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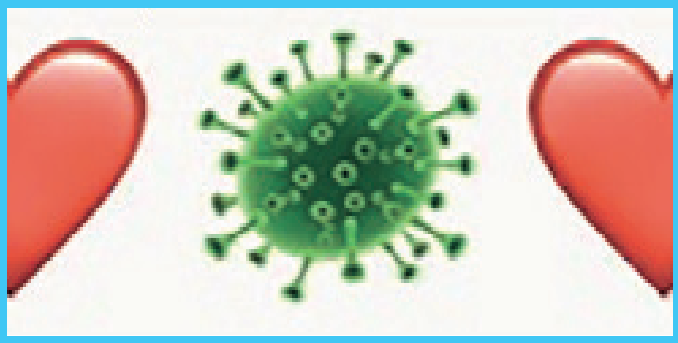
HIV and COVID-19 no. 4



HTB supplement (4): 1 June 2020

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HTB SUPPLEMENT ON HIV & COVID-19: ISSUE 4

Contents continued

EDITORIAL

This is the fourth HTB that is that it is produced as as a supplement on COVID-19.

Some HIV articles are still included though, including to remember leading US activists Ron Simmons and Larry Kramer who both died this week. We also have positive early results for using long-acting cabotegravir injections as HIV PrEP. Plus updates on HIV conferences, many of which have changed to virtual meetings.

But the rest of the contents are based on COVID-19 because this is he most important health information for people living with HIV right now. And there has been a lot to cover, even in the few weeks since the last issue.

We lead with a review of current studies on HIV and COVID-19 coinfection, five of which – from the UK, Spain, the US, Italy and Germany - were published in the last two weeks. Although most support BHIVA and ECAS statements of little additional risk from HIV in people on effective ART, most of these studies are small. And some - including the new case series from Kings College Hospital in South London – report higher rates of mortality and are more cautious.

We also include articles on many of the investigational treatments for COVID-19, including remdesivir, convalescent plasma, interferon, famotidine, tocilizumab and hydroxychloroquine (HCG).

Results from the randomised, placebo-controlled ACTT study provide the most convincing evidence of benefit to date - and supports the earlier decision for FDA approval. The UK MHRA have responded by lunching an early access programme across the country. In reporting the entry criteria we also comment that some important groups might be overlooked – and these guidelines tare reconsidered.

And now that remdesivir is now available in the the UK, ongoing COVID-19 studies should add it to current standard of care in many ongoing COVID-19 studies, and potentially for all particpants.

Undating research as the standard of care changes was always a community principle in HIV research - so that no participants receive less than the standard of care. Although this will improve care for participants, not doing this would jeopardise further enrolment and retainment.

For example, in the rendomised UK DISCOVERY trial. Although more than 10,600 participants are so far enrolled DISCOVERY hasn't reported preliminary results yet, or included a data review timeline in

the protocol. Other researchers have published negative results for some of the compoundsbeing used, such as monotherapy wirh lopinavir/r or HCQ. This includes a large HCQ meta-analysis published in the Lancet (We also report this study in detail).

Although the DISCOVERY study plans to continue its HCQ arm, the international WHO SOLIDARITY study (with a European branch called RECOVERY) has suspended the HCQ arm for further review.

DSMBs for large studies should looking at prompt discontinuation of study arms with no active benefit. Similar consideration should now be made to change single therapy arms to ones that include remdesivir as a basis for dual therapy,

In noting the lack of UK treatment guidelines for COVID-19, we review the NIHR listing for the 42 key research studies.

And we include reports on COVID-19 pathogenesis thanks to Mark Mascolini's reports on NATAP, a US community organisation that has been providing access to medical information on HIV and hepatitis for well over two decades.

Finally, we are hearing anecdotal reports of dramatically reduced cases of newly diagnosed COVID-19 in several London hospitals. This is hopefully being repeated through the rest of the UK.

We join our readers in the hope that this will be sustained, and the chance that the relaxing of at least some of the physical distancing measures will not lead to a second wave of COVID-19. Even managin smaller outbreaks though is untimately dependent on having effctive treatment and hopefully a future vaccine.

i-Base 2020 appeal:

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

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 receives 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 appeal supported by Wolfgang Tillmans Building 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:

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

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http://i-base.info/htb/about/subscribe

IN MEMORY

In the last week we heard that two long-time and prominent US community activists had died. Both were inspirational leaders who played key roles in fighting the AIDS epidemic.

Marc Thompson talks about how Ron Simmons influenced his activism and Ash Kotak remembers the impact Larry Kramer had on generating community response to HIV as a cofounder of GMHC and ACT-UP.

Dr Ron Simmons. Activist. Teacher. Mentor. Organiser. Leader. Survivor. Black gay icon.

By Marc Thompson, cofounder of Prepster

One of our elders has passed over.

I first met Ron Simmons in 1992 when he visited London and came to our Black gay men's group Let's Rap. He inspired us UK kids to organise, teach and support in those dark days of the epidemic.

On a visit to Washington DC in 1996 I had the honour of hanging out with Ron at Black gay pride over Memorial weekend. He invited me to his organisation Us Helping Us, set up to support Black folk living with HIV.

It changed my life.

I'd never been with so many Pos people that looked like me. I declared my status openly, in public for the first time. I remember Ron giving me the biggest hug and telling me everything was gonna be ok.

That evening I called my mum and told her I knew what my calling was. That my HIV was a gift for me to do good for my community.

Ron's strength and guidance enabled me to do that.

Even years later at conferences around the world, Ron would greet me with that beautiful smile and same big hug. He connected and impacted many of us across the diaspora and his legacy lives on in the work we do for Black queer men.

I often hear younger Black queer men say we don't have role models. Not entirely true.
I've been blessed to have had some amazing and inspiring 'uncles' that have guided my path and Dr Ron Simmons was at the front.

Rest in Power King.

Marc Thompson has worked for many HIV and sexual health organisations and is a cofounder of Prepster.

Selected links

Obituary in AU magazine
https://aumag.org/2016/12/19/ron-simmons-advocate

Obituary in Poz magazine
https://www.poz.com/article/rip-ron-simmons-phd-empowering-aids-advocate-gay-black-men

The Ubuntu Biography Project: Ron Simmons
https://ubuntubiographyproject.com/2018/03/02/ron-simmons

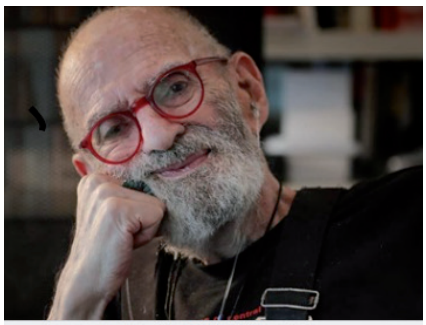
Short interview
https://www.youtube.com/watch?v=ZWXgycqtOUY

Larry Kramer, playwright, AIDS activist and writer (1935-2020)

by Ash Kotak, playwright and film-maker

Anyone who says one man cannot make a difference never met Larry Kramer, the playwright, author, essayist, screenwriter and activist who has died of pneumonia at the age of 84.

Bold, unpredictable, angry, articulate, a revolutionary with a sharp tongue but a surprising streak of tenderness, he stirred many to action as a co-founder of Gay Men's Health Crisis (GMHC) in 1982 and the AIDS Coalition To Unleash Power (ACT UP) in 1987.



Born in 1935 into a downwardly mobile Jewish family, Kramer was full of contradictions: a self-proclaimed loudmouth, he wrote with astonishing sensitivity.

He began his career writing for movies, winning an Oscar nomination in 1969 for director Ken Russell's "Women in Love", which he also produced. But he is probably best known as the author of the autobiographical Tony Award-winning play "The Normal Heart" about Ned Weeks, the founder of a gay advocacy group in early 1980s New York, which opened in Manhattan in 1985.

There have been more than 600 productions worldwide since, including a version staring Hollywood actor Martin Sheen in 1986 at London's Royal Court theatre. It later aired on HBO in 2014, having been adapted by Kramer, starring actors Mark Ruffalo and Julia Roberts.

His other works included a 1992 sequel, "The Destiny of Me", a finalist for the Pulitzer Prize for drama, which continued Weeks's story as he took part in an AIDS drug trial in the early 1980s whilst flashing back to the protagonist's early 1950s Jewish upbringing. The play won two Obie Awards.

In 1996, Kramer gained the American Academy of Arts and Letters Award for Literature.

"Faggots", published in 1979, proved to be his seminal novel. Deeply critical of the hedonistic lifestyle of gay men at the time – a constant whirl of drugs and sex – it provoked a firestorm among the LGBT+ community, before the advent of HIV/AIDS revealed the novel's prescient view of a section of society out of control.

But in his focus predominantly on white, gay men with AIDS, Kramer failed to fully grasp the issues faced by other communities at the epicentre of the pandemic: people of colour, the poor, the marginalised and women worldwide.

Yet he remained a powerful voice calling for greater recognition of the impact of HIV/AIDS worldwide.

His 5000-word essay, "1,112 and Counting", published on March 14, 1983 on the front page of The Native – New York's only significant gay publication at the time – caused just the stir he wanted. It was a wake-up call born out of his rage at the lack of serious attention paid to the crisis.

Kramer's targets were wide and many: healthcare professionals, scientists, the then US President Ronald Reagan, the closeted New York mayor Ed Koch. However, the gay men who represented the majority of deaths from AIDS-related illnesses were not absolved from criticism.

His anger was palpable. Three presidents stood accused of being "murderers" – Reagan, George Bush Snr and Bill Clinton. Others felt the full force of his rage, including the current COVID-19 tsar, Anthony Fauci, then director of the National Institute of Allergy and Infectious Diseases.

Without doubt, Kramer's voice and call to action saved hundreds of thousands of lives. He himself was diagnosed HIV-positive in 1988 and also with liver damage due to hepatitis B. He underwent a liver transplant in 2001 after causing a stink having been refused one due to his status.

And he never stopped fighting.

At the Reclaim Pride 50th anniversary of Stonewall event in Central Park in New York last summer, he upset the crowd by saying that they had failed the AIDS and the LGBT+ movement. He was furious that the hedonism had returned and the horrors of "the gay holocaust" and the memory of the dead was being so quickly ignored by a younger generation hooked on power, drugs and casual sex.

And his response to the novel form of coronavirus was typical: a new play, "An Army of Lovers Must Not Die", is likely to keep his fiery rage burning long after his death.

Ash Kotak is a playwright and film-maker and leads the #AIDSMemoryUK Campaign to establish a national tribute to HIV and AIDS in Britain. This was first published by Openly Thompson Reuters Foundation.

