prisons, general practice and SHSs.
- Testing for HIV and STIs in SHSs.
- Vaccination of gay, bisexual and other men who have sex with men (MSM) against Human Papillomavirus (HPV), hepatitis B (HBV) and hepatitis A (HAV).
- Diagnoses of viral hepatitis, HIV and STIs and hepatitis C (HCV) treatment initiations.

Also from June 2020, there was an increase in HIV, STIs and hepatitis tests and diagnoses, and hepatitis C virus (HCV) treatment, following the easing of national lockdown restrictions.

This reflects a partial recovery in service provision and demand.

Nevertheless, numbers of consultations, vaccinations, tests, diagnoses, and treatment initiations in the summer of 2020 were considerably lower than in corresponding months in 2019.

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PHE. The impact of the COVID-19 pandemic on prevention, testing, diagnosis and care for sexually transmitted infections, HIV and viral hepatitis in England: Provisional data: January to September 2020. (December 2020).

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OTHER NEWS

Significant increases in LGV in gay men from 2017 to 2019: latest PHE report

Simon Collins, HIV i-Base

On 9 December, Public Health England (PHE) published their latest report on Lymphogranuloma venereum (LGV). This included significant increases in this STI that predominantly affects gay men (95% of cases). [1]

Between 2018 and 2019 the number of clinical cases increased by 56% and laboratory diagnoses increased by 32%. This continues a similar trend from 2017 to 2018.

Although the number of tests also increased by 20% from about 10,500 to 12,600 (to include HIV negative men who were asymptomatic), the proportion of test with positive results also increased from 8.2% to 9.0% suggestion a real increase in transmission.

The report includes more detail on annual rates since 2011, age, HIV status, STI history, UK region and country of birth. It also notes that similar increases have been reported in other European countries including the Netherlands, France and Italy.

Although referring to social changes including reduced use of condoms and more frequent STI testing the report also refers to studies from 2016 and 2020 that suggest continued transmission might be explained by undiagnosed asymptomatic LGV infection. [2, 3]

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HIV criminalisation during 2020: cases continue but also legal advances

HIV Justice Network

A recent bulletin from HIV Justice Network includes the following summary of developments during 2020. [1]

The organisation reported at least 90 cases of unjust HIV criminalisation in 25 countries, with Russia and the United States being the worst offenders. Women living with HIV were accused in 25% of those cases. Three of these cases were for breastfeeding. In the United States, more than 50% of those accused in HIV criminalisation cases were people of colour.

2020 also saw Poland passing a new law against COVID-19 that also increased the criminal penalty for HIV exposure, and number of disappointing HIV criminalisation higher court appeals in the US (Ohio), and Canada (Ontario and Alberta) that appeared to ignore science over stigma.

And yet, despite the many difficulties of 2020, the movement to end unjust HIV criminalisation has continued to gain momentum.

In the United States, Washington State modernised its HIV-specific criminal law in March, reducing the 'crime' from a felony to a misdemeanour, adding in a number of defences, and eliminating the sex offender registration requirement. Earlier this month, legislators in Missouri published plans to modernise its HIV-specific criminal law next year.

In Europe, Sweden abolished the legal requirement to disclose HIV status in March, the Spanish Supreme Court set an important precedent for HIV criminalisation cases in May, and in June, Scottish police ended the stigmatising practice of marking people living with HIV as 'contagious' in their database.

In Francophone Africa, HIV-specific criminal law reform in Benin and across the region is looking likely thanks to a recognition that existing laws do not reflect up-to-date science.

And in Eastern Europe and Central Asia, a process to completely abolish the draconian HIV-specific criminal law in Belarus has begun.

The email bulletin is free and registration and back issues are also online. [2]

The bulletin from 8 January 2021 also reports an important editorial in the Lancet HIV calling for legal reform in the US. Unfortunately, this is not available as open access article. [3, 4]

Source:

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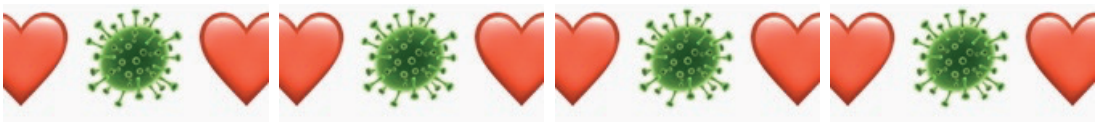
HTB SUPPLEMENT ON COVID-19: Issue 1 (January 2021)



COVID-19: HIV and COVID-19 COINFECTION

BHIVA and EACS updates HIV as higher risk for COVID-19: supports priority vaccine (January 2021)

Simon Collins, HIV i-Base

On 15 January 2021, the British HIV Association (BHIVA) and the European AIDS Clinical Society (EACS) published an updated review on HIV and COVID-19. [1]

This includes an overview of recent research covering transmission, treatment and the latest vaccines from an HIV perspective. This is jointly published with other HIV organisations from Germany, Poland, Portugal and Spain.

The review is especially useful for highlighting approaches to HIV and COVID-19 in different EU countries.

Important changes since August 2020 are included below.

- HIV is now linked to slightly higher risks from COVID-19. This is due to several large recent studies that are better powered to find small differences. Compared to the general population, HIV positive people are often affected at a lower average age.
- HIV factors linked to poorer outcomes in some studies include not being on ART or having a detectable viral load, a low CD4 count (<350 cells/mm^3) or the lowest-ever CD4 count (called CD4 nadir).
- Including HIV as an independent risk is important for access to COVID-19 vaccines across the EU. Currently, some countries do not include HIV as a health condition for earlier vaccine access.
- The newly approved vaccines are all discussed, including potential complications from using adenovirus vectors.
- The Statement references now WHO guidelines against use of hydroxychloroquine at any stage of COVID-19, including as prophylaxis.

- Recent evidence supporting use of IL-6 agonists including tocilizumab (including the REMCAP study, though not yet recommended in all countries.
- Famotidine and ivermectin are bother discussed, though with limited evidence.
- The overview includes another 20 references - now covering 82 studies.

Reference

BHIVA, DAIG, EACS, GESIDA, Polish Scientific AIDS Society and Portuguese Association for the clinical study of AIDS (APECS). Statement on risk of COVID-19 for people living with HIV (PLWH) and SARS-CoV-2 vaccine advice for adults living with HIV. (15 January 2021).

https://www.bhiva.org/joint-statement-on-risk-of-COVID-19-for-PLWH-and-SARS-CoV-2-vaccine-advice

Recent studies on HIV and COVID-19 coinfection

Simon Collins, HIV i-Base

The following papers have been published that include clinical outcomes on HIV positive people who were diagnosed with COVID-19, with brief summaries from the abstract.

