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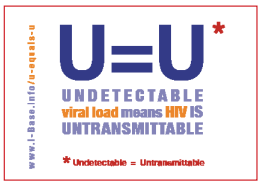

i-Base 2020 appeal

This year we are continuing a funding appeal to help i-Base continue to provide free publications and services during 2020.

i-base appeal 2020

i-Base now recieve more than 12,000 questions each year and the website has more than 500,000 view each month. We also distribute more than 80,000 booklets and leaflets free to UK clinics every year.

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EDITORIAL

Given the extent of the broadening COVID-19 pandemic we again expand our section on coronavirus - and the impact for HIV care.

This includes some of the first reports with data on how HIV affects risks of COVID-19 coinfection.

We include several papers on early treatments for COVID-19, often showing little benefit, and report on other studies that are ongoing, including the phase 3 studies with remdesivir with many UK sites.

And while the compounds are still in these early stages, we review Andrew Hill's analysis for production costs, should they prove effective, showing that pipeline compounds could be widely accessible in all settings.

In reporting a blog from the BMJ we highlight the importance of including HIV status and testing if needed within the management of COVID-19 - especially as HIV positive people with COVID-19 might not be treated at their HIV hospital.

We also signpost to BASHH resources on COVID-19 including a member survey reporting on how services have already been restructured.

But coverage from The CROI 2020 and Women & HIV Workshop planned for Boston are also included in this issue. These include an increased risk of diabetes in the ADVANCE study, more reassuring data on use of dolutegravir in pregnancy and an review by Richard Jefferys of vaccine approaches to delivering bNAbs that references a macaque study that recorded continued anti-SIV antibody levels out to six years.

The community experience from HIV unfortunately overlaps with much of the COVID-19 response. Certainly the lack of early treatment, the scramble to repurpose older drugs, a wide diversity of study designs, questions of pricing and access.Also, perhaps, having to manage unexpected grief and loss on individual and community settings.

And much of the clinical response to COVID-19 is directly lead by many nurses, doctors and other health workers being redirected from HIV and sexual health to the coronavirus response.

For all our colleagues and readers who are directly involved, we hope you are taking the best care you can, that you are resourced properly to protect your own health, and that you do this knowing we are very grateful.

CONFERENCE REPORTS

Conference on Retroviruses and Opportunistic Infections (CROI 2020)

8 – 11 March 2020, Boston

Introduction

We continue our coverage from CROI 2020 from March, which was run as a virtual conference.

All conference materials are now online.

Articles from the conference included in HTB are:

- Predicted diabetes risk with first-line ART regimens: results from the ADVANCE trial
- Dolutegravir-based ART is safe and effective for pregnant women: first results from the VESTED trial
- A step forward for AAV-mediated delivery of bNAbs

Predicted diabetes risk with first-line ART regimens: results from the ADVANCE trial

Polly Clayden, HIV i-Base

Increased risk of diabetes predicted for people receiving tenofovir alafenamide (TAF), emtricitabine (FTC) and dolutegravir (DTG) in the ADVANCE trial – according to an analysis presented at CROI 2020. [1]

In ADVANCE 1053 treatment-naive people in South Africa were randomised to one of three first-line ART regimens. More participants taking first-line TAF/FTC/DTG developed clinical obesity compared to tenofovir disoproxil fumarate (TDF)/FTC/DTG and TDF/FTC/efavirenz (EFV). [2]

The analysis of predicted risks associated with obesity in the study set out to answer the following research questions:

1. What changes are seen in markers of cardiovascular risk and diabetes?

2. Can we use risk equations to predict the risk of cardiovascular disease or diabetes from these changes?

At baseline characteristics were balanced across the three study arms, participants were 99% black and 59% women. The median age was 31 years, approximately 20% had viral load above 100,000 copies/mL and CD4 was about 350 cells/mm^3.

Women weighed more than men and had higher BMI: approximately 27 vs 21 kg/m^2. Just over half the participants had a normal BMI at baseline, and approximately a quarter were overweight.

Mean change in weight at week 96 was greater in women than men. Mean weight increase for women in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms was 8 kg, 5 kg and 3 kg, respectively. For men, mean weight increase for the respective regimens was 5 kg, 4 kg and 1 kg.

Treatment-emergent obesity occurred in 28%, 17% and 12% of women in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms, respectively. Compared to 7%, 5% and 3% of men in the respective treatment arms.

There was less increase in cholesterol in the TDF/FTC/DTG arm than in the other two arms (see Table 1). Total cholesterol and LDL increased in the TAF/FTC/DTG arm. Fasting glucose increased more in the TDF/FTC/EFV arm than the other two.

Metabolic syndrome (International Diabetes Federation definition – clinical obesity plus at least two of: raised triglycerides; reduced HDL cholesterol; raised blood pressure; raised fasting glucose) emerged in 8%, 6% and 3% of participants in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively. There were statistically significant differences between TAF/FTC/DTG and TDF/FTC/DTG at week 96 (p=0.031).

The investigators used three risk equations to calculate the risk of cardiovascular events or diabetes in ADVANCE participants.

The Framingham risk equation estimates the 10-year risk of heart attack or coronary death. According to this equation, the investigators reported no significant difference and low risk across arms at baseline: 2.37%, 2.53% and 2.24% in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

At week 96 there was a similar and very modest increase in risk: +0.43%, +0.22% and +0.28 across the respective treatment arms.

The QRISK equation estimates the 10-year risk of developing heart attack or stroke. This equation looks at a larger number of variables than Framingham – including black African ethnicity.

According to QRISK, the baseline 10-year risk of heart attack or stroke was very low: 0.6%, 0.6% and 0.5% in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

At week 96 there was a slightly lower borderline significant risk with TDF/FTC/EFV compared with TAF/FTC/DTG (p=0.027)

The QDiabetes score estimates the 10-year risk of developing diabetes. Black African ethnicity is also included among the variables in this equation.

The baseline 10 year risk score of developing diabetes was: 0.30%, 0.40% and 0.30% in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

At week 96, this increased to 0.90%, 0.50% and 0.70% in the respective arms. Compared with TDF/FTC/DTG, the risk of diabetes was significantly higher with TAF/FTC/DTG (p=0.004) and with TDF/FTC/EFV (p=0.005). There were no significant differences between TAF/FTC/DTG and TDF/FTC/EFV.

The investigators noted that among women treated with TAF/FTC/DTG, weight is continuing to increase, with no sign of a plateau. The predictive models do not account for additional weight gain after week 96.

COMMENT

There is very little additional risk of MI in this young population, but there is a significant increase in the predicted risk of diabetes for people taking TAF/FTC/DTG vs TDF/FTC/DTG.

For every 1000 people treated, these results suggest that an additional 4 people taking TAF/FTC/DTG would develop diabetes. The investigators have checked these results using another predictive equation (Cambridge algorithm) and seen the same.

In South Africa, with its vast HIV epidemic, this would translate into large numbers of additional diabetes cases.

WHO 2019 guidelines recommend TDF/FTC/DTG as first-line treatment. TAF/FTC/DTG is reserved only for special circumstances: people with osteoporosis or impaired renal function. The results from this analysis support the current WHO guidelines.

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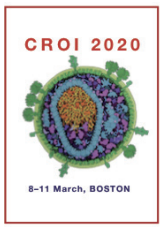
Table 1: Changes in laboratory parameters to week 96: median (IQR)

ART regimen/ comparison	1.TAF/FTC/DTG (n=185)	2.TDF/FTC/DTG (n=187)	3.TDF/FTC/EFV (n=191)	Arm 1 vs 3	Arm 1 vs 2	Arm 2 vs 3
Total cholesterol (mg/dL)	10.4 (-5.4 to 24)	1.5 (-13 to 19.7)	13.1 (-1.9 to 33.3)	p=0.022	p=0.007	p<0.001
LDL (mg/dL)	8.5 (-6.2 to 20.5)	2.3 (-10.8 to 12.4)	6.2 (-5.0 to 22.0)	p=0.82	p=0.007	p=0.013
HDL (mg/dL)	4.6 (-2.3 to 12.0)	3.9 (-2.3 to 12)	9.7 (2.3 to 19.3)	p<0.001	p=0.73	p<0.001
Fasting glucose (mg/dL)	19.3 (7.7 to 34.8)	19.3 (0.0 to 34.8)	27.1 (11.6 to 42.5)	p=0.0049	p=0.21	p<0.001
Systolic BP (mmHg)	3.0 (-7.0 to 11.0)	-1.0 (-12.0 to 8.0)	0.5 (-9.0 to 8.0)	p=0.19	p=0.03	p=0.35

Dolutegravir-based ART is safe and effective for pregnant women: first results from the VESTED trial

Polly Clayden, HIV i-Base

Dolutegravir (DTG)-based regimens safe and effective when started in pregnancy – according to findings presented at CROI 2020. [1]



IMPAACT 2010 or VESTED (Virologic Efficacy and Safety of Antiretroviral Therapy Combinations with TAF/TDF, EFV and DTG) is a phase 3, three arm, randomised, open-label trial comparing the safety and virologic efficacy of three ART regimens started by HIV positive women in pregnancy.

Pregnant women 14–28 weeks' gestation and ART-naive (up to 14 days ART in current pregnancy allowed) from nine countries were randomised to receive: DTG + tenofovir alafenamide (TAF) + emtricitabine (FTC) vs DTG + tenofovir disoproxil fumarate (TDF) + FTC vs efavirenz (EFV) + TDF + FTC.

Women are followed for 12–26 weeks up to delivery and mothers and infants for 50 weeks after delivery.

The study looked at whether treatment with DTG-based ART is non-inferior (-10% margin) to that with EFV (primary outcome viral load <200 copies/mL at delivery). It also assessed superiority after establishing non-inferiority.

Safety objectives included adverse pregnancy composite outcome (primary): preterm delivery (<37 weeks), small for gestational age (<10th centile), stillbirth or spontaneous abortion. The study also compared maternal and infant adverse events and neonatal death between arms.

Lameck Chinula showed data for 14 days follow up postpartum in women and 28 days postpartum neonates, at CROI 2020, on behalf of the VESTED investigators.

VESTED enrolled 643 women from Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, US and Zimbabwe. The majority (88%) of women were from African countries. Pregnancy outcomes were available for 640 and viral load results at delivery for 605 (94%).

At baseline women were a median of 26.6 years old, gestational age of 22 weeks, CD4 count 466 cells/mm^3 and viral load 903 copies/mL. The majority (83%) received ART for a median of 6 days before entry, only 16% had viral load <50 copies/mL. Median antepartum follow up was 17.4 weeks.

Women in the DTG arms were significantly more likely to have viral load <200 copies/mL at delivery than women in the EFV arm: 97.5% vs 91%, risk difference 6.5% (95% CI 2.0 to 10.7), p=0.005. Women receiving DTG also had a shorter time to viral suppression, p<0.001.

Fewer women in the DTG + FTC + TAF arm (24.1%) had an adverse pregnancy outcome (composite) than in the DTG + FTC + TDF (32.9%) or EFV + FTC + TDF (32.7%) arms; pairwise comparison p=0.043 and p=0.047 respectively.

