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HIV and COVID-19 no. 5

HTB supplement (5): 26 June 2020

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i-Base 2020 appeal

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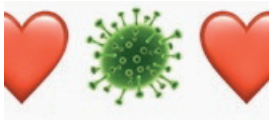
EDITORIAL



This edition of HTB includes that the programme is now online for the AIDS 2020 conference that will be held as a virtual meeting from 6 – 10 July 2020. Many of the original satellite meetings are also being held as virtual meetings, including the community HIV cure workshop. We will report from these meetings in the next issue of HTB.

We also continue coverage of COVID-19, even though the UK is steadily coming out of lockdown (and include the recent BHIVA statement on implications for HIV positive people.

As with previous issues, we start with new research on HIV and COVID-19 coinfection - adding a further eight studies since the previous issue. Although many of these are still small observational cohorts, the data from South Africa is notable for coming from a country with high HIV and TB prevalence, and also for reporting 2-3-fold worse outcomes in HIV positive people.

We also report both positive and negative results from different arms of the UK RECOVERY study. The good news is that dexamethasone significantly reduced 28-day mortality in a subset of people hospitalised with COVID-19 - in those requiring oxygen support, including mechanical ventilation. And a STOP PRESS that this pre-review paper is now online. The negative results come from reporting no impact of hydroxychloroquine (HCQ).

However, our editorial comments on this study cover the lack of published details on the statistical plan for the study that resulted in so many deaths in the HCQ arm that actually performed worse than no treatment. While recognising the efforts in establishing this important study, we ask whether an alternative statistical approach might have found an earlier answer, given more than 1100 people died (almost 400 people in the HCQ arm and more than 700 people in the control arm).

It is standard to include the statistical details in the online protocol, as the RECOVERY documents also refer to, but yet these are not available, with two of the study arms now stopped. This concern is for the remaining monotherapy groups, given that the aim of RECOVERY was to rapidly switch to better investigational compounds as the study progressed.

Many other studies have now discontinued HCQ arms, including the international WHO SOLIDARITY study.

Further treatment news includes remdesivir, (including a discussion on US pricing and on likely EU approval) and on recent papers on several investigational approaches.

CONFERENCE REPORTS

23rd International AIDS Conference (AIDS 2020)

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

The programme for the AIDS 2020 conference that will be held as a virtual meeting from 6 – 10 July 2020 is now online on the conference website, including late-breaker highlights.

Many of the original satellite meetings are also being held as virtual meetings, including the community HIV cure workshop. Programmes for these meetings are also being added.

https://www.aids2020.org

ANTIRETROVIRALS

FDA approves dolutegravir formulations to treat infants and young children

Polly Clayden, HIV i-Base

On 12 June 2020 the US Food and Drug Administration (FDA) approval dolutegravir (Tivicay) tablets and dolutegravir tablets for oral suspension (Tivicay PD) for infants and children in combination with other antiretrovirals.

Approval was granted to the originator manufacturer, ViiV Healthcare. The new formulations are indicated for paediatric patients at least 4 weeks old and weighing at least 3 kg who are ART-naive or ART-experienced but have not previously received an integrase strand transferase inhibitor (INSTI).

The safety and pharmacokinetics (PK) of the two formulations in this weight-band/age group were evaluated in the IMPAACT P1093 trial and two weight-band-based PK substudies of the PENTA ODYSSEY trial. Overall, the safety data in these paediatric studies were similar to those in adults and there was no clinically significant difference in dolutegravir exposure. IMPAACT P1093 is an ongoing, multicentre, open-label, non-comparative trial of paediatric participants aged 4 weeks to less than 18 years.

The safety analysis – based on week 24 data in 75 participants with a median age of 27 months – found 11% experienced drug-related clinical adverse events. Grade 1 to 2 drug-related IRIS was reported in two participants. No Grade 3 or 4 drug-related adverse events were reported. No participants discontinued due to adverse events.

The dolutegravir tablets for oral suspension are 5 mg dispersible: weight-based dosage for infants and young children aged 4 weeks and older at weighing at least 3 kg is shown in Table 1.

Table 1: Recommended weight-based dosage for dolutegravir tablets for oral suspension

Body weight	Once-daily dose*	Number of tablets
3 kg to less than 6 kg	5 mg	1
6 kg to less than 10 kg	15 mg	3
10 kg to less than 14 kg	20 mg	4
14 kg to less than 20 kg	25 mg	5
20 kg and greater	30 mg	6

*If administered with certain UGT1A or CYP3A inducers, administer twice-daily

The 5 mg tablets must be dispersed in 5 mL of drinking water (if using 1 or 3 tablets) or 10 mL (if using 4, 5, or 6 tablets) and the oral suspension administered within 30 minutes of mixing.

Alternatively, paediatric patients weighing 14 kg or more can receive dolutegravir oral 10 mg or 50 mg tablets (although the tablets for oral suspension are preferred in those weighing less than 20 mg). The dosages are 40 mg (4 x 10 mg tablets) and 50 mg (1 x 50 mg adult tablet) for the 14 to 20 kg and 20 kg and above weight-bands respectively. The 10 mg and 50 mg tablets cannot be crushed, cut, chewed or dispersed.

The label includes a warning that dolutegravir 10 mg tablets and 5 mg tablets for oral suspension are not bioequivalent (tablets for oral suspension approximately 1.6-fold that of oral tablets) so cannot be interchanged on a milligram-per-milligram basis and to follow the respective recommended dosing.

This application received priority review designation (usually within six months).

COMMENTS

This approval represents a welcome addition to the treatment of infants and young children with HIV and an excellent collaboration between the IMPAACT and PENTA networks.

A generic 10 mg scored, dispersible formulation of dolutegravir, to simplify weight-band dosing, is currently under review by the FDA (with approval expected by the end of the year) and another version close behind.