Impact of HIV on infection and mortality: literature review

A systematic literature review of 68 papers (including 11 prereview) reported that earlier small studies reported little difference between people living with HIV and the general population, larger studies.

However, larger studies (from South Africa, the UK and the US) reported a higher risk in multivariate analyses of severe responses including higher mortality (with relative risks from 1.7 to 2.3).

A significant difference included that serious COVID-19 events in people living with HIV were reported at a lower age.

Reference: Macallan D et al. Does HIV impact susceptibility to COVID-19 (SARS-CoV-2) infection and pathology? A review of the current literature. MedRxiv. DOI: 10.1101/2020.12.04.20240218. (7 December 2020).

https://www.medrxiv.org/content/10.1101/2020.12.04.20240218v1

HIV associated with higher COVID-19 mortality in New York State

A retrospective review based on surveillance data from >108,000 people living with HIV compared to 20 million people in general population with PCR-confirmed COVID-19 from 1 March to 7 June 2020.

The study measured diagnoses, hospitalisation (within 30 days of a positive test) and in-hospital deaths.

Demographics included age, sex and region with CD4, viral load and related information for those living with HIV and adjusted rate ratios (RR) included race and ethnicity.

Overall, 2998 HIV positive people were diagnosed with COVID-19 (27.6 vs 19.4/1,000 in general population) with an unadjusted RR: 1.43; 95%CI: 1.38 to 1.48). This effect was no longer significant though in an adjusted analysis (indirect standardized RR: 0.94; 95%CI: 0.91 to 0.97).

However, hospitalisation rates were significantly higher: 8.29 vs 3.15/1,000; RR after standarisation: 1.38 (95%CI: 1.29 to 1.47), as was in-hospital deaths. There were 207 deaths in HIV positive people with standardised mortality rate 1.23 (95%CI: 1.13 to 1.48).

Amongst HIV positive people, having undetectable viral load on ART was associated with reduced risk of COVID-19 diagnosis: RR 0.70 (95%CI: 0.61 to 0.80).

Reference: Tosojiero J et al. Elevated COVID-19 outcomes among persons living with diagnosed HIV infection in New York State: results from a population-level match of HIV, COVID-19, and hospitalization databases. MedRxiv. DOI: 10.1101/2020.11.04.20226118v1. (6 November 2020).

https://www.medrxiv.org/content/10.1101/2020.11.04.20226118v1

Lower CD4 count is associated with increased risk of severe COVID-19 in people living with HIV

A retrospective analysis of 175 HIV positive adults with PCR-confirmed COVID-19 from three local cohorts – in Italy (n=65), Spain (n=49) and Germany (n=61) – reported low CD4 counts as an independent risk for more severe COVID-19. The analysis adjusted for all key HIV and COVID-19 factors.

Overall, COVID-19 was mild-to-moderate in 126 (72%) and severe in 49 cases (28%) - of which 16/40 were critically ill.

Median CD4 count was 663 cells/mm3 (range: 69 to 1715) and 69% had a CD4 count >500 cells/mm3. However, 39% had a CD4 nadir <200 cells/mm3 and 31% had a previous AIDS-defining illness.

CD4 count and nadir was lowere in participants with severe vs mild to moderate infection: 449 (69–1,100) vs 717 (161–1,715) and 185 (1–650) vs 304 (4–1,336) for current and nadir counts respectively.

In multivariate analysis, only current CD4 count <350 cells/mm3 and presence of at least one cormorbidity were significantly associated with severity of COVID-19 with adj OR 2.85 (95% CI: 1.26–6.44), p=0.01, for severe disease.

Although nadir CD4 T-cell count < 200 cells/mm3 was the only factor associated with mortality (OR = 10.11; 95% CI: 1.19 to 86.10; p=0.03), the number of deaths was too low to run an adjusted analysis.

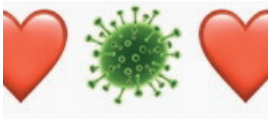
Reference

Hoffmann C et al. Immune deficiency is a risk factor for severe COVID-19 in people living with HIV. HIV Medicine. (27 December 2020).

https://onlinelibrary.wiley.com/doi/full/10.1111/hiv.13037

Very low-level viral load viraemia might continue after COVID-19

Simon Collins, HIV i-Base



A letter to CID reported a concern that higher HIV viral load levels might occur after HIV positive people on ART have recovered from COVID-19. However no significant differences were observed and no blips were reported above 20 copies/mL.

The results were from testing large volumes of HIV plasma using single copy viral load tests in 12 HIV positive people a median of 37 days (IQR: 29 to 62) after first COVID-19 symptoms compared to a control group of 17 HIV positive people the previous year.

Although not statistically significant, more people had detectable viral load in the COVID group: 83% vs 59%, whereas other characteristics were closely matched. The median viral load was also slightly higher: 1.59 vs 0.38 copies/mL in people with recent COVID-19 vs historical control.

Four of the COVID group had subsequent testing a median of 75 days (IQR: 58 to 90 days) with 3/4 still showing detectable viral load: median, 1.95 copies/mL (IQR: 0.1 to 14.53).

It is reassuring that the differences were small and without likely clinical significance. However, the low sample size suggest that larger studies are needed to know whether or not post-COVID viraemia might be a real effect.

Reference

Peluso MJ et al. A high percentage of people with HIV on antiretroviral therapy experience detectable low-level plasma HIV-1 RNA following COVID-19. Clinical Infectious Diseases, ciaa1754, DOI:10.1093/cid/ciaa1754. (19 November 2020).

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COVID-19: VACCINE RESEARCH

Pfizer COVID-19 vaccine might still overcome UK and SA variants

Simon Collins, HIV i-Base

The continued efficacy of current COVID-19 vaccines against two recent variants with multiple mutations in the S spike is an important and early concern.

Both recent variants linked to higher rates of transmission – B.1.1.7 in the UK and B.1.351 from South Africa - share the N501Y substitution in the S spike region. Similar unrelated variants have also been recently reported in Japan and Nigeria. [1]

An analysis published on 7 January 2021 from Pfizer reports likely continued activity for the their mRNA vaccine. However, the standard cautions apply for this paper not yet having been peer reviewed. [2]

The study reported continued impact on 16 isogenic viruses (essentially similar) developed with N501Y and tested immune response to these in samples from 20 participants who had previously received the Pfizer vaccine. These samples showed similar neutralising titres to both mutated and consensus viruses.

A limitation included in the paper includes that the N501Y viruses did not contain the full range of mutations in the UK and SA variants.

It also reported that the flexibility of mRNA technology would be able to respond to future emerging variants that might reduce vaccine responses. Continued ongoing surveillance research will be important for identifying new variants.

