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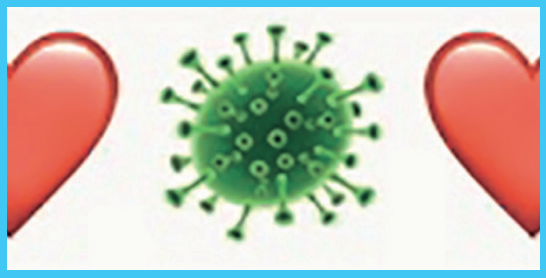
HTB no. 11 – HIV and COVID-19 no. 8

hiv treatment bulletin (e)



HIV Glasgow; HIV and COVID-19 (14 October 2020)

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Published by HIV i-Base

HTB no.10 – HIV and COVID-19 supplement ISSUE 7

Contents continued.

i-Base 2020 appeal

i-base appeal 2020

Please support i-Base with £5 or £10 a month...

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

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

If 1000 people support us with £5 a month we will be on course to meet our funding shortfall. All help is appreciated.

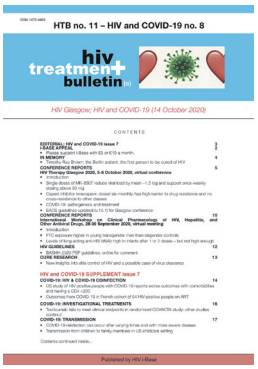
http://i-base.info/i-base-appeal-we-need-your-help

Plus a BIG thank you all all supporters over the years including in the recent Solidarity2020 campaign.

More than 70 people bought one or more posters curated by Wolfgang Tillmans and the Between Bridges Foundation, to who we are also really grateful :)

EDITORIAL

This double issue of HTB (covering September and October 2020) is again combined with a supplement on COVID-19.


HTB no. 11 – HIV and COVID-19 no. 8

hiv treatment+ bulletin

HIV Glasgow; HIV and COVID-19 (14 October 2020)

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Published by HIV i-Base

All readers are unfortunately already likely to know about our first news.

This issue leads with a tribute to Timothy Ray Brown - an inspiring activist and the first person to be cured of HIV. Timothy will always have a unique place in the history of HIV and his story brought hope to millions of people globally. But he took this further in working for a cure for the rest of us. He will be missed and our thoughts are with his partner, family and friends.

We then include reports from two conferences, both held as virtual meetings: the biennial HIV Glasgow and the annual PK Workshop.

As the UK is already being pulled into a second lockdown, virtual meetings are likely to be with us for some time. And Glasgow did particularly well in developing a web format that retained the tension of a real-time meeting. Prerecorded videos enabled webcasts to be posted at the end of each day, but speakers and panelists were also available to answer questions in real time after each session in the programme. Posters were similarly already loaded as PDF files and were easy to download.

The programme was current and topical, with many lectures and sessions covering COVID-19, women's health, side effects (notably weight gain) as well as presentations sessions on PrEP and pipeline compounds for treatment. First reports from this meeting are included in this issue and more will continue in the next.

Other HIV news included that BASHH PEP guidelines are now online for comment and an article on elite controllers and cure research by Richard Jefferys.

STOP PRESS news also includes that the EMA have given a positive opinion on approving long-active cabotegravir/rilpivirine injections for treatment. Also that this is for both monthly or two-monthly dosing.

And as the UK is on the brink of a second lockdown, the supplement on HIV and COVID-19 - now in its eight edition - also has extensive news.

This covers HIV coinfection, potential treatment, transmission news (including cases of reinfection) and more.

As always, we extend our appreciation to all health workers during this difficult

time - and hope all readers stay as safe as possible.

IN MEMORY:

Timothy Ray Brown: the Berlin patient, the first person to be cured of HIV

Timothy Ray Brown, filmed at IAS 2015 for 'Is a cure for HIV possible'. [6]

It is with great sadness that we report that on 29 September 2020, Timothy Ray Brown, the first person to be cured of HIV, died age 54, following a five-month battle with leukemia.

The news was announced by his partner Tim Hoeffgen on Timothy's Facebook page. [1]

Over the next few days, before this reached mainstream media, hundreds of people paid tributes online to the inspiration he had given them and many thousands more, connected in community networks internationally, shared this loss, remembering the unique impact he had on our lives.