Preterm delivery was less frequent with DTG + FTC + TAF (5.8%) than DTG + FTC + TDF (9.4%) or EFV + FTC + TDF (12.1%, p=0.023). Small for gestational age was also less frequent with DTG + FTC + TAF (16.3%) than DTG + FTC + TDF (22.5%) or EFV + FTC + TDF (20.5%) – but none of the by arm comparisons reached statistical significance.

Stillbirth was more frequent with DTG + FTC + TAF (3.7%) and DTG + FTC + TDF (5.2%) than EFV + FTC + TDF (1.9%); all p ≥0.05 (post-hoc). But neonatal death was more frequent with EFV + FTC + TDF (4.8%) than DTG + FTC + TAF (1.0%) or DTG + FTC + TDF (1.5%,); p=0.019 and p=0.053, respectively .

Overall, 23.0% women and 17.0% infants had one or more grade >3 AE; all p≥0.05.

Two infants were diagnosed with HIV at <14 days, one in each of the DTG arms. Maternal delivery viral loads were 58,590 and <40 copies/mL.

Maternal weight gain was significantly higher in the DTG + FTC + TAF arm than the DTG + FTC + TDF arm (p=0.011) or the EFV arm (p<0.001). But this was no greater than the recommended Institute of Medicine weight gain in second/third trimesters (0.42kg/week).

The investigators concluded that all three study regimens led to high rates of viral suppression and DTG-containing regimens had superior virologic efficacy at delivery compared with EFV.

DTG + FTC + TAF was associated with significantly fewer adverse pregnancy outcomes (driven by lower rates of preterm delivery and small for gestational age) and fewer neonatal deaths than EFV + FTC + TDF.

They concluded that these results affirm WHO recommendations to use DTG-based ART in all populations, including pregnant women. They note that TAF might be preferable to TDF in pregnancy.

C O M M E N T

VESTED is a key ART optimisation study. So these first results from an excellent randomised controlled trial, conducted in a population that will receive WHO-recommended first-line ART, have been greatly anticipated.

The DolPHIN 2 study also showed good virological suppression with DTG-based ART among women starting treatment in pregnancy (late pregnancy – from 28 weeks' gestation). [2] There were also more still births in this study in the DTG arm. But these were judged not related or unlikely to be related to ART.

The suggestion that TAF might be preferable to TDF in pregnancy needs to be carefully considered against the emerging data showing greater risk of weight gain – also shown in VESTED – with TAF and DTG containing ART. This seems to be more likely among black African women.

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CROI 2020: CURE RESEARCH

A step forward for AAV-mediated delivery of bNAbs

Richard Jefferys, TAG

Many years ago, Phil Johnson from the Children's Hospital of Philadelphia began pursuing a novel workaround to overcome the challenge of inducing broadly neutralising antibodies (bNAbs) against HIV.

The idea borrows from gene therapy, using adeno-associated virus (AAV) as a vector to deliver the genetic code for a bNAb into the body. The aim is for the AAV to persist inside cells and act as a factory for churning out the bNAb into systemic circulation.

As previously covered on the blog, promising results were obtained in macaques over a decade ago, but the first human trial (conducted in HIV negative volunteers) did not achieve detectable levels of the bNAb PG9 – likely due to the induction of anti-PG9 antibodies. [1, 2]

At CROI 2020, Joseph P. Casazza from the Vaccine Research Center (VRC) at the National Institutes of Health presented evidence that the approach may yet have promise. [3]

Casazza described preliminary results from an ongoing trial of the bNAb VRC07 delivered via an AAV serotype 8 (AAV8) vector. [4] The vector was designed by David Baltimore and Alejandro Balazs, and is different to the AAV serotype 1 vector used in the previous human trial. The study is recruiting people with HIV on ART with undetectable viral loads, and Casazza presented data from eight participants (six men and two women, with five African American and three Caucasian).

Three escalating doses are being evaluated, and Casazza's presentation included data from three recipients of the lowest dose, two recipients of the intermediate dose and three recipients of the highest dose. Follow up ranged from five months to a little over two years.

In contrast to the prior trial with AAV1, the bNAb VRC07 became persistently detectable in a majority of participants (six out of eight). In most cases, a pattern was observed in which an initial peak in levels occurred 2-4 weeks after injection, followed by a decline and then a rebound toward steady state levels after around 14-16 weeks.

Three participants developed anti-VRC07 antibodies, which has been the Achilles heel of the AAV-based delivery approach. In two of these individuals VRC07 levels became undetectable after the initial peak, and in the third the secondary peak was blunted. Casazza noted that anti-VRC07 antibodies did not appear to be the only factor influencing VRC07 levels, because one participant in the high dose group experienced a significant decline between weeks 22 and 40 which has yet to be explained.

Adverse events were minimal, with mild pain and tenderness at the injection sites reported in the high dose group and one case of muscle pain in the intermediate dose group—all resolved within seven days.

Casazza did not discuss the potential reasons for the greater success compared to the results achieved with AAV1-based delivery but, in addition to differences in the technical aspects of vector design, AAV8 is liver tropic and it's been suggested that this is more likely to lead to immunological tolerance of the delivered bNAb. [5]

Notably, the maximum VRC07 concentration achieved was a little over one ug/mL in the high dose group, which is low compared to the levels that are obtained by intravenous infusion of bNAbs. For example, levels of well over 50 ug/mL have been reported in studies involving IV administration of the bNAb VRC01. [6] In a recent trial that administered a combination of the bNAbs 3BNC117 and 10-1074 and then interrupted antiretroviral therapy (ART), an undetectable viral load was maintained for as long as the concentration of both antibodies was above 10 ug/mL. [7]

Casazza's results offer some hope that the use of AAV vectors to deliver bNAbs (or other therapeutic proteins) will turn out to be feasible. However, work remains to improve both the consistency and magnitude of bNAb production. In a preclinical macaque study in which an AAV8 vector was used to deliver VRC07, the addition of transient immune suppression with cyclosporine was able to increase average peak bNAb levels to ~40 ug/mL (compared to ~5 ug/mL without), however it's unclear if this approach could be practically adapted for human use. [8]

Casazza and his colleagues at the VRC are not the only research group still pursuing the idea. Michael Farzan from the Scripps Institute gave a talk at CROI describing the latest results obtained with AAV-based delivery of eCD4-Ig, a protein that inhibits HIV replication by binding the virus envelope at sites that attach to CD4 and CCR5 receptors on CD4 T cells. [9]

In a therapeutic experiment involving six macaques infected with the SIV/HIV hybrid virus SHIV-AD08, eCD4-Ig delivered by AAV (two injections, the first using an AAV8 vector and the second using an AAV1 vector) was able to maintain viral load control to varying degrees after an ART interruption. At the most recent timepoint after 80-90 weeks off ART, five animals have viral loads ≤15 copies/mL and the sixth has a viral load of 25 copies/mL. Concentrations of eCD4-Ig ranged from 4.7 to 10.3 ug/mL, and Farzan explained that they hope to further refine delivery to achieve higher levels.

The laboratory of Ron Desrosiers is also working on AAV delivery, focusing on payloads of combination bNAbs. Farzan cited the best known example of this work: the "Miami monkey," a recipient of AAV-delivered 3BNC117 and 10-1074 that has exhibited prolonged containment of a SHIV AD8 challenge at such vanishingly low levels that the virus has been extremely

challenging to even detect (at one point it was thought virus eradication may have occurred). [5]

On March 17th, Desrosiers and colleagues provided an update on another individual macaque that was originally part of a prevention study published in 2015. [10] This animal has now maintained high levels (240-350 ug/mL) of the anti-SIV antibody 5L7 for over six years. The researchers are now working to create this type of response more reliably and they conclude: "If satisfactory delivery methods are found, it becomes possible to envision long-term control of viral replication in the absence of antiretroviral treatment by delivering a combination of antibodies in people, and long-lasting protection when this approach is used in a prophylactic setting."

It may still be a big "if," but the data clearly justify efforts to solve the technological challenge.

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CONFERENCE REPORTS

10th International Workshop of HIV & Women

6 – 7 March 2020, Boston

Introduction

This annual workshop focuses on the latest developments in research and treatment of HIV positive women from a global perspective and 2020 was its 10th anniversary.

The meeting provides an interactive programme that includes: overview talks, oral abstract presentations, Q&A sessions, poster sessions and case studies.

This year it was the only CROI-affiliated event that went ahead in person.

The programme is available on the workshop website: https://www.virology-education.com

Abstracts together with most presentations and webcasts are available at:

https://www.academicmedicaleducation.com/hivwomen2020

We will include more reports from this workshop in the next edition of HTB.

Articles from the conference included in HTB are:

- No neural tube defects among pregnancies with periconception dolutegravir exposure in the Dolomite-EPPICC cohort study

No neural tube defects among pregnancies with periconception dolutegravir exposure in the Dolomite-EPPICC cohort study

Polly Clayden, HIV i-Base

Data from the European Dolomite-EPPICC cohort study, presented at the 10th International Workshop on HIV and Women, did not show any neural tube defects (NTD) among pregnancies with periconception dolutegravir (DTG) exposure. But the dataset is not yet large enough to rule out an increase in these rare events. [1]

In May 2018 the Tsepamo Study reported a significantly increased NTD risk in women conceiving on DTG (0.94%), leading to a safety alert and a lot of uncertainty and misinformation. [2]

Additional data, presented July 2019, showed NTD prevalence with periconception DTG to be lower than in the 2018 analysis, but still higher for other antiretroviral exposures (0.3% vs 0.1%). [3]

The Antiretroviral Pregnancy Registry reported 1 NTD with 312 periconception DTG exposures (0.3%) July 2019 – but the number of exposures is small. [4]

Dolomite-EPPICC is a multi-cohort European observational study: it includes pooled data from the Dolomite Study which was set up in 2017 to look at the use and safety of DTG in pregnant women and exposed infants in Europe and Canada within the NEAT-ID network, and EPPICC (the European Pregnancy and Paediatric Infections Cohort Collaboration).

The investigators conducted an analysis of prospectively collected data on all pregnancies with any prenatal DTG exposure and with birth outcomes reported by February 2019.

Periconception exposure was defined as within the first 6 weeks of gestation. The aim of the study is to assess pregnancy and neonatal outcomes following DTG use during pregnancy in real-world European settings.

The analysis included 453 pregnancies among 428 women from 6 countries: UK and Ireland (76%), Spain (9.9%), Switzerland (6.4%), Italy (6.4%) and Romania (0.7%). Women were mostly of black African (54%) and white (30%) ethnicity. Just over 10% were vertically infected.

Of 453 pregnancies (including outcomes from 10 twin pregnancies): 18 were terminated and 22 ended in spontaneous abortion.

There were 417 live-born infants; 280 with periconception exposure. There were 5 stillbirths, all exposed to periconception DTG, none with birth defects: 11.8 per 1000 (95% CI 3.9 to 27.4). One neonate died at 2 days (born at 23 gestational weeks) with periconception DTG exposure.

Among the 417 live-born infants there were 17 with reported birth defects: 4.1% (95% CI 2.4 to 6.5); one infant had 2 defects. Among infants with periconception exposure, 12/266 had reported birth defects: 4.5% (95% CI 3.9 to 5.1).