A letter to CID also reported a case of reinfection involving critical illness with the UK variant in a 78 year old man with multiple comorbidities who had previously experienced mild COVID-19 during the first wave in April 2020. [3]

The variant itself might not be the cause of the more serious outcomes as numerous cases of secondary infections with different outcomes have previously been reported before the recent variants. The letter also notes that this might also be the results of waning antibody responses from the first infection. [4]

Reference

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4. COVID-19 reinfection can occur after varying times and with more severe disease. HTB (14 October 2020).
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Novavax phase 3 vaccine study launched in the UK, South Africa, US, Mexico and Puerto Rico

Simon Collins, HIV i-Base

On 28 December, a press statement from Novavax publicised the launch of a new phase 3 study being run by Novavax in the US, Mexico and Puerto Rico. This randomised controlled study will enrol approximately 30,000 participants. [1, 2]

It also reported a similar phase 3 study enrolling 15,000 participants at 33 sites in the UK. [3]

An earlier phase 2 study with 4,400 participants is ongoing in South Africa. [4]

The vaccine candidate – NVX-CoV2373 – contains a full-length S spike protein (produced in insect cells) with a saponin-based adjuvant to enhance the immune response and to boost antibodies. It is stable at 2°C to 8°C and can be distributed with regular refrigeration.

As with other approved vaccines, it does not include an active virus and cannot cause COVID-19.

C O M M E N T

Although many serious preexisting conditions including immunosuppression are exclusion criteria, it is important that HIV is not specifically listed.

However, these placebo controlled studies are taking place during the roll-out of the UK national vaccination programme.

This means that study participants who are offered an NHS vaccine should have the option to be unblinded to the study arm as part of their decision to take up this offer.

A similar arrangement has been agreed in the US for participants in the phase 3 Pfizer and Moderna studies. The Vaccine Transition Option allows for participants to become unblinded to whether they were in the placebo arm, and to be given the active vaccine. [5]

References

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   https://ir.novavax.com/news-releases/news-release-details/novavax-announces-initiation-prevent-19-pivotal-phase-3-efficacy
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4. ClinicalTrials.gov. A study looking at the effectiveness and safety of a COVID-19 vaccine in South African adults. https://clinicaltrials.gov/ct2/show/NCT04533399
5. Vaccine Transition Option. https://www.covidvaccinestudy.com/participants

Merck/MSD withdraws two vaccine candidates from further research but continues focus on treatment

Simon Collins, HIV i-Base

On 25 January 2021, the US pharmaceutical company Merck announced that it was withdrawing two vaccine candidates against COVID-19 from further research.

This was due to the candidates – V590 and V591 – generating weaker responses in phase 1 studies compared to those seen after natural infection or to with other (unspecified) vaccines.

V590 was previously being developed in association with IAVI and results form both studies will be reported in peer-reviews journals.

Merck is still continuing to research potential treatments.

These include an antiviral drugs called molnupiravir (MK-4482) that is currently in four phase 2/3 studies as treatment and prevention, with results expected by May 2021.

A second compound, CD24Fc (MK-7110), is being studied to modulate inflammatory response to SARS-CoV-2. Interim phase 3 results reported 50% reduced mortality in people hospitalised with moderate to severe infection, although these are not yet published.

Further details on both treatment and vaccine candidates are included in the press release.

Outside the US, Merck is known as MSD.

C O M M E N T

Although the vaccine news is disappointing, this shows the high barrier set by the first vaccines. Even major companies with expertise in vaccine development are challenged with such high thresholds for efficacy and safety.

This doesn't diminish the need for new candidates that can meet the current global demand. There is also the potential for single-shot coverage, for formulations with easier delivery models than injections. that are easier to transport and that are less expensive.

It highlights that participants in vaccine research should still receive optimal standard of care. This should include the option to be unblinded from a research study if offered the chance of vaccination in the general NHS programme.

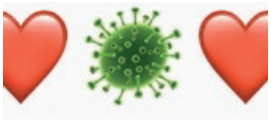
Reference

Merck press release. Merck discontinues development of SARS-CoV-2/COVID-19 vaccine candidates; continues development of two investigational therapeutic candidates. (25 January 2021).

https://www.merck.com/news/merck-discontinues-development-of-sars-cov-2-covid-19-vaccine-candidates-continues-development-of-two-investigational-therapeutic-candidates

Unprecedented rapid speed of COVID vaccine development

Simon Collins, HIV i-Base



Although HTB mainly includes reports with immediate clinical significance, a paper recently published in Annals of Internal Medicine is interesting for highlighting the unusually rapid development of vaccines against COVID-19.

Hopefully this sets a benchmark for future research.

A literature search, principally of studies listed on ClinicalTrials.gov, traced the likelihood of candidate vaccines for 23 new or emerging viral infections progressing from phase 2 to FDA approval and the associated timelines since 2005.

From 606 trials (involving 220 candidate vaccines and 267,000 participants) the probability of vaccines being approved within 10 years was 10% (95%CI: 2.6 to 16.9) with median time of 4.4 years (95%CI: 6.4 to 13.9). Most vaccines were against H1N1 or H5N1.

The study also concluded that any COVID vaccine developed within 18 months of phase 2 would be unprecedented.

Reference

MacPherson A et al. Probability of success and timelines for the development of vaccines for emerging and reemerged viral infectious diseases. Ann Intern Med. [Epub ahead of print]. doi:10.7326/M20-5350. (24 November 2020).

https://www.acpjournals.org/doi/10.7326/M20-5350

COVID-19: INVESTIGATIONAL DRUGS

Oral colchicine reduces hospitalisation in international randomised phase 3 outpatient study

Simon Collins, HIV i-Base

Top-line results from a large randomised phase 3 study report clinical benefits from the antiinflammatory drug colchicine and reduced mortality. This is an oral drug used that was studied in outpatients. [1, 2]

The ColCorona study randomised 4488 adults (>40 years old) with PCR-confirmed COVID-19 or clinical criteria, to either oral colchicine (0.5 mg twice daily for three days, then daily for 27 days) or placebo. This was a contactless study, with consultations by phone

Overall, the composite primary endpoint of death or hospitalisation occurred in 4.7% vs 5.8% of the colchicine and placebo groups respectively: OR 0.79 (95%CI: 0.61 to 1.03), p=0.08.

However, this became significant in the analysis of the 4159 participants with PCR-confirmed COVID-19: OR 0.75 (95%CI: 0.57 to 0.99), p=0.04. Events occurred in 4.5% vs 6.0% of the active vs placebo groups, respectively, and the colchicine group had a 25% risk reduction in the primary endpoint.

Although the press release reported that hospitalisation was reduced by 25%, mechanical ventilation by 50% and death by 44%, only hospitalisation results were statistically significant, with confidence intervals for ventilation and death crossing 1.0.