Reference
US FDA. FDA Approves drug to treat infants and children with HIV. 12 June 2020.
https://www.fda.gov/news-events/press-announcements/fda-approves-drug-treat-infants-and-children-hiv

HTB SUPPLEMENT ON COVID-19: Issue 5

COVID-19: HIV and COVID-19 COINFECTION

Latest studies on HIV and COVID-19 coinfection

Simon Collins, HIV i-Base

The previous issue of HTB included a review of approximately 20 published papers on HIV and COVID-19 coinfection. [1]

In the last few weeks another eight studies have been presented, from the US, China, and South Africa. [2, 3, 4, 5, 6, 7, 8, 9]

Although many of these are still relatively small cohorts, some report poorer outcomes, likely due to comorbidities and higher risk factors.

The results from South Africa, however, are important for providing the first large cohort from a country with high prevalence of both HIV and TB. The higher mortality from COVID-19 in people living with HIV in this study is controversial and are likely to be explained by issues specific to health care issues in South Africa. These data are reported in full in a separate article in this issue by Polly Clayden. [10]

Table 1: Recent studies reporting HIV/COVID-19 coinfection

Lead author	Notes	N	Refs
Okoh AK et al.	15 men, 12 women in Newark, New Jersey, US. Median age 58 years (IQR: 50 to 67), 25/27 were African American and 2/27 were Hispanic. Med. CD4 551 (IQR: 286, 710). Common comorbidities included hypertension (59%), diabetes mellitus (33%) and chronic kidney disease (27%). Three required ICU. The two deaths were complicated by septic shock and multi-organ dysfunction.	27 HIV+. 13/27 hospitalised. 2/27 died.	2
Ridgway JS et al.	N=5 Chicago, 4 women, 1 man. 4/5 African American. Median age 48 (range 38 to 53). All on effective ART with CD4 >200. 2/5 needed supplemental oxygen, but not mechanical ventilation. All discharged.	N=5 HIV+ All survived.	3
Hu Y et al.	N=12 (10 men, 2 women) from Wuhan, China. Median age 36 (IQR: 33 to 56; range 25 to 66). All on ART. Plus 2 men (age 25 and 37) diagnosed with late-stage HIV in hospital. Cases found using LGBT database and then by telephone contact.	N=14 HIV+ including 2 only diagnosed in hospital. 1/12 died (56 year old man who died at home).	4
Karmen-Tuohy S et al.	Case-control study of 21 HIV+ to 42 HIV negative with COVID-19 in NYC, matched for comorbidities. Median age 60. 23% African American. Reported similar outcomes. 3/21 died. Need larger study.	N=21 HIV+. 3/12 died.	5
Shekhar R et al.	Out of 125 patients at centre in New Mexico, only 5/125 (4%) were HIV+ (4 men, 1 woman). 3/5 hospitalised, 2/3 with thromboembolic events. All survived.	N=5 HIV+ (4%). All survived.	6
Calzo L et al.	Prospective observational study in 14 HIV+ with COVID-19 (9 men, 5 women) to study immune and viral responses, all on ART (13/14 with undetectable VL). Median age 52. Median CD4 count 612 cells/mm3 (IQR: 339, 886). 9/14 (64%) had one or more comorbidities. All recovered. No ICU admissions and no deaths.	14 HIV+. No ICU, no deaths.	7

Shalev N et al.	Retrospective review of 31 HIV+ from all 2159 adults (1.4%) at single centre for tertiary care in NYC. Mean age 60 (range, 23–89 years); 24 men and 7 women. Approx 52% non-Hispanic black, 29% Hispanic of any race, and 16) non-Hispanic white. 22/31 (71%) had at least one comorbidity. Mean CD4 396 (range: 89 to 924). VL <50 in 96%. 8/31 (25.8%) died and 2 (6.5%) were still in ICU. 4/8 were >65 years and 4 were between 50 and 65.	N=31. 8/31 died (25%) with 2 still on ICU at time of analysis.	8
Davies MA et al.	South African review of 12,987 COVID-19 cases in the public sector. Of 435 deaths, 52% were associated with diabetes, 12% with HIV, 2% to active TB and 4% to historical TB. HIV associated with 2-3-fold higher risk of death compared to 13-fold higher with uncontrolled diabetes.	Large public health database of 12,987 COVID-19 cases. 2-3-fold higher mortality associated with HIV. Likely explained by factors specific to south African setting.	9

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HIV positive people in South Africa at increased risk of dying from COVID-19: first data from country with high prevalence of HIV and TB

Polly Clayden, HIV i-Base

Preliminary data from the Western Cape, South Africa show people with HIV and TB have a two- to three- fold increased risk of death from COVID-19.

But the increases were much higher for other known risk factors. Older age increased the risk by 10 to 20 times (if over 50 or 70, respectively) and diabetes increased this by 5 to 13 times (depending on whether controlled or uncontrolled).

These findings were presented by Mary-Ann Davies from the Western Cape Department of Health, on a webinar organised by the Bhekisisa Centre for Health Journalism in collaboration with the Aurum Institute, South Africa.

For this analysis, which Professor Davies explained was not a formal study, the department reviewed 12, 987 COVID-19 cases seen in the public sector – this included 435 deaths. The analysis revealed that slightly above half of the deaths were associated with diabetes, about 12% HIV and 2% active TB.

These findings are important as this is the first data looking at risk factors for with COVID-19 from a country with two key high burden comorbidities: HIV and TB. There has been limited data so far on whether or not these comorbidities will increase the risk of poor outcomes from COVID-19.

To date, known risk factors from other settings include: older age, male sex, diabetes, cardiac disease, respiratory disease, kidney disease, liver disease, overweight/obesity, organ transplant and recently diagnosed cancer. Some risk factors may be linked, such as diabetes and overweight/obesity, but this data does not include information on BMI (or smoking).The analysis looked at factors associated with COVID-19 death in all adult public sector patients 20 years of age and above.

