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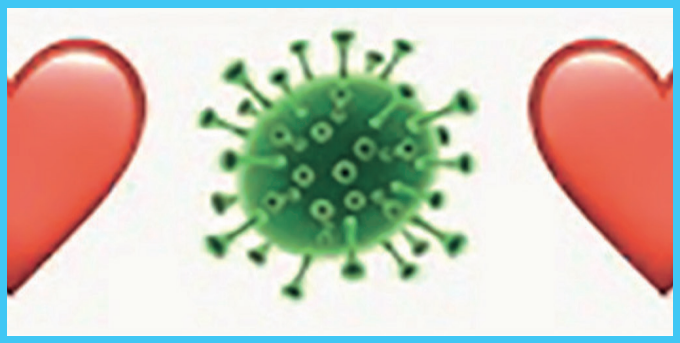
HIV and COVID-19 no. 3



HTB supplement (3): 14 May 2020

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HTB SUPPLEMENT ON COVID-19: ISSUE 3

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i-Base 2020 appeal

i-base appeal 2020

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

Please also see the new funding appreal supported by Wolfgang Tillmans Buildgin Bridges on page 3.

Each of the 16 posters are available for a donation of £50 / US$50 / 50 euros.

For full details please see:

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EDITORIAL

This is third HTB supplement on HIV and COVID-19 that is also now available as a separate PDF.

The publication aims to compile and review research over the last month - which has seen many new developments including more attention on the wider pathogenesis of COVID-19 beyond respiratory complications.

This issue also reports on new HIV/COVID-19 cohorts - still with small numbers - that still cautiously support no excess risk for people on effective ART.

Similarly, both BHIVA and EACS maintain that a good CD4 count on effective ART shouldn't affect risk from COVID-19, but also acknowledge that many people are also in higher risk categories due to our age and other comorbidities.

We also summarise the new BHIVA HIV treatment guidelines for COVID-19 that incorporate reduce/deferred monitoring and preferential use of bictegravir/F/TAF for first-line ART.

Several papers have focus on the complex pathogenesis of COVID-19 and that cells susceptible to CoV-2 infection are widely distributed throughout the body. There are increasing reports of complications from cardiovascular disease, blood clots, neurological complications and most recently the reports of hyperinflammatory shock in children in London and New York being described as atypical Kawasaki disease.

Some experimental treatments look more promising than others - including drugs to specifically target the inflammatory cytokine storm that characterizes the most severe stages of COVID-19. This issue includes information on anticoagulants (all formulations), anti-inflammatory drugs (tocilizumab, anakinra, baricitinib) and convalescent plasma. Less optimistic results are included on HIV drugs (lopinavir/r, darunavir, TAF), hydroxychloroquine and childhood BCG.

The most promising studies are using combination treatment but earlier access to all treatments seems important, even though most studies are still not being used 10-12 days after first symptoms.

During the last two weeks, remdesivir squeezed through the regulatory pathways with emergency approval in the US and Japan with a trade name Veklury. Although the indication is for severe hospitalised COVID-19, earlier use might be better. The limited data means this is currently an antiviral drug that in human studies shows no impact compared to placebo on viral load in throat swabs or lung tissue, and despite a relatively clean side effect profile, no apparent benefit from longer dosing in studies without a placebo or standard of care arm (10 vs 5 days).

This issue is produced during a time when the numbers of UK deaths have passed 32,000 and when there is still insufficient support for NHS staff and other key workers including in transport and retail, to be protected at work or for testing to be available widely enough to manage risks.

Under these circumstances we continue to be especially grateful for the continued commitment and care from the NHS and other services.

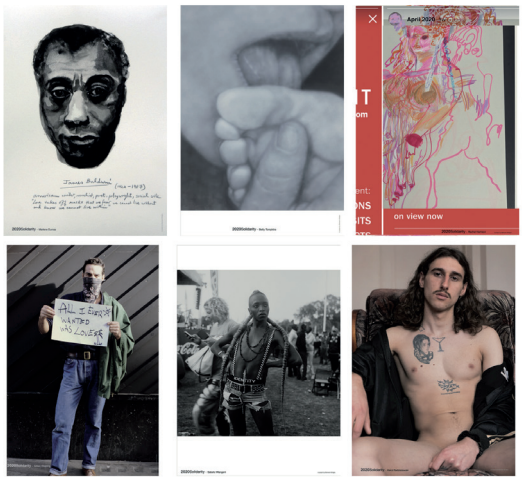
Support i-Base's work on HIV and COVID-19: posters curated by Wolfgang Tillmans

As part of the 2020Solidarity initiative launched by Between Bridges and Wolfgang Tillmans, please support i-Base's work on HIV and COVID-19.

Each of the 16 posters are available for a donation of £50 / US$50 / 50 euros.

For full details please see:

http://i-base.info/2020solidarity



COVID-19: HIV and COVID-19 COINFECTION

Higher rates of more serious outcomes in HIV and COVID-19 coinfection in Germany is interpreted cautiously

Simon Collins, HIV i-Base

The first detailed outcomes from a more sizable (but still small) cohort of 33 HIV positive people (30 men, 3 women) diagnosed with COVID-19 has been published in the May issue of the journal Infection. [1]

Until now, evidence of larger cohorts has been published (87/18107 in the ISARIC COVID-19 database and 43/5700 in the New York study reported below), but neither of these include clinical details. [2, 3] Otherwise, more detailed information has only trickled through in much smaller numbers, the largest of which was five people reported from Barcelona. [4]

The new study retrospectively analysed anonymous data from 33 people diagnosed with COVID-19 between 11 March and 17 April 2020 in 12 participating German HIV centres. Clinical outcomes were available for 32/33. Mean age was 48 years (range 26 to 82) and all were on ART. Viral load was below 50 copies/mL in all except two who were <1000) copies/mL when critically ill on ICU. Overall, 76% were classified as mild cases, 91% (n=29) recovered and 9% (n=3) died.

A wide range of ART combinations were being used, including all classes and ~ 20 using combinations with F/TAF or F/TDF backbone; 20 with INSTIs, 4 with PIs (all darunavir) and 9 with NNRTIs. 12 people had CD4:CD8 ratio $\geq$ 1.00.

Likely route of infection included 14 people with close contact with someone documented as CoV-2 positive and 14 with recent history of travel abroad. Most people were diagnosed with COVID-19 at outpatients (n=26) with seven diagnosed in hospital.

The median CD4 count before diagnosed SARS-CoV-2 was 670 cells/mm^3 (range 69 to 1715).

Overall, 14/33 (42%) were admitted to hospital and of these, 6/14 (43%) were treated in ICU. The three deaths included the 82 year old man (positive for 28 years and with detectable viral load before COVID-19), a 55 year old man with very low CD4 count of 69 cells/mm^3 (and CD4:CD8 ratio of 0.06) and a 59 year old man with hypertension, COPD and Type-2 diabetes.

C O M M E N T

Although this retrospective and uncontrolled series included a death rate more than double the death rate in HIV negative people in Germany (9% vs 3.7%), more severe cases (24% vs ~19%) and more hospitalisations (42% vs 17%), the authors did not conclude their data supported excess morbidity and mortality in people on controlled ART.

They comment that these figures might be overestimated due to caution in admitting HIV positive people to hospital and only including people who were symptomatic. However, mechanical ventilation was needed by both people whose viral load was detectable before COVID-19, perhaps showing the importance of controlled HIV.

These data should be interpreted cautiously but show the urgency for HIV status to be actively included at baseline in management of COVID-19 and for this to also be included in medical records and databases linked to the pandemic.

References

1. Härter G et al. Infection (2020). DOI: 10.1007/s15010-020-01438-z. (11 May 2020). https://link.springer.com/article/10.1007/s15010-020-01438-z
2. ISARIC Clinical data COVID-19 report (27 April 2020). https://media.tghn.org/medialibrary/2020/05/ISARIC_Data_Platform_COVID-19_Report_27APR20.pdf (PDF)
3. Collins S. HIV is not linked to higher risk of COVID-19 in large New York cohort. (12 May 2020). http://i-base.info/htb/37739
4. Collins S. Case series of five HIV positive people diagnosed with COVID-19 in Spain. (17 April 2020). http://i-base.info/htb/37661

HIV is not linked to higher risk of COVID-19 in large New York cohort

Simon Collins, HIV i-Base

Several papers have been recently published that include HIV status of people hospitalised with COVID-19.

The largest of these, published as an open access paper in JAMA, includes 5700 people hospitlised in the wider New York area between 1 March and 4 April 2020, where 43 were also recorded as being HIV positive (0.8%). [1]

This is a comprehensive dataset for demographics, comorbidities, home medications, symptoms, laboratory tests, electrocardiogram results and treatments. Clinical outcomes (including length of stay, discharge, readmission, and mortality) are presented for 2634/5700 patients who completed their hospital course at study end (discharged alive or dead). Please see the full paper for details (especially for details on hypertension and ACE inhibitors).

The population covered by the hospitals includes approximately 11.3 million people in the New York metropolitan, which has approximately 100, 000 people are HIV positive (1%).

Although the study doesn't include multivariate analyses for risk factors, the results are perhaps the most optimistic dataset to support HIV itself not being a risk factor for COVID-19.

Two other papers included smaller retrospective cohorts of just under 400 people. One is also from New York and one from Barcelona, which reported seven and five people respectively who were also HIV positive. [2, 3]

C O M M E N T

These results should be slightly reassuring for HIV positive people, although many of us also have other risk factors for COVID-19 that are common. However, the hospitals in this area are not the inner city clinics that are more commonly attended by people who are HIV positive.

Hopefully, as the largest cohort of HIV/COVID-19 coinfection so far, the researchers JAMA study could report characteristics of people with HIV coinfection.

It is important that HIV status is included for all people hospitalized with COVID-19 in the UK.