For most, this news was unexpected, even though during the previous week he had released a few interviews reporting how he was again seriously ill, though it was nothing to do with HIV. [2, 3]

Timothy was first known as the Berlin Patient. In 2007, while living in Germany, he had received an allogeneic stem cell transplant as a last treatment for refractory leukemia and he repeated this traumatic therapy in 2008 after the cancer returned. The second time, his doctors made the remarkable decision to use a donor with the CCR5 genetic deletion which blocks the most common form of HIV from establishing infection. This was the first time this had been tried in HIV and also involved stopping HIV treatment. Not only did this send the leukemia into remission, but HIV viral load also failed to rebound.

Establishing this as a definitive HIV cure however involved months of working closely with his doctors and providing countless tissue samples including lymph and gut biopsies. He also continued to do this to help answer research questions ever since.

This first case of an HIV cure was an astonishing achievement. Even though the procedure was so traumatic that Timothy was vocal about not wishing anyone else should have to go through it, his case inspired hope globally.

But Timothy then took it further, talking publicly about his experience and devoting most of the next decade to HIV activism. He was not content to just be cured for himself, he was determined to use his profile to raise the importance of finding an easier HIV cure for everyone else.

Everyone who met Timothy in this new role - likely many thousands - were immediately struck by his dedication and modesty. Or they could read about his story in any of the hundreds of interviews he gave to both mainstream and community press. [4, 5]

He was always happy to talk about his experience, no matter how many times he must have had to answer similar questions and he did this carefully because he could see how his story reached HIV positive people in all countries. Whether the meetings he spoke at were international conferences or smaller community meetings, he had time to talk to everyone, always smiling and always with humour and style.

He was an activist that led by a personal example that most of us never come close to and he leaves a wonderful legacy that challenges us to continue to find a cure. As he said many times "I don't want to be the man who says I am cured, I want to be the man who says we are cured." [6]

He will be remembered with kindness and our thoughts are with his partner, family and many many friends.

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CONFERENCE REPORTS

HIV Therapy Glasgow 2020

5-8 October 2020, virtual conference

Introduction

Simon Collins, HIV i-Base

This year, the biennial Glasgow HIV Congress was held from 5-8 October as a virtual meeting.

The conference website is easy to navigate, with most oral presentations already prerecorded but with presenters also being online for Q&A discussions afterwards.

The programme this year is particularly strong, with a focus on COVID-19 and how it affects people living with HIV and our care, and on important concerns about women's health and weight gain experienced by some people as a side effect of ART. As always, there are also exciting studies on next generation treatment.

For registered delegates, webcasts are being posted on the same day of the oral presentation and the meeting will be open access to everyone when the meeting closes.

https://virtual.hivglasgow.org

The following reports from the meeting are in this issue of HTB.

- Single doses of MK-8507 reduce viral load by mean –1.5 log and support once-weekly dosing above 80 mg
- Capsid inhibitor lenacapavir, dosed six-monthly, has high barrier to drug resistance and no cross-resistance to other classes
- COVID-19: pathogenesis and treatment
- EACS guidelines updated (v.10.1) for Glasgow conference

Single doses of MK-8507 reduce viral load by mean –1.5 log and support once-weekly dosing above 80 mg

Simon Collins, HIV i-Base

First PK and virological results were presented for MK-8507, a new NNRTI that shows potential for once-weekly dosing. [1]

This was a randomised proof of concept dose-ranging study of single fasted doses (40 mg, 80 mg and 600 mg) in 18 treatment-naive participants without NNRTI resistance. All were white men with a median age of 34 years (range: 22 to 56). Entry criteria included CD4 >200 cells/mm3 and viral load >10,000 copies/mL. Median viral load was 4.6 (range: 4.0 to 5.1) log copies/mL.

The primary virological endpoints was at 168 hours (one week) when ART was started. However, several participants delayed ART: three at 600 mg started at day 14 and one at 40 mg did not start ART. PK and safety follow-up extended to 14 and 21 days respectively.

Mean (95% CI) viral load reductions at day seven were –1.53 (1.84 to –1.23), –1.50 (–1.80 to –1.19) and –1.22 (–1.52 to –0.91) in the 600 mg, 80 mg and 40 mg arms respectively.

The PK target at one week of 300 nM (based on 6 x in vitro IC50 from other NNRTI monotherapy studies) was achieved by all participants in the 600 mg arm and most in the 80 mg arm. This led to a conclusion that doses above 80 mg per week would meet this target. The mean half-life was approximately 56 to 69 hours, supporting once-weekly dosing.