There were no defects among the stillborn infants. Of 18 induced abortions, 1 was carried out due to birth defects (at gestation week 29 for neuronal migration disorder and severe microcephaly). This terminated pregnancy had periconception DTG exposure.

The 18 defects were in the following systems: genitourinary (7), heart (3), limb addition (polydactyly, 3), gastrointestinal (2), other (3). No CNS defects were reported.

COMMENT

This dataset is the largest to date of European DTG use in pregnancy. The majority (70%) of pregnancies had periconception DTG exposure.

The overall prevalence of defects was 4.1% (3.1% if only EUROCAT defects). There were no NTDs reported but this is unsurprising as the sample size is too small to come to any conclusion about these rare events (2000 exposures required to rule out a three-fold increase).

But these data add to the current evidence base and the study is ongoing.

At the same meeting Lynne Mofenson provided a typically comprehensive overview of ART in pregnant women. This included an updated list of all published/presented data on NTD with periconception exposure to DTG to date. See Table 1.

Using the available prevalence data, Dr Mofensen calculated, preconception DTG NTD prevalence without food folate fortification: 0.27% (6/2233). This compares with the general population prevalence without food folate fortification: 0.09–0.1%.

With folate food fortification, preconception DTG NTD prevalence: 0.12% (1/847). Compared with general population prevalence with food folate fortification: 0.06%.

Table 1: Published or presented data on neural tube defects with preconception DTG

Study	Food folate fortification	NTD/pre-conception exposure
Tsepamo 2019 (NEJM 2019)	No	5/1683 (0.30%)
CDC-MoH Botswana	No	1/152 (0.66%)
Sibiude, France (CROI 2019)	No	0/41
Chouchana, France (JAIDS 2019)	No	0/49
Thorne, Dolomite-EPPICC 2020	No	0/266*
Weissmann, Germany (Glasgow 2018)	No	0/3
Kowalska, eastern Europe (Glasgow 2018)	No	0/24
Bornhede, Sweden (Eur J ID 2018)	No	0/14
Orrell, ARIA (Lancet HIV 2017)	No	0/1
APR July 2019	Most	1/312 (0.32%)
Brazil case-control (IAS 2019)	Yes	0/384
ADVANCE, S Africa (IAS 2019)	Yes	0/54
Money, Canada (BJOG)	Yes	0/69
Grayhack, US (AIDS 2018)	Yes	0/28

Source: Mofensen L. 10th International Workshop on HIV and Women 2020. *Dolomite-EPPICC updated to include presentation above.

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SIDE EFFECTS

Dolutegravir associated with hyperglycaemia in people switching first-line ART in Uganda

Polly Clayden, HIV i-Base

Hyperglycaemia was reported in Uganda among people switching first-line regimens to dolutegravir-based ART, in a letter to Lancet HIV, published online 24 February 2020.

The authors recommend that a monitoring plan for hyperglycaemia should be part of the clinical care package for people switching ART to dolutegravir-based regimens.

In March 2018, the Ugandan Government recommended dolutegravir-based ART for treatment-naive people with HIV and that eligible treatment-experienced patients be transitioned from their existing first-line regimens.

This programme originally started in specialised centres – including the Infectious Diseases Institute at Makerere University (Kampala, Uganda). A year later, 3417/6648 people on first-line regimens attending the facility had started dolutegravir. The authors noticed that some people developed symptomatic hyperglycaemia after switching to dolutegravir, so they documented these events. They compared cumulative incidence of symptomatic hyperglycaemia in people who started dolutegravir-based first-line regimens between 1 April 2018 and 31 March 2019 (cases), to that among all others on non-dolutegravir-based first-line regimens in the same period (controls).

There was 12 months follow up starting from 1 May 2018. The authors noted that this month had the highest frequency of starting dolutegravir.

The report revealed 16/3417 (0·47%) of people in the case group had new-onset hyperglycaemia vs 1/3230 (0·03%) in the control group (p=0·0004). Over 12 months this gave an incidence of 4·7 per 1000 vs 0·32 per 1000, in the case and control group respectively.

Among the cases, hyperglycaemia events were severe (in 15/16) and the majority were preceded by weight loss after starting dolutegravir rather than weight gain. Median time from starting dolutegravir to onset of hyperglycaemia was 4 months (IQR 2·5 to 4·5). People with hyperglycaemia were given antidiabetic medication and dolutegravir was stopped and substituted with an alternative antiretroviral.

Two people in the case group who initially presented with grade 3 hyperglycaemia reversed this after stopping dolutegravir. One no longer needed metformin after 6 weeks and the other after 6 months. Currently both are able to control their diabetes with diet alone.

The authors suggest that these findings could be subject to confounding: more people who transitioned to dolutegravir were older, male, or had been on ART for 5 years or more (p<0·0001 for each) vs those who did not transition to dolutegravir.

"Early recognition of potentially serious toxicities is crucial to inform the implementation of large-scale national ART programmes. This is especially true in settings in which pharmacovigilance systems are weak" they wrote. And they recommend that people switching ART to dolutegravir-based regimens be monitored for hyperglycaemia.

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HIV PREVENTION

PrEP recommended by NHS England (at last)

Simon Collins, HIV i-Base

On 15 March 2020, as the UK response to COVID-19 was becoming more critical, many health activists were surprised, in a good way, with a government announcement that PrEP would be available from NHS England. [1]

This included that local authorities will receive £16 million in 2020 to 2021 to deliver PrEP. The funding from the Department of Health and Social Care is to make sure that anyone who is at a high risk of contracting HIV has the option to receive PrEP from their local sexual health clinic.

This will also cover people enrolled in the last few months of the PrEP IMPACT trial, which is due to close on October 2020.

This access to PrEP was driven by health activists from all sectors: community, health workers, researchers and doctors. However, it still took more than five years after the UK PROUD study proved overwhelming PrEP efficacy in 2014. [2]

It is also almost four years after NHS England lost the legal challenge brought by the National AIDS Trust. [3]

Earlier access to PrEP could easily have prevented the many thousands of people who became HIV positive.

C O M M E N T

Although this was announced a few weeks ago, it is still important to include in this issue of HTB.

A coalition of Black and Minority Ethnic (BME) organisations, while welcoming the availability of PrEP called for new initiatives to broaden access to PrEP.

The rate of late diagnosis amongst black African heterosexual men rose to 69% in 2017 from 59% in 2015, in contrast to the overall late diagnosis rate which has fallen.

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HTB SUPPLEMENT ON COVID-19: ISSUE 2

HIV & COVID-19 COINFECTION

Why it is important to include HIV status and HIV testing in managing COVID-19

Simon Collins, HIV i-Base

The importance of HIV status being recorded for people diagnosed with pneumonia or other respiratory problems and who are hospitalised as part of the management of COVID-19 has been highlighted in a blog to the BMJ. [1]

There are several reasons for this.

Firstly, for those of us who are HIV positive, it will ensure that antiretroviral treatment (ART) is maintained during any period in hospital, including in intensive care. Interrupting ART will let viral load rebound which will increase immune inflammation at t time when this is one of the main difficulties in managing COVID-19. The lock down restrictions on physical movement means that HIV positive people with COIVD-19 might be seen in a hospital with less HIV experience. We need to know HIV is considered in all settings.

Secondly, it will start to generate a dataset that will inform statements and guidelines about the impact of COVID-19 on people living with HIV. All the generally optimistic statements and guidelines have emphasised the lack of actual data and that they are based on expert opinion. [2]

Thirdly, HIV will be a complicating factor for COVID-19 in people who are not on ART, and by definition this includes people who have not yet been diagnosed. Even though NICE guidelines include HIV testing for anyone admitted to intensive care with pneumonia and respiratory failure, this really needs to be emphasised. [3] A recent dataset set of 290 people hospitalised for COVID-19 included 2 people who were HIV positive but 47 people where HIV status was unknown or not recorded. [4]

Finally, at a time when doctors, nurses and laboratories involved in HIV testing and sexual health services are being diverted to deal with coronavirus, this will provide another chance for HIV diagnoses in people not currently aware of their status.

It will also make sure that the skills and experience form HIV services are included in the response to COVID-19.

C O M M E N T

Although there were anecdotal reports of initial reluctance to include HIV at some COVID-19 centres, this has since been integrated by many hospitals.

It has resulted in earlier diagnosis of HIV-associated pneumonia and cases of HIV and COVID-19 coinfection.

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COVID-19 symptoms in HIV positive people similar to general population in Wuhan

Simon Collins, HIV i-Base

The most substantial data to inform risk of HIV and COVID-19 coinfection so far is an analysis from China. However, this is based on self-reported symptoms and the paper is not yet peer reviewed – published only in draft form ahead of press in the Lancet.

Wuhan city in Hubei province has a population of about 9 million people which includes about 6000 people who are HIV positive.

During the coronavirus outbreak, and up to 2 March 2020, at least 49,300 people tested positive for CoV-2 and 2227 residents died from COVID-19.

This paper included a subset of 1178 HIV positive people in two central districts in Wuhan. All participants were prospectively contacted by telephone and those reporting symptoms tested by PCR for CoV-2 and by CT scan for COVID-19. Face-to-face contact was limited due to lock down restrictions. The two districts included approximately 1,800,000 residents and reported 9,000 cases of COVID-19.

Of the 12/1178 people who reported symptoms, 8/12 were confirmed as COVID-19 (6/8 by PCR, 2/8 by CT - and 4/12 were excluded). All eight had undetectable viral load (<20 copies/mL) and were taking NNRTI-based ART, 6/8 with CD4 counts >350 and 2/8 between 100 to 350 cells/mm^3.

Of these 8 cases, 6/8 were mild, 1 was severe, and 1 was a critical case who died.

Of the 1162 HIV positive people without symptoms, nine were in close household contact with people who had confirmed COVID-19. Of these, only 1/9 was confirmed positive for CoV-2 by PCR. This person had only recently been diagnosed with a very low CD4 count (27 cells/mm^3), had received ART for less than one month and was on chemotherapy for KS.

The cohort also included 41 people with CD4 counts <100 cells/mm^3, with only one of these having reported possible symptoms. In the discussion, the paper suggested that a low CD4 count might not reflect lower CoV-2 incidence but masking of symptoms of COVID-19 (but clearly not for the case mentioned above).

Based on self-reported symptoms the rate of COVID-19 in people living with HIV was estimated as 0.68% (95%CI: 0.29% to 1.34%). This was slightly higher than reported for general population in Wuhan (~0.5%) but similar to the overall estimated population rate of 0.83% (75 thousand out of 9 million).

In multivariate analysis, including age, gender, CD4 counts, viral load, and type of ART, only older age was significantly associated with higher risk of COVID-19 (p=0.010). The median age of the eight people with COVID-19 was 57.0 years old (95%CI: 47.5 to 61.5) compared to 36.0 (95%CI: 30.0 to 51.0) of those without COVID-19 (n=1166).