Significantly fewer serious adverse events were reported in colchicine arm: 4.9% vs 6.3%, p=0.05, with pneumonia in 2.9% vs 4.1%, respectively. Diarrhoea was more frequently reported with colchicine: 13.7% vs 7.3%, p<0.0001.

These results, were first published in a press release from the Montreal Heart Institute (MHI) that led this international study, with sites in Canada, the US, Brazil, South Africa and Spain. However, the pre-review paper was also published online soon after. [4]

Colchicine is an inexpensive medicine commonly used to treat gout and rheumatic disease.

References

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3. ColCorona website. https://www.colcorona.net
4. Tardif J-C et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. MedRxIV pre-review paper. doi: 10.1101/2021.01.26.21250494 (27 January 2021). https://doi.org/10.1101/2021.01.26.21250494

IL-6 agonists tocilizumab and sarilumab reduces mortality in severe COVID-19: interim results from REMAP-CAP study

Simon Collins, HIV i-Base

On 7 January 2021, preliminary results were published ahead of peer review from the international randomised adaptive platform REMAP-CAP study. This used two open label IL-6 agonists in adults with severe pneumonia in intensive care from COVID-19 and already needing organ support. [1, 2]

This led to announcements that both treatments would be immediately available for use in the UK.

Randomisation occurred within 24 of organ support with a primary outcome using an ordinal scale combining mortality in hospital and days without needing respiratory or cardiovascular support (up to day 21).

The study had a complicated design that included randomization, if eligible, to more than type of treatment (with each type referred to as a domain). It included predefined criteria for efficacy using routine interim analyses, and adapted based on changing standards of care.

Baseline characteristics were similar to cohorts hospitalised with COVID-19 and importantly ere balanced between active and control arms. Mean age was approximately 61 years (+/–12); 70% male; 73% white, 17% Asian, 4% black; with median BMI: 30 kg/m^2 (IQR: 27 to 35). Comorbidities were common (including diabetes mellitus 35%, respiratory 24% and kidney and severe cardiovascular each 10%).

High flow nasal oxygen was used by 28%, non-intensive ventilation by 41% and invasive mechanical ventilation by 30%.

The latest results, are based on outcomes from 803 participants from six countries, randomised to either of the monoclonal antibodies: initially to tocilizumab (n=353, 8 mg/kg) or later to sarilumab (n=48, 400 mg) - or to standard of care control (n=402). Tocilizumab was given twice (for 29%), 12-24 hours apart, but sarilumab could only be infused once. Corticosteroids were routinely included as part of standard of care by the majority of participants (610/654, 93%) although use was randomised for 158 of the earliest participants. Approximately one-third used remdesivir.

Other compounds in the immune modulator domain included an IL-1 receptor antagonist (anakinra) and interferon beta-1a. The results from these 69 participants are not included.

Statistical modelling was used to decide whether any effect was likely to be better or worse that other interventions or the control arm, based on posterior probability >99% or <0.25%, respectively. Differences were reported as odds ratios (with 95% credible interval) that were superior, equivalent or inferior,

An interim analysis on 28 October the DMSB reported that tocilizumab met the trigger to be superior to control (posterior probability 99.75%, OR: 1.87, 95%CrI: 1.20 to 2.76). Further randomisation to the control arm stopped on 19 November but continued to other immune modulators. At this time, 2,046 participants had been randomised to the study overall.

The median number of days without organ support were 10 (IQR: –1 to 16), 11 (IQR: 0 to 16) and 0 (IQR: –1 to 15) for tocilizumab, sarilumab and control, respectively.

The median adjusted OR were 1.64 (95% CrI: 1.25 to 2.14) for tocilizumab and 1.76 (95%CrI: 1.17 to 2.91) for sarilumab, with >99.9% and 99.5% posterior probabilities of superiority compared with control.

Mortality was 28.0% (98/350) for tocilizumab and 22.2% (10/45) for sarilumab compared to 35.8% (142/397) for control. Median OR for survival was 1.64 (95%CrI: 1.14 to 2.35) for tocilizumab and 2.01 (95% CrI: 1.18 to 4.71) for sarilumab.

All further outcomes and secondary and sensitivity analyses supported efficacy of these IL-6 receptor antagonists.

COMMENT

The peer-review version of this paper will be important given the complex statistical models. Also because of the choice of an unusual combined endpoint - mortality and time on organ support - even though mortality was independently associated with benefits.

This success doesn't mean there will be activity in earlier COVID-19.

Also, while the approximately 8% benefit compared to control was reportedly in addition to the protective impact of dexamethasone, the overall mortality still remained high in this study.

Earlier reports in HTB have included many earlier studies showing positive results although in August 2020 a lack of benefit in the phase 3 COVACTA led to an NIH recommendation against use, other than as part of a clinical trial.

References

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https://www.remapcap.org
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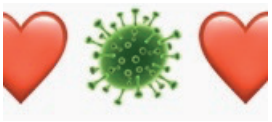
Two different dual antibody treatments each reduce SARS-CoV-2 viral load by >0.5 log

Simon Collins, HIV i-Base

Two studies, both published on 21 January 2021, report approximately 0.5 log greater reductions in SARS-CoV-2 viral load compared to placebo. The studies used different designs and were conducted in different study populations, but an early chance to reduce viral load, even by 0.5 log might have clinical benefits.



In one, early results were reported in JAMA from a randomised, placebo-controlled dose-ranging phase 2/3 study using bamlanivimab both as monotherapy and in combination with etesevimab. [1]

Both these monoclonal antibodies (also called LY-CoV555 and LT-CoV016 respectively) were derived from two patients with COVID-19 (in China and the US) and are in development with Eli Lilly.

The findings included a significant but small difference in the primary endpoint of reduction in viral load at day 11 for the combination arm compared to placebo, but no effect for the monotherapy arms.

The BLAZE-1 study included 577 participants with mild to moderate COVID-19 (with at least one symptom) at 49 trial sites in the US who received at least one randomised dose. In the initial stage, from 17 June to 21 August 2020, participants were randomised to one of three doses of bamlanivimab (700 mg [n=101], 2800 mg [n=107], or 7000 mg [n=101]) or placebo, with results already reported, and from 22 August to 3 September to dual therapy (2800 mg of bamlanivimab and 2800 mg of etesevimab [n=112]) vs placebo.

The final results (until 6 October), included a change in log viral load from baseline at day 11 was –3.72 for 700 mg, –4.08 for 2800 mg, –3.49 for 7000 mg, –4.37 for combination treatment, and –3.80 for placebo.

Only the combination therapy arm was significantly different compared to placebo: –0.57 (95%CI: –1.00 to –0.14], p=0.01.