Safety results were good, with only headache in 3/18 judged to be related to MK-8507. There were no significant trends

in other events or laboratory results.

No viral rebound occurred in any participants who started ART at day seven. However, a single F227C NNRTI mutation was detected in one of the three participants in the 600 mg arm who delayed ART until day 14. This person also experienced viral rebound at day 14, with F227C emergent at day 10. No viral rebound was detected by day 14 in the participant from the 40 mg dose who did not restart ART. However, no longer-term follow-up information was presented for this person.

Although the presentation dismissed this case with F227C as not being clinical relevant in the context of combination ART, most drug resistance emerges in context of suboptimal adherence. This also minimises the likely resistance for this person and doesn't comment on the implications for cross resistance to other NNRTIs.

The PK target for the 168 hour end of week trough was set at 300 nM (6 x IC50) and were met by doses above 80 mg. Further details of PK results were presented in a poster. [2]

These results support further development as a once-week treatment in dual therapy with weekly oral islatravir. This compound is in development with Merck/MSD.

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Unless stated otherwise, references are to the Programme and Abstracts of HIV Glasgow 2020, published as a supplement to JIAS; 23(7) October 2020. https://onlinelibrary.wiley.com/loi/17582652

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Capsid inhibitor lenacapavir, dosed six-monthly, has high barrier to drug resistance and no cross-resistance to other classes

Simon Collins, HIV i-Base

New data at the Glasgow conference on the capsid inhibitor lenacapavir included results on drug resistance. Although two participants in a proof-of-concept phase 1b dose finding study on each of the lowest doses developed a single resistance mutation, this will be overcome at the higher doses used for phase 2/3 development. [1]

Lenacapavir (previously GS-6207) is a first-in-class capsid inhibitor active at several stages of the viral lifecycle. It has high potency (30 - 100 pM) and as a new class, is sensitive to HIV that is drug resistant to other classes including maturation inhibitors. A single subcutaneous injection is expected to provide treatment coverage for six months.

This study randomised 39 treatment-naïve participants to a single dose of 20, 50, 150, 450 and 750 mg (n=6, 6, 6, 6 and 5) or placebo (n=10) as monotherapy. ART was started at day 10 (bictegravir/FTC/TAF) and follow-up continues to day 225.

Mean viral load responses at day 10, reported earlier this year at CROI, were dose-related and ranged from –1.3 log to –2.3 log in the 20 mg and 750 mg doses, respectively. [2]

In vitro passaging studies have previously identified seven mutations associated with reduced sensitivity to lenacapavir: at positions L56I, M66I, Q67H, K70N, N74D, N74S and T107N in HIV-1 capsid.

However, previous resistance studies found no pre-existing mutations in samples from 1500 treatment naïve samples and 51 experienced samples retained wild-type sensitivity.

In this study, all participants had wild-type susceptibility to lenacapavir at baseline with no detection of capsid mutations.

However, at day 10, two participants showed Q67H at lowest doses - one each in the 20 mg and 50 mg groups, at day 10 and day 7 respectively. From the group listed above, this mutation has the lowest impact on reduced sensitivity (approximately 6-fold).

No other substitutions were seen in capsid using next generation sequencing Seq-IT test.

The 20 mg case showed Q67Q/H mix at day 10, and VL reduction continued after adding BIC/F/TAF.

The 50 mg case showed Q67H at day 7, detected only by the more sensitive next generation sequencing, but with evidence of a viral rebound in the few days before ART at day 10.

Both participants achieved undetectable viral load on ART.

However, the presentation showed that drug resistance would be unlikely at higher doses. Maximal viral load reductions in dose response curves occurred between the 50 and 150 mg doses and this corresponded to mean lenacapavir concentrations at >4.4 ng/mL (IQ>1.1).

This is much lower than the predicted concentrations with the 300 mg and 600 mg doses selected for the phase 2/3 clinical programme which should range from 24 ng/mL (minimum) to 67 ng/mL (maximum), indicating an IQ >8 at six months and a very low probability of drug resistance.

Resistance has not yet been studies in HIV-2.

C O M M E N T

These data continue to be encouraging and are optimistic for future long-acting combinations.