The paper discussed the role of other antiretrovirals in COVID-19. Although no cases were reported among the 178 people taking lopinavir/r, the study was underpowered to comments on individual drugs. Any possible role (would be for antiviral activity in early stage infection rather than in later COVID-19 when organ damage is caused by inflammation.

This reason is given to support the Chinese guidelines (versions 1 to 6) to use corticosteroids to treat COVID-19 to suppress the inflammatory cytokine storm. Other experts, including WHO, disagree with this approach based on several meta-analyses that highlight risk of harm. [2, 3]

C O M M E N T

This study is welcome for providing some level of direct evidence that HIV positive people in Wuhan were not disproportionately affected by COVID-19. This is helpful in terms of concerns that incidence might be higher and outcomes might be worse.

The limitations from the study (other than lack of peer-review) is the reliance on self-reported symptoms and limiting testing to either those people who were symptomatic or at highest household risk. It doesn't therefore provide data on incidence and prevalence of CoV-2 which will need antibody testing.

Also, behavioural data on travel and risk was not available, including whether those with lowest CD4 counts were already self-isolating to minimise risk.

While these data are important, we still have much to learn.

It is therefore essential that all cases of COVID-19 in the UK have their HIV status recorded and that people without a recent negative result are routinely tested for HIV.

These two low-cost initiatives would improve the management of both HIV and COVID-19 care.

Recent studies of lopinavir/r have reported conflicting results but a recent UK study was announced also using dexamethasone. [3, 4, 5, 6]

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Case study of COVID-19 in HIV positive person with history of HCV

Simon Collins, HIV i-Base

With so few reports of outcomes of COVID-19 in HIV positive people yet available, case reports are important, in this case in someone with a history of HCV.

This was a 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/mm3 and HCV coinfection.

The case included persistently negative SARS-CoV-2 RNA on specimen samplings but positive for plasma anti-SARS-CoV-2 antibody although these were delayed.

Ref: 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).

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Case series of five HIV positive people diagnosed with COVID-19 in Spain

Simon Collins, HIV i-Base

A study reporting on the first 543 consecutive cases of COVID-19 admitted to the Hospital Clínic in Barcelona in the first two weeks of March 2020, included five people who were also HIV positive. Details of their management and outcomes have been published as a case series in Lancet HIV.

Overall, 62 (12%) were admitted to intensive care and 208 were discharged for supervised outpatient care.

The five HIV people (0.92%: 95%CI: 0.39 to 2.14) included three men, two were transgender and four identified as being gay men. Age ranged from 29 to 49. Community exposure risk included health work, sex work, time spent with someone diagnosed with COVID-19 and one reported a chemsex party six days earlier.

The four people on ART had undetectable viral load (two using boosted-darunavir-based and two using dolutegravir-based combinations) and CD4 counts >400 cells/mm^3. One was treatment-naive and was just diagnosed as a late presenter with a CD4 count of 11 cells/mm^3.

Two patients had upper-respiratory tract infections, and three had viral pneumonia, including two requiring admission to the intensive care unit with invasive and non-invasive mechanical ventilation.

Experimental approaches to management of COVID-19 included switching ART for most patients to lopinavir/r plus TDF/FTC; azithromycin was given as 500 mg once a day, with a loading dose on the first day, and then 250 mg once a day for 4 days; hydroxychloroquine was given as 400 mg twice a day with a loading dose on the first day and then 200 mg twice a day for 4 days, and interferon beta-1b was given as 250 µg (8 million units) every 48 h.

All three patients who had pneumonia had antibacterials, corticosteroids were given to two patients and tocilizumab in one.

Four patients have since been discharged and one remains in the intensive care unit

For further details please see the open access paper.

Ref: 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).

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COVID-19: TREATMENT

Evidence review for treatment: IDSA guidelines for COVID-19

Simon Collins, HIV i-Base

On 11 April 2020, the Infectious Diseases Society of America (ISDA) published an evidence review of the main compounds being studied for the management COVID-19. [1]

This document is planned in three parts. This first section deals with treatment and management. Part two on diagnostics, and part three on prevention, are due to be published shortly.

The guideline lists five investigational treatments of repurposed drugs for people who are hospitalised with COVID-19, all in the context of a clinical trial.

- Hydroxychloroquine/chloroquine.
- Hydroxychloroquine/chloroquine plus azithromycin.
- Lopinavir/ritonavir.
- Tocilizumab
- Convalescent plasma

Corticosteroids are not recommended in patients with COVID-19 pneumonia but are an option for COVID-19 that presents with other symptoms.

The detailed evidence review for each of these approaches is less than optimistic: none shows strong evidence for benefit and all include evidence of risk.

Additional compounds are also discussed.

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Remdesivir for COVID-19: first results from compassionate access programme

Simon Collins, HIV i-Base

Some of the earliest studies of repurposed compounds and drugs for the new coronavirus (CoV-2) include a nucleotide inhibitor prodrug in development with Gilead called remdesivir. Remdesivir has in-vitro activity against a panel of viruses including Ebola, MERS, SARS-CoV-1 and SARS-CoV-2, although studies for Ebola were not successful.

Although a dozen studies are now ongoing for CoV-2 none of these studies has yet published efficacy or safety results. [1]

So while first results in have now been published as an open access paper in the new England Journal of Medicine, these are only preliminary data from the first compassionate use, rather than from a controlled clinical study. [2]

The report is based on 53 patients who received at least one dose of remdesivir from 25 January to 7 March 2020 and who had follow up data available. This is an international cohort including the US (n=22), Europe or Canada (n=22) and Japan (n=9). A further 8 participants received remdesivir but were not included in the analysis, mainly due to missing data.

Entry criteria included being hospitalised with confirmed COVID-19 and either an oxygen saturation of 94% or less while breathing ambient air or a need for oxygen support. Although there were no formal primary endpoints, all key clinical factors and drug safety were recorded.

Baseline characteristics included median age 64 years (IQR: 48 to 71; range: 23 to 82), 75% men and 36 (68%) had a significant comorbidity. Clinical features included 30 patients (57%) on mechanical ventilation and 4 (8%) receiving extracorporeal membrane oxygenation. Median duration of symptoms before remdesivir was 12 days (IQR: 9 to 15).

Participants were able to receive a 10-day course of remdesivir, given IV: 200 mg on day 1, and then 100 mg daily. Overall, 40/53 (75%) received the 10-day course, 10 (19%) received 5 to 9 days of treatment, and 3 (6%) fewer than 5 days of treatment.

During a median follow-up of 18 days (95%CI: 13 to 23), 36 of 53 patients (68%) showed an improvement in the category of oxygen support, with 8 of 53 patients (15%) worsening. At most recent follow-up, 25/53 participants (47%) had been discharged (24% receiving invasive ventilation [8/34] and 89% [17/19] receiving noninvasive oxygen support).

Seven of the 53 participants (13%) died after remdesivir treatment, including 6/34 patients (18%) on invasive ventilation and 1/19 (5%) receiving noninvasive oxygen support.

Adverse events were reported in 30/53 participants (60%) many of which overlap with symptoms of COVID-19. Serious events in two or more people were multiple organ dysfunction (n=2), septic shock (n=2), acute kidney injury (n=2) and hypotension (n=2).

At 28 days post treatment, clinical improvement based on a six-point scale was reported for 84% of participants. Sex, country, coexisting conditions, and duration of symptoms before remdesivir were not significantly associated with clinical improvement.

Viral load data was not collected in this programme.

Although the paper refers to safety data from approximately 500 participants in the Ebola development programme, the NEJM paper doesn't report on the remdesivir arm and the EMA document in only animal data. [3, 4]

COMMENT

The urgency of effective treatment for COVID-19 makes the results from clinical studies essential, and hopefully the first of these might become available within the next few weeks.

Gilead have already announced plans for rapid large scale manufacturing and an expanded compassionate access programme. [5]

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No benefit of hydroxychloroquine and azithromycin in people hospitalised with COVID-19

Simon Collins, HIV i-Base

A prospective open label study of 11 people (7 men and 4 women) hospitalised with COVID-19 (10/11 with fever) at a single hospital in Paris, reported no benefits from using the antimalaria drug hydroxychloroquine with the antibiotic azithromycin. [1]

The results are important for challenging an earlier French study (from Gautret et al) that reported CoV-2 clearance in 6/26 people using this combination. It led to widespread speculation as an effective treatment that resulted in pharmacy stock-outs within 24 hours. [2, 3]

The new study was authored by Jean-Michel Molina and colleagues from Saint Louis Hospital, Paris and published ahead of print in the French journal Médecine et Maladies Infectieuses.

Baseline characteristics included mean age of 58 years (range: 20 to 77) and 8/11 had significant comorbidities associated with poor outcomes (obesity: 2; solid cancer: 3; hematological cancer: 2; HIV-infection: 1).

The treatment included hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5).

After five days, CoV-2 remained detectable by qualitative PCR in throat swabs in all participants.

Within five days, one patient died and two were transferred to intensive care units. One participant discontinued treatment after four days due to qT prolongation (from 405 ms to 460 and 470 ms).

The paper by Molina et al references a recent randomised study from China that also reported no benefit from hydroxychloroquine and azithromycin in 30 participants, with similar rates of clearance to a control group. In this study, throat swabs were negative by PCR at day seven in 86% of the active vs 93% of the standard of care control groups, and with no differences in clinical outcomes. [3]

It also references other studies showing no impact in other indications and was published as an alert to counter the high publicity given to this combination.

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High-dose chloroquine study for COVID-19 stopped with worse outcomes: high risk of cardiovascular events

Simon Collins, HIV i-Base

A randomised, double-blind phase 2 study of chloroquine (CQ) to treat COVID-19 in Brazil has discontinued further treatment in a high dose arm following early reports of significantly worse outcomes.

As with many new papers on COVID-19, the results are reported before peer-review. The paper had approximately 50 co-authors.

The recommendation from the Data and Safety Monitoring Board (DSMB) was based on the results from the first 81 participants (out of a planned 440) who were randomised to either high dose CQ (600 mg CQ twice daily for 10 days; total dose 12 g) or low dose CQ (450mg for 5 days, twice daily only on the first days; total dose 2.7g). All patients also received ceftriaxone and azithromycin.

History of heart diseases was higher in the high-dose group and participants older than 75 years (n=5) were also only included in this arm.

The high dose arm resulted in more QTc >500 ms (25%), and a trend toward higher mortality (17%) than the lower dosage. Two patients in the high dose arm had ventricular tachycardia before they died, . severe arrythmia associated when QTc is prolonged.

The mortality rate was 13.5% (95%CI: 6.9 to 23.0%) which overlaps with the CI of historical data from a meta-analysis of similar patients in two other studies not using CQ (95%CI: 14.5 to 19.2%). Two of the eleven deaths were in participants older than 75.

Many participants in this study were also taking oseltamivir (when seasonal influenza suspected) which can prong the QT interval.

The study also failed to show an antiviral effect of CQ with no evidence of viral clearance by day five, irrespective of dosage,

COMMENT

It is difficult to understand the rationale for either dose in this study. One likely to produce toxicity problems and the other being too low to see benefit.

The controversial study by Gautret et al used a dose of 600 mg/day and the high dose recommended in Chinese guidelines uses 10 mg/day.