Selected links

ACT-UP remembrances of Larry Kramer
https://actupny.com/post-your-remembrances-of-larry-kramer

Amfar: Larry Kramer: the most powerful voice on AIDS
https://www.amfar.org/Larry-Kramer

Obituary in Poz magazine
https://www.poz.com/article/rip-larry-kramer-84-author-aids-activist

Speech by Larry Kramer from Reclaim Pride
https://www.youtube.com/watch?v=3GZV3aU8WV0&feature=youtu.be

HIV PREVENTION

Cabotegravir long-acting injections prevent HIV but maybe less effective than oral PrEP in context of perfect adherence

Simon Collins, HIV i-Base

On 18 May 2020, the international phase 2b/3 HPTN 083 study reported that cabotegravir injections were effective at reducing the risk of HIV transmission. Compared to participants using daily oral PrEP (TDF/FTC) few participants using the injections became HIV positive. [1, 2]

However, because some participants did become HIV positive when using cabotegravir, explaining the full results might show that in the context of perfect adherence that oral TDF/FTC is technically more effective. When adherence is not good, the benefit is likely to come from using long-acting injections.

All participants will now be offered the injections, even though the study was planned to continue for another two years. Once approved, this will lead to a new way to prevent HIV infection, but the detailed results from this study are just as important as the headline news.

HTPN 083 randomised 4570 gay men and transgender women who have sex with men to either cabotegravir injections or daily oral TDF/FTC PrEP plus matching placebo for 153 weeks. The first five weeks was placebo-controlled oral formulations of both drugs. The study is being run in 40 sites in Argentina, Brazil, Peru, Thailand, the US, Vietnam, and South Africa. [3]

The study started in December 2018 and was due to finish in March 2022 but travel restrictions due to COVID-19 led to an early assessment of results by the independent data and safety monitoring board (DSMB). Although HPTN 083 was originally to test whether cabotegravir long acting (LA) was superior to TDF/FTC, the DSMB reported that changing to a non-inferior design would provide sufficient differences to show that cabotegravir LA is significantly more effective than oral TDF/ FTC. This led to a DSMB recommendation to discontinue the TDT/FTC arm early and offer cabotegravir injections to all participants.

The top-line results – all that have so far been released – reported that injectable PrEP was 69% more effective compared to oral PrEP. Overall, 50 participants became HIV positive: 12 in the cabotegravir arm vs 38 randomised to oral FTC/TDF. This produced an HIV incidence rate of 0.38% (95% CI: 0.20% to 0.66%) vs 1.21% (95% CI: 0.86% to 1.66%) in the cabotegravir vs FTC/TDF groups respectively.

The limited baseline demographics include that regionally 37% of participants are in the US, 43% are in Latin America, 16.5% in Asia and 3.5% in Africa. Mean age is 28 years old, with 40% less than 25 and 66% less than 30. It is significant that transgender women make up 12% of participants and that half of the participants in the United States identified as black or African American.

In an online press conference to present these results, tolerability and safety were also reported as generally good. Injections site reactions were more common in people receiving active injections – 80% vs 31% – with discontinuations at 2.2% vs 0, respectively.

A similar study that started a year later – HPTN 084 – is being run in 3200 cisgender women in Botswana, Kenya, Malawi, South Africa, Eswatini, Uganda and Zimbabwe. This study is almost recruited and already has 25% of follow-up. The same DSMB has recommended that this study should continue as planned. [4]

Both studies are a collaboration funded by the US NIAID with support from ViiV Healthcare and Gilead Sciences.

C O M M E N T

Results from HPTN 083 will be used as part of the regulatory submission for cabotegravir LA as PrEP to both the FDA and EMA, although the timeline for this was not announced.

These results are important as many people at high risk of HIV do not find oral PrEP an easy or acceptable option, but the results also need to be interpreted cautiously until the full analysis are presented and published.

Although in this study cabotegravir LA was more effective than oral PrEP this is likely to be explained by different levels of adherence in the two arms. Cabotegravir adherence should by definition have been 100% because it was given at study visits, whereas oral PrEP would depend on individual participants remembering to take a daily pill.

Although the press statements include that in a pharmacokinetic sub-study of HPTN-83, drug levels were generally good in the oral PrEP arm, the infections that did occur on oral PrEP are likely to be in people who missed doses. Other studies have reported true efficacy of oral PrEP in the context of good adherence is effectively 100%.

Strictly speaking, in the context of 100% adherence, cabotegravir injections appear to be less effective than oral PrEP. Further details to explain the new infections in the cabotegravir group, possibly because of early infections at the start of the study, lower drug levels at some timepoints and in some people, or development of drug resistance, will be important in the presentation of the full results.

For someone who is strictly adherent to oral PrEP, switching to cabotegravir LA injections now might therefore reduce their current level of protection against HIV. In someone where adherence is a difficult problem, the advantages of long-acting injections are likely to be better.Strictly speaking, in the context of 100% adherence, cabotegravir injections appear to be less effective than oral PrEP. Further details to explain the new infections in the cabotegravir group, possibly because of early infections at the start of the study or lower drug levels at some timepoints and in some people, will be an important aspect of the presentation of the full results.

For someone who is strictly adherent to oral PrEP, switching to cabotegravir LA injections now might therefore reduce their current level of protection against HIV.

References

1. HPTN press release. Long-acting injectable cabotegravir is highly effective for the prevention of HIV infection in cisgender men and transgender women who have sex with men. (18 May 2020).
   https://www.hptn.org/news-and-events/press-releases/long-acting-injectable-cabotegravir-highly-effective-prevention-hiv
2. ViiV press release. Global HIV prevention study to stop early after ViiV Healthcare's long-acting injectable formulation of cabotegravir dosed every two months shows higher efficacy than daily oral PrEP. (18 May 2020).
   https://viivhealthcare.com/en-gb/media/press-releases/2020/may/global-hiv-prevention-study-to-stop-early-after-viiv-healthcares
3. clinicaltrials.gov. Safety and efficacy study of injectable cabotegravir compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis in hiv-uninfected cisgender men and transgender women who have sex with men.
   https://clinicaltrials.gov/ct2/show/NCT02720094
4. clinicaltrials.gov. evaluating the safety and efficacy of long-acting injectable cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in hiv-uninfected women.
   https://clinicaltrials.gov/ct2/show/NCT03164564.

HTB SUPPLEMENT ON COVID-19: Issue 4

COVID-19: HIV and COVID-19 COINFECTION

HIV and COVID-19 coinfection: case reports, retrospective cohorts and outcomes

Simon Collins, HIV i-Base

In the last few weeks several new studies have reported on larger cohorts of HIV positive people with COVID-19 coinfection.

Data are still limited and hopefully larger national cohorts will be reported soon with more details on people living with HIV. There is also clearly a role for independent researchers to run meta-analyses from larger data sets.

Studies so far include from China, Germany, Italy, Spain, the UK and the US and are summarised in Table 1. [1 – 16]

This table will be added to as new data becomes available. Although other small case studies (n=1 to 4), have been reported and are referenced but as these add little to larger cohorts they are not included in the table. [17 – 20]

The most recent publications are:

A UK study describing 18 HIV positive people with COVID-19 at Kings College, South London. Most (17/18) were black, on long-term ART and undetectable but comorbidities were common. Five have died and one is still in hospital. [1]

A Spanish study of 51/2873 (1.8%) HIV positive people diagnosed with COVID-19 at a single hospital in Madrid. Six were critically ill and two have died. [2]

A case series of nine HIV positive people diagnosed with COVID-19 at a single centre in the South Bronx. All had comorbidities and 7/9 died (78%). [3]

An Italian study describes 47 HIV positive people referred to a single hospital between 21 February and 16 April 2020 with proven/probable COVID-19. Of these 45/47 (96%) fully recovered and two died. [4]

A German study on 33 HIV positive people, previously referred to in the joint BHIVA/EACS statement has also now been published in full. [5]

Generally, at least in statements by BHIVA and EACS, this is being taken as evidence that people on effective ART are not at any higher risk than the general population. [21]

However, the difficulties of interpreting outcomes in these small studies – whether different or similar to the general population – was also highlighted by UK researchers in correspondence to Lancet HIV. [22]

As larger studies become available, we will add them to this t

Table 1: Studies reporting HIV/COVID-19 coinfection

Lead author	Notes	N	Refs
Childs K et al.	Case series of 18 people (12 men, 6 women) with HIV and COVID-19 being treated at Kings College Hospital in South London. Median age was 52 years (IGR: 49 to 58). 17/18 were Black race. Median time since HIV diagnosis was 14 years (IQRL 10 to 23 years). All were on ART, with 17/18 having undetectable viral load. Latest CD4 count was median 395 cells/mm^3 (IQR: 238 to 680) but median CD4 nadir was only 97 cells/mm^3 (IQR: 45 to 143). Comorbidities were common, with 10/18 having BMI >30kg/m^2, 6/18 had hypertension, 4/18 had diabetes and 5/18 had chronic kidney disease. 12 pts were successfully discharged, one is still hospitalised and five died (median 5 days since admission (range: 3 to 28). Compared to our whole HIV cohort those hospitalised with COVID-19 were more likely to be of black ethnicity (OR 12.22 [95%CI: 1.62-92.00]) and to have lower CD4 count (395 vs. 573, p=0.03).	18 HIV+, 17/18 black. 5/28 died.	1
Vizcarra P et al.	Prospective, observational study of 51 people consecutively diagnosed with COVID-19 (8 women, 43 men) from a single HIV centre in Madrid from cohort of 2873 pts (incidence 1·8%, 95%CI: 1.3 to 2.3). 35/51 were lab confirmed and 28/51 were hospitalised. Age (range 31 to 75) and CD4 was similar to those without COVID-19 but 63% vs 38% had at least one comorbidity (mainly hypertension and diabetes). 6/51 (12%) were critically ill and two died.	51/2873 (1.8%), 2/51 died.	2
Suwanwongse K et al.	Case series of nine patients (seven men, two women) hospitalised with COVID-19 at a single centre in the South Bronx, New York from 25 March to 30 April 2020. Median age was 58 years (range: 30 to 76). All patients had comorbidities. CD4 count ranged from 179 to 1827 cells/mm^3. HIV viral load was <50 copies/mL is all (but unknown in one). Only 8/9 were on ART, which was discontinued for 4/8 (2 for kidney complications. 7/9 patients died (78%) Seven patients died (78%), four due to hypoxemic respiratory failure and three from septic shock and multi-organ failures.	9 HIV+. 7/9 died (78%).	3
Gervasoni C et al.	Retrospective Italian cohort from single hospital site in Milan from 21 February and 20 April 2020. 47/6000 HIV positive people identified. Mean age 51 (+/–11,) 36 men, 11 women. 28/47 were hospitalised. 45/47 recovered and 2/47 died. Minimal treatment but remdesivir + tocilizumab in one and tocilizumab alone in one.	47 HIV+, 2/47 died	4
Härter G et al.	Retrospective German cohort from 12 sites. 29/32 (91%) have recovered and 3/32 died. Mean age was 48 years (range 26–82 years) and 30/33 patients were men. Median CD4 was 670 cells/mm^3 (range 69 to 1715). Although this study reported increased hospitalisation and mortality for HIV positive people, this might be due to other factors. Mechanical ventilation needed by two people with detectable HIV viraemia.	33 HIV+. 3/33 died.	5