An interim analyses of a second study published in NEJM, with a combination of two neutralising IgG1 antibodies, also reported a similar impact on SARS-CoV-2 viral load: –0.56 log copies/mL at day 7 (in participants who were antibody negative at baseline). [3]

This was in a randomised dose-finding placebo-controlled phase 1-3 study of REGN-COV2, and preliminary results were reported for 275 participants. The combination was used to minimise the risk of treatment resistance that had been previously observed with single antibody treatment. The study is still ongoing and primary and secondary endpoints will only be reported at the end of the study. The key viral endpoint was time-weighted average change in viral load at day seven, with a clinical endpoint of the percentage of participants with COVID-19 medical visits (all levels including telemedicine) by day 28.

REGN-COV2 contains equal doses of casirivimab (REGN10933) and imdevimab (REGN10987) and the study used 2.4 mg and 8.0 mg doses of the combination. Participants needed to have confirmed PCR positive test no more than 72 hours before randomisation and sypmtoms no more than seven days before.

The median age of the patients in the trial was 44.0 years 49% were male 13% identified as Black or African American and 56% identified as Hispanic or Latino.

Results were reported for 228/275 participants with data. At baseline, 123 patients (45%) were antibody positive, 113 (41%) were antibody negative, and 39 (14%) had unknown antibody status. As expected, median baseline viral load was significantly higher in the antibody negative group: 7.18 vs 3.49 log copies/mL, respectively, and this also correlated with higher risk of medical visits.

The study hypothysis included an expectation that in an out-patient setting people would present at various stages of their own antibody responses but that REGN-COV-2 would be most effective before this had begun.

Viral load responses compared to placebo were –0.52 log lower (95% CI: –1.04 to 0.00) and –0.60 log lower (95%CI: –1.12 to –0.08) in the low and high dose groups respectively, and –0.56 log (95% CI: –1.02 to –0.11) in the combined REGN-COV2 group

Very few participants attended a clinic visit: 6% (n=6) in the placebo vs 3% (n=6) in the combined REGN-COV2 groups. Tolerabilty was also good with few side effects of interest, slightly high in the placebo group.

COMMENT

Although the dual combination significantly reduced SARS-CoV-2 viral load, it is unclear whether an approximate half log reduction in viral load will have clinical significance.

Some clinical benefits were reported for the pooled active vs placebo analysis in the first phase of the study, although these were in post hoc analyses. [2]

However, it is interesting that a similar viral load effect was associated with reduced hospital visits and admission with the Regn-CoV-2 dual antibody.

An editorial commentary commented on the higher risk of serious hospitalisation correlated with very high An editorial in NEJM from Mike Cohen commented on the higher risk of serious hospitalisation correlated with very high viral load and this might be limited by early antibody treatment or by a rapid autologous immune responses. [4]

Also, that combination monoclonal antibodies might have a protective role in people who need more rapid protection than offered by a vaccine.

No benefits are seen with these compounds in later infecftion perhaps because inflammation and coagulopathy play a greater role than viral replication.

A recent useful webinar sponsored by multiple organisations (including the Indian government, Wellcome and IAVI) is now online about global access to monoclonal antibodies. [5]

Reference

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5. Global access pathways for monoclonal antibodies: Can Covid-19 pave the way? (19 January 2021).
   https://vimeo.com/502655311/dbe55ca125

IV methylprednisolone pulse treatment for hospitalised severe COVID-19

Simon Collins, HIV i-Base

Results from a small single-blind randomised study using an immune suppressing treatment in severe COVID-19 published in ERJ reported benefits from reducing respiratory inflammation.

From April to June 2020, the study randomised 64 adults hospitalised with COVID-19 and at an early stage of pulmonary illness (before mechanical oxygen), to add methylprednisolone pulse therapy (250 mg/day IV for 3 days) to standard of care (hydroxychloroquine, lopinavir and naproxen) or to standard of care alone. However, six participants in the control group were also given methylprednisolone and were excluded from the ITT analysis.

Significant benefits were reported for the active arm for the primary endpoints of clinical progression (94% vs 57%) and mortality (5·9% vs 42.9%; p <0·001). Increased survival time by Kaplan-Meier estimates was also reported to benefit the active arm: HR: 0.293 (95% CI: 0.154 to 0.556), p<0·001.

C O M M E N T

This small study was conducted at the Imam Khomeini Hospital, Tehran more than six months ago and was only recently published.

It would be useful to know whether this treatment became more widely used and whether similar outcomes have continued to be seen.

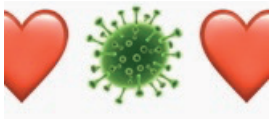
Reference

Edalatifard M et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. European Respiratory Journal 2020; DOI: 10.1183/13993003.02808-2020. (1 January 2021).

https://erj.ersjournals.com/content/early/2020/09/09/13993003.02808-2020

Monoclonal antibody bamlanivimab is not effective in advanced COVID-19: lack of early signal stops study early

Simon Collins, HIV i-Base



A phase 3 study using the COVID-19 monoclonal antibody bamlanivimab (formerly LY-CoV555) in advanced infection was stopped early due to lack of activity: other studies continue in earlier infection.

This was a randomised placebo-controlled study using a single infusion of bamlanivimab, with a primary endpoint of sustained recovery over 90 days. Results were published in the NEJM. [1]

On 9 November 2020, this compound received emergency use authorisation from the FDA. [2]

From 5 August to 13 October 2020, the study enrolled 326 participants in 31 sites (23 in the US, 7 in Denmark and 1 in Singapore). On 26 October however, the study was closed early after a recommendation from the Data and Safety Monitoring Board (DSMB). This was due to no impact on lung function at day 5 using a seven-category ordinal scale based on oxygen requirements. This is similar to the scale that showed faster recovery benefits with remdesivir.

If the five-day results had shown a benefit, the study would have advanced to enrol over 1000 participants.

At day five, 81 patients (50%) in the bamlanivimab group and 81 (54%) in the placebo group were in one of the two categories of the pulmonary scale.

Across all categories, the odds ratio of bamlanivimab participants being in a higher category was 0.85 (95% CI: 0.56 to 1.29), p=0.45.

There were no differences in the primary safety outcome (a composite of death, serious adverse events, or clinical grade 3 or 4 adverse events through day 5): 19% vs 14%, OR: 1.56 (95%CI: 0.78 to 3.10), p=0.020 or in the rate ratio for a sustained recovery: 1.06 (95% CI, 0.77 to 1.47).

C O M M E N T

This was the first of the US NIH-funded TICO (Therapeutics for Inpatients with Covid-19) studies to look at multiple monoclonal antibodies. The study will continue follow-up in participants who already received bamlanivimab.

Although these results are disappointing, the early analysis for lack of effect limited unnecessary risks for additional participants.