In the Q&A afterwards, there was no reference to which other long-acting drugs would be used with lenacapavir. However, Gilead recently bought the rights to two long-acting bNAbs from Rockefeller University, both of which might also allow 6-monthly dosing.

Technically, and perhaps as lower cost molecules, either a monthly islatravir oral pill or an annual islatravir implant would both be very acceptable options for people taking treatment.

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COVID-19: pathogenesis and treatment

Simon Collins, HIV i-Base

The keynote talk for Glasgow 2020 was an excellent review on current understanding of COVID-19 and strategies for treatment, including the implications for HIV care, given by Professor Karine Lacombe from Saint-Antoine Hospital, Paris. [1]

Part of the response to COVID-19 developed from experience with two earlier coronaviruses responsible for SARS-1 and MERS. However, although both were more pathogenic (with 7% and 35% mortality respectively), unlike SARS-CoV-2, neither were transmitted during asymptomatic infection.

This resulted in the extensive spread of the current coronavirus (> 35 million cases and >1 million deaths), which has so far been reported most severely in terms of both cases and mortality in North and South America and western Europe. While most countries experienced the first peak in March and April the widely predicted second wave is now established in most European countries, although so far with lower mortality.

The original early concern over a viral infection also rapidly expanded as it was quickly recognised that SARS-CoV-2 is a systemic disease with a complex pathology. Understanding this pathway is critical to the development of effective treatment.

Initial infection targets immune cells expressing ACE-2 receptors in the nose and throat that enable viral replication and then epithelial cells and marcrophages in lung tissue. In people where the infection progresses, this then produces an inflammatory response with overproduction of cytokines including IL-6, IP-10, MIP-1a, MIP-1b and MCP1 and resulting massive cell death restricting oxygenation.

The transmission timeline includes being infectious from an average of three days before symptoms to seven days after, and is complicated by a large percentage of people being asymptomatic but still infectious. Viral RNA is increasingly difficult to identify and culture from day ten, especially in mild and moderate disease, and, except in rare cases, is only detectable for a few days longer in severe disease.

Early clinical signs are now well described, most commonly fever, dry cough, shortness of breath, loss of taste and/or smell, fatigue, nausea and diarrhoea etc. X-ray shows multifocal ground glass opacities with peripheral and sub-pleural localisation but are not present in 18% of minor and 3% of severe infections. Extra pulmonary disease can be extensive and affect nearly all other organs including neurologic, renal, hepatic, GI, cardiac, endocrine and dermatological, including thrombosis and pulmonary embolism.

Neurological complications have also become an unexpected challenge - where people underestimate the severity of symptoms, continuing daily life even with severely depleted blood-oxygen levels, or focusing on daily responsibilities while about to be intubated. Mood instability and anxiety, similar to PTSD, are also commonly reported, sometimes for many months, after discharge from hospital.

Although surrogate markers for severe disease are not widely established, with similar presenting symptoms, four recent papers have suggested immune markers that might be predictive. [2, 3, 4, 5]

The three stages in the natural history - viral, pulmonary and hyperinflammation phases - have different targets for potential interventions. That these phases overlap and vary between individual patients, clearly suggest a role for combination therapy, for example, to include both antiviral and anti-inflammatory compounds. A fourth stage is also increasingly recognised of delayed recovery lasting many months, called 'long COVID'.

Early targets for treatment include ACE-2 and angiotensin-II blockers, fusion inhibitors (baricitinib), endosomal acidification inhibitors (hydroxychloroquine), antiviral polymerase inhibitors (remdesivir, favipiravir, ribavirin, TDF/FTC), protease inhibitors (lopinavir/r), more than 20 immunomodulators (corticosteroids, tocilizumab etc) and passive immunisation. There is already considerable well-publicised evidence to support the efficacy of some of these compounds (remdesivir and dexamethasone), or the definitive lack of benefit (hydroxychloroquine, lopinavir/r).

Of the two approved treatments, remdesivir is associated with faster recovery but only dexamethasone has reduced mortality, and then only in people with advanced disease who are already requiring supportive oxygen.

Although promising, with ongoing studies, there have been conflicting results from using the IL-6 inhibitor tocilizumab. Of three randomised trials, the CONVICTA study reported no benefit, CORIMUNO-TOCI reported reduced mortality or need for oxygen at day 14 and EMPACTA has reported both reduced mortality and need for intubation. However, several meta-analyses have supported efficacy, though this might only be in a subset of patients, perhaps before the increase in proinflammatory proteins. [6]

Research importantly covers many other aspects of care including different strategies for oxygen support and intubation and prevention of thrombosis.