Anecdotal reports of 13 people diagnosed with COVID-19 at a central London clinic included 13 who are also HIV positive. Approximately half of these people were on ART that contained TDF/FTC, showing that HIV PrEP is not effective at preventing COVID-19. [4]

The data on ART use in these cohorts could perhaps inform an ongoing study for coronavirus prophylaxis in health workers is that is proposing to study TDF/FTC as prophylaxis for COVID-19. [5]

References

1. Richardson S et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. doi:10.1001/jama.2020.6775. (22 April 2020). https://jamanetwork.com/journals/jama/fullarticle/2765184
2. Goyal P et al. Clinical Characteristics of Covid-19 in New York City. NEJM. DOI: 10.1056/NEJMc2010419. (17 April 2020). https://www.nejm.org/doi/full/10.1056/NEJMc2010419
3. Case series of five HIV positive people diagnosed with COVID-19 in Spain. HTB (17 April 2020). http://i-base.info/htb/37661
4. Personal communication.
5. COVID-19 prophylaxis using TDF/FTC and low-dose hydroxychloroquine in Spanish health workers. HTB (17 April 2020). http://i-base.info/htb/37625

Case study shows darunavir does not protect against CoV-2

Simon Collins, HIV i-Base

Although in vitro studies reported possible antiviral activity of boosted darunavir (DRV) against CoV-2, in March 2020 Janssen issued an early statement advising against using this drug in research against COVID 19. [1]

Nevertheless, and to confirm lack of protection, three cases have been reported of HIV positive people (two men and one woman) who were diagnosed with COVID-19 despite using boosted-darunavir-based ART. [2]

The historical details of the three cases are not worth reporting, as the approach to management is already out of date

and against current guidelines (ie - switching DRV to lopinavir/r and adding hydroxychloroquine).

References
1. Janssen press statement. Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. (16 March 2020). https://www.janssen.com/uk/sars-cov-2-treatment
2. Riva D et al. Darunavir does not prevent SARS-CoV-2 infection in HIV patients. Pharmacological Research (157), 104826 (20 April 2020). https://www.sciencedirect.com/science/article/pii/S1043661820311348

COVID-19: TREATMENT ACCESS

COVID-19 could lead 500,000 excess HIV-related deaths in Sub-Saharan Africa including from interruptions in ART

Polly Clayden, HIV i-Base

COVID-19 associated disruptions to HIV services could lead to over 500,000 excess adult deaths and approximately double the rate of vertical transmission – according to modelling published ahead of print 11 May 2020. [1, 2]

Investigators from the HIV Modelling Consortium set out to predict the potential effects of disruptions associated with the COVID-19 epidemic on HIV-related deaths and new infections.

They combined results from five independent models of HIV epidemics (Goals, Optima HIV, HIV Synthesis, an Imperial College London Model and EMOD) to estimate the effect of various potential scenarios on HIV treatment and prevention services.

Unsurprisingly, disruptions to all aspects of HIV care were associated with increases in mortality risks. Most importantly interruptions to the supply of ART leading to treatment discontinuation.

The modelling predicted that 6-months interruption of ART supply across the HIV population could lead to approximately 2-fold increase in mortality risk (from 1.87- to 2.80-fold across models) over a one year period compared with no disruption.

There was also an effect predicted in the years following the 6-month disruption of around 40% (35% to 41% across models) excess death for each of the next five years.

In countries and regions in sub-Saharan Africa this suggested an excess of over 500,000 (range: 471,000 to 673,000) excess HIV deaths following the 6-month disruption.

A more sporadic interruption of ART supply (across only a proportion of the population or for a shorter time) would have less effect on mortality: 1.05- and 1.17-fold increase compared with current annual deaths for a 3- and 6 month interruption respectively (1.00- and 1.03-fold increase over 5 years).

The authors noted that even in a scenario with largely dolutegravir-based ART, interruptions would lead to an increase in drug resistance and a 1% lower proportion of people with undetectable viral load in the next 5 years.

An interruption in the supply of cotrimoxazole was predicted to result in an increase in HIV mortality of 8% over one year.

Stopping maternal/infant HIV activities could lead to significant increases in the number of vertical infections: 78% Malawi, 37% Mozambique, 104% Uganda and 78% Zimbabwe. The impact of ART interruption on vertical transmission was predicted to be an excess of 1.67 and 2.07 times more babies born with HIV in one year as a result of 3 and 6 months disruption, respectively.

Disruption to outreach and condom programmes could lead to increases in new HIV infections of up to 25% a year. PrEP programmes are currently small in most settings but a 6-month disruption was predicted to lead to a 1% rise in HIV incidence over one year.

The authors concluded that, when considering plans to manage the effects of the COVID-19, it is critical that governments, donors, suppliers and communities focus on maintaining the supply of ART for people with HIV to avoid excess deaths, and the provision of other prevention strategies to stop any increase in HIV incidence.

References
1. Jewell B et al for the HIV Modelling consortium. **Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple models.** Pre-print 11 may 2020.
https://doi.org/10.6084/m9.figshare.12279914.v1
https://doi.org/10.6084/m9.figshare.12279932.v1

2. WHO press release. The cost of inaction: COVID-19-related service disruptions could cause hundreds of thousands of extra deaths from HIV. 11 May 2020.
https://www.who.int/news-room/detail/11-05-2020-the-cost-of-inaction-covid-19-related-service-disruptions-could-cause-hundreds-of-thousands-of-extra-deaths-from-hiv

COVID-19: INVESTIGATIONAL DRUGS

Remdesivir for COVID-19: randomised study shows similar antiviral effect to placebo

Simon Collins, HIV i-Base

Leaked results from a study of the antiviral drug remdesivir, have reported no benefit when used in late-stage COVID-19. The top-line results were posted online on the WHO website and have since been taken down, but a screen shot is still available, included in a report from STAT news. [1]

The summary results showed that 237 participants hospitalised with severe COVID-19 were randomised to remdesivir (n=158) or control (n=79). There were no differences in clinical outcomes: clinical improvement [HR 1.23 (95%CI: 0.87 to 1.75)] or mortality at 28 days [13.9% vs 12.8%, difference 1.1 (95%CI: –8,1 to +10.3)]. The summary results also include no difference in viral load (PCR) although further details are not included. Both groups reported side effects in about 65% of participants. More people stopped treatment due to side effects in the remdesivir group: 18 (11%) vs 4 (5%).

That is all though. A press release from Gilead Sciences, the company developing remdesivir, confirmed that the results were released before they had been peer-reviewed, and that the study, being run in China, had been stopped early due to low recruitment. [2]

The results are important because they provide randomised data where remdesivir use is compared to a control group not getting this drug. The only other published data on remdesivir is from open-label use in an expanded programme. These results were difficut to interpret because some people recovered (as they would anyway) and some people still died (just showing that remdevisir cannot help everyone in late-stage COVID-19). [3]

However, remdesivir was being used in late stage COVID-19 when it might be more effective much earlier. Remdesivir is an antiviral drug that was previously studied to treat Ebola virus. In-vitro studies showed activity against a range of viruses, including SARS-1, SARS-2 and Ebola virus, though this did not translate to clinical benefit for Ebola. Recently published studies show antiviral activity against COVID-19 and MERS in monkeys and improved clinical results when used early in infection. [4, 5]

Without commenting further on other issues about study design and leaking of early data remdesivir levels of coronavirus have already dropped once COVID-19 has become a severe inflammatory disease. So there is plausibility that earlier use might show a benefit. This is the second time that early data has been leaked before being peer-reviewed and published by STAT news. [6]

A simplified description of COVID-19 has three different stages (which might also overlap), each lasting around a week, and getting progressively worse.[7]

1. An initial viral infection in throat and upper respiratory tract. This will be positive to PCR throat swabs and is when someone will also be very infectious.
2. Move to upper and then lower lungs where this becomes an inflammatory (not viral) disease. The immune response steadily blocks the lungs with pus and dead cells as a result of a cytokine storm, blocking oxygen from getting into the blood.
3. A severe stage of immune activation, with oxygen depletion, risk of major organ failure, use of mechanical ventilators (after medically induced coma) etc.

C O M M E N T

Mainstream press emphasised the negative results in articles that fail to analyse the mechanism of action for remdesivir or the stage of COVID-19. The report in the Guardian went further by questioning early access to investigational compounds. [8, 9, 10]

Expanded access programmes were an achievement of AIDS activism that kept thousands of HIV positive people alive

until the drugs were approved. If remdesivir - or any other antiviral - shows benefits in early infection, then demands for expanded access before approval will be just as important now.

This highlights the urgency of wider access to testing - and also to run studies in earlier COVID-19 infection.

Two phase 3 remdesivir studies are already ongoing in the UK in moderate and severe stage COVID-19. [11] The Data and Safety Monitoring Boards (DSMB) for these studies should be alert for any signals of earlier benefit.

Note: the paper has now been published in the Lancet. [12]

Although the full results include a numerically faster time to clinical improvement in the remdesivir vs placebo arms for people who started treatment earlier (less than ten days since symptoms), this was not statistically significant (hazard ratio 1·52; 95%CI: 0·95 to 2·43).

Of greater concern is the lack of difference in viral load reductions between the active and placebo group, given that remdesivir would be expected to have a direct antiviral effect.