Guo et al.	Subset of 1178/6000 HIV positive people in Wuhan City who were contacted by telephone. 8/1178 who self-reported symptoms were later confirmed with COVID-19 (0.68%). 6/8 were mild, 1/8 was severe and 1/8 died. Only 1/9 HIV positive people in close household contact with COVID-19 became coinfected with COVID-19 (late diagnosed with CD4: 27 cells/mm^3).	8/1178 HIV (0.68%) positive people were coinfected with COVID-19.	6
Karmen-Tuohy S et al.	Case-control study in NYC matching 21 HIV positive people to 42 HIV negative people reporting similar outcomes in both groups - and that HIV doesn't impact this.	21 HIV+ and 42 HIV – controls.	7
Richardson S et al.	Characteristics, symptoms, and outcomes of 5700 patients hospitalised with COVID-19 in 12 hospitals in outer NYC boroughs between 1 March and 4 April 2020. Although no clinical details were presented separately for the 43 people (0.8%) who also had HIV positive status recorded, it provided an indication that HIV might not be over-represented.	43/5700 (0.8%) were HIV positive.	8
ISARIC reports.	ISARIC published paper and online COVID-19 report (27 April 2020). The published paper on general population includes >16,000 people with COVID-19. Median age was 72 years [IQR 57, 82; range 0, 104]. Only data provided on HIV positive people is number of people where HIV positive status was recorded. This may not be comprehensive as an earlier report included a large percentage with unknown status.	At least 120 HIV positive people in the UK have been diagnosed with COVID-19, with > 40 deaths.	9, 10, 11
Goyal P et al.	Characteristics and outcomes of first 393 consecutive patients with COVID-19 hospitalised at a single community hospital in NYC. No clinical details were presented for the 7/393 who were also HIV positive.	7/393 were HIV positive.	12
Blanco JL et al.	Characteristics and outcomes of first 543 consecutive patients with COVID-19 hospitalised at a single community hospital in Barcelona. Clinical details for the 5/543 (0.92%) who were also HIV positive included ART, risk factors and outcomes. 1/5 was diagnosed as a late presenter with CD4: 11 cells/mm^3. All since discharged.	5/543 (0.92%) were HIV positive	13
Miro JM et al.	Updated numbers to the Spanish cohort above (Blanco et al) reported in correspondence, included 42 HIV/COVID-19 coinfections. 32/42 were hospitalised including one new HIV diagnosis. This was 42/5649 (0.7%) of the HIV cohort, 1·9% of the 2215 emergency department visits for COVID-19 and 1·5% of the 2102 hospital clinic admissions.	32/2102 hospitalised were coinfected. Approx. 0.7% of HIV cohort reported COVID-19.	14
Riva D et al.	Three case studies of COVID-19 coinfection in HIV positive people on darunavir-based ART.	3 case studies.	15
Zhao J et al.	38-year-old Chinese gay man diagnosed with COVID-19 on 25 January who had travelled to Wuhan several weeks earlier. He had been diagnosed with HIV in 2016 with a CD4 count of 84 cells/mm^3 and HCV coinfection.	Single case study, included earlier HCV coinfection.	16

References

1. Childs K et al. Hospitalised patients with COVID-19 and HIV: a case series. Clinical Infectious Diseases, ciaa657, DOI: 10.1093/cid/ciaa657 (27 May 2020)
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa657/5847856
2. Vizcarra P et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. The Lancet. DOI: 10.1016/S2352-3018(20)30164-8. (28 May 2020).
https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30164-8/fulltext
3. Suwanwongse K et al. Clinical features and outcome of HIV/SARS□CoV□2 co□infected patients in the Bronx, New York City. Jour Med Vir. DOI: 10.1002/jmv.26077. (28 May 2020).
https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.26077 (abstract)
https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.26077 (PDF)
4. Gervasoni C et al. Clinical features and outcomes of HIV patients with coronavirus disease 2019. Clinical Infectious Diseases, ciaa579, DOI: 10.1093/cid/ciaa579/ (14 May 2020).
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa579/5837155
5. Härter G et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. Infection. DOI: 10.1007/s15010-020-01438-z. (11 May 2020).
https://link.springer.com/article/10.1007%2Fs15010-020-01438-z

6. Guo W et al . A survey for COVID-19 among HIV/AIDS patients in two districts of Wuhan China. Lancet. DOI: 10.2139/ssrn.3550029 (13 March 2020). https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3550029
7. Karmen-Tuohy S et al. Outcomes among HIV-positive patients hospitalised with COVID-19. Ahead of peer review. https://www.medrxiv.org/content/10.1101/2020.05.07.20094797v1
8. 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
9. Docherty AB et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO clinical characterization protocol. medRxiv preprint DOI: 10.1101/2020.04.23.20076042. (28 April 2020). https://www.medrxiv.org/content/10.1101/2020.04.23.20076042v1
10. 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)
11. Personal communication.
12. 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
13. Blanco JL et al. COVID-19 in patients with HIV: clinical case series. Lancet HIV. Correspondence. DOI: 10.1016/S2352-3018(20)30111-9. (15 April 2020). https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30111-9/fulltext
14. Miro JM et al. COVID-19 in patients with HIV. Lancet HIV, Correspondence. (14 May 2020). https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30140-5/fulltext
15. 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
16. Zhao J et al. Early virus clearance and delayed antibody response in a case of COVID-19 with a history of co-infection with HIV-1 and HCV. Clinical Infectious Diseases, ciaa408, DOI: 10.1093/cid/ciaa408. (09 April 2020). https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa408/5818121
17. Wu Q et al. Recovery from COVID-19 in two patients with coexisted HIV infection. J Med Virol. DOI: 10.1002/jmv.26006. (13 May 2020). https://onlinelibrary.wiley.com/doi/10.1002/jmv.26006
18. Patel RH et al COVID□19 in a patient with HIV infection. J Med Vir. (22 May 2020). https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.26049
19. Baluku JB et al. HIV and SARS-CoV-2 Co-Infection: A Case Report From Uganda. J Med Virol DOI: 10.1002/jmv.26044. (21 May 2020). https://pubmed.ncbi.nlm.nih.gov/32437000/
20. Aydin OA et al. HIV/SARS-CoV-2 co-infected patients in Istanbul, Turkey. J Med Virol. DOI: 10.1002/jmv.25955. (29 April 2020) https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25955
21. BHIVA, DAIG, EACS, GESIDA & Polish Scientific AIDS Society Statement on risk of COVID-19 for people living with HIV (PLWH). (25 May 2020). https://www.bhiva.org/BHIVA-DAIG-EACS-GESIDA-Polish-Scientific-AIDS-Society-statement-on-risk-of-COVID-19-for-PLWH
22. Jones R et al. COVID-19 in patients with HIV. Lancet HIV. Correspondence. DOI: 10.1016/S2352-3018(20)30139-9 (14 May 2020). https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30139-9/fulltext

COVID-19: TREATMENT ACCESS

UK access to remdesivir approved: but MHRA criteria exclude some who could benefit

Simon Collins, HIV i-Base

On 26 May 2020 the Medicines and Healthcare products Regulatory Agency (MHRA) issued a press release and guidelines to outline criteria for UK access to remdesivir, the first drug to be approved in the US to treat COVID-19. [1]

However, some people who could benefit are not included. Also, ongoing COVID-19 studies should also now include remdesivir as part of the new standard of care. This is a principle from community engagement in HIV research.

Access to remdesivir will use a programme that allows people with life-threatening illnesses to have early access to medicines that already have proven benefits but that are still going through full approval.

To reach this stage an advisory group (the Commission on Human Medicines) has reviewed the available evidence and recommended that remdesivir is both effective and safe enough for early access. [2, 3]

The UK indication is for:

- The treatment of adults and adolescent patients aged ≥ 12 years and weighing at least 40 kg hospitalised with suspected or laboratory confirmed SARS-CoV-2 infection and severe disease.
- Severe disease is defined as an SpO2 ≤ 94% on room air or requiring supplemental oxygen or requiring non-invasive or invasive ventilation or extracorporeal membrane oxygenation (ECMO).

However the document then suggests than remdesivir should be more effective in earlier infection but also that this should benefit those at higher risk, and then includes criteria for access. [4]

The criteria are listed below.

Early access criteria

- Age 12 years or older on the date of starting treatment.
- Weight ≥40kg on the date of starting treatment.
- Creatinine clearance above 50ml/min (upper level defined).
- AST/ALT below 5 times upper limit of normal and no history of chronic liver disease defined as Child-Pugh C.

Risk score

Access dependent on having at least four of the following factors (or three if the radiographic severity score threshold is reached).

- Radiographic severity score >3.
- Male gender.
- Non-white ethnicity.
- Diabetes.
- Hypertension.
- Neutrophils >8.0 10 /L.
- Age >40 years.
- CRP >40 mg/L.

Diagnostic criteria

- Less than 10 days from onset of symptoms
- Hospitalised with SARS-CoV-2 infection confirmed by PCR collected in preceding 72 hours

Illness severity and organ support criteria

- Discussion about the eligibility for escalation to critical care including invasive mechanical ventilation, multi-organ support and CPR should be considered through shared decision making in line with the NICE guidance NG159 (using the Clinical Frailty Score). [5] Some patients not eligible for escalation may be suitable for access to remdesivir as determined by mutildisciplinary assessment.
- Patients who require FiO2 ≥ 0.4% to maintain O2 sats >94% with standard oxygen therapy (Hudson mask) measured on two occasions at least 1 hour apart; OR who are within 24h of commencing CPAP or HFNO2 to maintain O2 sats >94% and have not been previously mechanically ventilated for treatment of COVID-19
- Not requiring invasive mechanical ventilation, ECMO, cardiovascular support (pressor, inotrope or mechanical) at the time of drug initiation. Those starting on the drug should continue if they subsequently need invasive mechanical ventilation. The evidence of benefit has not been demonstrated for those on ventilation. There may be some patients just starting on ventilation in the early phase of the infection who may be suitable for access to remdesivir as determined by mutildisciplinary assessment.

Reporting safety and outcome data is a requirement for use of remdesivir.

Logistic details are outlined for each UK country but trusts will be allocated stock upfront. They will be able to preorder supplies based on caseload and expected need.

C O M M E N T

The early access to remdesivir is important. It should immediately improve the outcomes for many people who are ill with COVID-19. Even though the protocol requires people to be hospitalised, it should encourage people with confirmed COVID-19 to seek hospital treatment earlier.

Remdesivir has the potential to save lives and earlier access will improve the chance of better outcomes.

So whilst the data clearly show benefit of remdesivir in hospitalised patients, especially for those requiring supplemental oxygen therapy, there remains an issue of supply of remdesivir and therefore the need to prioritise sickest and 'most at risk'

patients, and exclude patients likely to have poor outcomes.

The current criteria are justifiably stringent in this regard, and will, hopefully become less stringent, as supplies improve over the coming months. There are, however, two criteria that deserve immediate attention.

Patients who are thought unsuitable for 'escalation' or Intensive Care are excluded, unless an MDT decides that they are suitable. Actually, this is exactly the group most likely to benefit, if there was a reasonable short to medium term prognosis from a general health point of view, since remdesivir could prevent both progression and the need for ventilatory support.

The second group that should be reconsidered is patients presenting beyond 10 days of symptom onset. These people would also benefit from added anti-inflammatory therapy, however as the ACTT-1 trial showed, time from onset of symptoms was not an important factor for achieving primary outcome.