New antibodies already added in the next stage of the ACTIV-3 study include VIR-7831 from GSK and a dual combination of BRII-196 and BRII-198 from Brii Sciences. [3]

Other studies using bamlanivimab continue in earlier stage infection. [4]

References

1. ACTIV-3/TICO LY-CoV555 study group. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. NEJM. DOI: 10.1056/NEJMoa2033130 l. (22 December 2020). https://www.nejm.org/doi/full/10.1056/NEJMoa2033130
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4. ClinicalTrials.gov. ACTIV-2: A study for outpatients with COVID-19. https://clinicaltrials.gov/ct2/show/NCT04518410

RECOVERY study reports no benefits from azithromycin monotherapy for COVID-19: 1500 further deaths

Simon Collins, HIV i-Base

On 14 December 2020, the large randomised UK RECOVERY study announced that azithromycin had no benefit for the treatment of COVID-19. [1]

Previous results from this study included positive results for dexamethasone in last-stage infection but negative results for hydroxychloroquine and lopinavir/r.

Azithromycin had been chosen as a macrolide antibiotic that in additional to antibacterial activity can also reduce proinflammatory cytokines and has in vitro antiviral activity, including against SARS-CoV-2. Macrolide antibiotics are used to treat bacterial pneumonia and chronic inflammatory lung disease.

On 27 November 2020, the trial steering committee closed the azithromycin arm based on 'sufficient patients having been enrolled to establish clearly whether or not the drug had a meaningful benefit'. This shows that the timing was based on predetermined statistical calculations, rather than close observations from the Data and Safety Monitoring Board (DSMB).

Between 7 April and 27 November, 7,764 participants were randomised 1:2 to either azithromycin (n=2582) or standard of care (n=5182). However, more than 16,000 people were recruited to the RECOVERY study and just over 7000 were excluded from this randomisation because of contraindications to azithromycin or unavailability of drug. Roughly 15% of both the azithromycin and control participants were also enrolled in a second randomisation to another experimental drug.

Azithromycin (500 mg) was to given by mouth, nasogastric tube, or intravenous injection once daily for 10 days or until discharge, if sooner. In practice, the median duration of azithromycin was 6 days (IQR: 3 to 9 days). This was open-label for participants and local health workers, but study investigators were blinded to the outcomes.

Baseline characteristics included mean age 65 years (SD +/–15) with 58% being <70, 23% 70 to 80 and 19% >80 years. Ethnicity included 73% white, 14% BAME and 14% unknown; and 62% were men. Overall, 58% had a history of previous complications including diabetes (27%), heart disease (26%) or chronic lung disease (25%).

The median time since symptom onset was 8 days (IQR: 5 to 11 days) and time since admission to hospital was median 2 days (IQR: 1 to 4).

Other treatments of note included 46% using a corticosteroid, 20% using remdesivir and 17% using convalescent plasma. Supplemental oxygen was given to 76% and an additional 6% needed invasive mechanical ventilation.

Results

The interim results were based on 73% of participants. Follow up will be complete by the end of December for the 27% who hadn't reached this endpoint when this arm of the study was stopped.

Overall, 19% of participants died in each arm: 496 vs 997 in the azithromycin vs control arms respectively.

There was no difference in the primary endpoint of all-cause mortality at day 28 (RR 1.00; 95% CI 0.90 to 1.12), p=0.99). There were also no differences in use of mechanical ventilation, duration in hospital or in subgroup analyses (including age, sex, ethnicity, level of respiratory support, days since symptom onset, use of corticosteroids, and predicted 28-day mortality risk).

The pre-review paper summarising these results was also posted online, with much of the important details included in supplementary material. [2]

Statistical analysis

The study was based on a predetermined decision that a 20% reduction in 28-day mortality would be clinically significant. This was used to calculated numbers of participants needed to provide at least 90% power at two-sided p=0.01, adjusted by the background mortality reported in the study.

For example if mortality was 20% then the blinded Trail Steering Committee (TSC) calculated that the study would need 2000 participants in the experimental arm and 4000 in the control arm. As mortality in the study was lower, the TSC recommended these numbers increase to 2500 and 5000 respectively.

The trial protocol refers to the possibility of the trial stopping early due to benefit (needing "at least a 3 to 3·5 standard error reduction in mortality".

However, the protocol does not appear to consider earlier options for lack of benefit.

C O M M E N T

Few people will be surprised at these results as three smaller RCTs have already published similar outcomes. [3, 4, 5]

The time taken to find this lack of benefit though is disturbing and upsetting, together with the overall (accumulating) mortality.

More than 20,000 participants have now been enrolled in RECOVERY. Mortality rates suggest that more than 4,000 people will have died, and that perhaps fewer than 100 participants had their lives saved in the study (if enrolled to the early dexamethasone arm).

Although the study design was approved as acceptable eight months ago, the independent Data Monitoring Committee should arguably have a more active role in the event of no signal of benefit.

Allowing experimental arms to continue for so long while waiting for the primary endpoint of significant benefit is no longer acceptable. Including an early threshold for activity should be considered for the remaining study arms: tocilizumab, convalescent plasma, REGEN-COV2 (two monoclonal antibodies), aspirin, and colchicine.

This high over mortality in the ineffective arms - and the control arm - urgently raises questions about the stop/go thresholds for deciding whether or not there is sufficient signal of benefit for the ineffective treatments to continue.

References

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   https://www.medrxiv.org/content/10.1101/2020.12.10.20245944v1.supplementary-material
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COVID-19: GUIDELINES

WHO strongly recommended against using hydroxychloroquine or lopinavir/r at any stage of COVID-19

Simon Collins, HIV i-Base

On 17 December 2020, the World Health Organization (WHO) issued important new guidelines that reverse previous support for using either hydroxychloroquine or lopinavir/r for COVID-19. [1]

Early in the epidemic both drugs were thought by some researchers to have potential activity against COVID-19. However, results from randomised controlled studies throughout 2020 convincingly proved that neither drug has any role in preventing or treating COVID-19.

This third update to the guidelines were based on a meta-analysis of 30 trials with 10921 participants for hydroxychloroquine and seven trials with 7429 participants for lopinavir-ritonavir, including the WHO SOLIDARITY study. [2]

Importantly, “contextual factors including resources, feasibility, acceptability, and equity for countries and health care systems did not alter the recommendation”.

The guidelines made a strong recommendation supporting the use of corticosteroids in severe and critical COVID-19 and a weak recommendation against their use in earlier non-severe infection.

More controversially, the document also includes a weak recommendation against using remdesivir at any stage, even though this is approved in Europe and the US where it is included in the standard of care for reducing recovery time in people hospitalised with COVID-19.

C O M M E N T

The decision by WHO to withdraw the earlier support for both hydroxychloroquine and lopinavir/r is a clear signal that continued use is now clearly unethical.