References

1. Gilead press statement. Gilead Sciences statement on data from remdesivir study in patients With severe COVID-19 in China. (23 April 2020). https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-data-from-remdesivir-study-in-patients-with-severe-covid-19-in-china
2. Silverman E. New data on Gilead's remdesivir released by accident show no benefit for coronavirus patients. Company still sees reason for hope. (23 April 2020). https://www.statnews.com/2020/04/23/data-on-gileads-remdesivir-released-by-accident-show-no-benefit-for-coronavirus-patients/
3. Collins S. Remdesivir for COVID-19: first results from compassionate access programme. HTB (17 April 2020). http://i-base.info/htb/37593
4. Williamson B et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. BioRxiv (ahead or peer review). doi: 10.1101/2020.04.15.043166. https://www.biorxiv.org/content/10.1101/2020.04.15.043166v1
5. de Wit et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. PNAS March 24, 2020 117 (12) 6771-6776. (13 February 2020). https://www.pnas.org/content/117/12/6771
6. Silverman E. Pharmalittle: Early data suggests Gilead Covid-19 drug works; did FDA drop standards too far in hunt for chloroquine? STAT news. (17 April 2020). https://www.statnews.com/pharmalot/2020/04/17/gilead-fda-covid19-coronavirus-remdesivir-choloroquine/
7. A clinical-therapeutic staging proposal for COVID-19. HTB (17 April 2020). http://i-base.info/htb/37627
8. Boseley S. First trial for potential Covid-19 drug shows it has no effect. The Guardian. (23 April 2020). https://www.theguardian.com/world/2020/apr/23/high-hopes-drug-for-covid-19-treatment-failed-in-full-trial
9. Manchini DP. Gilead antiviral drug remdesivir flops in first trial. Financial Times. (23 April 2020). https://www.ft.com/content/0a4872d1-4cac-4040-846f-ce32daa09d99
10. BBC. Hopes dashed as coronavirus drug remdesivir 'fails first trial'. (24 April 2020). https://www.bbc.co.uk/news/world-52406261
11. Gilead expand UK sites for two phase-3 studies of remdesivir to treat COVID-19. HTB (17 April 2010). http://i-base.info/htb/37520
12. Wang Y et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. DOI: 10.1016/S0140-6736(20)31022-9. (29 April 2020). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

Other remdesivir news: top results from NIH and Gilead studies - emergency approval in US and Japan

Simon Collins, HIV i-Base

On the same day that the Lancet published the results of the Chinese placebo-controlled study reporting a lack of effect (see article above [1]), top-line results were released from two other studies.

The highest profile of these was probably the placebo-controlled NIAID study that enrolled more than 1000 people hospitalised with COVID-19.

NIH ACTT study

The Adaptive COVID-19 Treatment Trial (ACTT) study had started on 21 February 2020, and randomised 1063 participants. On 27 April, the DSMB reported 31% shorter time to recovery (the primary endpoint, defined as well-enough for hospital discharge) in the remdesivir compared to the placebo group ($p<0.001$). [2, 3]

The median time to recovery was 11 days vs 15 days for the remdesivir vs placebo groups. The difference in mortality also showed a trend towards benefit: 8.0% vs 11.6% ($p=0.059$). Further details have still to be released.

Gilead SIMPLE study

Also on 29 April 2020, Gilead Sciences issued a press statement releasing top-line results from the phase 3 SIMPLE study that randomised 397 hospitalised participants with symptoms of severe COVID-19 to either 5-day or 10-day remdesivir. [4]

The results included similar clinical outcomes at day 14 in both groups (OR: 0.75 [95% CI 0.51 to 1.12]). Importantly though, there is no control group receiving placebo or only standard of care.

Clinical improvement was defined by moving at least two points on a seven point scale (ranging from hospital discharge to death). Time to improvement was 10 vs 11 days in the 5 vs 10-day groups. More than half the participants in each group were discharged by day 14: 60% (120/200) vs 52% (103/197); p=0.14. At Day 14, 65% (129/200) vs 54% (106/197 achieved clinical recovery, both in 5 vs 10 day groups respectively.

Although the differences were not statistically significant, it is perhaps unusual that numerically all three of these parameters favoured the shorter 5-day dose.

In what sounds like a pooled post-hoc analysis, the press release states that earlier access to treatment (within 10 days of first symptoms) led to 62% vs 49% being discharged from hospital.

There were no difference between the two groups in terms of deaths (n=16 vs 21; 8% vs 11%, p=0.7) or serious adverse events.

FDA emergency authorisation

On 1 May 2020, on the basis of only the top-line results from the ACTT and SIMPLE studies, the US FDA issued an emergency use authorisation for remdesivir as a 'potential' new treatment for severe COVID-19 (defined as oxygen depletion <94% on room air or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). [5, 6]

The FDA letter of approval based the decision on three criteria:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus.
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that remdesivir may be effective in treating COVID-19, and that, when used under the conditions described in this authorisation, the known and potential benefits of remdesivir when used to treat COVID-19 outweigh the known and potential risks of such products.
3. There is no adequate, approved, and available alternative to the emergency use of remdesivir for the treatment of COVID-19.

Approval in Japan

On 7 May 2020, Gilead also announced approval of remdesivir in Japan under an 'exceptional approval pathway'. The trade name is Veklury. [7]

Access to remdesivir in Japan will be provided free to patients by government hospitals.

C O M M E N T

Remdesivir has an indication for severe COVID-19 (although hinting at data that suggests earlier use might be better), an antiviral profile that shows no impact compared to placebo on PCR in throat swabs or lung tissue, and despite a relatively clean side effect profile, no benefit from longer dosing (10 vs 5 days) in studies without a placebo or standard of care arm.

It is not so much (in a nod to the BHIVA/EACS statement) that full data are eagerly awaited, but a difficulty understanding these approvals without a more substantive data set being shared in the public domain.

Although there is recent animal data to support remdesivir being clinically effective in rhesus macaque studies using a comparable dose to that used in humans, with some reductions in viral load, the faster progression in macaques makes commenting on timing difficult. Nevertheless this paper discussed the potential benefits of using remdesivir as early as possible to get the maximum treatment effect. [8]

References
1. Wang et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext
2. NIAID press statement. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. (29 April 2020). https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

3. NIH clinical trial of remdesivir to treat COVID-19 begins/ (25 February 2020).
https://www.niaid.nih.gov/news-events/nih-clinical-trial-remdesivir-treat-covid-19-begins
4. Gilead press release. Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. (29 April 2020).
https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19
5. FDA news release. Coronavirus (COVID-19) Update: FDA issues emergency use authorization for potential COVID-19 treatment. (1 May 2020).
https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment
6. Remdesivir Safety information.
https://www.fda.gov/media/137566/download
7. Gilead press release. Gilead announces approval of Veklury (remdesivir) in Japan for patients with severe COVID-19. (7 May 2020).
https://www.gilead.com/news-and-press/press-room/press-releases/2020/5/gilead-announces-approval-of-veklury-remdesivir-in-japan-for-patients-with-severe-covid19
8. B. Williamson, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Pre-peer review. DOI: 10.1101/2020.04.15.043166. (22 April 2020).
https://www.biorxiv.org/content/10.1101/2020.04.15.043166v2

Potential for tocilizumab to treat moderate to severe COVID-19

Simon Collins, HIV i-Base

A study published in PNAS includes encouraging reports from use of the anti-IL-6 monoclonal antibody tocilizumab as treatment for COVID-19 and a press release issued by INSERM two days earlier promises significant results but includes no further details.

The Chinese study ran from 5 to 14 February at a single site in Wuhan and included 21 participants (18 men, 3 women): mean age 56 years (± 16, range 25 to 88). Baseline symptoms included fever (21/21), cough (14/21), phlegm (9/21), fatigue (6/21), tight chest (6/21). Overall, 17/21 were judged severe and 4/21 critical with 9/20 using high flow oxygen, 7/20 using nasal canula, 2/10 using invasive ventilation, 1/21 using non-invasive ventilation and 1/21 using an oxygen mask. [1]

Fever and body temperature returned to normal on day one in all participants. Other symptoms improved within a few days including reductions in CRP (from 75.06 mg/L ± 66.80 before tocilizumab to 2.72 ± 3.60 (day 5), although IL-6 remained very elevated (274.90 ± 414.08 at day 5). Oxygen saturation improved and 15/20 had lowered oxygen intake by day 5.

No serious events were associated with tocilizumab with no reports of elevated transaminase, neutropenia, infection, etc. There were no emerging bacterial, fungal, or viral infections were observed during the treatment.

All participants were discharged within mean 15 days (+/– 5.8, range 10 to 31 days).

Two days earlier, a press release from the French INSERM network reported positive results but only with the most limited results. This is from a multicentre study that randomised 129 participants with moderate to severe COVID-19 pneumonia to open label tocilizumab in addition to standard of care compared to standard of care alone, and that had significantly fewer composite primary endpoints of the need for ventilation or deaths at day 14. [2]

However, although the results have been submitted for publication, further details were not made available in terms of participant responses or the degree of benefit, and the study apparently is still ongoing.

The CORIMUNO-19 study was started on 27 March 2020 to evaluate the efficacy and tolerance of various immune modulators and other treatments in adult patients with severe COVID-19 infection and is still ongoing.

Approximately 30 other studies are planned or ongoing on clinicaltrials.gov. Another dozen studies are using sarilumab and one study in Russia is using olokizumab. [3]

References

1. Xu X et al. Effective treatment of severe COVID-19 patients with tocilizumab. PNAS, DOI: 10.1073/pnas.2005615117. (29 April 2020).
https://www.pnas.org/content/early/2020/04/27/2005615117
2. INSERM press release. Tocilizumab improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia. (27 April 2020).
https://pipelinereview.com/index.php/2020042874458/Antibodies/Tocilizumab-improves-significantly-clinical-outcomes-of-patients-with-moderate-or-severe-COVID-19-pneumonia.html
https://translate.google.com/translate?hl=en&sl=fr&u=https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinical-outcomes-patients-moderate-or-severe-covid-19&prev=search\
3. clinicaltrials.gov. Search results for tocilizumab and COVID-19.
https://clinicaltrials.gov/ct2/results?cond=&term=tocilizumab+covid-19&cntry=&state=&city=&dist=

Detectable viral load and IL-6: a role for tocilizumab or anti-JAK inhibitor baricitinib?

Simon Collins, HIV i-Base

A study of 48 participants (31 men, 17 women) enrolled in a COVID-19 hospital in Wuhan City, China, reported a close correlation between disease severity and both RNA viral load in serum and elevated levels of IL-6.