It is shocking to see the mortality reported for oldest participants who were at highest both for COVID-19 and CG side effects.

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COVID-19: TREATMENT ACCESS

Potential treatments for COVID-19 could be manufactured for $1 a day or less

Polly Clayden, HIV i-Base

If repurposed drugs, currently under investigation for COVID-19, show efficacy, they could be manufactured profitably at very low costs – according to an analysis published in the Journal of Virus Eradication on 8 April 2020. [1]

As the SARS-CoV-2 pandemic grows daily, clinical trials are underway worldwide looking at potential ways to prevent new infections, treat those already infected and reduce the severity of the disease.

Results from randomised controlled trials of repurposed drugs – ie those currently indicated for other diseases so shortening the drug discovery and development timeline – are expected between May and September of this year.

Andrew Hill and colleagues – whose group have previously reliably predicted the minimum costs of drugs for hepatitis C and other diseases – calculated the costs of new potential treatments for COVID-19.

The authors used established methods to make these calculations. They estimated the minimum costs of drug production by calculating the cost of active pharmaceutical ingredients (API), added to costs of excipients, formulation, packaging and a profit margin of 10%, to calculate the price of the final finished product (FFP) – the drug ready for use.

The selected treatments were: remdesivir (previously used unsuccessfully against Ebola); favipiravir (influenza), lopinavir/ritonavir (HIV), chloroquine and hydroxychloroquine (malaria) and sofosbuvir and daclatasvir (HCV), azithromycin (pneumonia), and pirfenidone and tocilizumab (improve lung function and reduce inflammation).

Remdesvir

Remdesvir is given by IV infusion. A 10-day course of treatment is under investigation at a dose of 200 mg on the first day and 100 mg the following days.

The authors estimated the cost per treatment to be approximately $9 per person – an estimated daily cost of $0.93.

They note that costs for non-drug components associated with IV infusion were not included in this estimate: saline, equipment (syringe, sterile water and IV lines) and staff time.

Favipiravir

Favipiravir is an oral treatment dosed at 600 mg twice daily. A 14-day course is being evaluated. The estimated cost of production for this course is $20 or $1.45 per day.

The authors added that favipiravir was launched for sale in China in late February 2020 at a price of $231 per 14-day course.

Lopinavir/ritonavir

The standard dose of lopinavir/ritonavir is 400/100 mg oral combined pill twice daily. A 14-day course is also being evaluated.

The estimated cost for this course is $4 or $0.28 per day.

So far there has been no clear evidence of efficacy for lopinavir/ritonavir against COVID-19.

Current list prices for a 14-day course range from $503 in the US to $15 in South Africa (and available through the Global Fund to low- middle-income countries for a medium of $9).

Hydroxychloroquine and chloroquine

These old malaria treatments (since the 50's) were calculated at 400 mg and 155 mg daily doses for 14 days of hydroxychloroquine and chloroquine, respectively.

The estimated costs were $1 per course or $0.08 per day and $0.3 or $0.08 per day for the respective drugs.

Available list prices for a 14-day course of hydroxychloroquine ranged from $19 in China to $2 in India.

For chloroquine these prices ranged from $93 in US to $0.2 in Bangladesh for a course. The authors note that the Bangladesh price was lower than their estimate and the US one might be considered an outlier (by a considerable amount as the next most expensive price for a 14-day course, in the UK, was $8).

Azithromycin

Used in small pilot studies with hydrochloroquine (and contradictory results) to prevent bacterial superinfection.

A 14-day course at a dose of 500 mg per day was calculated at $1.40 or $0.10 per day.

List prices for azithromycin range between $63 per 14-day course in the US and $5 in India and Bangladesh.

Sofosbuvir/daclatasvir

Under evaluation in Iran for people with moderate to severe COVID-19 symptoms at a daily dosage of sofosbuvir/daclatasvir 400/600 mg.

The estimated cost is $5 per 14-day course or $0.39 per day.

These drugs were launched by originator manufacturers for treatment of Hepatitis C at eye-watering prices, which have fallen significantly in recent years.

Earlier estimates of minimum price for generic production by Hill et al in 2016 were equivalent to $7.8 per 14-day course, so the new estimates represent a 6.6-fold reduction since the group's original calculations.

Fourteen-day list prices range from $18,610 in the US and $7 in India or $6 in Pakistan.

Pirfenidone

A dose of 801 mg three times a day for four weeks is being evaluated. The estimated cost for a 4-week course is $31 or $1.09 per day. List prices for a 4-week course range from $9,606 in the US to $124 in Bangladesh and $100 in India for a generic version.

The authors explained that at $100, the lowest list prices are still higher than their estimate.

Tocilizumab

This monoclonal antibody is dosed as an IV infusion. Doses are based on weight (8 mg/kg) with a maximum single dose of 800 mg every 12 hours.

The authors assumed an average bodyweight of 70 kg and a single dose of 560 mg.

There were no API data available for tocilizumab – so they were unable to estimate the minimum cost of production.

List prices for 560 mg single dose varied from $3,383 in the US to $510 in Pakistan.

Several biosimilars are currently under development but these have yet to be approved and launched.

Biosimilars can offer healthcare systems the potential to lower costs significantly. The UK is expected to save up to £200–300 million a year through the uptake of better-value biological medicines.

Conclusion

The authors emphasised that we do not know yet which or any of these drugs will show benefit. But this analysis shows that if that was the case they all could be manufactured for very low prices.

Repurposed drugs might be the only option to treat COVID-19 for the next 12–18 months, until effective vaccines can be developed and manufactured at scale.

Some of the treatments are already available as generic, with prices close to the cost of manufacture for low- and middle-income countries.

Treatments for HIV, TB and malaria are distributed worldwide by the Global Fund and PEPFAR at prices close the cost of manufacture. These prices allow generic companies to make acceptable profits. The authors recommend that a similar model of drug distribution be adopted for COVID-19.

They made four recommendations to ensure that anyone with COVID-19, in any country, would be able to access the treatment they need:

1. Treatments showing efficacy in well-powered clinical trials should be made available worldwide at prices close to the cost of manufacture.
2. There should be parallel manufacture by at least three different companies for each product, sourcing their API from different countries. Production of drugs in a range of countries will protect us from disruption or shortages in individual countries.
3. There should be no intellectual property barriers preventing mass production of these treatments worldwide. We need open 'technology transfer' so that the methods used to manufacture the key drugs can be shared with any country deciding to produce the drugs locally.
4. Results and databases from all COVID-19 clinical trials should be fully accessible so others can learn from them. To speed up access to these drugs, countries could rely on recognition of the review and approval of key treatments by regulatory authorities in the US or Europe, or other stringent regulatory authorities. There may not be time for the normal times of regulatory review by all individual countries.

C O M M E N T

The authors looked at costs of production for the main treatments currently being tested in clinical trials. These drugs could be mass produced for $1 per day, often for a lot less, and distributed through mechanisms like those used for HIV, TB and malaria.

Even remdesivir, the new potential treatment from Gilead, could be mass produced for $9 for a 10-day treatment course. The cost of the saline (and other non-drug components) would be higher than the remdesivir, when given by IV infusion.

Some of these treatments have US list prices 100 times higher than the cost of production. The Presidential-favourite untested COVID-19 candidate is over 10 times as much in US as the UK.

Anyone with COVID-19, in any country, should be able to access these new treatments if the prices can be kept close to production costs.

Previous minimum cost estimates by Hill et al have been invaluable to support price negotiations for treatments for other diseases. Among many others, MSF welcomed the COVID-19 estimates. [2] "Literally every single person on earth is susceptible to this pandemic – now is not the time for price gouging and pandemic profiteering" they wrote.

At the moment, countries are becoming insular, competing for limited supplies of drugs, ventilators and PPE, in bidding wars, rather than engaging in a collaborative system for resources to be prioritised for areas of greatest need.

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MSF calls for no patents or profiteering on COVID-19 drugs, tests, and vaccines in pandemic

MSF press release

On 27 March 2020, Médecins Sans Frontières/Doctors Without Borders (MSF) issued a press release calling for no patents or profiteering on drugs, tests, or vaccines used for the COVID-19 pandemic, and for governments to prepare to suspend and override patents and take other measures, such as price controls, to ensure availability, reduce prices and save more lives.

Already, Canada, Chile, Ecuador and Germany have taken steps to make it easier to override patents by issuing 'compulsory licenses' for COVID-19 medicines, vaccines and other medical tools. Similarly, the government of Israel issued a compulsory license for patents on a medicine they were investigating for use for COVID-19.

The press releases states: "MSF is deeply concerned about access to any forthcoming drugs, tests, and vaccines for COVID-19 in places where MSF works and in other countries affected by this pandemic, and is urging governments to prepare to suspend or override patents for COVID-19 medical tools by issuing compulsory licenses. Removing patents and other barriers is critical to help ensure that there are sufficient suppliers selling at prices everyone can afford."

Ref: MSF calls for no patents or profiteering on COVID-19 drugs, tests, and vaccines in pandemic (27 March 2020)

https://msfaccess.org/msf-calls-no-patents-or-profiteering-covid-19-drugs-tests-and-vaccines-pandemic

COVID-19: NEW RESEARCH

Gilead expand UK sites for two phase-3 studies of remdesivir to treat COVID-19

Simon Collins, HIV i-Base

On 1 April 2020, Gilead Sciences announced that two new studies of the investigational compound remdesivir were launched in the UK, in participants with moderate and severe COVID-19.

These are both part of large international phase 3 studies, announced in February, with more than 100 sites in the US and ten countries in Europe, China and South East Asia. [2]

The current listings state the studies will randomise 1000 participants overall to either a five-day or ten-day course of remdesivir (200 mg on day 1 and 100 mg on subsequent days), given as an infusion, or to placebo. The primary composite endpoint is improved clinical outcomes (reduced fever and oxygen normalisation). [3, 4]

However, these studies are now expected to enrol more than 4000 participants globally, including in the UK, and clinical outcome at 28 days is included in the primary endpoint. Both studies also include safety as secondary endpoints. [5]

The 15 UK sites include five London clinics and ten centres across the rest of the UK:

Royal Free London NHS Foundation Trust.

London North West University Healthcare NHS Trust.

University College London Hospitals NHS Foundation Trust.

King's College Hospital NHS Foundation Trust.

Imperial College Healthcare NHS Trust.

Liverpool University Hospitals NHS Foundation Trust.

Manchester Royal Infirmary.

Sheffield Teaching Hospitals NHS Foundation Trust (adult services).

Wythenshawe Hospital.

Hull University Teaching Hospitals NHS Trust.

The Pennine Acute Hospitals NHS Trust.

Royal Lancaster Infirmary.

Glasgow Queen Elizabeth University Hospital.

Edinburgh Western General Hospital.

University Hospitals Plymouth NHS Trust.

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Prospective cohorts to study COVID-19 including HIV

Simon Collins, HIV i-Base

New prospective study to understand the natural history, especially in special populations, for example with HIV are already underway.

These should be started as soon as possible and hopefully using similar or shared methodology that will enable data from multiple studies to be combined when larger power is needed to see smaller signals, for example for genetic markers.