Although few studies continue using either drug, the proposal to include both in a widely publicised international study in 13 African countries launched in December, justified continued use by their inclusion in WHO recommendations. [3]

The publication in BMJ has several confusing contradictions, likely proofing errors, including apparent contradictions between the body text and the simplified graphics and not updating the date of webpages (still showing 20 September initial version).

Reference
1. A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. DOIi: 10.1136/bmj.m3379 (17 December 2020). https://www.bmj.com/content/370/bmj.m3379
2. WHO SOLIDARITY study published in NEJM. HTB (9 December 2020). https://i-base.info/htb/39498
3. International COVID-19 study launches in Africa but with drugs that have little chance of working (ANTICOV). HTB (9 December 2020). https://i-base.info/htb/39419

NICE issue guidelines on long COVID

Simon Collins, HIV i-Base

On 18 December 2020, NICE issued brief guidelines on 'identifying, assessing and managing the long-term effects of COVID-19'.

It includes recommendations for adults, children and young people.

The guidelines also include advice on services to support people with long COVID.

Long COVID is defined in three categories: acute, ongoing symptomatic and a post-COVID syndrome.

- Acute symptoms that last longer than four weeks.
- New or ongoing symptoms from 4-12 weeks or more after the start of acute COVID-19.
- Post-COVID symptoms consistent with COVID-19 that continue for more than 12 weeks and are not explained by an alternative diagnosis.

The risk of developing long COVID is not thought to be linked to the severity of the acute COVID19 (including whether they were in hospital).

Potential symptoms include.

- Respiratory (difficulty breathing, cough, chest pain, palpitations).
- General (tiredness, fever, pain).
- Neurological (brain fog, memory, headache, poor sleep, neuropathy, dizziness, delirium)
- Gastrointestinal (nausea, diarrhea, abdominal pain, anorexia).
- Musculoskeletal (joint or muscle pain).
- Psychological/psychiatric (depression).
- Ear, nose and throat (tinnitus, earache, sore throat and loss of taste and/or smell.
- Dermatological (rashes).

The guidelines refer to the importance of individualising care, based on involving relevant specialists to manage symptoms. This should ideally be through a multidisciplinary service with a single point of care.

They include research questions based on areas of limited evidence (such as impact of age, sex and ethnicity on long COVID).

C O M M E N T

The guidelines are for health workers and commissioners.

This means that technically the document does not include information for people who actually have COVID-19.

They do not include specific treatment or management recommendations or address the situation if referral services are not immediately available.

Webcasts from an important 2-day NIH workshop on Long COVID are now online. [2]

An important international community study on Long COVID Community study on long COVID has recently been published as a pre-review draft and will be reviewed in the next edition of HTB. [3]

References
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3. Davis HE et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. Pre-review draft. MedRxiv. DOI: 10.1101/2020.12.24.20248802. (27 December 2020).
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Updated US guidelines for treating COVID-19

Simon Collins, HIV i-Base

The volume of rapidly expanding research on COVID-19 has meant that the main US treatment guidelines are often updated several times a month.

It is important to not only note four updates in December highlighted below but to regularly check for future updates.

Clinical spectrum of symptoms

The guidelines expanded the description and discussion of persistent symptoms or organ dysfunction following acute COVID-19. It also noted that more research was needed to understand post-infection complications.

PrEP

Two studies were added showing that hydroxychloroquine shows no benefit in preventing COVID-19 in healthworkers.

Antithrombotic treatment

The review of data on use of antithrombotic therapy were been updated to include recommendations during pregnancy.

Baricitinib

Guidelines about recent FDA Emergency Use Authorization (EUA) for the use of baricitinib, but based on limited data to recommend for or against its use with remdesivir, when corticosteroids can be used.

Also on the importance of clinical trials for informing use.

Guidelines on clinical management

This section had been expanded to include a new summary and a more detailed discussion of the processes that are thought to drive the pathogenesis of COVID-19

Casirivimab plus imdevimab (REGN-COV2)

Guidelines about recent FDA EUA for the monoclonal antibody combination of casirivimab plus imdevimab for the non-hospitalised patients with COVID-19 who are at high risk for progressing to severe disease and/or hospitalisation.

References

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (17 December 2020).

https://www.covid19treatmentguidelines.nih.gov

https://www.covid19treatmentguidelines.nih.gov/whats-new

US guidelines for using mRNA vaccines against COVID-19

Simon Collins, HIV i-Base

On 30 December 2020, the US guidelines on vaccines against COVID-19 were updated. As with other guidelines on COVID-19, they are likely to be updated frequently.

Main summary

- The current guidelines only cover the two mRNA vaccines approved in the US (Pfizer and Moderna).
- Both vaccines require two doses - 21 and 28 days apart for the Pfizer and Moderna vaccines, respectively.
- Caution is given it the second dose is given within a shorter window.
- Neither vaccines has a maximum time within which the second dose should be given.
- Although there is no preference between these two vaccines, both doses should be with the same vaccine. There is no data with mixed dosing.
- Any other vaccines should be ideally separated by a two-week window,
- Further boosting doses are not recommended until further data become available.
- Vaccines can be used by people with previous COVID-19.
- To include patient counselling on efficacy and safety.

Deferring vaccination

- People who received monoclonal antibodies against COVID-19 or convalescent plasma are recommended to wait 90 days before using a vaccine.
- People with current symptoms or a recent confirmed exposure should wait until quarantine restrictions are ended before having a vaccine.

Contraindications

The only people who are not recommended to use these vaccines

- Severe allergy after previous mRNA COVID 19 vaccine or any of its components (listed in an appendix).
- Any previous allergic reaction to polyethylene glycol or polysorbate.
- A history of severe allergy reactions to other vaccines, medicines and foods is not a contraindication to COVID-19 vaccines.
- No underlying health conditions are a contraindication against the COVID-19 vaccines.

Appendices

Several appendices are included on triage for vaccinations, ingredients in each vaccine and characterising allergic reactions.

Reference

US CDC. Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States. (30 December 2020).

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

US update guidelines on access to COVID vaccines

Simon Collins, HIV i-Base

On 20 December US guidelines were updated on the plans for access to vaccines against COVID-19. [1]

The initial guidance on 1 December was that health care workers and residents in long term care receive first priority (phase 1a).

In phase 1b, COVID-19 vaccine should be offered to the approximately 49 million people aged ≥75 years and non–health care frontline essential workers, and in phase 1c, to people aged 65–74 years, persons aged 16–64 years with high-risk medical conditions, and essential workers not included in Phase 1b.

Phase 2 includes everyone aged ≥16 years not already recommended for vaccination in earlier phases.

Recommendations for children and adolescents will only be made when a COVID-19 vaccine is approved for people aged less than 16 years.