No cases were categorised as mild; 21 were moderate (43%), 10 severe cases (21%), and 17 critically ill cases (35%). Although viral load in throat samples was positive in all patients, serum PCR was only positive in five patients who were critically ill, two of whom died.

Peripheral blood leukocytes inversely correlated with severity of COVID-19 and IL-6 was sharply increased in critical patients, 10-fold higher than that in severe patients, all exceeding 100 pg/mL.

RNA and IL-6 were both closely correlated with severe illness (r=0.902) and patients with higher levels had great risk of organ damage.

The researchers concluded with a discussion on plausible benefit from using anti-inflammatory drugs such as tocilizumab or the anti-JAK inhibitor baricitinib, currently licensed and with safety data to treat rheumatoid arthritis, some of which have already reported encouraging results in open-label uncontrolled studies. [2, 3]

Reference

1. Chen X et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clin Infect Dis. 2020 Apr 17: ciaa449. DOI: doi: 10.1093/cid/ciaa449. (17 April 2020). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184354
2. Xu X et al. Effective treatment of severe COVID-19 patients with tocilizumab. PNAS, DOI: 10.1073/pnas.2005615117. (29 April 2020). https://www.pnas.org/content/early/2020/04/27/2005615117
3. Cantini F et al. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect. doi: 10.1016/j.jinf.2020.04.017. (23 April 2020). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177073

Rheumatoid arthritis drug anakinra in small study to treat COVID-19

Simon Collins, HIV i-Base

A small observational study reported in Lancet Rheumatology used the rheumatoid arthritis drug anakinra, a recombinant interleukin-1 receptor antagonist, for the treatment of COVID-19. [1]

The study was conducted in Milan in 29 patients hospitalised with COVID-19 (median age 62, many with comorbidities) who received daily high-dose intravenous infusions of anakinra at 10 mg/kg bodyweight for 21 days in addition to standard of care (non-invasive ventilation (CPAP), hydroxychloroquine, and lopinavir/r). Results were compared to a non-randomised control group of 16 people who only received standard of care.

Respiratory improvements and reduced signs of cytokine activity including reduced C-reactive protein was reported in 72% (21/29) of patients. Survival was 90% (26 out of 29). Five of 29 patients (17%) needed mechanical ventilation.

This compared to persistent or recurrent increases in C-reactive protein in most of the control group. Respiratory function improved for half of the patients (8 patients, 50%), and 56% (nine of 16) survived. One patient received mechanical ventilation (6%).

The authors commented that anakinra has a stronger safety record compared with other cytokine-blocking agents and a shorter half-life, making it suitable for critically ill patients, but that their findings needed to be tested in larger randomised studies.

The study is also part of the prospective 1000-person COVID-19 Biobank study looking for predictors of response and outcomes to COVID-19. [2]

Reference

1. Cavalli G et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatology DOI: 10.1016/S2665-9913(20)30127-2. (7 May 2020). https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext
2. clinicaltrials.gov. COVID-19 patients characterization, biobank, treatment response and outcome predictor (COVID-BioB). https://clinicaltrials.gov/ct2/show/NCT04318366

Anticoagulants associated with improved survival rates in people hospitalised with COVID-19

Simon Collins, HIV i-Base

A large retrospective analysis from researchers at Mount Sinai School of Medicine in New York reported that people hosptitalised with COVID-19 who were treated with anticoagulant treatment (AC) had reduced mortality, but also higher rates of bleeding complications. [1]

Recent studies have reported increased cardiovascular complications including life-threatening clots in patients hospitalised with COVID-19, and post-mortem biopsies have reported blood clots in major organs, including lung and kidney tissue. [2, 3]

The current study involved 2773 participants hospitalised with confirmed COVID-19 between 14 March and 11 April 2020, 786 (28%) received oral, subcutaneous, or intravenous AC. The study is published as a research letter in the Journal of the American College of Cardiology.

Results were adjusted for age, sex, ethnicity, body mass index, history of hypertension, heart failure, atrial fibrillation, type 2 diabetes, AC use prior to hospitalisation, and admission date. AC treatment duration was used as a covariate while intubation was treated as a time-dependent variable.

The median time in hospital was 5 days (IQR: 3-8 days) and median time from admission to AC initiation was 2 days (IQR: 0-5 days). AC treatment lasted a median of 3 days (IQR: 2-7 days).

In-hospital mortality and median survival was 22.5% and 21 days, compared to 22.8% and 14 days in those with and without AC respectively. Participants receiving AC were more likely to require invasive mechanical ventilation (29.8% vs 8.1%, p<0.001).

In patients who required mechanical ventilation (N=395), in-hospital mortality and median survival was 29.1% and 21 days compared to 62.7% and 9 days, with vs without AC respectively. In multivariate analysis, longer duration of AC was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89, p<0.001).

However, use of AC was also associated with higher rates of major bleeding events in 24 (3%) vs 38 (1.9%) in those with AC vs no AC respectively.

Of the 24 patients with bleeding events on AC, 15 (63%) had bleeding events after starting AC vs 9 (37%) before starting AC. Bleeding events were more common among patients intubated (30/395; 7.5%) than among non-intubated patients (32/2378; 1.35%).

The study concluded that AC was likely used for more severe clinical presentations and that AC was associated with improved survival after adjusting for mechanical ventilation, but that randomised studies were needed to confirm the results.

References

1. Paranjpe I et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. Journal of the American College of Cardiology, DOI: 10.1016/j.jacc.2020.05.001 (May 2020)
   http://www.onlinejacc.org/content/early/2020/05/05/j.jacc.2020.05.001
2. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J. Thromb. Haemost. 2020. https://doi.org/10.1111/jth.14781. (24 March 2020).
   https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14781
3. Zhang Y et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020; 382:e38. DOI: 10.1056/NEJMc2007575. (23 April 2020).

Monoclonal antibodies identified in convalescent plasma COVID-19

Simon Collins, HIV i-Base

Italian researchers from GSK report on isolation of broadly neuralising monoclonal antibodies from convalescent plasma that will be lead candidates as potential treatment for COVID-19.

This study, currently online before peer review, involved screening more than 1,100 memory B cells from seven people who had recovered from COVID-19 and incubation cells for two weeks to allow natural production of antibodies. Of these, 318 B cells expressed human monoclonal antibodies that inhibited the spike protein in vitro, 74 of which inhibited binding to receptors on Vero E6 cells, and 17 neutralised CoV-2 in vitro.

These will be further studied as lead compounds for further development as potential treatments.

Reference

Andreano E et al. Identification of neutralizing human monoclonal antibodies from Italian Covid-19 convalescent patients. Published before peer review. https://www.biorxiv.org/content/10.1101/2020.05.05.078154v2

Studies reporting lack of benefit from hydroxychloroquine to treat COVID-19

Simon Collins, HIV i-Base

Several studies have recently reported a lack of benefit from using hydroxychloroquine (HCQ) to treat COVID-19, with or without use of azithromycin (AZ).

These results are important for further challenging a controversial French study reported that an initial benefit that led to more than 100 new studies investigating this potential treatment, including some based in the UK, and despite higher risk of serious side effects.

The first observational study, published in the NEJM, reported no association between HCQ and intubation or death in 1446 consecutive patients at a single centre in New York from 7 March to 8 April 2020, 70 were excluded due to intubation, death, or discharged within 24 hours.

In the remaining 1376 patients, 811 (58.9%) received HCQ (600 mg twice on day 1, then 400 mg daily for a median of 5 days) during a median follow-up of 22.5 days.

Just under half (45%) were treated within 24 hours of admission to ER and 86% within 48 hours. Participants receiving HCQ were more severely ill at baseline. Overall, 346 patients (25.1%) had a primary end-point event (180 patients were intubated, of whom 66 subsequently died, and 166 died without intubation). In the main analysis, there was no significant association between HCQ use and intubation or death (HR: 1.04, 95%CI: 0.82 to 1.32). A small percentage of patients also used tocilizumab or remdesivir. Results were similar in multiple sensitivity analyses.

Given the observational design and the relatively wide confidence interval, the researchers concluded that their findings did not rule out either benefit or harm of HCQ treatment, but that they also did not support use of HCW outside of a research setting.

The second report is a retrospective analysis of 368 patients hospitalised with COVID-19 in the US Veterans Affairs hospitals (n=97 HCQ; n=113 HCQ+AZ, n=113; n=158 no HCQ) and published ahead of peer review. [1]

The two primary outcomes were death and the need for mechanical ventilation and results used propensity scores to calculate adjusted hazard ratios (adj HR) for clinical characteristics.

Baseline characteristics included median age 70 years (youngest 59), 100% male and 66% black.

Rates of death were 27.8%, 22.1%, 11.4% and ventilation were 13.3%, 6.9%, 14.1% in the HCQ, HCQ+AZ, and no HC groups, respectively.

Compared to the no HCQ group, the risk of death from any cause was higher in participants using HCQ (adj. hazard ratio, 2.61; 95% CI: 1.10 to 6.17; p=0.03) but not in the HCQ+AZ group (adj. HR 1.14; 95% CI: 0.56 to 2.32; p=0.72).

Also compared to the no HC group, the risk of ventilation was similar in participants using either HCQ (adj. HR, 1.43; 95% CI: 0.53 to 3.79; p=0.48) and HCQ+AZ group (ad. HR, 0.43; 95% CI: 0.16 to 1.12; p=0.09),

These researchers emphasised the importance of results of prospective, randomised, controlled studies before general use of these drugs.

A third study, ahead of review for Nature Research reported lack of effect from HCQ in vitro and also in macaques. [3]

The abstract reports that HCQ showed antiviral activity in African green monkey kidney (VeroE6) cells but not in a model of reconstituted human airway epithelium. Also that in macaques, neither HCQ nor HCQ + azithromycin compared to placebo, showed a significant effect on the viral load levels in any of the tested compartments, including before and after peak viral load.