These studies should be developed with the involvement of community advocates and should be listed on clinicaltrials.gov (where dozens already planned) or another clinical trials registry.

A few initiatives are listed below as reference for other researchers looking to start similar projects.

COVID-19 in UK general population

Queen Mary College London and collaborators are planning a prospective observational cohort of 12,000 participants in the UK general population aged 16 and over. The primary outcome is COVID-19 diagnosis with numerous clinical secondary outcomes.

This study is due to start in April 2020 and will run for five years.

Ref: clinicaltrials.gov. Longitudinal Population-based Observational Study of Coronavirus Disease in the UK Population (COVIDENCE). NCT04330599.

https://clinicaltrials.gov/ct2/show/NCT04330599

NEAT-ID develop COVID-19 dashboard for European data

The last issue of HTB included news that the NEAT ID network has developed a simple database dashboard to monitor the progress of COVID-19 in HIV positive people across Europe for researchers to contribute to.

Please see the report in the last issue for details and contact information.

http://i-base.info/htb/37439

COVID-19 and HIV: a prospective observational study in the US

The University of Missouri is running multi-centre prospective observational study in 500 participants coinfected with HIV and COVID-19. [1, 2]

They aim is to characterise the clinical presentation and clinical course of COVID-19 in people living with HIV.

The primary outcome is 30-day mortality with serious comorbidities are secondary outcomes.

The study opened in April and will run until October.

Additional info is also available at this link.

https://drive.google.com/drive/folders/1qi9l8-JpCYzpOhe9C3cvdEBwpVDcTZGU

Ref: clinicaltrials.gov. COVID-19 in Patients With HIV. NCT04333953.
https://clinicaltrials.gov/ct2/show/NCT04333953

HIV cure researchers in US launch HIV and COVID-19 coinfection database

An initiative in the US called Coronavirus Under Research Exclusion (CURE HIV-COVID) has launched an adult database to monitor and report on outcomes of COVID-19 occurring in HIV patients. [1]

They want US doctors to report all cases of COVID-19, regardless of severity and including asymptomatic patients detected through public health screening. Cases should be confirmed COVID-19 with at least seven days of follow-up. Each case is easy to report only and will take about five minutes. [2]

However, although the database only plans to use de-identified data, and does not count as human research requiring IRB approval, it is unclear how confidential patient information will be managed.

Referencess

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COVID-19 prophylaxis using TDF/FTC and low-dose hydroxychloroquine in Spanish health workers

Simon Collins, HIV i-Base

A large randomised phase 3 placebo-controlled study in Spain is using the HIV PrEP combination TDF/FTC and low-dose hydroxychloroquine (HCQ) as prophylaxis for COVID-19 in health workers. [1]

Although in-vitro data support potential antiviral activity of TDF/FTC against CoV-2, the rationale was also driven by anecdotal reports of fewer cases of severe COVID-19 in Spain in HIV positive people on ART.

The study plans to enroll 4000 participants who will be randomised to one of three active arms or an inactive placebo group. The active arms are TDF/FTC, hydroxychloroquine (200 mg daily) and a dual combination of TDF/FTC plus HCQ.

The study is due to start in April 2020 and will run until July.

C O M M E N T

The decision to investigate TDF/FTC for PrEP does not mean that there this will be effective.

Some HIV positive people are diagnosed with COVID-19 even though there are on TDF/TFC-containing ART.

Reference

clinicaltrials.gov. Randomized clinical trial for the prevention of SARS-CoV-2 infection (COVID-19) in healthcare personnel (EPICOS).

https://clinicaltrials.gov/ct2/show/study/NCT04334928

Community survey on impact of COVID-19 and chemsex

European Chemsex Forum

The community chemsex forum is carrying out an international online survey on the impact of COVID-19 in different cities and countries.

The survey is especially collecting information on drug users, sex

workers, trans people, migrants and gay men.

Please send responses by Tuesday 21 April 2020.

https://www.surveymonkey.co.uk/r/B6X7CMW

European rapid community assessment reports for COVID-19

EATG

The European AIDS Treatment Group (EATG) have launched an online rapid assessment report for HIV positive people and organisations to report impact of COVID-19 on HIV care across Europe.

The group plans to compile results every two weeks.

This questionnaire will take about 15-30 minutes to complete.

https://form.jotform.com/200852077808054

COVID-19: PATHOGENESIS

A clinical-therapeutic staging proposal for COVID-19

Simon Collins, HIV i-Base

This short paper proposes a three-stage classification for COVID-19, with increasing severity that corresponds with distinct clinical findings, responses to therapy and clinical outcomes.

Stage I (mild) – early infection

The initial stage occurs at the time of inoculation and early establishment of disease. For most people, this involves an incubation period associated with mild and often non-specific symptoms such as malaise, fever and a dry cough.

Stage II (moderate) - pulmonary involvement (IIa) without and (IIb) with hypoxia:

In the second stage of established pulmonary disease, viral multiplication and localized inflammation in the lung is the norm. During this stage, patients develop a viral pneumonia, with cough, fever and possibly hypoxia (defined as a PaO2/FiO2 of <300 mmHg).

Stage III (severe) – systemic hyperinflammation:

A minority of COVID-19 patients will transition into the third and most severe stage of illness, which manifests as an extra-pulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation appear to be elevated. COVID-19 infection results in a decrease in helper, suppressor and regulatory T cell counts.

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https://www.jhltonline.org/article/S1053-2498(20)31473-X/pdf (PDF)

COVID-19: TRANSMISSION

Four papers on CoV-2 transmission

Simon Collins, HIV i-Base

These following four papers are interesting for different aspects relating to CoV-2 transmission

A paper in the New England Journal of Medicine from Zou et al reported similar levels of viral load in an asymptomatic patients and symptomatic patients which suggests the transmission potential of people who are asymptomatic or minimally symptomatic. [1]

Two other papers are examples of CoV-2 failed to be transmitted even to people at high risk and might help reduce anxiety for contacts of people who are later diagnosed with COVID-19.

The first describes the first person-to-person transmission in the US between partners at home. However, 347 contacts of other cases including 152 community contacts and 195 health workers found no other transmissions. This included 43 people under special investigation who all tested negative for SARS-CoV-2. [2]

The second, also from the US, included a case of someone diagnosed with COVID-19 but with mild symptoms who continued to remain PCR positive for 18 days after diagnosis. However, there were no further transmissions to 16 contacts. Of these 11/16 (69%) had high-risk exposure, including 1 intimate contact, and 5 (31%) had medium-risk exposure. [3]

Lastly, a retrospective study, but before peer-review, of household transmission in Wuhan, after the city had been locked down, reported that each index case resulted in approximately three other infections. [4]

Of the 85 original cases, there were 155 close contacts overall. Of these, 104 contacts received PCR testing, with 47 (30%) positive cases and 57 (37%) negative cases. The other 51 (33%) cases were not tested because they were asymptomatic during the 2 weeks of quarantine. The infection rates were 38%, 50% and 31% for households with one, two and three contacts, respectively.

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Studies stoke concern about coronavirus contagion through air via speech

Mark Mascolini, natap.org

Accumulating evidence indicates that simply speaking can emit coronavirus-containing particles that wafts through air for tens of meters, hover there, and possibly transmit SARS-CoV-2 to a person who inhales these virus-tainted aerosols.

"Based on the trend in the increase of [SARS-CoV-2] infections, and understanding the basic science of viral infection spread," Australian and Chinese researchers write, "we strongly believe that the virus is likely to be spreading through the air". [1]

They "plead that the international and national authorities acknowledge the reality that the virus spreads through air, and recommend that adequate control measures . . . be implemented to prevent further spread of the SARS-CoV-2 virus."

Since the days after World War II, researchers recognised that merely speaking produces oral fluid droplets [2] that can carry infectious virus particles. Big droplets quickly fall to the ground, but small droplets can dehydrate and linger in the air as "droplet nuclei" [3] that "behave like an aerosol and thereby expand the spatial extent of emitted infectious particles" [4]

Researchers from the National Institutes of Health (NIH) and the University of Pennsylvania conducted a laser light-scattering experiment that visualised speech-generated droplets and determined how they spread and linger [4]. A researcher spoke through an opening in one side of a carboard box painted black inside, repeating the words "stay healthy" at different volumes, without or with a damp washcloth over his mouth. An iPhone 11 Pro video camera positioned at the other end of the box aimed at a laser light sheet through which droplets passed. Ultrahigh-resolution recordings estimated the size of these droplets, represented by flashes of light.

The brightness of flashes reflected particle size and time present in a 16.7-msec video frame. The number of flashes in a single video frame ranged from 227 at low-volume speech to 347 at the highest volume. Flashes in a single frame reached their maximum with the tongue-on-teeth "th" sound in "healthy." When the researcher spoke through a slightly damp washcloth, the flash count fell to the background level averaging 0.1 flashes.

The investigators note that droplets emitted during speaking in one study were smaller than those ejected during coughing or sneezing [4]. But some research found the same ***number*** of droplets during speaking and coughing [5]. The NIH-UPenn team did not assess the potential roles of speech-propelled droplets and aerosols in viral transmission.

Writing about this experiment, Harvard researcher Matthew Meselson explains that larger droplets and smaller aerosols take different routes if inhaled [6]. The bigger droplets settle in the upper respiratory tract, from which they can be removed in nasal secretions or ascend the "mucociliary escalator" and then be expelled or swallowed. But smaller aerosolized particles can descend deeply into the lung, nest in alveoli, and start infecting lung cells.

Merelson sites another recent study showing that aerosols containing SARS-CoV-2 remain infectious in tissue culture assays for three hours [7]. That finding suggests to Merelson that aerosols from infected people may "pose an inhalation threat even at considerable distances and in enclosed spaces, particularly if there is poor ventilation." He suggests "wearing a suitable mask" when infected people may be nearby or providing adequate ventilation in enclosed spaces currently or recently inhabited by SARS-CoV-2-infected people.

Hand washing and 6-foot social distancing remain the primary measures for avoiding SARS-CoV-2 infection. But Australian and Chinese researchers Lidia Morawska and Junji Cao argue those strategies "do not prevent infection by inhalation of small droplets exhaled by an infected person that can travel . . . meters or tens of meters in the air and carry their viral content". [1, 8]

Morawska and Cao remind readers that SARS-CoV-1 did spread in air, a route that explained transmission of this coronavirus in Hong Kong's Prince of Wales Hospital and in healthcare facilities in Toronto [1]. They site studies demonstrating airborne transmission of Norwalk-like virus in school children and influenza A/H5N1 in ferrets. At a single choir practice near Seattle, Washington, speaking and singing apparently contributed to SARS-CoV-2 spreading to 45 of 60 choir members. [9]

Findings like these, Morawska and Cao say, mean "it is highly likely that the SARS-CoV-2 virus also spreads by air" [1].

Measures that can lower chances of indoor transmission, Morawska and Cao propose [1], include:

- Increased ventilation rate.
- Natural ventilation.
- Avoiding air recirculation.
- Avoiding staying in another person's direct air flow.
- Minimising the number of people sharing the same space.