A French study from 2015 reported a positive effect on 90-day mortality of nasal high flow oxygen on ARDS compared to other methods of oxygen delivery and a recent paper from New York on higher responsiveness to prone position in COVID-19 in order to delay mechanical ventilation in ICU. [7, 8]

The limited evidence on anticoagulation includes no benefit on 28-day mortality in a preventative randomised study in China (although a benefit was seen in those with coagulopathy). [9] Reduced mortality was reported in a large retrospective US cohort analysis (29% vs 62%) in people who were intubated (but not in others). [10]

Promising, or preliminary results on other compounds include MK-4428 (potentially active against remdesivir resistance), baricitinib, immunomodulators (anti-IL-1, anti-C5a), passive transfer of immunity (convalescent plasma), monoclonal and polyclonal antibodies - and, of course, vaccines.

Of these, another French study recently reported benefits of convalescent plasma in 17 participants with B-cell depletion with protracted COVID-19. [11]

Finally, the talk referred to the difficulty during COVID-19 of reduced services for other infectious diseases including suspension of many STI services and restricting hospital care to emergency services. Among many others, this has led to delayed diagnosis of acute HCV and hepatic cancer, or support for people living with TB or HIV who need support for adherence.

The Q&A after the talk included little likelihood that vitamin D would have any significant effect and the comment included above that tocilizumab might be more likely to work if used before the pro-inflammatory cytokine response. Also, although reinfection cases have been reported, these have often been in those who might have generated low antibody responses to their initial mild infection.

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EACS guidelines updated (v.10.1) for Glasgow conference

Simon Collins, HIV i-Base

The latest update to the EACS HIV guidelines (version 10.1) is now available (English version), with minor updates to all sections.

They are available as a free app, an interactive web version and as an online PDF.

A useful five minute YouTube introduction is also online:

https://www.youtube.com/watch?v=MwLBoy12cZ0

The main changes in each section are included below.

ART section

- First-line combinations are now categorised as 'recommended', 'alternative' and 'other'.
- Recommended regimens include unboosted INSTI (DTG, BIC or RAL) plus 2 NRTIs or the dual combination 3TC/DTG (which no longer has a CD4 restriction].
- Dual DRV/b + DTG is now included as a switch option.
- Recommendations for viral failure is now: "New regimen will usually use at least one fully active PI/b (e.g. DRV/b) plus a drug remaining fully active despite resistance to other drugs from the class (e.g. INSTI, NNRTI) and/or from a class not used previously (e.g. INSTI, NNRTI, PI, CCR5 antagonist (if tropism test shows R5 virus only) assessed by genotypic testing".
- TAF is now allowed for women who become pregnant while on ART.
- TAF/FTC+DTG is now included as a recommended regimen for ART-naïve pregnant women.
- Alternative PEP drugs now include DRV/b and drop AZT/3TC.

Drug-drug interaction (DDI) section

- All tables include changes in the HIV drug interaction website (University of Liverpool).
- EFV + atorvastatin: changed to amber due to the decrease in atorvastatin exposure requiring the monitoring of lipid values.
- RPV + chloroquine, methadone or pimozide were changed to amber due to the known risk for QT interval prolongation associated with the comedication.
- A note on the risk of DDI with ibalizumab has been added to the footnote of each DDI table.
- Ibalizumab has been added in the table for people with swallowing difficulties and the tables for dose adjustment in case of renal and hepatic impairment.

Co-morbidity section and complications

- Increased risk of neural tube defects associated with DTG.
- An HIV-specific reference has been included for the PCSK9 inhibitor, evolocumab.

- An indication to intervene if BMI ≥ 30 kg/m2 or ≥ 25 kg/m2 and weight-related complications (diabetes mellitus, hypertension) with expanded detail regarding exercise, dietary, behavioural and therapeutic management.
- In sero-discordant couples, fully effective ART should be a primary goal. If not achieved, PrEP can be used if the couple are looking to conceive.
- In PLWH at high risk of STI, three-monthly STI screening is recommended.
- Treatment for gonorrhoea has been updated to single dose ceftriaxone 1g IM.