No benefit was seen when HCQ was tested as a pre-exposure prophylaxis (PrEP).

C O M M E N T

These studies do not comment on the use of zinc supplement that is hypothesised to increase likelihood of benefit with HCQ.

Many comments posted online about the pre-peer review paper from Geleris et al emphasise the higher rate of hospitalisation in the HCQ group and the limited characteristics for many patients.

The independent publication Prescrire also failed to find evidence of efficacy in it's review of new data on HCQ, following several earlier articles cautioning positive data. [4]

The FDA have issued a cautioned against the use of HCQ outside of clinical studies due to the risk of cardiovascular toxicity and that strongly recommends close supervision. [5]

References

1. Geleris J et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. DOI: 10.1056/NEJMoa2012410. (7 May 2020).
   https://www.nejm.org/doi/full/10.1056/NEJMoa2012410
2. Magagnoli J et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. DOI: 10.1101/2020.04.16.20065920. (23 April 2020).
   https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2
3. Maisonnasse P et al. Hydroxychloroquine in the treatment and prophylaxis of SARS-CoV-2 infection in non- human primates. Nature Research. In Review. (6 May 2020).
   https://www.researchsquare.com/article/rs-27223/v1
4. Prescrire. Covid-19 and hydroxychloroquine (Plaquenil): new data show no evidence of efficacy.
   https://english.prescrire.org/en/81/168/58639/0/NewsDetails.aspx
5. FDA press releases. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. (24 April 2020).
   https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

Israeli cohort shows no protection against COVID-19 from childhood BCG vaccination

Simon Collins, HIV i-Base

A large observational analysis has reported no relationship between rates or severity of COVID-19 in adults and whether or not they received a BCG vaccination in childhood. [1]

These results, published in the Journal of American Medicine (JAMA) are disappointing as it was hoped this vaccine might have offered broad protection to respiratory infections. Several papers have also suggested that COVID-19 might have lower prevalence in countries with higher use of the vaccine.

Changes in vaccination policy in Israel meant that BCG was routinely given to newborn babies from 1955 to 1982 but only subsequently given to migrants from countries with a high prevalence of TB. This allowed researchers to compare two similar aged groups for any evidence of protection against COVID-19.

Of 72 060 test results reviewed, 3064 were from patients born between 1979 and 1981 (and 2869 were among likely unvaccinated people born between 1983 and 1985. Both groups were approximately 50% male with mean age 40 and 35 years respectively.

There was no significant difference in the proportion of positive test results in the BCG vs no-BCG group: 361 (11.7%) vs 299 (10.4%); difference, 1.3%; 95%CI: –0.3% to 2.9%; p=0.09). There was also no difference in positivity rates per 100 000: 121 vs 100; difference, 21 per 100 000; 95%CI: –10 to 50 per 100 000; p=0.15).

One case of severe disease was reported in each group with no deaths.

C O M M E N T

The implications of these results are unclear for studies that have already been designed to look at prospective use of BCG vaccination.

At least ten ongoing studies are already either planned or ongoing that use BCG vaccinations as COVID-19 prophylaxis for adult health workers. [2, 3, 4]

Unless there is still a mechanism for plausibility of protection, health workers should be allowed to use more promising options. Those that continue for any reason should have a very tightly defined mandate to recognise early futility.

References

1. Hamiel U et al. SARS-CoV-2 rates in BCG-vaccinated and unvaccinated young adults. JAMA, research letter. doi:10.1001/jama.2020.8189. (13 May 2020).
   https://jamanetwork.com/journals/jama/fullarticle/2766182

2. clinicltrials.gov. BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE). (n=4170) https://clinicaltrials.gov/ct2/show/NCT0432720
3. clinicltrials.gov. BCG Vaccination for Healthcare Workers in COVID-19 Pandemic (n=500) https://clinicaltrials.gov/ct2/show/NCT04379336
4. Using BCG Vaccine to Protect Health Care Workers in the COVID-19 Pandemic. (n=1500) https://clinicaltrials.gov/ct2/show/NCT04373291

COVID-19: COMPLICATIONS

Obesity associated with worse outcomes in younger people hospitalised with COVID-19 in the US

Simon Collins, HIV i-Base

A study from researchers at Johns Hopkins who noted higher rates of obesity in younger patients in the US compared to previous reports from China and Italy has reported reduced mortality with use of anti-coagulation treatment (AC).

The current study included 265 people (58% male) in intensive care units at five hospitals in New York, Florida, Pennsylvania, Cincinnati and Washington and limited results were published in a letter to the Lancet. [1]

The median BMI was 29·3 kg/m^2, with only 25% of individuals having a BMI of less than 26 kg/m^2, and 25% exceeding a BMI of 34·7 kg/m^2.

In multivariate linear regression analysis, there was a significant association between body-mass index (BMI) and age in patients with COVID-19 in which younger individuals admitted to hospital were more likely to be obese (r2 = 0.051, p=0.0002).

The researchers also noted that obesity can restrict ventilation by impeding diaphragm excursion, impairs immune responses to viral infection, is pro-inflammatory, and induces diabetes and oxidant stress to adversely affect cardiovascular function. [2, 3]

C O M M E N T

The evidence supporting additional risk from obesity and high BMI in people diagnosed with COVID-19 (currently at around ten studies) are also summarised in a useful short report by the International Severe Acute Respiratory and Emerging infection Consortium (ISARIC). [4]

References
1. Kass DA et al. Obesity could shift severe COVID-19 disease to younger ages. Lancet. doi: 10.1016/S0140-6736(20)31024-2. (4 May 2020). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31024-2/fulltext
2. Honce R et al. Impact of obesity on influenza A virus pathogenesis, immune response, and evolution. Front Immunol. 2019; 101071. (10 May 2019). https://www.frontiersin.org/articles/10.3389/fimmu.2019.01071/full
3. Afshin A et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017; 377: 13-27. (16 July 2017). https://www.nejm.org/doi/full/10.1056/NEJMoa1614362
4. ISARIC Rapid Review team. Obesity: An independent risk factor for COVID-19 severity? (9 April 2020). https://media.tghn.org/medialibrary/2020/04/Obesity_and_COVID-19_09APR2020.pdf (PDF)

ACE inhibitors and angiotensin receptor blockers do not boost risk of COVID-19 or flu

Mark Mascolini, for NATAP.org

Large studies in the United States, Italy, and the United Kingdom (UK) should ease fears that taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) raise the risk of COVID-19 or influenza [1-3]. In fact the UK study found that these popular antihypertensives *lower* flu risk.

Because SARS-CoV-2, the COVID-19 virus, uses angiotensin-converting enzyme 2 (ACE-2) to enter target cells, some feared that drugs interfering with the renin-angiotensin–aldosterone system – like ACE

inhibitors and ARBs – may make COVID-19 more likely. [1, 2]

Influenza A (including subtypes H7N9, H1N1, and H5N1) uses the ACE-2 receptor to mediate lung damage. [3]

Researchers at New York University (NYU) in New York City analysed medical records of everyone tested for COVID-19 between 1 March and 15 April 2020. [1] Among 12,594 people tested, 5894 (46.8%) had COVID-19 and 1002 (17% of 5894) had severe illness (intensive care, mechanical ventilation, or death). More than one third (4357; 34.6%) had a history of hypertension, of whom 2573 (59.1%) had COVID-19 and 634 (24.6% of 2573) had severe COVID-19.

The NYU team assessed relations between previous treatment with ACE inhibitors, ARBs, beta-blockers, calcium-channel blockers, or thiazide diuretics and a positive or negative COVID-19 test plus the likelihood of severe illness among those with COVID-19. Bayesian methods showed no association between any medication class and greater chance of a positive COVID-19 test or a substantially increased risk of severe COVID-19.

In Italy's Lombardy region, researchers matched 6272 people with SARS-CoV-2 infection to 30,759 people without the virus by age, sex, and municipality. [2]

Both groups averaged 68 years in age and 37% were women. People with COVID-19 took ACE inhibitors and ARBs more often than the control group because they had a higher prevalence of cardiovascular disease. But statistical analysis detected no association between ARBs or ACE inhibitors and COVID-19 risk overall or COVID-19 risk in people with a severe or fatal disease course.

UK researchers used electronic health records to determine flu incidence in adults who got an ACE inhibitor, an ARB, or neither from 1998 through 2016. [3]

While 700,994 people got an ACE inhibitor prescription, 230,028 were prescribed an ARB and 4,742,017 got neither drug or the direct renin inhibitor aliskiren. After a median 8.7 years of follow-up, an analysis adjusted for age, sex, smoking history, influenza vaccination, obesity, and 12 comorbidities determined that people taking an ACE inhibitor had a one third lower risk of flu than those who did not (adjusted hazard ratio [aHR] 0.66, 95% confidence interval [CI] 0.62 to 0.70). Taking an ARB halved the flu risk (aHR 0.52, 95% CI 0.47 to 0.57). Further analysis showed that the longer people took ACE or ARB agents, the lower their flu risk.

Professional societies and expert panels recommend not stopping ACE inhibitors or ARBs for fear that they may raise the risk of COVID-19 infection, severity, or death. [4, 5, 6]

References

1. Reynolds HR et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2008975. https://www.nejm.org/doi/full/10.1056/NEJMoa2008975
2. Mancia G et al. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2006923. https://www.nejm.org/doi/full/10.1056/NEJMoa2006923
3. Chung SC et al. Association between angiotensin blockade and incidence of influenza in the United Kingdom. N Engl J Med. May 8, 2020. DOI: 10.1056/NEJMc2005396. https://www.nejm.org/doi/full/10.1056/NEJMc2005396
4. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. March 17, 2020. https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19
5. European Society of Cardiology. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. March 13, 2020.
6. Vaduganathan M et al. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653-1659.