The analysis looked at factors associated with COVID-19 death in all adult public sector patients 20 years of age and above. Western Cape public sector data is brought together in the Public Health Data Centre (PHDC) using a unique identifier across all systems: primary care, hospitals, emergency, disease specific, laboratory, dispensing, community, births and deaths. Several comorbidities can be inferred from lab tests and medication dispensed: diabetes, hypertension, chronic kidney disease, chronic respiratory disease/asthma, TB and HIV. But the data does not capture other risk factors such as overweight/obesity, smoking and socio-economic status.

Table 1 shows the adjusted hazard ratios for dying from COVID-19 for different risk factors.

Table 1: Chances of dying from COVID-19 for different risk factors

Patient characteristics	Adjusted hazard ratio	95% confidence interval
Sex		
Female	1	
Male	1.4	1.16 to 1.7
Age (years)		
Less than 40	1	
40–49	3.12	1.88 to 5.17
50–59	9.92	6.34 to 15.54
60– 69	13.55	8.55 to 21.48
70 and above	19.53	12.20 to 31.26
Non-communicable disease		
None	1	
Diabetes well-controlled	4.65	3.19 to 6.79
Diabetes poorly-controlled	8,99	6.65 to 15.54
Diabetes uncontrolled	13.02	8.55 to 21.48
Diabetes – no measure of control	3.34	12.20 to 31.26
Hypertension	1.46	1.18 to 1.81
Chronic kidney disease	2.02	1.55 to 2.62
Chronic pulmonary disease	0.98	0.75 to 1.30
TB		
Never TB	1	
Previous TB	1.41	1.05 to 1.90
Current TB	2.58	1.53 to 4.37
HIV		
Negative	1	
Positive	2.75	2.09 to 3.61

Older age of 70 years and above was the highest risk factor giving an approximately 20-fold risk of death compared to that in people aged 40 and below. Diabetes was associated with an approximately 13-fold risk if uncontrolled and just below 5-fold risk if well-controlled.

Both HIV and active TB were associated with a 2- to 3-fold risk of dying from COVID-19. Notably there was no difference by viral suppression among people with HIV dying from COVID-19.

Men were more at risk than women but this difference was small.

Professor Davies explained that for every 100 people in the public sector who have died from COVID-19, 52 can be attributed to diabetes, 12 to HIV, 2 to current TB and 4 to previous TB.

As these data are limited to the public setting the group calculated the Standardised Mortality Ratios (SMR) for the increase in COVID-19 death in people with vs without HIV in Western Cape: 2.33 (95% CI 1.83 to 2.91). So across the public and private sector, about 8% of COVID-19 deaths were due to HIV.

She added that the risk might be over-estimated if the analysis was not able to disentangle all comorbidities and risks eg overweight and socio-economic status. And that those with HIV and TB tend to be younger where overall risk of COVID-19 death is low.

C O M M E N T

These data are extremely important as he first from a setting with large numbers of people with HIV and TB. Professor Davies said that although the numbers of people dying of COVID-19 with these comorbidities might have been expected to be much higher, HIV and TB need to be included in the risk groups.

Francois Venter from Ezintsha at Wits University's faculty of health sciences, and discussant on the webinar, stressed the importance of these data: "First proper African data to compare ourselves to the rest of the world…(with) huge implications for how we manage our health programmes."

He noted that the allocation of resources to COVID-19 as well as the draconian measures originally taken in lockdown has had an impact on HIV and TB services in South Africa. Health seeking behaviour for HIV has been affected including people being afraid to go to health facilities and pick up their ART. They are scared of catching COVID-19 (including from visiting their clinic), scared of being arrested going the the clinic (for breaking strict lockdown regulations) and scared of being tested and forcibly quarantined.

This is likely to have led to treatment interruptions of both HIV and TB treatment and delayed diagnosis of new TB infections. Nevertheless, approximately two-thirds of COVID-19 deaths in HIV positive people were in people with undetectable viral load.

Venter expects huge challenges over the six months and suggests that policy decisions should have instead learned lessons from HIV experiences with community engagement for successful treatment and prevention programmes rather than using police and military.

But he added that a few things have been fast-tracked, since COVID-19 that were already being discussed. This includes multi-month dispensing and triaging people with respiratory illnesses.

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Update on Western Cape data: people with HIV have small increased risks from COVID-19

Polly Clayden, HIV i-Base

Routine public sector data from Western Cape South Africa, showing a modestly increased risk of mortality from COVID-19 among people living with HIV (and the largest assessment of SARS-CoV-2 and HIV coinfected people to date), were presented on a webinar and widely-reported earlier in June. [1, 2]

These data have been slightly updated and published on 22 June 2020 by the National Institute for Communicable Diseases. [3]

Between 1 March and 4 June 2020, there were 12,522 people, aged 20 and above, diagnosed with COVID-19 and alive at the time of analysis and 435 COVID-19 deaths.

The proportion of men was lower among COVID-19 cases vs non-cases (30% vs 42%) – the authors suggest that this was likely due to early cases occurring in essential workers in sectors largely employing women.

Slightly higher proportions of COVID-19 cases had diabetes mellitus (13% vs 8%), hypertension (20% vs 16%) and HIV (18% vs 16%).

COVID-19 patients who died were considerably older than those who survived: median 63 years (IQR 54 to 71) vs 37 (IQR 30 to 48).

Of the people with HIV and COVID-19 who died and survived, 69% and 66% were considered "well on ART" (by the definition of the analysis).

The authors also looked at whether the association between HIV and COVID-19 mortality could be associated with unmeasured confounding eg by socio-economic status or raised BMI – which was not captured in the analysis.

They calculated the E-value for an unmeasured confounder for both above analyses. This value is an estimate of how strong the association between a confounder and the outcome would need to be to account for all of the association between, in this case, HIV and COVID-19 death.

They found the E-value for analysis among all public sector patients to be 4.94 (3.60 for the lower bound of the CI). This suggests that there would need to be a strong association between both HIV and low socio-economic status (or raised BMI), and COVID-19 death to account for all the association between HIV and COVID-19 death.