For patients needing mechanical ventilatory support/ECMO there is clearly a need for added anti-inflammatory therapy.

Finally, all future studies of antiviral and anti-inflammatory or immunomodulatory therapy now need to consider remdesivir as the new 'standard of care' for comparison.

Rapidly responding to advances in the standard of care was a basic principle of community engagement with HIV research and it is just as important for COVID-19.

STOP PRESS: As this issue of HIV and COVID-19 was being finalised for distribution, Gilead issued a press release on the SIMPLE-Moderate study. Top-line results showed that in moderate COVID-19 disease – those with pneumonia who do not require supplemental oxygen – a 5-day course of remdesivir led to greater clinical improvement than standard of care alone. [6]

References

1. MHRA. MHRA issues a scientific opinion for the first medicine to treat COVID-19 in the UK. (26 May 2020).
https://www.gov.uk/government/news/mhra-supports-the-use-of-remdesivir-as-the-first-medicine-to-treat-covid-19-in-the-uk
2. MHRA. Early access to medicines scheme (EAMS) scientific opinion: remdesivir in the treatment of patients hospitalised with suspected or laboratory-confirmed SARS-CoV-2 infection who meet the clinical criteria. (26 May 2020).
https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-remdesivir-in-the-treatment-of-patients-hospitalised-with-suspected-or-laboratory-confirme
3. Product information for healthcare professionals.
https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-remdesivir-in-the-treatment-of-patients-hospitalised-with-suspected-or-laboratory-confirme
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/887275/EAMS__11972_0002__TP__HCP_Solution.pdf (PDF direct link)
4. COVID-19 Therapeutic Alert. Early Access to Medicines Scheme for remdesivir in the treatment of COVID-19. Implementation of the scheme and management of supply. CEM/CMO/2020/025 Issue date: 26 May 2020
https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103046
https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103580 (PDF download)
5. NICE. COVID-19 rapid guideline: critical care in adults. NICE guideline [NG159]. (Last update 29 April 2020).
https://www.nice.org.uk/guidance/ng159
7. Gilead press statement. Gilead announces results from phase 3 trial of remdesivir in patients with moderate COVID-19. (1 June 2020).
https://www.gilead.com

EMA recommends expanding access to remdesivir

EMA press release

EMA's human medicines committee (CHMP) has recommended expanding the compassionate use of the investigational medicine remdesivir so that more patients with severe COVID19 can be treated.

In addition to patients undergoing invasive mechanical ventilation, the compassionate use recommendations now cover the treatment of hospitalised patients requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices or ECMO (extracorporeal membrane oxygenation).

The updated recommendations are based on preliminary results from the NIAID-ACTT study, which suggest a beneficial effect of remdesivir in the treatment of hospitalised patients with severe COVID-19. EMA is currently evaluating these data in the context of the rolling review of remdesivir.

In addition, a treatment duration of 5 days has been introduced alongside the longer 10-day course, based on preliminary results from another study (GS-US-540-5773) suggesting that for patients not requiring mechanical ventilation or ECMO, the treatment course may be shortened from 10 to 5 days without any loss of efficacy. Patients who receive a 5-day treatment course but do not show clinical improvement will be eligible to continue receiving remdesivir for an additional 5 days. The option to shorten treatment duration also means that more patients may be able to receive the medicine, which is in very high demand worldwide.

Although remdesivir is not yet authorised for marketing in the European Union, these recommendations for compassionate use will help some patients with severe COVID-19 access the medicine while EMA evaluates data on its benefits and risks. When the evaluation is complete, EMA will make a recommendation on whether or not remdesivir should receive a marketing authorisation.

On 30 April 2020, the EMA also announced the start of a rolling review for data related to evaluating remdesivir in the EU, [2]

C O M M E N T

The UK MHRA have already approved access to remdesivir, although criteria exclude important people who could benefit.

Remdesivir should be considered the new standard of care in appropriate research studies.

References
1. EMA recommends expanding remdesivir compassionate use to patients not on mechanical ventilation (11 May 2020). https://www.ema.europa.eu/en/news/ema-recommends-expanding-remdesivir-compassionate-use-patients-not-mechanical-ventilation
2. EMA starts rolling review of remdesivir for COVID-19. (30 April 2020). https://www.ema.europa.eu/en/news/ema-starts-rolling-review-remdesivir-covid-19

COVID-19: INVESTIGATIONAL TREATMENT

Remdesivir improves recovery time in early COVID-19 infection: first definitive results of benefit

Simon Collins, HIV i-Base

On 22 May 2020, the first clear results in favour of remdesivir being active against COVID-19, from the US NIAID ACTT study were published in the New England Journal of Medicine. [1]

Until now, even though recently approved in both the US and Japan, the data supporting remdesivir was contradictory, and top-line results had only been available by press release.

The preliminary results are sufficient to warrant widespread early access to remdesivir, including by compassionate access in Europe. They should also challenge other ongoing studies to look at adding remdesivir to current standard of care for all participants.

The international Adaptive Covid-19 Treatment Trial (ACTT-1) study is a phase 3, double-blind, placebo-controlled study that randomised 1063 participants to either intravenous remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The study was conducted in more than 60 sites in Denmark, Germany, Greece, Japan, Korea, Mexico, Singapore, Spain, the UK and the US.

The primary outcome was the time to recovery - although this had been changed during the study as more was learnt about COVID-19. This was defined by either discharge from hospital or remaining in hospital to reduce transmission (rather than for clinical reasons).

Baseline characteristics were well balanced between arms and included mean age 58.9 (±15.0); 64% male and 53% white, 23% Hispanic/Latino, 21% black or African American, 12% Asian. Median time from symptoms to randomisation was 9 days (IQR: 6 to 12). Just over 50% in each arm had two or more comorbidities, mainly hypertension (49%), obesity (37%) and type-2 diabetes (29%).

Randomisation was stratified by disease severity. Although baseline ordinal score (4 to 7) was generally balanced, more advanced oxygen support requiring invasive mechanical ventilation or ECMO (baseline score of 7) was 28% of placebo recipients (compared to 23% in the remdesivir group). Overall, 88% were classified as having severe stage disease (defined by one or more of: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an SpO2 ≤ 94% on room air, or respiratory rate ≥ 24 breaths per minute).

On 27 April 2020, the independent data and safety monitoring board (DSMB) for the study recommended early unblinding of the results due to significant differences in favour of remdesivir.

Preliminary results from 1049 participants (531 remdesivir vs 518 placebo) included a median recovery time of 11 days (95% CI: 9 to 12) vs 15 days (95% CI: 13 to 19) with a significant rate ratio of 1.32; 95% CI, 1.12 to 1.55; p<0.001).

Although there were numerically fewer deaths by day 14 in the remdesivir arm (n=32 vs 54; 7.1% vs 11.9%), the Kaplan-Meier estimates of mortality did not reach statistical significance (HR: 0.70; 95% CI: 0.47 to 1.04). All but two of the deaths (one in each arm) had severe stage disease at study entry.

Kaplan-Meier estimates of recovery only favoured remdesivir for participants with a baseline score of 5 (less severe illness) but not for participants with more advanced disease, see Table 1. However, an analysis adjusting for baseline ordinal score produced a similar treatment-effect estimate (RR 1.31; 95% CI, 1.12 to 1.54; 1017 patients).

Table 1: results by baseline ordinal score

Baseline ordinal score *	n	RR for recovery (95%CI)
4	127	1.38 (95% CI, 0.94 to 2.03)
5	421	1.47 (95% CI, 1.17 to 1.84)
6	197	1.20 (95% CI, 0.79 to 1.81)
7	272	0.95 (95% CI, 0.64 to 1.42)

* Key: 4 = not requiring oxygen; 5 = requiring supplemental oxygen; 6 = non-invasive ventilation or high-flow oxygen devices; 7 = mechanical ventilation or ECMO.

Serious adverse events occurred less frequently in the remdesivir arm 114/541 (21.1%) vs 141/522 patients (27.0%) in the placebo group. This included serious respiratory failure adverse events in 28 (5.2%) vs 42 (8.0%) of the remdesivir vs placebo participants respectively. No deaths were judged related to remdesivir/placebo. Grade 3 or 4 events also occurred less frequently in the remdesivir arm: 156 (28.8%) vs 172 (33.0%), respectively.

The study also concludes that the high mortality even with remdesivir suggests that treatment with an antiviral drug alone is unlikely to be sufficient and that combination therapy should still be investigated. However, no viral load results have been presented for this study and this is not listed as a secondary endpoint in the information on clinicaltrials.gov registry for other phase 3 studies.

C O M M E N T

These results provide the first evidence that remdesivir can significantly improve outcomes, although early access and use seems important. This should increase demand for compassionate access in the UK, at earlier stages of infection. [2]

Although the initial primary endpoint was difference in clinical status, defined by 8-point ordinal scale at day 15, this was changed a priori to time to recovery (ordinal scale score 1,2 or 3) during the 28 days after enrolment.

There was an overall difference between the arms with regard to median recovery time, but no statistically significant benefit in terms of overall mortality. This suggests that optimal benefit is for patients hospitalised, requiring oxygen or non-invasive ventilation. However, less of an effect for patients requiring mechanical ventilation or ECMO.

The Gilead 5774 Simple study in moderate infection will provide data on the impact of remdesivir 5 days vs 10 days vs standard of care in a larger number of hospitalised patients not needing oxygen supplementation or with O2 >94% on air. This should be reporting soon.

The DISCOVERY Trial (the European arm of the adaptive-platform Solidarity study) should provide data on Sars-CoV-2 RNA, at least in terms of time to undetectability. This includes remdesivir as one of the treatment arms.

Additional remdesivir studies in the UK are comparing 5-day vs 10-day remdesivir treatment.

Even though not yet approved in Europe, other ongoing studies that currently use standard of care control arms should also consider remdesivir to current standard of care.

Remdesivir was approved by the FDA on 1 May 2020. [3, 4] The EMA has already announced that remdesivir will be evaluated using a rolling review process to accelerate this decision in Europe.

Gilead has signed non-exclusive licensing agreements with five generic drug makers to manufacture remdesivir for distribution in 127 countries and to expand the supply of remdesivir for COVID-19. [6]

The agreements are with Cipla, Ferozsons, Hetero, Jubilant Lifesciences and Mylan and the countries include nearly all low-income and lower-middle income countries, as well as several upper-middle- and high-income countries that face significant obstacles to healthcare access.