ACE inhibitors and angiotensin receptor blockers for hypertension tied to lower death risk with COVID-19

Mark Mascolini, for natap.org

Taking a step toward resolving a prickly clinical conundrum, a retrospective analysis of COVID-19 in patients taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) for hypertension found that the treated group had almost a 60% lower risk of all-cause mortality than hypertensive COVID-19 patients not taking ACEIs or ARBs. [1]

That association held true in diverse models adjusted for variables that may affect death risk.

NEJM Journal Watch analysts Allan Brett and David Rind frame the problem as deciding whether ACEIs and ARBs have potentially harmful – or potentially beneficial – effects on the natural history of COVID-19. [2, 3]

Angiotensin-converting enzyme 2 (ACE2) plays a role in SARS-CoV-2 entry into human cells, and ACEIs and ARBs may boost expression of ACE2 and so worsen the course of COVID-19. On the other hand, experts invoke other mechanisms suggesting

that ACEIs and ARBs could benefit people with COVID-19. For example, ACE2 transforms angiotensin II to angiotensin-(1-7), and angiotensin-(1-7) may enhance vasodilation and stifle inflammation.

Researchers working in Wuhan, the initial site of the COVID-19 epidemic, did not address specific ACE2-related mechanisms but instead weighed the impact of ACEIs or ARBs on the ultimate outcome – all-cause mortality after 28 days – in people taking those agents for hypertension while in the hospital for COVID-19. [1]

All 1128 people in the analysis had hypertension, and 188 of them (17%) took an ACEI or an ARB for their high blood pressure. The comparison group took other antihypertensives (alpha or beta blockers) or no blood pressure medication. Both groups had a median age of 64 years, and about 53% in both groups were men.

A slightly (but significantly) higher proportion of the ACEI/ARB group than the control group received antiviral medication (88.8% versus 81.7%, p=0.02), and a higher proportion received a beta blocker (28.2% versus 17.9%, p=0.002) or lipid-lowering drug (22.9% versus 10.0%, p=1.51(E-6)). But the groups did not differ significantly in use of systemic corticosteroids, antibiotics, vasoactive drugs, or use of invasive or noninvasive ventilation.

Unadjusted 28-day all-cause mortality stood at 3.7% in the ACEI/ARB group, less than half the 9.8% mortality in the comparison group, a significant difference (p=0.01). A Cox model that adjusted for age, gender, comorbidities, and in-hospital medication determined that ACEI/ARB takers had almost a 60% lower risk of death than hypertensive people not taking these drugs (adjusted hazard ratio [aHR] 0.42, 95% confidence interval [CI] 0.19 to 0.92, p=0.03). A propensity score-matched analysis that adjusted for imbalanced variables in a mixed-effect Cox model determined that ACEI/ARB treatment cut the risk of death by almost two thirds (aHR 0.37, 95% CI 0.15 to 0.89, p=0.03). A similar analysis found that, compared with use of other antihypertensives, ACEI/ARB therapy sliced the death risk 70% (aHR 0.30, 95% CI 0.12 to 0.70, p=0.01).

The American College of Cardiology and the American Heart Association recommend continued use of ACEI/ARB agents by people already taking those drugs when diagnosed with COVID-19 [4]. The Wuhan team concludes that their findings support that recommendation.

References

1. Zhang P et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020 Apr 17. doi: 10.1161/CIRCRESAHA.120.317134. https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.120.317134
2. Brett AS, Rind DM. ACE inhibitors and ARBs during the COVID-19 pandemic. NEJM Journal Watch. April 9, 2020. https://www.jwatch.org/na51345/2020/04/09/ace-inhibitors-and-arbs-during-covid-19-pandemic
3. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: What is the evidence? JAMA 2020 Mar 24; [e-pub]. https://doi.org/10.1001/jama.2020.4812 4
4. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. ACC News Story. March 17, 2020. https://viajwat.ch/2REZU2H

COVID-19: PAEDIATRICS

Reports of Kawasaki-like disease in children after the start of the SARS-CoV-2 epidemic in Italy

Polly Clayden, HIV i-Base

A paediatric hospital in the Bergamo province, Italy reported a 30-fold increased incidence of Kawasaki-like disease after the start of the SARS-CoV-2 epidemic. [1]

These findings were described in a retrospective review, published online in The Lancet 13 May 2020.

In children, the respiratory symptoms that are typical in adults appear to be more benign, with almost no deaths reported in this age group.

Kawasaki disease causes swelling of the blood vessels, which can lead to complications in the coronary arteries and almost exclusively affects children. The study authors noted that despite half a century having passed since Tomisaku Kawasaki first reported 50 cases in Japan, the cause of the disease remains unknown. The generally accepted hypothesis supports an abnormal response of the immune system to one or more unidentified pathogens in genetically predisposed patients.

The Bergamo province, has been hugely affected by the SARS-CoV-2 epidemic – the City of Bergamo has the highest rates of deaths from COVID-19 in Italy.

The authors retrospectively reviewed the notes of children diagnosed with Kawasaki disease admitted to the General Paediatric Unit of Hospital Papa Giovanni XXIII between 1 January 2015 and 20 April 2020.

The aim of the study was to describe the incidence and characteristics of new cases of Kawasaki-like presentations admitted to the unit during the SARS-CoV-2 epidemic.

All children diagnosed with a Kawasaki-like disease over the study period were stratified by symptoms before (group 1) or after (group 2) the beginning of the SARS-CoV-2 epidemic.

Kawasaki disease shock syndrome (KDSS) was defined by presence of circulatory dysfunction. Macrophage activation syndrome (MAS) was defined according to the Paediatric Rheumatology International Trials Organisation criteria.

Current or previous infection was diagnosed using reverse-transcriptase quantitative PCR in nasopharyngeal and oropharyngeal swabs, and by serological qualitative test detecting SARS-CoV-2 IgM and IgG, respectively.

Group 1 included 19 children: 7 boys and 12 girls, mean aged 3 years (SD 2·5), diagnosed between 1 January 2015 and 17 February 17 2020. Group 2 included 10 children: 7 boys and 3 girls, mean age 7·5 years (SD 3·5), diagnosed between 18 February and 20 April 2020; 8 of 10 were positive for IgG or IgM, or both.

The authors reported the following differences among children in group 1 vs group 2, respectively: disease incidence, 0·3 vs 10 per month; mean age, 3 vs 7·5 years; abnormal echocardiogram, 2/19 vs 6/10, p=0·0089; met criteria for KDSS and MAS, 0/19 vs 5/10, p=0·02; Kobayashi score of 5 or more, 2/19 vs 7/10, p=0·0021; and need for adjunctive steroid treatment, 4/19 vs 8/10, p=0·0045.

The authors suggest that the association between SARS-CoV-2 and Kawasaki-like disease should be taken into account in the paediatric population. But, they added, the Kawasaki-like disease described here remains a rare condition, probably affecting no more than one in 1000 children exposed to SARS-CoV-2. And this estimate is based on the limited data from the case series in this region.

COMMENT

In an accompanying commentary, the authors explain that although studies from several countries have confirmed that severe illness and death due to COVID-19 among children are rare, attention has now shifted in the understanding of the role of the disease in children. [2]

First, as the degree to which children transmit COVID-19 is key to how countries resume activities after lockdown. Second, the new concerns about a novel severe Kawasaki-like disease in children related to COVID-19, including that described in the Bergamo region above.

Experts in the UK have formulated a case definition for what is provisionally called Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). This has been published by the Royal College of Paediatrics and Child Health. [3]

Correspondence in The Lancet on 6 May 2020, describing nine children with PIMS-TS needing critical care in south London highlights the severe end of this disease. [4]

As that correspondence went to press, one week after the initial submission, the Evelina London Children's Hospital paediatric intensive care unit had managed more than 20 children with similar symptoms.

References

1. Verdoni L et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet. Published online. 13 May 2020.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31103-X/fulltext
2. Viner RM and Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. Published online 13 May 2020.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31129-6/fulltext
3. Royal College of Paediatrics and Child Health Guidance –Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 5 May 2020.
https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19
4. Shelley Riphagen et al. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. Published online 6 May 2020.
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31094-1.pdf (PDF)

COVID-19: HIV GUIDELINES

New BHIVA guidelines: B/F/TAF now preferred first-line ART and reduced HIV monitoring in the UK during COVID-19

Simon Collins, HIV i-Base

On 1 May 2020, BHIVA published the first guidelines specifically for the management of HIV care in the UK during COVID-19.

The new guidelines include specific recommendations for monitoring and treatment that are briefly summarised below. The document also includes recommendations for health workers providing services, for example for service planning and providing leadership during the epidemic.

The most significant changes are reducing monitoring and the related recommendation to use the bictegravir-based fixed dose combination B/F/TAF as first-line combination (so long as this is medically appropriate). This assumes good adherence and no side effects.

Please refer to the full document published on the BHIVA website in PDF format, together with other information and statements about COVID-19. This is linked below and the full draft is also published as an html page in this issue of HTB.

Summary of new HIV management guidelines

- ART should continue being used without interruption. This includes by people diagnosed with COVID-19. Services will continue to provide HIV drugs to all people living with HIV.
- ART should not be switched or stopped unless there is a medical need to do this. Lopinavir/r (Kaletra) is not recommended as treatment for COVID-19.
- Monitoring CD4 and viral load tests will be deferred, unless this is clinically needed (for example, to start or change treatment). This assumes good adherence and no side effects.
- Minimise ART switching until after COVID-19 unless clinically needed. This assumes good adherence and no side effects.
- Providing six-months of ART. This assumes good adherence and no side effects.
- Viral failure (to change ART) is now defined as two viral load results above 200 copies/mL or a single rebound above 1000 copies/mL. ART with low barrier to resistance (NNRTI-based ART) should be changed to ART with a high barrier to resistance. These generally include dolutegravir-, bictegravir- or boosted darunavir-based combinations.
- B/F/TAF (bictegravir/tenofovir-alafenamide/emtricitabine, trade name Biktarvy) is proactively recommended for first-line ART. Exceptions include new pregnancy, drug interactions or intolerance.
- Monitoring after new or changed treatment should involve:
  - A two-month initial drug supply.
  - Viral load monitoring after one month,
  - Follow-up with four months drug supply.
- All prescribing during COVID-19 should be later reviewed by a multidisplinary team (MDT).
- Limitations or problems with home delivery can be overcome with collection from pharmacy, Royal Mail and courier services.
- Supporting government policies about population health for reducing transmission of COVID-19 including self-isolation/distancing generally and shielding for people who are extremely vulnerable.
- Shielding is recommended for people living with HIV who have a CD4 count <50 cells/mm^3, other serious comorbidities or a detectable viral load.