Among all public and private sector diagnosed COVID-19 cases, there were 97 deaths among an estimated population of approximately 520,000 people with HIV in the Western Cape province (187 deaths/million) vs 573 deaths among 6.36 million people without HIV (90 deaths/million).

The SMR for COVID-19 mortality in people with HIV, relative to HIV negative people, was 2.33 (95% CI 1.83 to 2.91) and 8.2% (95% CI: 5.3 to 11.2) of deaths were considered to be associated with HIV.

C O M M E N T

Although the published findings do not differ from those presented earlier by webinar, it is worth reading the more comprehensive data set.

And it is important that the authors have now looked at potential unmeasured confounding for the association between HIV and COVID-19 in this setting.

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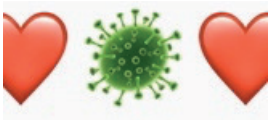
COVID-19: INVESTIGATIONAL TREATMENTS

STOP PRESS: The pre-review paper from this study is also now available online; 32 of the study participants were HIV positive. While relative rates impressively benefitted the active arm, the mortality in both arms is sobering. It shows the need for much better and more effective treatments for COVID-19. [7]

Dexamethasone significantly reduces mortality in subset of patients hospitalised with advanced COVID-19: UK RECOVERY study

Simon Collins, HIV i-Base



On 14 June 2020, top-line results from one arm of the UK RECOVERY study, included significant benefits from using the anti-inflammatory drug dexamethasone to treat COVID-19. [1]

In patients with the most advanced stages of COVID-19 - those either on mechanical ventilation or assisted breathing - dexamethasone reduced the risk of death by approximately one-third and one-fifth, respectively. No benefit was seen in people with less advanced infection who were not using oxygen support.

The results are based on 6335 participants who were randomised (1:2) to either dexamethasone (n=2104) or a control arm using standard of care (n=4321). Dexamethasone was dosed at 6 mg daily for ten days, either orally or by IV injection.

The dexamethasone arm was stopped early on 8 June 2020 after the trial steering committee decided enough participants had been recruited to show significant results based on the primary endpoint of survival at day-28 - reached by 94% of participants. The statistical basis for this decision though or the timeline and review plan for other arms are not included in study protocol online. [2]

Mortality overall correlated with severity of COVID-19: 41% in people on mechanical ventilation, 25% in those needing oxygen only and 13% in people not needing respiratory support.

Overall, dexamethasone reduced the 28-day mortality rate by 17% (RR 0.83; 95%CI: 0.74 to 0.92, p=0.0007) with a highly significant trend showing greatest benefit among those patients requiring ventilation (test for trend p<0.001).

The press release includes that dexamethasone reduced deaths by one-third in ventilated patients (RR: 0.65; 95% CI: 0.48 to 0.88, p=0.0003) and by one fifth in other patients receiving oxygen only (RR: 0.80; 95%CI: 0.67 to 0.96, p=0.0021). Also, that there was no benefit among participants who did not receive respiratory support (RR: 1.22; 95% CI: 0.86 to 1.75, p=0.14).

The study included 176 clinic sites throughout the UK and funders included the UK NIHR, Wellcome and the Bill and Melinda Gates Foundation, DFID and the MRC, with details on the study website.

C O M M E N T

These results are good news. Although only the top-line, the UK government has already announced that dexamethasone is already included in the new standard of care for people hospitalised with COVID-19 and using oxygen support. [3]

This should also include other participants in the RECOVERY study who are currently randomised to monotherapy treatment using other single investigational drugs. These include lopinavir/r, azithromycin, tocilizumab and convalescent plasma.

Community participation in research has always included the principle of responding to new standards of care that change while a study is ongoing.

Dexamethasone is an inexpensive and widely used generic drug that can be accessed immediately. It is already included on the WHO list of essential medicines. This will enable wide use including in low- and middle-income countries (LMICs), although mechanical ventilation is often extremely limited in these settings and might require different guidelines [4]

The full analysis will hopefully explain the lack of benefit in people hospitalised in earlier stages who are not using oxygen, even though they should also be at a stage of immune inflammation.

The RECOVERY study was launched in March 2020 and has now randomised more than 11,500 participants to one of six investigational treatments for COVID-19 or to a control group that receives standard of care. Earlier this month, the hydroxychloroquine (HCQ) arm was stopped early after an MHRA-requested review showed no benefit. [5]

This raised concerns, including in a report from i-Base, about the duration of time participants were kept on ineffective treatment and the lack of transparency about the timeline and details of the statistical analysis plan that has still not been made publicly available. [6]

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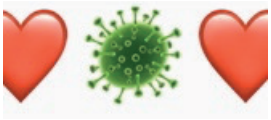
Modeling paper suggests hydroxychloroquine dosing was too low to be active against COVID-19 and that higher doses would risk toxicity

Simon Collins, HIV i-Base



A paper published on 21 May 2020 in Clinical Infectious Diseases by Fan and colleagues, modelled drug levels of hydroxychloroquine (HCQ) in vitro to show that dosing for human studies was unlikely to be effective. [1]

The paper suggests that in vitro EC50/EC90 values for HCQ should be compared to the in vivo free extracellular tissue concentration (which is similar to the free plasma HQC concentration).

it also concludes that none of the current studies using HCQ as treatment for COVID-19 are/were using a high enough dose to expect to see a significant clinical effect and that dosing any higher would lead to unacceptable toxicity.

The range of ongoing studies registered to use hydroxychloroquine to treat or prevent COVID-19 already shows wide difference on the most appropriate dose. At least one study was stopped early due to excessing overdosing and serious side effects. [2]

Many other studies have reported no benefit. This includes the UK RECOVERY study, closing this arm of the study and contributing to the International WHO SOLIDARITY study also discontinuing HCQ. [3, 4, 5]

This paper modeling dosing suggests that activity against CoV-2 is unlikely at any of the current doses and that higher doses need for activity would risk toxicity.