The CDC open meeting that allowed representatives to speak on the importance of access for different communities was broadcast live. These hearings are also available as webcasts. [2]

References

1. Dooling K et al. The Advisory Committee on Immunization Practices' updated interim recommendation for allocation of COVID-19 vaccine — United States, December 2020. MMWR ePub. DOI: 10.15585/mmwr.mm695152e2. (22 December 2020). https://www.cdc.gov/mmwr/volumes/69/wr/mm695152e2.htm
2. Advisory Committee on Immunization Practices' (ACIP) live meetings. https://www.youtube.com/playlist?feature=edit_ok&list=PLvrp9iOILTQb6D9e1YZWpbUvzfptNMKx2

COVID-19: PATHOGENESIS

Long COVID: webcasts from two-day US workshop on now online

Simon Collins, HIV i-Base

The increasing awareness of the complexity on post-acute symptoms related to COVID-19 was covered in a two day workshop organised by the US National Institutes of Health (NIH).

The workshop, including breakout sessions, in now webcast with open access.

The workshop opens with an overview of the current challenges and includes talks on clinical observations (both US and international), and some insights from the patient's perspective.

Further talks cover pathology coronaviruses as well as host immune responses.

The second day starts with a talk on social determinants of health and race/ethnicity that are expanded in focus groups.

DAY 1

https://videocast.nih.gov/watch=38878

Session 1: Post-acute COVID-19: clinical observations

- Epidemiological and clinical landscape
- Experience from U.S. clinics
- Global perspective: experience from South Africa
- The post-acute COVID-19 xxperience

Session 2: Viral pathogenic features and host immune response

Immunological responses to SARS-CoV-2 infection and potential role in post-acute sequelae

- B cells/antibodies
- T cells
- Multisystem Inflammatory Syndrome in children
- Pathogenic features of coronaviruses and manifestations of extrapulmonary infection
- Approaches to researching post-acute sequelae of SARS-CoV-2 infection

Session 3: Post-acute COVID-19 perspectives

Neurological/psychiatric/neuromuscular, cardiovascular, pulmonary, renal/GI/metabolic, immunologic/rheumatologic, paediatric

DAY 2

https://videocast.nih.gov/watch=38879

Impact of Social Determinants of Health, Race and Ethnicity on Post-Acute COVID-19 Sequelae

Reports from breakout sessions.

1. Neurological/Psychiatric/Neuromuscular https://videocast.nih.gov/watch=38882
2. Cardiovascular https://videocast.nih.gov/watch=38880
3. Pulmonary https://videocast.nih.gov/watch=38884
4. Renal/GI/Metabolic https://videocast.nih.gov/watch=38883
5. Immunologic/Rheumatologic https://videocast.nih.gov/watch=38885
6. Pediatric https://videocast.nih.gov/watch=38881

C O M M E N T

An international community study on Long COVID Community study on long COVID has recently been published as a pre-review draft and will be reviewed in the next edition of HTB. [2]

References

1. NIH Workshop. 3-4 December 2020.
2. Davis HE et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. Pre-review draft. MedRxiv. DOI: 10.1101/2020.12.24.20248802. (27 December 2020).
   https://www.medrxiv.org/content/10.1101/2020.12.24.20248802v2

Most people hospitalised with COVID-19 have at least one symptoms after 6 months: Wuhan cohort

Simon Collins, HIV i-Base

A study by Huang and colleagues and published in the Lancet provides important results on longer-term outcomes from COVID-19 and importantly highlights the longer recovery times that are now starting to get more attention. [1]

This study includes results from 1,733 adults (from a total of nearly 2500) who were discharged from Jin Yin-tan Hospital in Wuhan, China, between 7 January and 29 May 2020.

Median age was 57 years (IQR: to). Follow-up visits were done from 16 June to 3 September 2020, and the median follow-up time was 186 days (IQR: to). This included subset of 390 with results from lung functions tests and 94 with antibody serology.

At follow-up, 76% of patients (1,265/1,655) reported at least one ongoing symptom. The most common were fatigue or muscle weakness (63%, 1,038/1,655), sleep difficulties (26%, 437/1,655) and anxiety or depression (23%, 367/1,733).

Antibody responses were significantly lower over time in the subset of participants with these results, with 96% vs 58 testing seropositive in acute vs follow-up samples and with median titres of 19 vs 10, respectively.

Reduced kidney was reported by 13% (107/822) of participants with previous normal kidney function based on eGFR levels being above vs below 90 mL per 1.73 m^2.

In 349 participants who completed the lung function test, those with more severe illness commonly had reduced lung function. There also reported slightly worse outcomes in a six-minute walking test: 29% at severity scale 5–6 walked less than the lower limit of the normal range (compared with 24% at scale 3, and 22% for scale 4).

However, only 4% of participants had been admitted to ICU during their hospitalisation, therefore underreporting the long-term outcomes from the most severe infections.

Reference

Huang C et al. Six-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet, DOI:10.1016/ S0140-6736(20)32656-8. (8 January 2021).

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32656-8/fulltext (website)

http://www.thelancet-press.com/embargo/longcovid.pdf (PDF)

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)

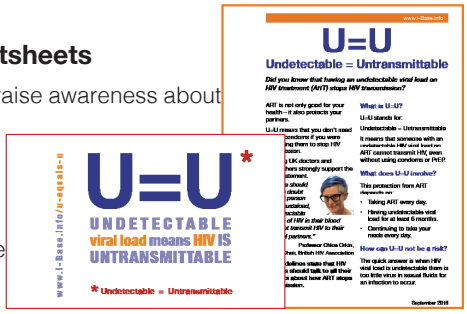
Pocket guides

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.

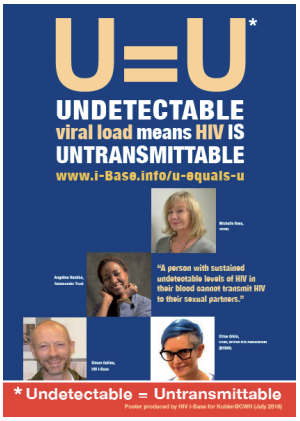
This project was developed with the Kobler Centre in London.

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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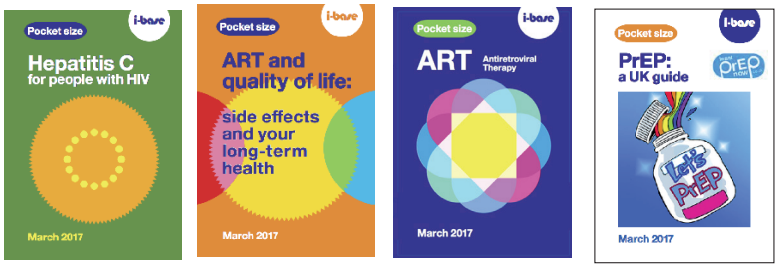

h-tb

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