C O M M E N T

These guidelines are welcomed.

Over the last two months, NHS services have been considerably restructured to minimise care that is defined as 'non-essential'. This has involved moving many doctors, nurses and supporting staff and laboratories from HIV care to COVID-19.

Some changes have worked well to ensure HIV care remains high and the risk of COVID-19 is reduced. The move to telephone/virtual HIV consultations has reduced the need for travelling and use of public transport, especially since the UK shut-down from 23 March. Virtual appointments might now be easier to make.

People who are stable on effective HIV treatment should have no difference in their overall care. This is defined as having an undetectable viral load for the previous six months on ART that is manageable and that is without complications or side effects. Luckily, this covers the majority of people who are living with HIV in the UK.

When the situation is more complicated and face-to-face consultations are needed, or additional tests, HIV clinics are now less busy and appointments can be arranged with minimal waiting time and minimal contact with other clients and staff.

Reference

BHIVA. BHIVA COVID-19 ART guidelines 1May 2020.

https://www.bhiva.org/BHIVA-COVID-19-interim-adult-antiretroviral-guidance
https://www.bhiva.org/file/5eac2b1e84f0f/BHIVA-interim-ART-guidelines-COVID-19-01052020.pdf (direct PDF)

Joint BHIVA/EACS update on HIV and COVID-19

Simon Collins, HIV i-Base

On 30 April 2020, BHIVA and EACS published a summary of recent research into COVID-19. [1]

Main points are quoted below but please see full report for details including references.

- Latest studies reporting no evidence so far on increased risk from COVID-19 in people on effective ART compared to HIV negative people. [2, 3, 4]
- The risk of severe illness increases with age, male sex and with certain chronic medical problems such as cardiovascular disease, chronic lung disease and diabetes. Although people living with HIV who are on treatment with a normal CD4 T-cell count and suppressed viral load may not be at an increased risk of serious illness, many people living with HIV have other conditions that increase their risk. Indeed, almost half of people living with HIV in Europe are older than 50 years – and chronic medical problems, such as cardiovascular and chronic lung disease, are more common in people living with HIV. Smoking is a risk factor for respiratory infections; smoking cessation should therefore be encouraged for all patients. Influenza and pneumococcal vaccinations should be kept up to date.
- It assumes that immune suppression, indicated by a low CD4 T-cell count (<200 cells/mm3), or not receiving ART, will also be associated with an increased risk for a more severe disease presentation. OI prophylaxis should be used in these cases.
- Evidence supports potential for COVID-19 vertical transmission [5, 6, 7], although so far clinical outcome for the newborn have been very good.
- Existing national guidelines should be followed in terms of reducing risk for acquiring a COVID-19 infection and managing symptoms.
- No benefit has been seen with use of lopinavir/r (Kaletra) for treating COVID-19 and that there is no evidence to support the use of other antiretrovirals, including protease inhibitors; indeed, structural analysis demonstrates no darunavir binding to COVID-19 protease.
- Despite a lack of in-vitro data to support antiviral activity of TDF/FTC against CoV-2, and only limited evidence of molecular docking and binding data, a large randomised phase 3 placebo-controlled study in Spain using the HIV PrEP combination TDF/FTC and low-dose hydroxychloroquine (HCQ) as prophylaxis for COVID-19 in health workers is planned. Documented COVID-19 infections in people who are HIV positive on TDF/TAF containing ART suggests that complete protection is unlikely.
- In discussing ongoing HCQ as a treatment for COVID-19, with or without azithromycin, the document notes that no acute viral infection has ever been successfully treated with either product.
- Comments on remdesivir are slightly more positive. While noting a lack of effect in some studies the statement refers to a press release from a US NIAID study in which 1063 hospitalised patients with advanced COVID-19 and lung involvement randomised to remdesivir recovered faster than similar patients who received placebo. Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (p=0.059) [8]. Gilead also reported top-line results from their late-stage SIMPLE study, that a five-day dosing duration of remdesivir led to “similar improvement in clinical status” as the 10-day treatment course being evaluated in the NIAID study and other ongoing trials. [9] The initial phase of the SIMPLE trial, which is not placebo-controlled, randomised 397 hospitalised patients with severe manifestations of COVID-19

disease to receive intravenous remdesivir until either day five or 10, on top of standard care. An expansion phase of the study has recently been added and will enroll an additional 5600 patients, including patients on mechanical ventilation. The full results from these trials, as well as other ongoing clinical trials especially in early COVID-19 disease, are eagerly awaited

- A new website is recommended from Liverpool University on drug interactions with COVID-19 treatments.

  www.covid19-druginteractions.org

- Two new resources are recommended for data collection on COVID-19.

  i) www.NEAT-ID.org and if your centre has not signed up, you can do so via this link.

  https://mailchi.mp/neat-id/covid-19-hiv-co-infection-data-dashboard-4783628

  ii) The Lean European Open Survey on SARS-CoV-2 Infected Patients (LEOSS) launched by the German Society for Infectious Diseases (DGI) and ESCMID's Emerging Infections Task Force (EITaF).

  https://leoss.net/statistics

References

1. EACS & BHIVA Statement on risk of COVID-19 for people living with HIV (PLWH). (30 April 2020). https://www.bhiva.org/EACS-BHIVA-statement-on-risk-of-COVID-19-for-people-living-with-HIV-PLWH
2. Blanco JL et al. COVID-19 in patients with HIV: clinical case series. Lancet HIV. 2020 Apr 15. pii: S2352-3018(20)30111-9.
3. Härter G et al. Infection (2020). DOI: 10.1007/s15010-020-01438-z. (11 May 2020). https://link.springer.com/article/10.1007/s15010-020-01438-z
4. Guo W et al. A survey for COVID-19 among HIV/AIDS patients in two districts of Wuhan, China. Preprint research paper, The Lancet, 2020.
5. Zeng L, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr 2020; DOI: 10.1001/jamapediatrics.2020.0878.
6. Alzamora MC et al. Severe COVID-19 during pregnancy and possible vertical transmission. Am J Perinatol. 2020 Apr 18. doi: 10.1055/s-0040-1710050. [Epub ahead of print]
7. Zamaniyan M et al. Preterm delivery in pregnant woman with critical COVID-19 pneumonia and vertical transmission. Prenat Diagn. 2020 Apr 17. doi: 10.1002/pd.5713. [Epub ahead of print]
8. NIAID press release. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. (29 April 2020). https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19
9. Gilead press release. Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. (29 April 2020). https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19

Interim US guidance for coinfection COVID-19 and HIV

Simon Collins, HIV i-Base

On 21 April 2020, the US Department for Health and Human Services (HHS) updated their guidelines for management of people with HIV and COVID-19 coinfection. [1]

This included new recommendations that people living with HIV who are diagnosed with COVID-19 have an excellent prognosis, and they should be clinically managed the same as persons in the general population with COVID-19, including when making medical care triage determinations.

Other recommendations are similar to many earlier BHIVA guidelines. [2]

- Deferring monitoring in people on stable ART and reducing face-to-face consultations unless urgent - with a preference to have virtual or telephone appointments.
- Following similar guidelines to general populations for reducing risk of infection and transmission.
- Additional caution in individuals aged >60 years and those with diabetes, hypertension, cardiovascular disease, pulmonary disease, or obesity and in current smokers.
- Additional caution in those with CD4 counts <200 cells/mm^3 or with detectable viral load.

- Ensuring continued supply of ART, preferably at least three months and at least one month.
- Keeping influenza and pneumococcal vaccinations up to date.
- To follow Substance Abuse and Mental Health Service Administration (SAMHSA) guidelines for maintaining access to opioid substitution therapy. (https://www.samhsa.gov/medication-assisted-treatment/statutes-regulations-guidelines/covid-19-guidance-otp)
- That HIV positive people with COVID-19 should also contact their HIV provider, whether hosptialised or managing symptoms at home with self-isolation.
- That ART should be continued if hospitalised for COVID-19, including access to investigational HIV medicines if part of a research study.
- That HIV should not be an exclusion criterion for enrolling in investigational treatments for COVID-19.
- That people with HIV may need additional assistance with food, housing, transportation, and childcare during times of crisis and economic fragility. To enhance care engagement and continuity of ARV therapy, clinicians should make every attempt to assess their patients' need for additional social assistance and connect them with resources, including navigator services when possible.
- During this crisis, social distancing and isolation may exacerbate mental health and substance use issues for some persons with HIV. Doctors should assess and address these patient concerns and arrange for additional consultations, preferably virtual, as needed.

For more information please refer to full guidelines.

References

1. Interim Guidance for COVID-19 and Persons with HIV. (Updated 21 April 2020).
   https://aidsinfo.nih.gov/guidelines/html/8/covid-19-and-persons-with-hiv--interim-guidance-/0 (summary)
   https://aidsinfo.nih.gov/guidelines/html/8/covid-19-and-persons-with-hiv--interim-guidance-/554/interim-guidance-for-covid-19-and-persons-with-hiv (full version).
2. BHIVA statements and guidelines on COVID-19.
   https://www.bhiva.org/Coronavirus-COVID-19

COVID-19: PATHOGENESIS

COVID-19 pathogenisis: potential for CoV-2 to be widely distributed in the body

Simon Collins, HIV i-Base

These two papers are based on analyses from single-cell sequencing datasets and support the idea that COVID-19 is not just a respiratory disease but an illness that can affect multiple organs.