Implementing measures like these depends on countries recognizing the risk of airborne transmission, but "currently, this is not the case anywhere in the world". [1]

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https://members.bashh.org/Documents/COVID-19/COVID BASHH GC.pdf (PDF)
Advice from the BASHH Guideline writing group on treating gonorrhoea with limited face to face services.
4. Guide to services that can assist and support vulnerable patients during COVID-19 pandemic in London [update 09.04.2020]
https://members.bashh.org/Documents/COVID-19/Guide for vulnerable patients COVID 09042020.docx
A compendium of resources to help when you encounter a vulnerable patient who has any difficulty accessing food or medication, or is isolated without any support network (credit Indrajit Ghosh).
5. Updated COVID-19 guidance: provision of sexual health services to the community.
zContingency planning for out-patient Genitourinary Medicine, Contraception and Sexual Health Services (including online) and HIV services

COVID-19: UK HEALTH SERVICES

BASHH responses to impact of COVID-19 on sexual health services

Simon Collins, HIV i-Base

A rapid survey to members of BASHH about the UK response to COVID-19, reports that most sexual health services have already restructured many of their services.

The first results of the survey from 13-16 March 2020 included feedback from 44 members on local COVID-19 contingency plans and the importance of sharing of tips and advice.

BASHH have also already published several recommendations for managing sexual health services when clinic appointments are reduced.

These include policies on social distancing, treating gonorrhoea and a guide to services to support vulnerable people. [2, 3, 4, 5]

References

COVID-19: BLOOD DONATION

US COVID-19 crisis relaxes restrictions on gay men as blood donors

Simon Collins, HIV i-Base

On 2 April 2020, an indication of the impact of the COVID-19 health crisis in the US has been new FDA recommendations that reduces earlier restrictions on gay men (or straight partners of gay men) donating blood.

The 12-month period of abstinence has been reduced to not having had sex in the previous three months.

The guidelines notes that the urgent need for the crisis response doesn't allow time for public consultation, but that the recommendations are only to cover this COVID-19 crisis period.

Reference

FDA. Revised recommendations for reducing the risk of HIV transmission by blood and blood products (2 April 2020).

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/revised-recommendations-reducing-risk-human-immunodeficiency-virus-transmission-blood-and-blood

https://www.fda.gov/media/92490/download (direct download)

CoV-2 identified in blood donations in China

Simon Collins, HIV i-Base

Concern over screening for blood donation services was raised by a report from China that identified CoV-2 in samples from asymptomatic donors and on the donation service response in contact tracing and testing.

The report details the screening measures that were started in blood centres in Wuhan from 25 January 2020 and are published as a research letter in the journal Emerging Infectious Diseases. [1]

The first PCR testing performed on pooled samples in real time and retrospectively found positive viral RNA from four donors, none of whom had symptoms of COVID-19. By 4 March, 2,430 samples had been prospectively screened (1656 platelets and 774 whole blood plasma).

Donors were contacted and quarantined until two consecutive throat swabs were confirmed negative.

Retrospective screening of 4,995 donations collected from 21 December to 22 January found two additional positive samples, none of which had been used. The donors were again contacted to be quarantined at home.

All donors for January and February were contacted by telephone and 33 people reporting fever since donating had their samples taken out of circulation.

Although the study notes limitation on the information about some donors and that finding CoV-2 RNA does not confirm infectivity and risk of transmission, this potential risk should not be ignored.

The service also emphasises screening prospective donors for symptoms and on the need to actively report fever and other symptoms if these occur after donating.

Reference

1. Chang L et al. Severe Acute Respiratory Syndrome Coronavirus 2 RNA Detected in Blood Donations. Research Letter. Emerg Infect Dis. 2020, 26(7) July 2020. DOI: 10.3201/eid2607.200839
   https://wwwnc.cdc.gov/eid/article/26/7/20-0839_article

COVID-19: VACCINE RESEARCH

COVID-19 vaccine study opens for recruitment in UK

Simon Collins, HIV i-Base

Researchers at University of Oxford working on a preventative COVID-19 vaccine have started screening healthy volunteers (aged 18-55).

This is for an upcoming ChAdOx1 nCoV-19 vaccine trial in the Thames Valley Region. The vaccine based on an adenovirus vaccine vector and the SARS-CoV-2 spike protein is already in production but will not be available for several weeks.

The study will enrol 510 participants who will receive the vaccine or a placebo.

Ref: Oxford COVID-19 vaccine programme opens for clinical trial recruitment. (27 March 2020).

http://www.ox.ac.uk/news/2020-03-27-oxford-covid-19-vaccine-programme-opens-clinical-trial-recruitment#

US NIH vaccine chief optimistic on prospects for SARS-CoV-2 vaccine

Mark Mascolini, natap.org

In a video by fivethirtyeight.com editor Anna Rothschild, the director of the Vaccine Research Center at the US National Institutes of Health, John Mascola, says, "I am quite hopeful that we will . . . find a vaccine that works [against SARS-CoV-2] in the time frames that people like Dr. Fauci have been talking about [within 18 months]. . . . I think the data we have from the laboratory side of things suggests that a vaccine should work against a coronavirus."

The Rothschild video, "How Close Are We to a COVID-19 Vaccine?", can be viewed online or assessed via the following slightly abbreviated and edited transcript.

These are the key points:

- A phase 1 trial of a SARS-CoV-2 vaccine has begun, the fastest a vaccine has ever entered clinical trials in the United States.
- The tested vaccine is an mRNA vaccine, and if licensed it would be the first mRNA vaccine against a human disease.
- mRNA vaccines are easy to design and make in quantities needed for human trials, but no facilities are set up to produce large quantities of an mRNA vaccine right now.
- The new coronavirus does mutate but not as fast as HIV mutates, for example. So Dr. Mascola does not expect that SARS-CoV-2 would mutate away from a vaccine within months or years.
- Preliminary reports have circulated about some recovered

COVID-19 patients producing very low levels of antibodies. That might mean that some people could get COVID-19 more than once.

- Dr. Mascola said that should not affect prospects for coronavirus vaccine efficacy, because such a vaccine would be designed to promote a strong immune response.

Ref: How Close Are We to a COVID-19 Vaccine?

https://fivethirtyeight.com/videos/how-close-are-we-to-a-covid-19-vaccine/

Sanofi and GSK collaborate on COVID-19 vaccine

Company press release

On 14 April 2020, Sanofi and GSK announced they would be collaborating to develop an adjuvanted vaccine for COVID-19, using innovative technology from both companies.

Sanofi will contribute its S-protein COVID-19 antigen, which is based on recombinant DNA technology. This technology has produced an exact genetic match to proteins found on the surface of the virus, and the DNA sequence encoding this antigen has been combined into the DNA of the baculovirus expression platform, the basis of Sanofi's licensed recombinant influenza product in the US.

GSK will contribute its proven pandemic adjuvant technology to the collaboration. The use of an adjuvant can be of particular importance in a pandemic situation since it may reduce the amount of vaccine protein required per dose, allowing more vaccine doses to be produced and therefore contributing to protect more people.

Candidate vaccine expected to enter phase 1 trials in the second half of 2020 and, if successful, to be available in the second half of 2021

Ref: Sanofi and GSK to join forces in unprecedented vaccine collaboration to fight COVID-19 (14 April 2020).

https://www.gsk.com/en-gb/media/press-releases/sanofi-and-gsk-to-join-forces-in-unprecedented-vaccine-collaboration-to-fight-covid-19

Trial trackers for vaccine studies

Several organisations have already compiled listings of pipeline research for a CoV-2 vaccine.

AVAC: Ongoing studies for the treatment and prevention of the COVID-19 virus

https://www.avac.org/resource/ongoing-studies-2019-ncov-prevention-and-treatment

COVID-19: Projected Timeline for Treatment and Prevention, from SynBioBeta

https://synbiobeta.com/covid19

COVID-19 R&D Tracker, from the Global Health Technologies Coalition

https://www.ghtcoalition.org/resources-item/covid-19-r-d-tracker

COVID-19 Vaccine Tracker, from the Regulatory Affairs Professionals Society (RAPS)

https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

COVID-19 diagnostic resources including pipeline & test tracker, from FIND

https://www.finddx.org/covid-19/

Every Vaccine and Treatment in Development for COVID-19, So Far, from the Visual Capitalist

https://www.visualcapitalist.com/every-vaccine-treatment-covid-19-so-far/

COVID-19: HEALTHCARE AND HUMAN RIGHTS

COVID-19 and threats to human rights: another HIV parallel

Simon Collins, HIV i-Base

Nearly all the early reports on the new coronavirus outbreak - whether in mainstream or scientific journals - tagged the coronavirus outbreak in relation to its location in Wuhan and/or China. Although this was soon changed to using the appropriate medical name of coronavirus-2 or SARS-CoV-2 - one outcome was to associate the early epidemic with racist reactions.

Even in late March 2020, global responses from the G20 virtual summit were hampered by US instance of referring to the Wuhan Virus.

In some Western countries, including the UK and the US, people stopped visiting Chinese restaurants (when restaurants were still open) and there were cases of individuals being assaulted.

The opening session of CROI 2020 - the leading US scientific HIV conference - noted the importance of bringing our shared experience from HIV to coronavirus.

Now that CoV-2 has been declared a global pandemic that has threatened healthcare services in every country the importance of equitable access to care also has similarities to the HIV response, with the urgency to make sure marginalised communities are not excluded.

The following articles include related statements and links.

UNAIDS condemns misuse and abuse of emergency powers

On 9 April 2020, UNAIDS issued a statement on countries using emergency powers or public health justifications to restrict rights related to personal autonomy, gender identity, freedom of speech and sexual and reproductive health and rights.

There have also been concerning reports of increases in criminal penalties in relation to HIV transmission, exposure and non-disclosure and the use of police powers to target, through arrests and brutality, vulnerable and criminalised groups, such as sex workers, people who use drugs, people living with HIV and lesbian, gay, bisexual, transgender and intersex (LGBTI) people.

For example:

- In Hungary, a new bill has been introduced to remove the right of people to change their gender and name on official documents in order to ensure conformity with their gender identity, in clear breach of international human rights to legal recognition of gender identity.
- In Poland, a fast-tracked amendment to the criminal law that increases the penalties for HIV exposure, non-disclosure and transmission to at least six months in prison and up to eight years in prison has been passed—a clear contravention of international human rights obligations to remove HIV-specific criminal laws.
- In Kenya, civil society organisations, prompted by concerns about actions being not consistent with a human-rights based epidemic response, released an advisory opinion calling for a human rights-based approach to be adopted in the COVID-19 response and have released a letter calling for a focus on community engagement and what works for prevention and treatment rather than disproportionate and coercive approaches.

Source: UNAIDS press statement. UNAIDS condemns misuse and abuse of emergency powers to target marginalized and vulnerable populations. (9 April 2020)

https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2020/april/20200409_laws-covid19

Statement from HIV Justice

On 25 March 2020, a coalition of HIV community advocacy groups published a joint statement on criminalisation related to COVID-19.