Viral Hepatitis Co-infections section

- Updated tables on HCV treatment and DDIs.
- Resistance testing guidance before re-treatment with DAAs has been modified.
- No changes in sections on HBV, HDV and HEV.

Opportunistic Infections section

- Minor stylistic changes were made to all OI tables.
- Cidofovir was deleted as secondary prophylaxis/maintenance therapy for CMV.
- Rifabutin was added to the list of drugs for primary prophylaxis of Non-Tuberculosis Mycobacteria.
- Moxifloxacin was added to the list of drugs for treatment of MAC.

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CONFERENCE REPORTS

International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs

28-30 September 2020, virtual meeting

This annual workshop was held as a virtual meeting this year.

The following report is included in this issue of HTB, thanks to NATAP.org.

- FTC Exposure Higher in Young Transgender Men Than Cisgender Controls
- Levels of long-acting anti-HIV bNAb high in infants after 1 or 2 doses – but not high enough

Further NATAP reports fomr the meeting are at this link:

https://www.natap.org/2020/Pharm/Pharm.htm

FTC exposure higher in young transgender men than cisgender controls

Mark Mascolini for NATAP and Virology Education

By two measures, transgender men (TM) had somewhat higher plasma emtricitabine (FTC) exposure than historical cisgender men taking FTC as part of TDF/FTC preexposure prophylaxis (PrEP). [1]

And TM had higher FTC exposure than transgender women (TW). TW had 25% higher tenofovir (TFV) troughs (Ctau) than historical cisgender women.

Transgender people run a higher risk of HIV infection in the United States than the general population, noted University of Colorado, Aurora researchers who conducted this study with colleagues from other centres. But relatively little is known about the pharmacokinetics of PrEP constituents TFV and FTC in TM or TW because those groups have not been well represented in PrEP trials.

And the potential impact of cross-sex hormone therapy (csHT) on PrEP remains inadequately studied. As a result, effectiveness of PrEP remains poorly understood in these groups at high risk for HIV infection.

To address these issues, researchers from the University of Colorado, Aurora, and colleagues conducted a TFV/FTC pharmacokinetic study in TM and TW and compared results to those in historical cisgender controls. Participating HIV-negative TM and TW were receiving a stable csHT dose and had not taken tenofovir disoproxil fumarate (TDF)/FTC PrEP within 3 months. All TM and TW participants were between the ages of 15 and 24.

Enrollees took daily observed TDF/FTC for 4 weeks. Intensive pharmacokinetic sampling after an overnight fast was conducted 2-3 weeks after first dosing. Researchers compared results to those in 9 cisgender men and 10 cisgender women without HIV and with a median age of 30.5 years who followed the same protocol in the Cell-PrEP study. [2]

The transgender group included 24 TW and 23 TM with a median age of 21 years (range 16 to 24) and median creatinine clearance of 146 mL/min (range 69 to 197) for TW and 115 mL/min (range 75 to 243) for TM. Three quarters of participants (76%) were white, 22% Hispanic, and 13% black. Among 24 TW, 12 used oral or sublingual estrogen and 12 used intramuscular estrogen. Eighteen of 23 TM had intramuscular testosterone injections and 5 had subcutaneous injections.

TFV area under the concentration-time curve (AUCtau) was similar for TW and TM (geometric mean 2628 and 2770 ng*h/mL), as was TFV trough concentration (Ctau) (57.3 and 55.3 ng/mL). Compared with TM, TW had 20% lower FTC exposure (AUCtau 10,706 vs 13,445 vs ng*h/mL, p=0.0005) and 24% lower FTC maximum concentration (Cmax 1665 vs 2191 ng/mL $P = 0.004$) but similar FTC troughs.

TW had 25% higher TFV Ctau than Cell-PrEP cisgender women (57.3 vs 45.7 ng/mL, $P = 0.049$) but a similar TFV Cmax and AUCtau. FTC concentrations did not differ significantly between TW and cisgender control women. TM did not differ much from Cell-PrEP cisgender men in TFV or FTC Ctau, but TM had 20% higher TFV AUCtau than control men (2770 vs 2301 ng*h/mL, p=0.039), 36% higher FTC Cmax (2191 vs 1608 ng/mL, p=0.001), and 33% higher FTC AUCtau (13,445 vs 10,125 ng*h/mL, p<0.0001).

The University of Colorado team concluded that daily PrEP with TDF/FTC should continue to be recommended for transgender adolescents and young adults who run a risk of HIV infection.