On 26 May 2020, the UK MHRA agreed expanded access to remdesivir. [7]

STOP PRESS: As this issue of HIV and COVID-19 was being finalised for distribution, Gilead issued a press release on the SIMPLE-Moderate study. Top-line results showed that in moderate COVID-19 disease – those with pneumonia who do not require supplemental oxygen – a 5-day course of remdesivir led to greater clinical improvement than standard of care alone. [8]

References
1. Beigel JH et al. Remdesivir for the treatment of covid-19 – preliminary report. NEJM, DOI: 10.1056/NEJMoa2007764. (22 May 2020). https://www.nejm.org/doi/full/10.1056/NEJMoa2007764
2. European Medicine's Agency press statement. EMA provides recommendations on compassionate use of remdesivir for COVID-19. (3 April 2020). https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19
3. 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
4. Remdesivir Safety information.https://www.fda.gov/media/137566/download
5. European Medicine's Agency press statement. EMA starts rolling review of remdesivir for COVID-19. (30 April 2020). https://www.ema.europa.eu/en/news/ema-starts-rolling-review-remdesivir-covid-19
6. Gilead press statement. Voluntary licensing agreements for remdesivir. https://www.gilead.com/purpose/advancing-global-health/covid-19/voluntary-licensing-agreements-for-remdesivir
7. UK access to remdesivir approved: but MHRA criteria exclude some who could benefit. HTB. (28 May 2020). http://i-base.info/htb/38051
8. Gilead press statement. Gilead announces results from phase 3 trial of remdesivir in patients with moderate COVID-19. (1 June 2020). https://www.gilead.com

Convalescent plasma therapy for COVID-19

Simon Collins, HIV i-Base

Several papers have reviewed the potential benefits of using convalescent plasma therapy with immunoglobulins to treat COVID-19.

Although data s currently very limited, many more studies are already underway including in the UK RECOVERY study.

The first report of convalescent plasma to successfully treat five people critically ill with COVID-19 was published in JAMA. [1]

All participants (aged 36 to 73 years, 2/5 were women) had severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment, methylprednisolone and mechanical ventilation. None were smokers and none had pre-existing comorbidities. Convalescent plasma was given between 10 and 22 days after admission with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 and a neutralisation titre >40 that had been obtained from five patients (aged 18 to 60) who recovered from COVID-19 approximately 11 days after discharge.

In 4/5 patients, body temperature normalised within three days, the SOFA score decreased, and P/F oxygen ratio increased within 12 days (range, 172-276 before and 284-366 after). Viral load also became negative within 12 days of the transfusion. SARS-CoV-2–specific ELISA and neutralising antibody titres increased following the transfusion (range, 40-60 before and 80-320 on day 7). Acute respiratory distress syndrome (ARDS) resolved in 4/5 patients at 12 days, and 3/5 were weaned from mechanical ventilation within 2 weeks of treatment.

At last follow-up, 3/5 have been discharged from hospital (after 53, 51, and 55 days), and two are in stable condition at 37 days after transfusion.

Kai Duan and colleagues also published outcomes from six men and four women with severe COVID-19 treated with a single infusion (200 mL) of convalescent plasma. [3] The primary endpoint was safety with secondary endpoints of clinical improvement and laboratory parameters within 3 days after transfusion. [2]

Median age was 52 years old (IQR: 45 to 59) and median time from symptoms to hospitalisation and transfusion was 6 days (IQR: 2.5 to 8.5) and 16.5 days (IQR,:11.0 to 19.3), respectively.

After transfusion, neutralising antibody levels increased rapidly up to 1:640 in five cases, and was maintained at a high level (1:640) in four others. The clinical symptoms significantly improved within three days. Other improvements included increased lymphocyte counts (0.65×10^9/L vs. 0.76×10^9/L) and reduced C-reactive protein (55.98 mg/L vs. 18.13 mg/L). Viral load in seven participants become undetectable.

However, nine patients received the antiviral treatment, mainly umifenovir in combination with remdesivir, ribavirin, or peramivir. Antibacterial or antifungal treatment was used when patients had coinfection. Six patients received IV methylprednisolone.

Another paper from Korea included two cases (a 71 year old man and a 67 year old woman) who used convalescent plasma (from donors in their 20s), who were admitted for tertiary care, were unresponsive to lopinavir/r, hydroxychloroquine and antibiotics and who had progressed to intubation. [3]

Both had improvements in fever and need for oxygen decreased following convalescent plasma and were successfully weaned off intubation. Both showed an increasing trend in viral load that began to decrease right after the use of convalescent plasma, but because neither were in early phase infection (22 and 7 days after onset of symptoms) this cannot be ruled out as part of natural pathology.

Unfortunately, less successful outcomes were reported by Qing-Lee Zeng and colleagues for six patients with COVID-19 and respiratory failure who received convalescent plasma for a median of 21.5 days after viral shedding was first found. Although all tested negative for SARS-CoV-2 RNA within three days after infusion, 5/6 people eventually died. [4]

This led the researchers to conclude that convalescent plasma treatment can stop SARS-CoV-2 shedding but cannot reduce the mortality rate in critically ill patients with end-stage COVID-19, and treatment should be initiated earlier.

Many other papers have discussed use of convalescent plasma for COVID-19 including a recent paper in Lancet Infectious Diseases by Chen and colleagues, who reviewed historical use to treat SARS-1, MERS, H1N1 and related viral infections and on possible use to treat SARS-CoV-2. [5] Earlier reviews have also reported potential benefits with few risks but are based on small low-quality studies without control groups. [6]

A useful review of 10 ongoing studies in Nature, mostly controlled, including with placebos, and ranging from 60 to over 420 participants and due to end from May to December 2020, will produce stronger evidence. [7]

However, this doesn't include the UK RECOVERY study that has already randomised more than 10,600 participants (2:1 control:active arms) to standard of care defined at no treatment or to one of several active arms including lopinavir/r (Kaletra), low-dose dexamethasone, hydroxychloroquine (related to an anti-malarial drug), azithromycin, tocilizumab or convalescent plasma. It is unclear whether all these arms are still ongoing. [8]

Finally, the UK has also already launched a campaign to collect convalescent plasma. [9]

In the US, a large-scale open-label study had registered more than 2000 sites by 30 April 2020, enrolled 7,774 patients and provided transfusion to 3,809 of them. [10]

C O M M E N T

These papers show the potential for both successful and unsuccessful outcomes from use of convalescent plasma and without controls is it difficult to evaluate the impact of treatment.

Despite critical illness the initial case study included younger patients who did not have comorbidities that predict worse outcomes and they also received other antiviral treatment.

In other papers, convalescent plasma is used with other potential treatments, and combination therapy is increasingly thought to be more effective than monotherapy with any single treatment.

Most also comment, either in the original paper or in correspondence that optimal timing for plasma infusion still needs to be determined but earlier use might be important.

It is similarly important for ongoing studies now responding to use multiple treatments, even if the UK is currently hopefully coming to the end of the initial first wave of COVID-19.

References

1. Shen C et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020 323(16): 1582–1589. doi: 10.1001/jama.2020.4783. (27 Mar 2020).
https://jamanetwork.com/journals/jama/fullarticle/2763983
2. Duan et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. PNAS, PNAS 117 (17) 9490-9496; DOI: 10.1073/pnas.2004168117. (6 April 2020).
https://www.pnas.org/content/117/17/9490
3 Ahn JY et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci. 2020;35:e.149. doi: 10.3346/jkms.2020.35.e149.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7152526
4. Zeng Q-L. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. Journal of Infectious Diseases, jiaa228, DOI: 10.1093/infdis/jiaa228. (29 April 2020)
https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985
5. Chen L et al. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020; 20:398–400. doi: 10.1016/S1473-3099(20)30141-9. (20 April 2020).
https://www.thelancet.com/article/S1473-3099(20)30141-9/fulltext
6. Mair-Jenkins J et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015 Jan 1; 211(1): 80–90. doi: 10.1093/infdis/jiu396.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264590
7. Sheridan C. Convalescent serum lines up as first-choice treatment for coronavirus. Nature Biotechnology. doi: 10.1038/d41587-020-00011-1. (7 May 2020).
https://www.nature.com/articles/d41587-020-00011-1

8. The UK RECOVERY study.
https://www.recoverytrial.net
https://www.recoverytrial.net/files/recovery-protocol-v6-0-2020-05-14.pdf (protocol PDF)
9. NHS. Convalescent plasma programme.
https://www.nhsbt.nhs.uk/covid-19-research/plasma-programme
10. Expanded access to convalescent plasma for the treatment of patients with COVID-19. (15 May 2020).
https://www.uscovidplasma.org/pdf/COVID-19 Plasma EAP.pdf (protocol PDF)
https://clinicaltrials.gov/ct2/show/NCT04338360 (trial listing).

Treatment with interferon in early COVID-19

Simon Collins, HIV i-Base

Two studies have been recently published that report potential benefits from using interferon treatment in mild of early stage COVID-19.

A study by Zhou and colleagues reported the outcomes of 77 participants with moderate COVID-19 who were admitted to the Union Hospital in Shanghai between 16 January and 20 February 2020 and who were randomised to receive either nebulised IFN-□-2b (n=7), the antiviral umifenovir (UFV) (n=24) or dual treatment (n=46). [1]

Participants receiving IFN treatment had faster viral load clearance and reduced levels of inflammatory proteins IL-6 and C-reactive protein, regardless of age, sex and comorbidities.

Baseline characteristics that varied between groups included median age (IQR) 41 vs 40 vs 64 (p<0.001) the percentage of men 0%, 43% and 45% (p=0.076) and percentage with comorbidities 14%, 15% and 54% (p=0.002), in the IFN, dual and UFV arms respectively.

The dual therapy group was also treated approximately nine days later after symptoms, median 8, 17 and 8 days respectively, p=0.004.

None of the participants required oxygen supplementation, intubation or intensive care. Approximately 50% had fever 38°C that was managed by ibuprofen.

Mean days to viral clearance was approximately 21 vs 20 vs 28 days from the onset of symptoms for the IFN, dual and UFV arms respectively (p=0.002).

The dual therapy arms included 16/46 cases (34.8%) IFN was started after UFV and 24 cases where IFN was continued after UFV was stopped.

Although this was an exploratory, small, non-randomised, uncontrolled study with significant baseline differences between the groups the effects of IFN treatment on accelerated viral clearance and reductions in circulating IL-6 and CRP levels remained significant after adjusting for age, sex and comorbidities.

At least one publication has reported no benefit from using umifenovir against COVID-19. [2]

An open-label, randomised, phase 2 trial from Hung and colleagues using a triple combination regimen of interferon beta-1b, lopinavir/r and ribavirin reported better outcomes compared to a control arm using lopinavir/r alone. [3]

The triple therapy arm had significantly reduced time to negative throat PCR: 7 days (IQR: 5 to 11) vs 12 days (IQR: 8 to 15) [HR: 4.37 (95%CI: 1.86 to 10.24)], symptom alleviation: 0 of 4 days (IQR 3 to 8) vs 8 days (IQR: 7 to 9); [HR 3.92; 95%CI: 1.66 to 9.23], and duration of hospital stay (9.0 days (IQR: 7.0 to 13.0] vs 14.5 days (IQR: 9·3 to 16·0); HR 2.72 (95%CI: 1.2 to 6.13).

Although this is important for being a prospective study, participants were in early mild or moderate COVID-19 and there was no mortality in either group.