An excellent editorial article by Charles Flexner et al in Clinical Infectious Diseases further explains the complex pharmacokinetics of HCQ and the problems of dosing for different indications. [6]

This was included in reference to two papers in the same journal using contradictory approaches to study design. [7, 8]

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FDA contraindication for remdesivir and hydroxychloroquine (HCQ): immediate impact on current HCQ research

Simon Collins, HIV i-Base

On 15 June 2020, the US FDA issued a warning over a potential serious drug interaction between remdesivir and hydroxychloroquine that makes the two drugs contraindicated. [1]

The warning is based on a recently completed study that showed that HCQ could reduce concentrations of remdesivir, although further details on the interaction are not given

This should stop continued enrolment into ongoing HCQ studies in settings where remdesivir is available (if any such studies are still continuing).

Access to remdesivir as a proven and approved treatment now outweighs the scientific interest in HCQ, however novel the original study design, especially given recent reports that HCQ has no activity against COVID-19. [2]

The FDA also revoked the Emergency Use Authorisation (EUA) that was issued in March 2020 to enable access and research into HCQ for COVID-19. [3]

C O M M E N T

The Liverpool Drug Interaction databases (both for HIV and COVID-19) categorise this DDI as serious with a red alert contraindication.

Ongoing HCQ studies need to rapidly consider best outcomes for their participants that will prioritise immediate access to remdesivir as an FDA-approved active drug compared to scientific interest in HCQ as an investigational drug that has now reported outcomes that are worse than standard of care (ie no intervention).

This should limit further randomisations to studies that include HCQ arms when remdesivir is now available.

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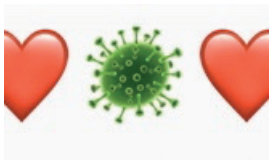
UK RECOVERY study stops hydroxychloroquine (HCQ) for COVID-19: more than 1100 deaths question ethics and safety overall

Simon Collins, HIV i-Base



On 5 June 2020, the large randomised RECOVERY study announced that hydroxychloroquine (HCQ) will no longer be used to treat COVID-19. [1]

The results show that hundreds of people died - both taking HCQ and in the comparison group receiving no investigational drugs - and yet the study was only closed because of a safety request by the UK Medicines and Healthcare products Regulatory Agency (MHRA).

This very large study – with more than 11,000 participants – should have been looking for early signals that experimental treatment might be effective. Instead, the results announced yesterday call for an urgent analysis of other ongoing arms plus immediate use of drugs that are now known to be effective.

The press release states that people receiving HCQ did no better than people who were given no additional drugs - also called the standard of care. Actually, it is not that HCQ didn't make enough difference for the results to be significantly better. It looks like people taking HCQ did worse than adding nothing, at least numerically. It is very worrying that this analysis was only carried out because of a request by the MHRA.

For the main study endpoint – the number of people still alive after 28 days – approximately 25.7% of the 1542 people who received HCQ died compared to 23.5% of the 3132 people who were given no treatment. In a study this large, this signal of no active benefit from an experimental treatment should have been found much earlier. There were also apparently no benefit in other measures, such as length of hospital stay or other clinical factors.

How many deaths were these researchers going to allow to continue before they would have stopped the study themselves? Almost 400 people in the HCQ arm and more than 700 people in the control arm died and the study still planned to continue?

Many researchers will not be surprised at the lack of effect with HCQ - but they should be shocked at the time taken to hear this result. Over the last few weeks, other studies have been published showing that HCQ was unlikely to work. [2-6]

One of these - a very large study published in the Lancet reported that HCQ was not effective, and prompted the RECOVERY study to look at their own results. And they came back saying their study should continue unchanged. [7]

Anyone reading that letter from the RECOVERY researchers on 22 May 2020, would expect results to perhaps already show a trend towards ***benefit***from HCQ. This would support continuing to allow participants to take a risk until the study reached a conclusion that was statistically significant.

Instead, nothing close to a benefit could have been happening. It doesn't even matter that the Lancet study has since been retracted – another complicated story [8, 9] – the important thing is that three weeks ago the RECOVERY study insisted that their data supported continuing to use HCQ.

Today's results showing no suggestion of benefit are important for several reasons.

Firstly, the large RECOVERY study is continuing with other single therapy arms, some of which have even less evidence than HCQ to show they might work. These include monotherapy (single drug) using an old HIV drug called lopinavir/r (LPV/r). Actually, in March 2020, an earlier randomised study was published showing no benefit from lopinavir/r. [10] For RECOVERY to be continuing with this drug, it needs to already be showing a strong trend towards benefit. Anything less, and LPV/r should also be pulled like HCQ. The RECOVERY study should not be looking for small marginal benefits, but for clear signals that the experimental drugs are considerably better than standard of care.

RECOVERY is also studying a single antibiotic called azithromycin (AZM). Actually, previous studies claiming a benefit from HCQ used it together with AZM. This does not make it plausible that AZM monotherapy will be a success. Again, anything less than clear benefit compared to standard of care, and this arm should be pulled too. And with a study this large, the results should have been available weeks ago. This shouldn't need a prompt letter from the MHRA over safety. The DSMB in the RECOVERY study, should be analysing every death, with a low threshold of benefit to continue and a similarly low threshold to stop.

Secondly, the statistical plans and timeline for analysing early results should be part of the RECOVERY study protocol - as it is for other major studies. The protocol should publish the start/stop criteria and the thresholds that are being used. It is not good enough for the study to say, as it currently does, that it will look at the results every two weeks. If this is the case, why has it taken an MHRA directive to look again now?

Thirdly, we need to remember the context for COVID-19. Large numbers of participants who are already hospitalised have trusted the researchers to take experimental drugs that have some chance of working (and the chance of no drugs). By joining RECOVERY, people are by default not joining another study - and the UK already has another 20 or so ongoing treatment trials. [11]

Finally, on 26 May 2020, the new availability of remdesivir, a proven treatment for COVID-19, should have led this to be offered to all participants in RECOVERY. Based on published results from the large randomised ACTT study showing remdesivir to be effective, the MHRA announced a compassionate access programme to enable widespread access. It is also notable that the conclusions of the ACTT paper emphasise the importance of using combination treatment with more than one investigational drug. The RECOVERY has not made any announcement for the use of combination therapy. [12, 13, 14]

An established principal in ethical research, at least from HIV studies, is that no study participant should use less than current standard of care. When the standard of care changes, research studies need to rapidly change too, to ensure their participants do not use anything less.