C O M M E N T

This study is important for providing PK data for transgender people who as a group are likely to use and depend on PrEP as an option to protect against HIV.

The study only reported plasma levels of these NRTIs, as surrogate markers for TFV-DP and FTC-TP intracellular levels in genital tissue.

Daily dosing is still recommended as the higher plasma levels in transmen is not likely to translate to protective levels needed in genital tissue.

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Levels of long-acting anti-HIV bNAb high in infants after 1 or 2 doses – but not high enough

Mark Mascolini for NATAP and Virology Education

Population pharmacokinetic modelling of the HIV-specific broadly neutralising antibody (bNAb) VRC01LS in infants indicated that concentrations would stay above 20 mcg/mL for 6 months after doses at 0 and 12 weeks in almost all infants. [1]

However, the target is 50 mcg/mL. Early infant growth had a large impact on VRC01LS concentration, according to results reported by University of California, San Diego researchers and collaborators at other centers.

The monoclonal antibody VRC01LS, the first long-acting anti-HIV bNAb, has activity against up to 90% of HIV-1 strains. Because of its long half-life, VRC01LS has emerged as an HIV PrEP candidate and as possible treatment for infants, in whom treatment adherence remains a challenge.

A phase 1 dose-escalation study of VRC01LS in healthy adults measured a half-life more than 4-fold higher than that of wild-type bNAb VRC01, a result suggesting the possibility of maintaining therapeutic levels with less frequent and lower doses. [2]

VRC01LS is a modified version of the bNAb VRC01; both target the CD4 binding site HIV uses to enter cells.

The new study set out to describe the population pharmacokinetics of subcutaneous VRC01LS in early infancy among HIV-exposed African and US infants participating in the phase 1 IMPAACT P1112 trial. [3]

The 21 healthy infants entered the trial at a median age of 2 days (range 0 to 4) and a median weight of 2.8 kg (range 2.5 to 3.8). They received a subcutaneous dose of 80 mg if weighing less than 4.5 kg and 100 mg if weighing 4.5 kg or more. While 10 nonbreastfed infants got a single dose on day 1, 11 breastfed infants received a second dose at week 12.

Researchers collected pharmacokinetic samples 24 hours and 2, 4, 8, 12, 14, 16, and 24 weeks after VRC01LS dosing in breastfed infants, and at those times plus 36 and 48 weeks in nonbreastfed infants. Before assessing other potential covariates, the investigators incorporated allometric scaling into the population pharmacokinetic model with clearance (CL/F) scaled as (WT/70)^0.85 and volume of distribution (VD) as (WT/70)^1.0. Potential covariates included infant age, infant sex, breastfeeding, and location (US or Africa). The research team used 1000 Monte Carlo simulations to predict concentrations of VRC01LS 12 and 24 weeks after dosing.

A one-compartment model proved sufficient to describe the data. Final model parameters were CL/F 71.04 x (WT/70)^0.85 mL/day and V/F 8.46 x (WT/70) x 0.84^Day past 84 days. Weight rose from 3.3 kg at birth to 5.7 kg at week 12 and had a significant impact on pharmacokinetic values. Over that time VD rose 37% from 423 mL to 579 mL and CL/F climbed 59% from 5.30 to 8.43 mL/day.

The target serum concentration was 50 mcg/mL or more for 6 months or more. The 1000 simulations predicted that a single 80-mg dose would yield a median VRC01LS concentration of 43.7 mcg/mL at week 12, when 27.1% of trough concentrations would lie at or above 50 mcg/mL and 99.8% at or above 20 mcg/mL. With a single 100-mg dose, 66.9% of trough concentrations would lie at or above 50 mcg/mL at week 12 and 99.9% at or above 20 mcg/mL. With a first dose of 80 mg and a second dose of 100 mg at week 12, 60% of trough concentrations would lie at or above 50 mcg/mL at week 24 and >99% at or above 20 mcg/mL.

The researchers concluded that a higher dose or more frequent dosing will be needed to keep VRC01LS concentrations above 50 mcg/mL in most infants. The dilution effect from early infant growth, they stressed, contributes to the drop in VRC01LA concentrations.

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HIV GUIDELINES

BASHH 2020 PEP guidelines: online for comment

Simon Collins, HIV i-Base

The new draft BASHH 2020 PEP guidelines are now available for consultation.