References

1. Zhou Q et al. Interferon-□2b Treatment for COVID-19. Front. Immunol., DOI: 10.3389/fimmu.2020.01061. (15 May 2020).
https://www.frontiersin.org/articles/10.3389/fimmu.2020.01061/full
2. Lian N et al. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clin Bicrociol and Inf. DOI:https://doi.org/10.1016/j.cmi.2020.04.026. (25 April 2020).
https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30234-2/fulltext
3. Hung IF-N et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020; DOI: 10.1016/S0140-6736(20)31042-4. (8 May 2020).
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext

Famotidine associated with improved clinical outcomes in people hospitalised with COVID-19

Simon Collins, HIV i-Base

A retrospective analysis reports a positive association between open label use of antacid famotidine (an H2 receptor agonist with antiviral properties) and better clinical outcomes in people hospitalised with COVID-19, compared to a control group matched by baseline characteristics. [1]

Famotidine had previously been identified from a database of potential compounds screened for repurposing for COVID-19 based on computational analysis of structures encoded by SARS-CoV-2 proteins. [2]

This paper reported on clinical outcomes from 84/1,620 (5%) adults who were given famotodine within 24 hours of admission to a single centre from 25 February to 13 April 2020 with PCR confirmed COVID-19. Comparison to a control group used propensity score matching was balance the baseline characteristics of patients who did and did not use famotidine.

Factors in the analysis included pre-existing diabetes, hypertension, coronary artery disease (CAD), heart failure, end-stage renal disease or chronic kidney disease, and chronic pulmonary disorders; obesity, based on BMI; and age, classified as <50 years old, 50-65 years old, and >65 years old.

Overall, 340/1,620 (21%) met the composite primary endpoint of progression to intubation (n=142, 8.8%) or death (n=238, 15%). In adjusted analysis, famotidine was associated with reduced risk for intubation or death (aHR) 0.43; 95% CI: 0.21 to 0.88) and also for death alone (aHR 0.30; 95% CI: 0.11 to 0.80), both p<0.01. When those who died prior to intubation were excluded, there was no association between use of famotidine and intubation (log-rank p=0.40)

Participants using famotidine received a total median dose of 136 mg (63 – 233 mg) for a median 5.8 days. 28% of all famotidine doses were intravenous; 47% were 20 mg, 35% were 40 mg, and 17% were 10 mg. Famotidine was used prior to admission by 15% of those who used famotidine while hospitalised compared to 1% of those who did not (p<0.01).

The results were similar in several sensitivity analyses, including use of proton pump inhibitors that had no impact on either endpoint, indicating any mechanism was unrelated to acid suppression.

The study reported that a lower peak ferritin value was observed among users of famotidine, supporting the hypothesis that use of famotidine may decrease cytokine release in the setting of SARS-CoV-2 infection.

A randomised phase study of high-dose IV famotidine with hydroxychloroquine (HCQ) vs HCQ is already underway in 1170 participants with mild or moderate COVID-19. [3]

References

1. Freedberg DE et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. PRe-peer review. DOI: 10.1101/2020.05.01.20086694.(19 May 2020). https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v2
2. Wu C et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102550
3. clinicaltrials.gov. A multi-site, randomized, double-blind, multi-arm historical control, comparative trial of the safety and efficacy of hydroxychloroquine, and the combination of HCQ and famotidine for the treatment of COVID-19 (MATCH). NCT04370262. https://clinicaltrials.gov/ct2/show/NCT04370262

Tocilizumab and remdesivir in dual therapy study

Simon Collins, HIV i-Base

As dual and triple combination therapy becomes an important approach for COVID-19 a new randomised phase 3 study a new study has been announced that will use tocilizumab plus remdesivir with a control arm using remdesivir alone.

The study (called REMDACTA) is not yet listed on clinicaltrials.gov. [1, 2]

It is supported by Roche and Gilead (manufacturers of tocilizumab and remdesivir, resptectively) and is expected to begin enrol 450 participants globally from June 2020.

More than 40 studies of tocilizumab are listed on clincaltrials.gov registry as either ongoing or planned. This includes the large multi-arm UK RECOVERY study that has already enrolled more than 10,500 participants.. [2]

References
1. Roche press release. Roche initiates phase III clinical trial of Actemra/RoActemra plus remdesivir in hospitalised patients with severe COVID-19 pneumonia. (28 May 2020).
https://www.roche.com/media/releases/med-cor-2020-05-28.htm
2. clinicaltrials.gov. Randomized evaluation of COVID-19 therapy (RECOVERY). NCT04381936.
https://clinicaltrials.gov/ct2/show/NCT04381936

No benefit from hydroxychloroquine, with or without macrolide antibiotics in analysis of 96,000 patients

Simon Collins, HIV i-Base

On 22 May 2020, a large retrospective international meta-analysis published in the Lancet failed to show a benefit of either hydroxychloroquine (HCQ) or chloroquine (CQ) for treating COVID-19, with or without a macrolide antibiotic (generally azithromycin or clarithromycin) but did report increased risk of side effects. [1]

The results are important given the extensive ongoing studies using HCQ (largely based on variable results from small uncontrolled studies), especially since positive results have now been reported for remdesivir in a large placebo controlled study. [2]

Off-label use of HCQ has also been reported, including as prophylaxis for COVID-19, and stockpiling drugs have led to shortages for people with approved indications.

This analysis included results from more than 96,000 people hospitalised with PCR-confirmed COVID-19 between 20 December 2019 and 14 April 2020, and involved 671 hospitals in six continents.

The analysis included 14,888 people in four treatments (started within 48 hours): chloroquine alone (n=1868), chloroquine with a macrolide (n=3783), hydroxychloroquine alone (n=3016), or hydroxychloroquine with a macrolide (n=62210. This left 81,144 in the control group. Main outcomes included time in hospital for efficacy against COVID-19 and new ventricular arrhythmias as a safety measure. Starting treatment when on mechanical ventilation and use of remdesivir were exclusion criteria.

Baseline characteristics include mean age 53.8 years and 53.7% were men. Mean BMI was 27.6 kg/m^2 (SD +/–5·5) and 30.7% were obese (BMI ≥30). The mean length of stay in hospital was 9.1 days (SD 6·4), with an overall in-hospital mortality of 11·1%.

Geographically, participants were from North America (65·9%), Europe (17·3%), Asia (7·9%), Africa (4·6%), South America (3·7%), and Australia (0·6%).

Overall, 10698 (11·1%) people died in hospital. In multivariate analysis, controlling for age, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity) all four treatment groups had significantly higher rates of in-hospital mortality and new ventricular arrhythmias compared to the control group, see Table 1.

The commonly reported risk factors associated with poor outcomes to COVID-19 were significantly associated with higher risk of mortality, and with use of all four treatment groups, hence the importance of adjusted analysis.

Table 1: risk of in-hospital mortality with COVID-19

Treatment arm	Mortality rate	HR (95%CI)	New ventricular arrhythmias	HR (95%CI)
control group	9.3%		0.3%	
HCQ	18.0%	1.335 (1.223 to 1.457)	6.1%	2.369 (1.935 to 2.900)
HCQ + macrolide	23.8%	1.447 (1.368 to 1.531)	8.1%	5.106 (4.106 to 5.983)
CQ	16.4%	1.365 (1.218 to 1.531)	4.3%	3.561 (2.760 to 4.596)
CQ + macrolide	22.2%	1.368 (1.273 to 1.469)	6.5%	4.011 (3.344 to 4.812)

Other independent predictors of higher rates of in-hospital mortality included:

- Black race HR: 1.344 (95%CI: 1.276 to 1.415).
- Hispanic race HR: 1.495 (95%CI: 1.400 to 1.597).
- Congestive heart failure HR: 1.756 (95%CI: 1.609 to 1.915).
- Arrhythmia HR: 1.626 (95%CI: 1.504 to 1.758).
- Oxygen saturation (SPO2) <94% HR: 1.664 (95%CI: 1.587 to 1.746).

Protective factors associated with a reduced risk included:

- Asian race (HR: 0.717; 95%CI: 0.668 to 0.769).
- Use of an ACE inhibitor (HR: 0.566; 95%CI: 0.514 to 0.624).
- Use of a statin (HR: 0.793; 95%CI: 0.736 to 0.855) and
- Quick sepsis-related organ failure assessment (qSOFA) <1 (HR: 0.758; 95%CI: 0.726 to 0.792.

Independent predictors of ventricular arrythmia included:

- Coronary artery disease HR: 1.830 (95%CI: 1.613 to 2.076).
- Congestive heart failure HR: 3.914 (95%CI: 3.283 to 4.665).
- History of cardiac arrhythmia HR: 4.119 (95%CI: 3.525 to 4.812).
- COPD HR: 1.585 (95%CI: 1.256 to 2.001).

The discussion included a data review of other studies, largely reporting similar lack of benefit.

Although the investigators noted limitations from observational data they concluded that this large-scale, international, real-world analysis supports the absence of a clinical benefit of chloroquine and hydroxychloroquine and points to potential harm in hospitalised patients with COVID-19.

They suggested that these drug regimens should not be used outside of clinical trials and urgent that confirmation from randomised clinical trials is needed.

C O M M E N T

Although this article was peer reviewed and published in the Lancet, the study has also been criticised for methodology relating to the dataset and for suggestions that finding such a large safety effect linked to treatment might be linked to unadjusted confounding.

For example, that in the context of patients hospitalised for COVID-19, HCQ or CQ could easily have been more readily prescribed for people with the most rapid deterioration when management of cardiovascular event might also have been less optimum. Also, while presented as a collaborative large international study, the paper is authored by four commercial researchers who are not directly connected to any of the datasets that are included.

However, its advantages include the size of the dataset and that it is representative of people in many different countries.

Also, a growing number of studies are now questioning the use of HCQ or CQ for COVID-19 based on unlikely efficacy or increased risk of toxicity.

Studies questioning efficacy include a recent article (ahead of peer review) support in-vitro and animal studies as relevant models for studying COVID-19 but did not find data to support antiviral or clinical efficacy of HCQ as either treatment or PrEP. [3]

The large randomised UK RECOVERY study (n>9000) currently being run in the UK has published MHRA support to still continue the HCQ arm. [4]

The large international WHO SOLIDARITY trial (called DISCOVER in Europe) has just closed its HCQ arm. [5]

A paper focused on the risk of serious toxicity based on drug levels from intentional overdose studies reported that peak concentrations >13 umol/L (95%CI: 10 to 16) would be associated with >1% mortality. [6]

Use of an adult dose of 600 mg twice-daily for 10 days results in peak concentrations >10 umol/L in >60% of adults weighing 70 kg. It also notes that among more than 90 ongoing HCQ of CQ studies for COVID-19, only 0.2% adults weighing >70 kg in other high-dose studies would be expected to achieve peak drug levels >10 umol/L.

This paper also reports that the high dose arm (600 mg base chloroquine twice daily for ten days) used in the Brazilian study that was recently stopped due to serious high toxicity, represented the standard malaria loading dose repeated 19 times at 12 hour intervals. [7]

It also suggests that there may have been confusion between salt and base weights. The Chinese guidelines on which the Brazilian study was based recommended 500 mg salt twice daily (two tablets of 250 mg, comprising 155 mg base each).