The RECOVERY researchers have publicised how quickly they launched their study. They also claim that early signals will be acted on quickly to stop ineffective drugs and to prioritise newly effective ones. If this was really true, it shouldn't have taken a request from the MHRA to look again at the HCQ arm. The investigators and the independent data and safety monitoring board (DSMB) for the study should have done this already. The study should also have publicised whether more recent compounds with positive data have been considered - for example using anticoagulants or ACE inhibitors or the anti-rheumatoid anakinra. [15, 16, 17]

The fact that RECOVERY didn't stop the HCQ arm based on its own analysis plan, nor announce plans to look at other ongoing arms, are a concern for the study overall, and especially for participants who put their trust in these researchers.

The press release concludes "These data convincingly rule out any meaningful mortality benefit of hydroxychloroquine in patients hospitalised with COVID-19". If this is really the case, then slightly less convincing data should have been enough to stop this study arm much earlier and allowed participants the option to use other drugs that stood a better chance of benefit.

C O M M E N T

The degree of failure in this study is not an unfortunate scientific event. Unless the data review on 23 May showed a clear benefit for HCQ that reversed over the last few weeks, this arm of the study is a failure.

Many of these issues, including on the data plans and timeline, the decision to continue using HCQ and access to remdesivir were raised by email with the RECOVERY coinvestigator Peter W Horby on 24 May 2020. This email has neither been acknowledged nor answered.

Instead, hundreds of people have died using an intervention that has no signal of benefit, or because they were randomised to standard of care with no potentially active treatment.

These results should prompt an urgent review of the other study arms in the RECOVERY study and an investigation for why such ineffective treatment continued for so long. Even though the study says the DSMB have been reviewing results every two weeks, the predefined rules to close or continue a study might not be appropriate - but as these have been excluded from the protocol it is difficult to comment.

This study - and no doubt others - should be using drugs that have a better indication of efficacy. Study participants deserve better.

On 17 June 2020, the WHO announced that the HCQ arm in the international SOLIDARITY study has now discontinued the HCQ arm. [18]

Two other large studies have reported that HCQ was also not effective as PEP. [19, 20, 21]

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SIMPLE study reports benefit from 5-day but not 10-day remdesivir on moderate COVID-19

Simon Collins, HIV i-Base

On 1 June 2020, top-line results were reported in a company press release from the phase 3 SIMPLE remdesivir study.

This study compared 5-day vs 10-day dosing vs standard of care (SoC) in people with moderate COVID-19 pneumonia but without reduced oxygen levels.

The primary endpoint was based on a 7-point scale of clinical symptoms at day 11.

The results reported that 5-day treatment significantly improved outcomes at day 11 compared to the control arm: OR 1.65 (95% CI: 1.09 to 2.48); p=0.017.

Results for the 10-day treatment however were not significantly different from the standard of care arm: OR 1.31 (95% CI: 0.88 to 1.95}; p=0.18.

The most common adverse events occurring in more than 5% of patients in both treatment groups were nausea (10% vs 9% vs 3%), diarrhoea (5% vs 5% vs 7%) and headache (5% vs 5% vs 3%), in 5-day vs 10-day vs SoC, respectively.

Key efficacy and safety results from the press release are included in Table 1.

Table 1: Key efficacy and safety results from SIMPLE study

	5-Day RDV n=191	10-Day RDV n=193	SoC n=200
Clinical Efficacy Outcomes at Day 11			
≥ 2-point improvement in ordinal scale	134 (70)	126 (65)	121 (61)
≥ 1-point improvement in ordinal scale	146 (76)	135 (70)	132 (66)
Requiring any oxygen support	12 (6)	13 (7)	22 (11)
≥ 1-point worsening in ordinal scale	6 (3)	12 (6)	22 (11)
Death	0	2 (1)	4 (2)
Safety			
Any adverse event (AE)	97 (51)	106 (55)	90 (45)
Grade ≥3 AE	20 (10)	21 (11)	24 (12)
Any serious adverse event (SAE)	8 (4)	7 (4)	18 (9)

C O M M E N T

Even when statistically significant, the summary result in Table 1 do not show especially large differences compared to the SoC inactive control arms. It is also difficult to understand why slightly longer treatment would not replicate the 5-day treatment.

Nevertheless, these results will be used to support 5-day dosing, which will ensure twice as many people are able to access the limited supplies of remdesivir - both in expanded access and when fully available.

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Recent papers on convalescent plasma and on ACE inhibitors and angiotensin receptor blockers

Simon Collins, HIV i-Base

This article includes recent papers that add to the knowledge of investigational approaches to treat COVID-19, that are currently in clinical studies in the UK.

Convalescent plasma and antibody research

The previous edition of HTB included a review of studies looking at convalescent plasma to treat COVID-19. [1]

A further study - the largest so far - has recently reported no benefit. [2]

The investigators reported a 7-day mortality rate of 14.9%, which is similar to the natural history of severe COVID-19. The incidence of severe adverse events was <1%.