The links are to a preprint article published on bioRxiv on 21 April 2020 and a related review that shows that other potential target cells also producing ACE2 and TMPRSS2 are common throughout the body – including in the heart, bladder, pancreas, kidney, nose, eyes and brain.

Many are epithelial cells lining the outer surface of organs and the new findings add to an emerging picture of SARS-CoV-2 as a virus that can target cells in many places in the human body, rather than being focused on a particular organ or part of the respiratory tract.

Receptors for SARS-CoV-2 present in wide variety of human cells.

Baraniuk C. Science. (29 Apr 2020).

https://www.the-scientist.com/news-opinion/receptors-for-sars-cov-2-present-in-wide-variety-of-human-cells-67496

Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells.

Muus C et al. DOI: 10.1101/2020.04.19.049254. (21 April 2020).

https://www.biorxiv.org/content/10.1101/2020.04.19.049254v2

Debate over development of pathogenic strains of CoV-2

Simon Collins, HIV i-Base

In the last couple of weeks different research groups have presented various analyses on whether or not CoV-2 mutated into a more pathogenic and easier to transmit form.

Related articles are included below.

Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2.

Korber B al. bioRxiv. doi: 10.1101/2020.04.29.069054

https://www.biorxiv.org/content/10.1101/2020.04.29.069054v2

This 33-page report raises concerns that the virus has mutated into a more severe from. Although from established researchers (with a history of HIV-related research), it is a bioRxiv preprint that has not been peer reviewed.

SARS-CoV-2 viral spike G614 mutation exhibits higher case fatality rate

Manuel Becerra-Flores and Timothy Cardozo, Int J Clin Pract. 2020 May 6. doi: 10.1111/ijcp.13525.

https://pubmed.ncbi.nlm.nih.gov/32374903

This study from NYU supports the more pathogenic mutation from Korber et al.

The problem with stories about dangerous coronavirus mutations.

Yong E. The Atlantic.

https://www.theatlantic.com/health/archive/2020/05/coronavirus-strains-transmissible/611239/

A new report that is critical of the findings.

Details discussed in this Twitter thread

https://twitter.com/trvrb/status/1257825352660877313

Trevor Bedford (of Fred Hutchinson/https://nextstrain.org/).

Some coronaviruses can reinfect the same person quickly: will that happen with SARS-CoV-2?

Mark Mascolini report for NATAP.org

http://natap.org/2020/COVID/043020_04.htm

Study finds nearly everyone who recovers from COVID-19 makes coronavirus antibodies.

Francis Collins, NIH Directors Blog.

https://directorsblog.nih.gov/2020/05/07/study-finds-nearly-everyone-who-recovers-from-covid-19-makes-coronavirus-antibodies

Antibody responses to SARS-CoV-2 in patients with COVID-19.

Long QX et al. Nat Med. (29 April 2020).

https://www.ncbi.nlm.nih.gov/pubmed/32350462

COVID-19: PREVENTION

Coronavirus: the risks - know them - avoid them

This blog by Dr Erin Bromage, an associate professor of biology, is a very readable non-technical overview of the kinetics and risk of CoV-2 transmission.

It includes a breakdown of the risks involved in common daily activities and how to reduce these in order to stay safe as lockdown steadily relaxes.

https://www.erinbromage.com/post/the-risks-know-them-avoid-them

Articles supporting wider use of face masks

The following two articles cover benefits of universal use of face masks to reduce transmission of CoV-2.

The time for universal masking of the public for COVID-19 is now.

Monica Gandhi and Diane Havlir, Open Forum Infect Dis. (15 April 2020).

https://academic.oup.com/ofid/article/7/4/ofaa131/5820544

Face masks for the public during the COVID-19 crisis.

Greenhaulgh T et al. BMJ 2020; 369:m1435. doi: 10.1136/bmj.m1435 (09 April 2020).

https://www.bmj.com/content/369/bmj.m1442

COVID-19: ON THE WEB

Guide to homecare and COVID-19

A helpful US-based communinty guide to homecare during COVID-19.

https://covidhomecare.ca/Covid19-Practical-Home-Care-bd4ea23fe5654737a93ea578c2ea1d02

Reviews on immunology of COVID-19

Simon Collins, HIV i-Base

Two useful overviews on current approaches to understanding immunology of COVID-19.

Immunology of COVID-19: current state of the science. Immunity (2020).

Vabret N et al. j.immuni.2020.05.002. DOI: 10.1016/j.immuni.2020.05.002

https://www.cell.com/action/showPdf?pii=S1074-7613%2820%2930183-7

This review summarise the current state of knowledge of innate and adaptive immune responses from SARS-CoV-2 and the immunological pathways that are likely to contribute to disease severity and death.

It also discusses the rationale and clinical outcome of current approaches to treatment and is sufficiently updated to include all recent remdesivir studies. It also reviews some of the prospective clinical trials to prevent or treat SARS-CoV-2 infection.

The many faces of the anti-COVID immune response.

Vardhana SA et al. JEM, 216(6) (30 April 2020).

https://rupress.org/jem/article-standard/217/6/e20200678/151725/The-many-faces-of-the-anti-COVID-immune-responseA

A review of active vs innate immune activation and COVID-19, that also cautions about this being an IL-6-mediated cytokine release syndrome.

COVID-19: OTHER NEWS

US groups protest political cuts to COVID-19 research

COVID-19 Working Group NYC

On May 1, 2020, Science Magazine reported the mid-term cancellation of a major grant to the EcoHealth Alliance, an international collaboration studying how coronaviruses transmitting in bats can evolve to spread in human populations.

Based on emails reviewed by Science, this decision appears to be directly related to the Trump administration's belief in the conspiracy theory that the SARS-CoV-2 virus, the cause of COVID-19, was purposefully or accidentally released from the Wuhan Institute of Virology.

The Wuhan Institute of Virology was a participant in the EcoHealth Alliance grant that was cancelled.

Beyond the critical importance of the research the NIH defunded, political interference in grantmaking is a disturbing trend that would allow politicians to effectively squash research that does not align with their political desires. Industry influence in research, the silencing of climate science, and long term harm of American science in the global climate become increasingly likely if politicians can easily meddle in grantmaking.

We must stand united as a community of clinicians, scientists, activists, and citizens to demand the best – most transparent – scientific decision making process in this moment of crisis, and always.

For further information about related protests please see this link:

https://docs.google.com/forms/d/e/1FAIpQLSfR1jfnqi10a8pNqRAXx5fQzwdtbRDg8-ZtZ8IyeLHbYxo9kA/viewform

COVID-19: RESCHEDULED MEETINGS

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

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

Community Reclaiming the Global Response (HIV 2020)

CANCELLED (was 5 – 7 July 2020, Mexico City)

https://www.hiv2020.org/registration

23rd International AIDS Conference (AIDS 2020)
6 – 10 July 2020 (NOW VIRTUAL ONLY

www.aids2020.org

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

12 – 13 September 2020, New York

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

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

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

www.virology-education.com

11th International Workshop on HIV & Ageing (2020)

1 – 2 October 2020, NYC

https://www.virology-education.com

HIV Glasgow Congress 2020

NOW VIRTUAL ONLY - 4 – 7 October 2020, Glasgow

www.hivglasgow.org

International Workshop on HIV Paediatrics 2020

16 - 17 November 2020, San Francisco, USA.

www.virology-education.com

26th Annual BHIVA Conference (BHIVA 2020)

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

www.bhiva.org

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

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

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

expected: planned follow-up to continue to two years. HTB (1 December

HIV Research for Prevention (HIV R4P 2020)

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

https://www.hivr4p.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

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

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

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

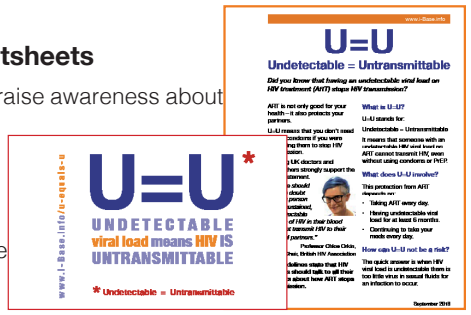
Pocket guides

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

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

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

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



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

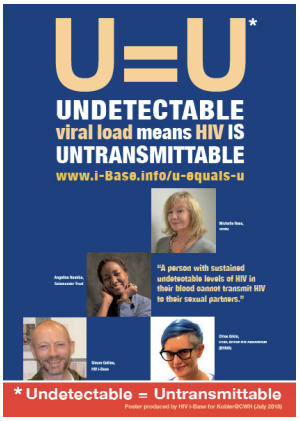
This project was developed with the Kobler Centre in London.

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

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

email: subscriptions@i-base.org.uk

Customise U=U posters for your clinic



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

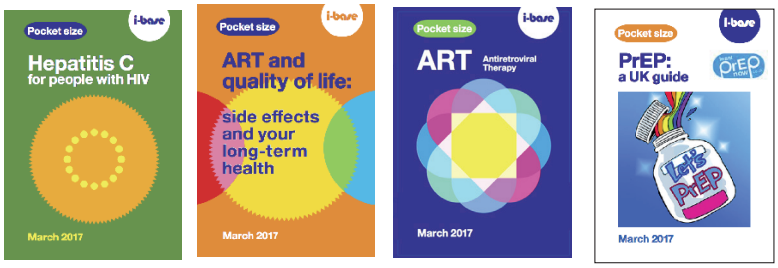
Personalising these for your clinic is cheap and easy and might be an especially nice way to highlight the good news.

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

roy.trevelion@i-Base.org.uk

Order publications and subscribe online

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



h-tb

HIV TREATMENT BULLETIN

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

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