References

1. Mehra MR et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet. DOI: 10.1016/ S0140-6736(20)31180-6. (22 May 2020).
   https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext
2. Collins S. Remdesivir improves recovery time in early COVID-19 infection: first definitive results of benefit. HTB (22 May 2020).
   http://i-base.info/htb/37976
3. Maisonnasse P et al. Hydroxychloroquine in the treatment and prophylaxis of SARS-CoV-2 infection in non-human primates. NatureReseach. Pre-peer-review article. 10.21203/rs.3.rs-27223/v1. (6 May 2020).
   https://www.researchsquare.com/article/rs-27223/v1
4. RECOVERY trial statement. Recruitment to the RECOVERY trial (including the Hydroxychloroquine arm) REMAINS OPEN. (22 May 2020).
   https://www.recoverytrial.net/files/professional-downloads/recovery_noticetoinvestigators_2020-05-24_1422.pdf (PDF)
5. WHO SOLIDARITY trial (DISCOVERY trial in Europe).
   https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
6. Watson JA et al. Concentration-dependent mortality of chloroquine in overdose. Before peer review. DOI: 10.1101/2020.04.24.20078303. (29 April 2020).
   https://www.medrxiv.org/content/10.1101/2020.04.24.20078303v1
7. Borba M et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). medRxix doi: 10.1101/2020.04.07.20056424.
   https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v1

COVID-19: HIV MANAGEMENT GUIDELINES

BHIVA advice for HIV positive people hospitalised with COVID-19

Simon Collins, HIV i-Base

On 15 May 2020, BHIVA published an online factsheet to help HIV positive people who need to go to hospital because of COVID-19. [1]

The leaflet covers HIV disclosure in hospital, continuing to take ART, access to intensive care if needed and where to get more information.

i-Base have adapted the leaflet as an i-Base Q&A web page, This also includes information about treatment for COVID-19. [2]

References

1. BHIVA. What to do if you're HIV positive and are admitted to hospital with COVID-19 – advice from the British HIV Association (BHIVA). (15 May 2020).
   https://www.bhiva.org/what-to-do-if-youre-HIV-positive-and-are-admitted-to-hospital-with-COVID-19
2. i-Base Q&A. What should HIV positive people do if hospitalised with COVID-19.
   http://i-base.info/qa/15765

BHIVA guidelines on shielding: advice for HIV clinicians, GPs and people living with HIV

BHIVA press release

On 23 April, BHIVA published guidance on COVID-19 and shielding. [1]

This guidance addresses two key issues related to COVID-19 and shielding.

1. People considered to be at highest clinical risk who are not on the official CMO list.
2. People who have incorrectly received Government advice to shield.

Much of this guidance is applicable to all countries in the UK, but some outlined processes are specific to England.

It also refers to the Royal College of General Practitioners (RCGP) useful summary of shielding actions and advice for each nation, which can be accessed on their website. [2]

References

1. BHIVA. COVID-19 & shielding: advice for HIV clinicians, GPs and people living with HIV. (23 April 2020). https://www.bhiva.org/COVID-19-and-shielding-advice-for-HIV-clinicians-GPs-and-people-living-with-HIV
2. RCGP. Latest advice on COVID-19 from RCGP. https://www.rcgp.org.uk/covid-19/latest-covid-19-guidance-in-your-area.aspx

European consensus on COVID-19: UK, European, Spanish, German and Polish HIV organisations

Simon Collins, HIV i-Base

The latest monthly joint statement from BHIVA and EACS on COVID-19 has also become a collaboration with the German (DAIG, Deutsche AIDS Gesellschaft), Spanish (GeSIDA Grupo de Estudio de SIDA) and Polish AIDS Societies. [1]

This statement reviews new studies on risk to people living with HIV, maintaining the same conclusion that being on effective ART is similar to the general population. It still notes however, the high percentage of HIV positive people who have risk factors (including age, gender, cormorbidities and smoking) for more serious outcomes from COVID-19. [2, 3]

Information on the potential treatments for COVID-19 has been updated to include recently published studies reporting the potential risks from hydroxychloroquine and the potential benefits from remdesivir. [4, 5, 6]

It also includes a new reference to an article in Science reports potential benefits of famotidine. [7]

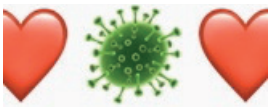
Most of the new research is also reviewed in articles in this issue of *HIV and COVID-19*.

References

1. BHIVA, DAIG, EACS, GESIDA & Polish Scientific AIDS Society Statement on risk of COVID-19 for people living with HIV (PLWH). (25 May 2020). https://www.bhiva.org/BHIVA-DAIG-EACS-GESIDA-Polish-Scientific-AIDS-Society-statement-on-risk-of-COVID-19-for-PLWH
2. Härter G et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. Infection. Infections. DOI: 10.1007/s15010-020-01438-z. (11 May 2020). https://link.springer.com/article/10.1007%2Fs15010-020-01438-z
3. Gervasoni C et al. Clinical features and outcomes of HIV patients with coronavirus disease 2019. Clin Infect Dis. pii: ciaa579. DOI: 10.1093/cid/ciaa579. (14 May 2020). https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa579/5837155
4. Geleris J et al. Observational Study of Hydroxychloroquine in Hospitalized Patients With Covid-19. N Engl J Med 2020 May 7;NEJMoa2012410. doi: 10.1056/NEJMoa2012410. Online ahead of print
5. Mehra MR et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020, Published online May 22, 2020. https://doi.org/10.1016/S0140-6736(20)31180-6 https://doi.org/10.1016/S0140-6736(20)31180-6
6. Beigel JH for the ACTT-1 study group members. Remdesivir for the treatment of covid-19 – preliminary report. N Engl J Med 2020. DOI: 10.1056/NEJMoa2007764. (22 May 2020). https://www.nejm.org/doi/full/10.1056/NEJMoa2007764
7. New York clinical trial quietly tests heartburn remedy against coronavirus. Science. (26 April 2020). https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus#

UK guidelines for the treatment of COVID-19: ongoing research

Simon Collins, HIV i-Base



There are currently no UK national or regional guidelines on treatment of COVID-19.

However, there is an information support tool from the Network of High Consequence Infectious Diseases (HCID) and this is updated regularly. [1]

This 25-page document includes a review of key and prioritised UK research studies and a data review for key compounds with proposed antiviral activity.

Ongoing UK studies

The National Institute for Health Research (NIHR) also publishes a directory of prioritised research studies that currently includes 42 trials. [2]

These currently include observational, interventional and preclinical studies both for prevention al treatment. The interventions for treatment include remdesivir (3), tocilizumab (1), canakinumab (1), otilimab (1), Gemtuzumab ozogamicin (1), baricitinib and ravulizumab (1), IFN (1), HCQ +/– azithromycin (2), Ruxolitimib (1), Brensocatib (1).

Three studies use variations of adaptive design to study multiple treatment. including some of the same compounds above: (i) Zilucoplan, Bemcentinib, Medi3506, Acalabrutinib (ACCORD), (ii) LPV/r, steroid, HCQ, azithromycin, tocilizumab (TACTIC-R) and (iii) LPV/r, steroid, HCQ, tocilizumab, interferon-beta, anakinra, convalescent plasma, therapeutic anticoagulation (REMAO-CAP)

About 20 studies are largely observational to look at specialist management (for example with ventilation), or outcomes in various populations (including in pregnancy) and for genetic and genomics. Or are looking at prevention in various populations including health workers. Three studies involve vaccine research and four have no further information, including one using IL-7 and preclinical studies.

A European initiative. led by French researchers at INSERM, Cochrane France and University of Paris, but with partners from Ireland, Germany, Denmark and Chile is also tracking studies, with weekly updates. [3]

This project currently includes almost 1000 studies, almost 600 of which are recruiting and 66 of which were added in the last week.

C O M M E N T

Given NICE has published guideline for prevention – and also on patient rights and decisions for end-of-life care - the lack of information guidance on COVID-19 is a significant oversight.

Guidelines on treatment are especially for people who are faced with life-threatening treatment decisions. Even if they largely stress the limited evidence from randomised clinical studies, guidelines could also be useful to outline the most important ongoing studies and different approaches to treatment.

Some of the larger adaptive trials, including RECOVERY include experimental treatments with compounds than might not now be thought likely to work than when the study was first planned.

For example, although the RECOVERY group have reported that HCQ will continue to be used, given the study size (more than 10,600 participants ae now enrolled), it is difficult to believe that lopinavir/r is showing a significant benefit compared to standard of care.

Given the size of this study, and the rapid course of COVID-19, it is notable that no arms have so far been stopped due to limited effects, especially as randomisation is 2:1 in favour of standard of care control to open-label compounds. The online protocol for RECOVERY doesn't appear include a detailed timeline for data review

Recent MHRA approval should hopefully result in research studies promptly including remdesivir in all arms as this is the new standard of care and investigational compounds should also now be studied in addition to the best standard of care.

As new cases of COVID-19 become less common - the primary outcome we all want – this will reduce the number of participants for research studies. The availability of open-label access to remdesivir – and other treatments with evidence to support inclusion in the changing standard of care – will also deter participants from enrolling in research studies where these are not routinely included in the control arms.

References

1. Network of High Consequence Infectious Diseases (HCID). Position Statement: Use of investigational antiviral medicines for COVID-19 in adults:Interim support for UK hospital clinicians. (last update: 22 May 2020).
https://www.ctag-support.org.uk/antivirals

2. NIHR. Urgent Public Health COVID-19 Studies
https://www.nihr.ac.uk/covid-studies
3. Living mapping and living systematic review of Covid-19 studies.
https://covid-nma.com

COVID-19: PATHOGENESIS

Changes in taste and smell as key symptoms of COVID-19

Simon Collins, HIV i-Base

On 20 April 2020, based on accumulated evidence, the i-Base Q&A service included information about changes and taste being a common symptom of COVID-19. [1]

Early anecdotal reports in the US also included taste and smell changes and this was now supported by a published study that confirmed these as symptoms. [2]

The US study reported that smell and taste loss were reported in 68% (40/59) and 71% (42/59) of people who had COVID-19, respectively. This compared to only 16% (33/203) and 17% (35/203) of people that did not have COVID-19. People reporting smell and taste changes were about ten times more likely to have COVID-19.

Two other studies have reported more details. [3, 4]

The letter in JAMA reported that taste and smell changes occurred in about 1 in 3 people with coronavirus. Also, that this could occur at any time – ie before or after other symptoms. In a few people (about 3%) this was the only symptom of coronavirus.

Approximately a month later the UK government also added changes in taste and smell as key symptoms that would enable someone to test for COVID-19. [5]

References

1. i-Base Q&A. Are taste and smell changes common with COVID-19?
http://i-base.info/qa/15688
2. Yan CH et al. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. International Forum of Allergy & Rhinology, 2020; DOI: 10.1002/alr.22579.
https://pubmed.ncbi.nlm.nih.gov/32279441/
3. Giacomelli A et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020;ciaa330. Published online March 26, 2020. doi:10.1093/cid/ciaa330. (26 March 2020).
http://dx.doi.org/10.1093/cid/ciaa330
4. Spinato G et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA, research letter. (22 April 2020).
https://jamanetwork.com/journals/jama/fullarticle/2765183
5. gov.uk. Everyone in the United Kingdom with symptoms now eligible for coronavirus tests (18 May 2020)
https://www.gov.uk/government/news/everyone-in-the-united-kingdom-with-symptoms-now-eligible-for-coronavirus-tests

Low CD4s and CD8s and older age predict COVID-19 progression – but not viral genetics

Mark Mascolini for NATAP.org

Low CD4 and CD8 T-cell counts and other host factors predicted COVID-19 progression in 326 people in Shanghai early in the epidemic's course. SARS-CoV-2, the virus that causes COVID-19, stayed genetically stable over time and did not affect disease outcomes.