An editorial viewpoint in JAMA also discusses this research in more detail. [3]

A third study that randomised 103 participants with severe or life-saving COVID-19 to either open-label convalescent plasma or standard of care reported no difference in clinical recovery or PCR changes by day 28. Evolving standard of care during the study included antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications. However, this study was original planned to include 200 participants but was closed early due to lack of new cases after COVID-19 was contained in China. [4]

ACE inhibitors and angiotensin receptor blockers

HTB has previously reported on the potentially beneficial impact of ACW inhibitors and angiotensin receptor blockers (ACEI/ARBs), previously reported in HTB. [5, 6]

Several papers have added to this literature, including a study in JAMA reporting that ACEI/ARB therapy is not associated with increased susceptibility to SARS-CoV-2 infection or increased severity of COVID-19. This was based on 30-day mortality in a retrospective cohort of 4480 patients with COVID-19 (adj HR: 0.83 [95% CI: 0.67 to 1.03]). A nested case-control analysis within a cohort of 494,170 patients with hypertension also concluded that among patients with pre-existing hypertension, those receiving ACEI/ARBs did not have a significantly higher risk of acquiring COVID-19 than patients receiving other antihypertensive medications (HR: 1.05 [95% CI: 0.80 to 1.36]). [7]

An accompanying editorial is again useful for reviewing this data in the context of other research. [8]

Although this study confirms that ACEI/ARBs are safe to continue in context of COVID-19, they didn't report a beneficial effect.

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COVID-19: GUIDELINES

BHIVA/THT updated guidelines for social distancing in the UK

Simon Collins, HIV i-Base

On 23 June 2020, BHIVA/THT updated guidance to reflect changes in government advice on COVID-19 in the UK.

From 6 July

- People can meet in groups of up to six people from outside your household, outdoors. This still involves social distancing and not sharing items such as cups and plates.
- If you live alone (or are a lone adult with dependent children under 18), you can form a support bubble with another household.

From 1 August

- There is no need to shield. You can visit shops and places of worship, with strict social distancing.

The guidance about shielding is slightly different if you live in Scotland, Wales or Northern Ireland.

For HIV positive people shielding due to a very low CD4 count or recent serious illness related to HIV, please speak to your HIV doctor. This is especially if you are worried about stopping shielding.

However, shielding support from the Government will only continue until the end of July.

Please be careful to continue social distancing and hand washing. Also, to avoid any contact with people who are diagnosed with COVID-19 or who have possible symptoms.

Please see the full guidance for additional links and details.

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COVID-19: PREVENTION

Two PEP studies report no benefit of hydroxychloroquine for preventing CoV-2 infection

Simon Collins, HIV i-Base

Two studies reported lack of benefit from using hydroxychloroquine (HCQ) as PEP.

One was a randomised, double-blind, placebo-controlled trial in 821 participants reporting high-risk exposure and who started HCQ PEP within three days. Results reported no difference in COVID-19 between the two arms and were published in the NEJM. [1]

COVID-19 was confirmed in 49/414 (11.8%) vs 58/407 (14.3%) of active vs placebo arms: diff –2.4% (95% CI: –7.0 to 2.2), p=0.35.

The second was a Spanish study that randomised more than 2300 people exposed to the CoV-2 to either HCQ or the usual care. Although not yet published, the top-line results of no difference between the two arms was reported in Science journal online. [2, 3]

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COVID-19: ON THE WEB

Independent SAGE: UK COVID-19 policy responses

An independent Scientific Advisory Group for Emergencies (i-SAGE) has been hosting online meetings and producing comprehensive reports for the UK.

The group is convened by former UK government Chief Scientific Adviser Sir David King. For more details please see the website and YouTube channel.

https://www.independentsage.org (website)

https://www.youtube.com/channel/UCqqwC56XTP8F9zeEUCOttPQ (YouTube channel)

Four comprehensive reports are already online.

Report 1: COVID-19: what are the options for the UK? (12 May 2020)

https://www.independentsage.org/wp-content/uploads/2020/05/The-Independent-SAGE-Report.pdf (PDF)

Report 2: Should schools reopen? (22 May 2020)

https://www.independentsage.org/wp-content/uploads/2020/05/Independent-Sage-Brief-Report-on-Schools.pdf (PDF)

Report 3: When should a school reopen? (28 May 2020)

https://www.independentsage.org/wp-content/uploads/2020/06/Independent-Sage-Brief-Report-on-Schools.pdf (PDF)

Report 4: Towards an integrated find, test, trace, isolate, support (FTTIS) response to the pandemic. (9 June 2020)

https://www.independentsage.org/wp-content/uploads/2020/06/IndependentSAGE-report-4.pdf (PDF)

COVID-19 harm reduction programmes in Central and Eastern Europe and Central Asia

Eurasian Harm Reduction Network (EHRA)

EHRA recently finalised the review of harm reduction programmes during the COVID-19 crisis in Central and Eastern Europe and Central Asia.

The excellent report was developed as a result of online discussions between members from 22 countries between 14 to 23 April 14 2020.

In most countries of the CEECA region, opioid substitution therapy (OST) and sterile needle/syringe programmes (NSP) – key components of an evidence-based and comprehensive harm reduction (HR) programme – continue to operate under COVID-19 quarantine measures. Such work requires flexibility, readiness for mutual partnerships and strong advocacy by community and harm reduction activists. Unfortunately, the practice of amnesty of prisoners for drug-related crimes because of COVID-19 quarantine requirements has not been implemented in the region.

Key changes in harm reduction services include the following:

Provision of take–home OST. For many countries of the region, OST medications have been made available to take home for the first time, for periods of 5 to 14 days and sometimes up to one month. The opportunity to get take-home OST (both buprenorphine and methadone) became available to all clients in every country of the region except for Azerbaijan, Belarus and Kazakhstan. Initially, there were difficulties in some countries in enrolling new clients onto such programmes. Some countries developed partnerships, such as mobile outpatient clinics, to deliver OST medications and, often, together with antiretroviral therapy (ART) drugs to clients in remote locations.

Harm reduction works remotely. In all countries of the region, organisations have managed to deliver a range of commodities such as sterile needles and syringes, masks, disinfectant, hygiene materials, naloxone, tests, and information materials for people who use drugs (PWUD). As a result of the restriction in movement caused by COVID-19, such service providers have found it necessary to deliver sufficient supplies at one time to cover the needs of an individual for 1-2 weeks. Often, materials are provided by mobile outpatient clinics, including social workers delivering such assistance by use of their own car or through use of a courier. Organisations have arranged online counselling for clients and, wherever possible, HIV testing through self-test kits delivered to clients. In providing such remote services, social workers and psychologists have needed to urgently develop additional skills and the management of organisations have had to introduce a flexible system of monitoring for the new service modalities.