The organisations include AIDS Action Europe**;** AIDS and Rights Alliance for Southern Africa (ARASA)**;** Canadian HIV/AIDS Legal Network**;** Global Network of People Living with HIV (GNP+)**;** HIV Justice Network**;** International Community of Women Living with HIV (ICW)**;** Positive Women's Network – USA**;** Sero Project**; and** Southern Africa Litigation Centre**.**

Source:

HIV Justice press statement. HIV justice worldwide steering committee statement on COVID-19 criminalisation. (25 March 2020).

http://www.hivjustice.net/news/hiv-justice-worldwide-steering-committee-statement-on-covid-19-criminalisation/

NAT statement on employment issues

NAT (National AIDS Trust) have updated their information on HIV and coronavirus (COVID-19).

This is especially for people who need to isolate themselves but have not yet had a conversation with their employer or others close to them about their HIV status.

Source:

NAT. Employers must support people living with HIV to follow guidance on coronavirus (COVID-19),

https://loopedin.nat.org.uk/content-section/employers-must-support-people-living-with-hiv-to-follow-guidance-on-coronavirus-covid-19

Sex workers must not be left behind in the response to COVID-19

NSWP and UNAIDS

On 8 April 2020, the Global Network of Sex Work Projects (NSWP) and UNAIDS issued a press statement about the particular hardships and concerns facing sex workers globally. It called on countries to ensure the respect, protection and fulfilment of sex workers' human rights.

The COVID-19 pandemic, as with other health crises, exposes existing inequalities and disproportionately affects people already criminalised, marginalized and living in financially precarious situations, often outside social protection mechanisms.

As a result of the COVID-19 pandemic, sex workers all over the world are experiencing hardship, a total loss of income and increased discrimination and harassment. The criminalization of various aspects of sex work in the majority of countries serves to magnify the already precarious situation of sex workers in the informal economy. As sex workers and their clients self-isolate, sex workers are left unprotected, increasingly vulnerable and unable to provide for themselves and their families.

Sex worker-led organizations from all regions are reporting a lack of access to national social protection schemes and exclusion from emergency social protection measures being put in place for other workers, particularly where sex work is criminalized. Whenever and wherever possible, sex workers are responsibly self-isolating in response to governments' calls. However, when they are excluded from COVID-19 social protection responses, sex workers are faced with putting their safety, their health and their lives at increased risk just to survive.

NSWP and UNAIDS are furthermore concerned at reports of punitive crackdowns against sex workers, resulting in the raiding of homes, compulsory COVID-19 testing, arrest and threatened deportation of migrant sex workers.

UNAIDS calls on countries to take immediate, critical action, grounded in human rights principles, to protect the health and rights of sex workers. Measures should include:

- Access to national social protection schemes for sex workers, including income support schemes.
- An immediate firewall between health services and immigration authorities in order to ensure that migrant sex workers can access health services.
- Emergency financial support for sex workers facing

destitution, particularly migrants who are unable to access residency-based financial support.

- An immediate end to evictions and access to appropriate emergency housing for homeless sex workers.
- Stopping raids on sex workers' homes and sex work premises and ensuring that all measures to protect public health are proportionate.
- An immediate halt to arrests and prosecutions for sex work-related activity, moving away from punitive measures and criminalization towards reaching and serving those most in need.
- An immediate end to the use of criminal law to enforce COVID-19-related restrictions, including forced COVID-19 testing and related prosecutions.
- Automatic extensions on visas due to expire as travel restrictions tighten. Immigration detention systems must support detainees in safe accommodation.
- The engagement of sex worker communities in responses—the meaningful involvement of sex worker-led organizations in emergency public health planning groups.

UNAIDS, as ever, stands ready to support countries in the implementation of the above recommendations.

Harm reduction for people who inject drugs and for people in prison

Safer drug use during the COVID-19 outbreak: harm reduction tips

Some of these are easier to do than others, and some may seem impossible depending on your current situation. Do the best you can. Reach out to friends, harm reduction, syringe service providers (SSP), and other health or social service providers to plan for what to do to so you can stay safe and take care of one another.

https://harmreduction.org/miscellaneous/covid-19-guidance-for-people-who-use-drugs-and-harm-reduction-programs/

Providing care for people who inject drugs and for people in prison

Practical tips for harm reduction and OST clients and harm reduction/OST service providers is provided by UNODC .

https://www.unodc.org/unodc/en/hiv-aids/new/covid-19-and-hiv.html

Importance of harm reduction services during the COVID-19 crisis

A community statement from harm reduction networks include 12 demands for care of people who use drugs.

People Who Use Drugs (PWUDs) can be considered as a risk group in the COVID-19 epidemic. They often live in the margins of society with low or no access to housing, employment, financial resources, social and health care, and face systematic discrimination and criminalisation in majority of countries.

Many have multiple health problems that can increase the risk of a (fatal) COVID-19 infection (including long-term diseases such as COPD, HIV, TB, cancer, and other conditions which reduce the immune system).

Harm reduction services are often the one and only contact point for PWUDs to access the health service. They provide health and social services as well as other basic support, and function as an essential link to other live-saving services.

Ref: The position of Correlation-European Harm Reduction Network and the Eurasian Harm Reduction Association on the continuity of harm reduction services during the COVID-19 crisis (19 March 2020)

https://www.correlation-net.org/harm-reduction-must-go-on

https://harmreductioneurasia.org/the-position-during-the-covid-19

COVID-19: ON THE WEB

medRxiv and bioRxiv websites

This two websites, supported by Yale University and the British Medical Journal (BMJ) are holding platforms for draft manuscripts that have been submitted for publication but that have not yet been peer-reviewed.

All papers come with a cautious that results have not undergone this rigourous check,

As an indication of the volume of papers linked to COVID-19 SARS-CoV-2 there are already 1,687 articles online in PDF format (1,316 for medRxiv and 371 for bioRxiv).

https://connect.medrxiv.org/relate/content/181

Resources from WHO on COVID-19

WHO have published a wide range of important resources

Q&A on coronaviruses (COVID-19)

https://www.who.int/news-room/q-a-detail/q-a-coronaviruses

Q&A on COVID-19, HIV and antiretrovirals

https://www.who.int/news-room/q-a-detail/q-a-on-covid-19-hiv-and-antiretrovirals

Coronavirus myth busters

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters

Includes:

Being in the sun or at high temperature does not protect against COVID-19.

Being able to hold your breath does not mean you are free from

coronavirus.

Alcohol does not protect against COVID-19. Neither does garlic.

Cold weather and snow doesn't kill coronavirus and hot climates are still at high risk.

Coronavirus is not transmitted by mosquito bites.

Will pneumonia and flu vaccines help?

Q&A on COVID-19, pregnancy, childbirth and breastfeeding

https://www.who.int/news-room/q-a-detail/q-a-on-covid-19-pregnancy-childbirth-and-breastfeeding

Q&A: Similarities and differences – COVID-19 and influenza

https://www.who.int/news-room/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza

WHO guidance on severe acute respiratory infection when COVID-19 is suspected

This document is intended for doctors taking care of hospitalised adult and paediatric patients with severe acute respiratory infection (SARI) when a nCoV infection is suspected.

It is not meant to replace clinical judgment or specialist consultation but rather to strengthen clinical management of these patients and provide to up-to-date guidance.

Best practices for SARI including IPC and optimised supportive care for severely ill patients are essential.

Ref: WHO. WHO guidance on clinical management of severe acute respiratory infection when COVID-19 is suspected. (13 March 2020).

https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

WHO daily situation reports

WHO now publishes daily updates on incidence and suspected routes of transmission in all countries and regions.

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

Comparing HIV/AIDS and COVID-19 pandemics

Articles that draw parallels between the COVID-19 health crisis and the response to HIV/AIDS.

How to survive yet another plague: I lived through the AIDS epidemic - here's how to live through coronavirus.

Mark Shoofs. (20 March 2020).

https://www.buzzfeednews.com/article/markschoofs/how-to-survive-yet-another-plague

Lessons the AIDS epidemic has for coronavirus

Brandon Tensley, CNN

https://www.cnn.com/2020/04/05/politics/coronavirus-aids-hiv-sarah-schulman/index.html

For HIV survivors, a feeling of weary déjà vu

Jacob Bernstein. (8 April 2020)

https://www.nytimes.com/2020/04/08/style/coronavirus-hiv.html

Lessons of Aids for Covid-19: Don't sacrifice science to expediency

Robin Gorna. (9 April 2020).

https://www.dailymaverick.co.za/article/2020-04-09-lessons-of-aids-for-covid-19-dont-sacrifice-science-to-expediency

COVID-19: The HIV research advocacy movement offers lessons

Stacey Hannah. (6 April 2020).

https://www.avac.org/blog/covid-19-hiv-research-advocacy-movement-offers-lessons

New COVID-19 webinars

Free online course on coronavirus

Free online course on coronavirus that includes short lectures and presentations of various kinds (each lasts no more than six minutes). You take the course at your own pace, although they suggest four hours a week for three weeks.

The course is developed by Future Learn and the London School of Hygeine and Tropical Medicine.

Give the rapid developments in this field, the course will be updated in a few weeks.

https://www.futurelearn.com/courses/covid19-novel-coronavirus

AVAC COVID and HIV Webinars

The Impact of COVID-19 on Clinical Trials in Sub-Saharan Africa (9 April 2020)

https://www.avac.org/event/webinar-impact-covid-19-clinical-trials-sub-saharan-africa

Talks with community engagement practitioners from trial site communities across Africa on how HIV clinical trials are being affected by the global response to COVID 19.

Pandemic Vaccine Development and Lessons for COVID-19 (2 April 2020)

https://www.avac.org/event/webinar-pandemic-vaccine-

development-and-lessons-covid-19

Mark Feinberg of IAVI and Helen Rees of Wits RHI talk about lessons for COVID-19 from Ebola and HIV vaccine development.

Global Advocates' Teleconference: COVID-19 & HIV update (23 March 2020)

https://www.youtube.com/watch?v=DgUkiivCrRQ&feature=youtu.be

Carl Dieffenbach, NIH's Director of the Division of AIDS (DAIDS) talks about how the response to HIV and COVID-19 impact each other. Also covers an advocacy agenda for COVID-19 in sub-Saharan Africa.

COVID-19: RESCHEDULED MEETINGS

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

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

Community Reclaiming the Global Response (HIV 2020)

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

https://www.hiv2020.org/registration

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

www.aids2020.org

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

12 – 13 September 2020, New York

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

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

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

www.virology-education.com

11th International Workshop on HIV & Ageing (2020)

1 – 2 October 2020, NYC

https://www.virology-education.com

HIV Glasgow Congress 2020

4 – 7 October 2020, Glasgow (expects to continue)

www.hivglasgow.org

HIV Research for Prevention (HIV R4P 2020)

11 – 15 October 2020, Cape Town

https://www.hivr4p.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

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

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

Fax: 0208 616 1250

Other i-Base resources can still be ordered online as usual.

http://i-base.info/forms/order.php

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

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- **HIV Treatment Bulletin (HTB) every two weeks** ☐ **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: Guide to HIV testing and risks of sexual transmission *(Jan 2020): 32-page A5 booklet* **quantity** _____

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: guide to side effects and long-term health *(Sept 2016): 96-page A5* **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