Researchers from Shanghai's Fudan University and collaborators from other centres conducted this study to identify progression predictors in 326 people with PCR-confirmed COVID-19 seen between January 20 and February 25, 2020 in Shanghai. Five people had no symptoms, 293 had mild disease (fever and radiologic manifestations of pneumonia), 12 people had severe disease (dyspnea and early expanding ground-glass opacity on lung x-ray), and 16 people had critical disease (acute respiratory distress syndrome that required mechanical ventilation or oxygen support). Through 1 April, six people had died and 315 had been discharged from the hospital.

The researchers sequenced 112 SARS-CoV-2 samples collected from sputum or oropharyngeal swabs. Using viral genomes from 94 study participants plus 221 sequences from the database of the Global Initiative on Sharing All Influenza Data (GISAID), the researchers identified two major clades (viral groups), and both clades included people diagnosed in early December 2019. The Shanghai study population had sequences throughout these two major clades. Neither the two major clades nor subclades expanded in the Shanghai population. Study participants with clade I or clade II virus did not differ in viral mutation rate or transmissibility.

Clinical manifestations of COVID-19 did not differ much between people with clade I or clade II virus, including disease severity (p=0.88), T-cell count (p=0.79), CD3 T-cell count (p=0.21), C-reactive protein (an inflammation marker) (p=0.83), D-dimer (a coagulation marker) (p=0.19), or duration of viral shedding after onset (p=0.79). Neither did the researchers find differences in disease severity among the 13 most frequent viral sequence variations.

The Shanghai team did find clinical markers of progression. Lymphocyte counts dropped progressively, particularly in people with severe or critical COVID-19, whether measured as CD3 T cells (p<10[-6]), CD4 T cells (p<10[-6]), or CD8 T cells (p=1 x 10[-5]). Yet T cell counts fell significantly not only in people with severe or critical disease, but also in those with asymptomatic or mild disease. Although CD19 B cells dropped significantly in people with critical disease (p=1 x 10[-5]), they did not fall significantly in those with asymptomatic, mild, or severe disease.

During follow-up, COVID-19 progression proved significantly more likely in people with coexisting conditions (p=0.01). Univariate analysis identified four predictors of disease progression: older age (*p*<0.0001), lower lymphocyte count upon admission (p<0.00001), comorbidities (p=0.01), and male gender (p=0.014). Multivariate analysis singled out two independent predictors of progression: lower lymphocyte count (p=0.002) and older age (p=0.002).

Among 11 cytokines measured at admission and during treatment, IL-6 (p<10[-6]) and IL-8 (p=1 x 10[-5]) rose the most and correlated inversely with lymphocytes (the higher the cytokine level, the lower the lymphocyte count). IL-6 levels (p=0.001) and IL-8 levels (p=0.006) were significantly higher in the critical COVID-19 group than in the other groups.

The researchers conclude that their analysis of recently treated people in Shanghai 'provides further evidence that the viral genome is largely stable.' They write that reasons for the relationships they found between virologic activity, cytokine release, and low lymphocytes remain unclear. They "hypothesise that the immunopathological response against SARS-CoV-2 involving cytokine storm and loss of CD3+ T lymphocytes could constitute, at least in part, an underlying mechanism for disease progression and fatality."

Reference

Zhang X, Tan Y, Ling Y, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature. 2020 May 20. doi: 10.1038/s41586-020-2355-0.

https://pubmed.ncbi.nlm.nih.gov/32434211

Autopsies show how COVID-19 damages lungs more than flu

Mark Mascolini for NATAP.org

COVID-19 wreaks more havoc in the lung than influenza A(H1N1), according to an autopsy comparison by German researchers. [1]

The greater damage with COVID-19 included widespread thrombosis with microangiopathy, 9-fold more prevalent alveolar capillary microthrombi, and almost 3-fold more aberrant angiogenesis (new blood vessel growth) than seen with influenza A.

Researchers at the University of Witten-Herdecke and colleagues at other centers note that respiratory disease is the hallmark of infection with SARS-CoV-2, the virus that causes COVID-19, but the precise morphologic (structural) and molecular changes remain poorly defined. To address that gap, they compared 3 sets of lung biopsies from (1) 7 people who died from COVID-19 respiratory failure, (2) 7 people who died from acute respiratory distress syndrome (ARDS) caused by influenza A(H1N1), and 10 age-matched uninfected control lungs. They used several methods to analyse lung biopsies: 7-color immunohistochemical analysis, microcomputed tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurement of gene expression.

In people who died from COVID-19 or influenza A, the peripheral lung histologic (microscopic anatomy) pattern was diffuse alveolar damage and perivascular T-cell infiltration. In people with COVID-19, the researchers characterised alveolar damage as necrosis of alveolar lining cells, pneumocyte type 2 hyperplasia, and linear intraalveolar fibrin deposition. In flu patients, "florid diffuse" alveolar damage was marked by "massive interstitial edema and extensive fibrin deposition."

The researchers found no angiotensin-converting enzyme 2 (ACE2)-positive lymphocytes in perivascular tissue or alveoli of uninfected control lungs, but they did find ACE2-positive lymphocytes in the COVID-19 group and the influenza A group. CD4 T cells proved more numerous in COVID-19 lungs than in flu lungs (average 13.6 versus 5.8 within a 200-µm radius of precapillary and postcapillary vessel walls in 20 fields of examination per patient, p=0.04). But COVID-19 lung had significantly fewer CD8 T cells than flu lungs (average 5.3 versus 11.6, p=0.008).

Alveolar capillary microthrombi proved more than 9 times more prevalent with COVID-19 than with influenza A (average 159 versus 16 thrombi per square centimeter of vascular lumen area, p=0.002). But in postcapillary venules less than 1 mm in diameter, COVID-19 lungs had fewer thrombi than flu lungs (average 12 versus 35, p=0.02). Three-dimensional microCT showed that lung in both groups had "nearly total occlusions of precapillary and postcapillary vessels."

Imaging showed structurally deformed capillaries in COVID-19 lung, marked by "sudden changes in caliber and the presence of intussusceptive pillars* in capillaries." In the COVID-19 group, transmission electron microscopy showed ultrastructural damage to the endothelium and both intracellular and extracellular SARS-CoV-2.

The researchers found 2.7-fold greater density of intussusceptive angiogenic features* in COVID-19 lungs (average 60.7 features per field) than in flu lungs (average 22.5) or uninfected control lungs (average 2.1) ($p<0.001$ for both comparisons). In people with COVID-19, degree of intussusceptive angiogenesis increased significantly with longer time in the hospital ($p<0.001$). In contrast, flu patients had no increase in intussusceptive angiogenesis over time.

The investigators summarised three features that distinguished COVID-19 lungs from influenza A lungs:

1. Severe endothelial injury associated with intracellular SARS-CoV-2 virus and disrupted endothelial cell membranes.
2. Widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries, and
3. Significant new vessel growth through a mechanism of intussusceptive angiogenesis.

The authors call this last finding unexpected and suggest that more endothelialitis and thrombosis may contribute to the intussusceptive angiogenesis documented in COVID-19 lungs. They caution that how their findings affect the clinical course of COVID-19 remains to be defined.

*Compared with normal sprouting angiogenesis, intussusceptive angiogenesis is a "splitting process" marked by invasion of existing blood vessels by other tissues, forming damaging "tissue pillars". [2]

References

1. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020 May 21. doi: 10.1056/NEJMoa2015432.
   https://www.nejm.org/doi/full/10.1056/NEJMoa2015432
2. Adair TH, Montani JP. Angiogenesis. San Rafael (CA): Morgan & Claypool Life Sciences. 2010.
   https://www.ncbi.nlm.nih.gov/books/NBK53238

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)

Now reprogrammed as a series of 2-hour zoom sessions between July and October 2020. (Was 5-7 July, Mexico City).

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

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)

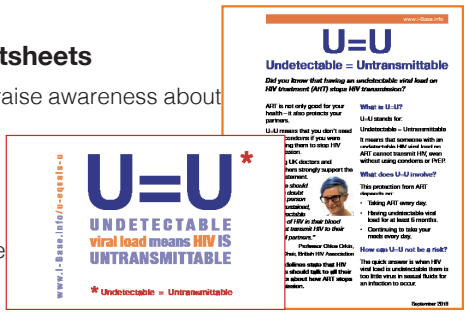
Pocket guides

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.

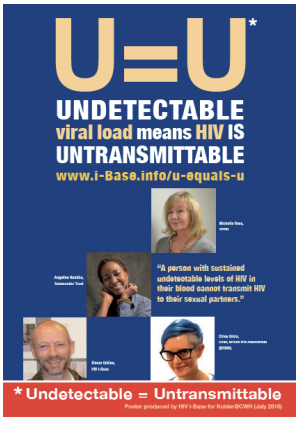
This project was developed with the Kobler Centre in London.

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.

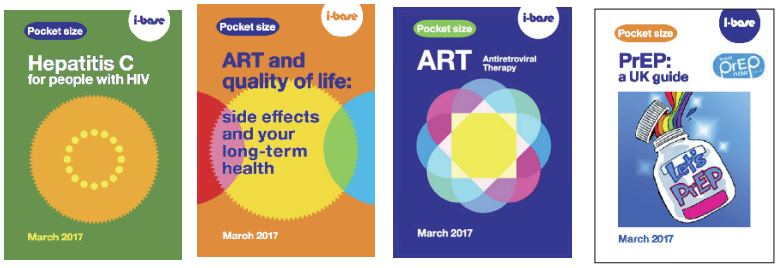
Personalising these for your clinic is cheap and easy and might be an especially nice way to highlight the good news.

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

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http://www.i-Base.info

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- **Pocket leaflets** - *A7 small concertina-folded leaflets (2017)*

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

- **Booklets about HIV treatment**

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

NEW: UK Guide To PrEP *(November 2019): 24-page A5 booklet* **quantity** _____

ART in pictures: HIV treatment explained *(June 2019): 32-page A4 booklet* **quantity** _____

Guide to HIV, pregnancy and women's health *(April 2019): 36-page A5 booklet* **quantity** _____

Guide to changing treatment: what if viral load rebounds *(Jan 2018): 24-page A5 booklet* **quantity** _____

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

Guide to HIV testing and risks of sexual transmission *(July 2016): 52-page A5 booklet* **quantity** _____

Guide to hepatitis C coinfection *(April 2017): 52-page A5 booklet* **quantity** _____

- **Other resources**

U=U resources:

A3 posters quantity _____ **A5 leaflets quantity** _____ **A6 postcards quantity** _____

HIV Treatment 'Passports' - Booklets for patients to record their own medical history **quantity** _____

Phoneline *posters (A4)* **quantity** _____

Please post to the above address, or email a request to HIV i-Base:

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