Providing the essentials – food and shelter. For a large number of problematic users of psychoactive substances, quarantine restrictions and curfews have restricted access to temporary accommodation and made it impossible for them to earn money to find drugs. Responding to such basic needs, some organisations have re-planned budgets (as has been the case, for example, for EHRA members in Czechia, Kazakhstan, Montenegro, and Slovakia), or organised crowdfunding campaigns to be able to feed those in need (as undertaken by the Pink House in Bulgaria). In some countries, partnerships have been established to make it possible to provide shelter to PWUD and women who are victims of violence. In Azerbaijan and Kazakhstan, harm reduction organisations have helped their clients to receive specific assistance for unemployed people in connection with COVID-19.

Partnership in the integration of services. In most countries, the crisis situation has prompted medical centres and non-governmental organisations (NGOs) of various types to partner in the daily provision and delivery of necessary preventive materials, substitution therapy and ART drugs, and food supplies to clients, especially in remote areas.

Flexibility of services in response to changes in the drug scene. Due to the closure of international borders as a result of COVID-19, the drug scene has changed in many countries, with access to some drugs becoming more difficult, resulting in people having to use everything that they can find, including various prescription drugs mixed with alcohol. Many clients need advice to reduce harm in using new psychoactive substances (NPS), as well as help to prevent overdose. In some countries, such as Kazakhstan, Lithuania, and Serbia, such consultations are already under development. In Prague, because crystal methamphetamine is less available, community organisations have pushed for the introduction of substitution therapy for stimulant users.

Risk of service interruption due to deficiencies in the supply chain. The closure of international borders has also led to a disruption in the supply of substitution therapy medications in Moldova; similar risks exist in other countries. In addition, government authorities responsible for OST and other harm reduction programmes in several countries have not issued a tender for the purchase of medications from public organisations providing harm reduction services; this is particularly critical in Bulgaria and Montenegro.

Ref: EHRA. Review of harm reduction programs in the situation of the COVID-19 crisis in 22 CEECA countries is published. (26 May 2020),

https://harmreductioneurasia.org/hr-programs-overview-in-a-covid-19-situation

https://harmreductioneurasia.org/wp-content/uploads/2020/05/regional-review_-FINAL_ENG.pdf (PDF)

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).

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

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

Global HIV Clinical Forum 2020

Virtual meeting, 30 June – 1 July

https://www.hiv-clinical-forum.org/global-2020

Community Reclaiming the Global Response (HIV 2020)

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

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

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

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

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

www.aids2020.org

IAS COVID-19 Conference

NOW VIRTUAL.

6 – 10 July 202

https://covid19.aids2020.org/programme-at-a-glance

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

NOW VIRTUAL.

12 – 13 September 2020, New York

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

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

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

www.virology-education.com

11th International Workshop on HIV & Ageing (2020)

NOW VIRTUAL.

1 – 2 October 2020, NYC

https://www.virology-education.com

HIV Glasgow Congress 2020

NOW VIRTUAL

5 – 8 October 2020, Glasgow

www.hivglasgow.org

International Workshop on HIV Paediatrics 2020

16 – 17 November 2020, San Francisco, USA.

www.virology-education.com

26th Annual BHIVA Conference (BHIVA 2020)

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

www.bhiva.org

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

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

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

HIV Research for Prevention (HIV R4P 2020)

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

https://www.hivr4p.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

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

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

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

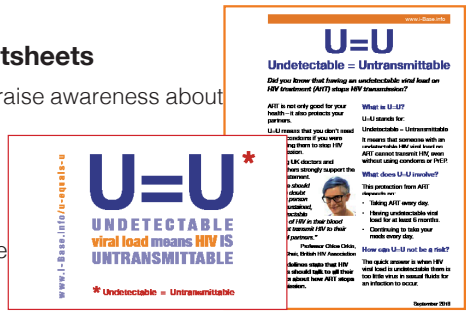
Pocket guides

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

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

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

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



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

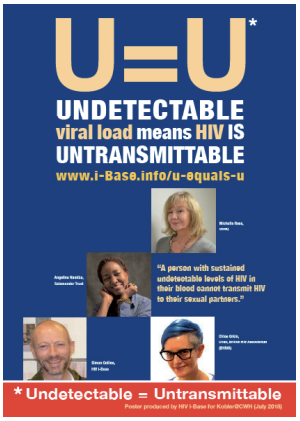
This project was developed with the Kobler Centre in London.

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

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

email: subscriptions@i-base.org.uk

Customise U=U posters for your clinic



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

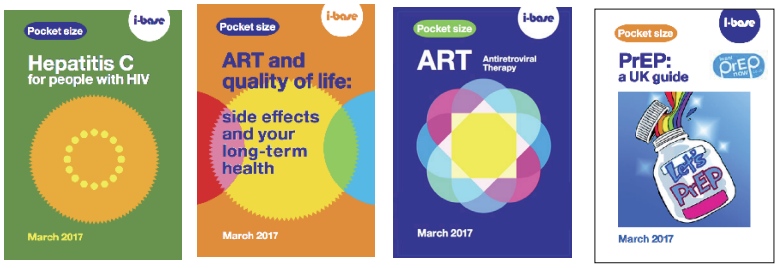
Personalising these for your clinic is cheap and easy and might be an especially nice way to highlight the good news.

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

roy.trevelion@i-Base.org.uk

Order publications and subscribe online

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



h-tb

HIV TREATMENT BULLETIN

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

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

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http://www.i-Base.info

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

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

- **Booklets about HIV treatment**

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

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

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

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

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

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

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

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

- **Other resources**

U=U resources:

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

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

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

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

subscriptions@i-Base.org.uk