This is an update to the 2015 BASHH guideline on PEP following sexual exposures and the 2008 Expert Advisory Group on AIDS guidelines on HIV PEP.

These comprehensive guidelines (with almost 200 references) include evidence on the efficacy of PEP and most appropriate treatment (though data for both are limited). It also covers different levels of risk with occupational and sexual exposure, special circumstances including pregnancy, injecting drug use, HBV infection and in relation to PrEP.

Significant changes include basing criteria for providing PEP on prevalence of detectable viral load within the source population rather than prevalence of HIV. It also includes a new section on situations when PEP is not recommended because of the negligible (or zero) risk of transmission.

Importantly, PEP is now generally not recommended after receptive or insertive sex or shared injecting use just because the partner is from a high risk (high prevalence?) group.

The deadline for comments by 27 November 2020.

The draft guidelines together with details for how to provide feedback are at this link:

https://www.bashhguidelines.org/documents-for-consultation/guidelines-out-for-consultation

HIV CURE RESEARCH

New insights into elite control of HIV and a possible case of virus clearance

Richard Jefferys, TAG

Several media outlets are reporting on a newly published study of elite controllers, a rare subset of people with HIV who suppress viral load to low or undetectable levels without treatment. [1]

A major impetus for the interest is a finding that one long-term elite controller, Loreen Willenberg, may have cleared all the intact HIV from her body. The study was published today in the journal Nature (paired with an open access commentary by Nicolas Chomont) [2], and Apoorva Mandavilli covered the research in a story for the New York Times. [3] Jon Cohen has authored an excellent explanatory article for Science. [4]

The study results offer potentially important clues about how HIV may be cured in some circumstances, but unfortunately do not directly help design interventions that might produce similar outcomes in the majority of people living with the virus (who are not elite controllers).

The crux of the new paper is that elite controllers appear to preferentially deplete the HIV-infected cells from their bodies that contain virus capable of replicating, likely due to potent anti-HIV immune responses (particularly HIV-specific CD8 and CD4 T cells). The HIV-infected cells that are left behind preferentially harbor viral DNA in regions of the cell's genetic code that are inactive, essentially entombing the virus and preventing its reemergence. In some cases, the HIV DNA is not intact, which also prevents further replication. For Loreen Willenberg, analyses of huge numbers of cells from both the blood and gut could not find any intact HIV, leading to the suggestion that all virus capable of replicating (referred to as replication-competent HIV) has been eliminated over time.

In the New York Times article, scientist Steve Deeks notes that a somewhat similar phenomenon may occur in people with HIV on long term antiretroviral therapy (ART), raising the possibility that over a period of decades cells containing replication-competent virus might be eliminated. Deeks intends to investigate this scenario in people on very long-term ART. However, it's important to note that the evidence is very thin—the most detailed paper indicating the phenomenon might be occurring involves only three individuals on ART. [5]

Furthermore, the Nature paper compares elite controllers with people on ART, finding that the entombment of HIV in cells is far more common in the former group than the latter. Given the significant uncertainty, people on long-term ART shouldn't attempt to interrupt treatment outside of research studies.

Another way researchers are attempting to translate the knowledge gleaned from elite controllers is by testing approaches that may be able to enhance immune responses against HIV. Examples include therapeutic vaccines, broadly neutralising antibodies, toll-like receptor agonists and gene therapies (see TAG's Research Toward a Cure clinical trials listing and 2020 Pipeline Report). [6, 7]

Success to date has been limited, and part of the challenge may be that elite controllers tend to possess particular genetic traits associated with superior HIV-specific immunity.

While the Nature paper was published today, the content was partially known to people who follow HIV research. Xu Yu described some of the data, including the case of Loreen Willenberg, at the IAS 2019 conference. [8]

Loreen was subsequently profiled in an article for Leapsmag by Bob Roehr. [9] In a tour-de-force plenary talk on cure research at CROI 2020 earlier this year, Sharon Lewin highlighted the need to consider how much of the HIV reservoir that persists on ART is replication-competent and able to reemerge if treatment is interrupted. Lewin cited the work of the Nature paper's lead author Chenyang Jiang, who also presented during the conference. [11]

Source

Jefferys R. TAG Basic Science Project. (26 August 2020).

https://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2020/08/new-insights-into-elite-control-of-hiv-and-a-possible-case-of-virus-clearance.html

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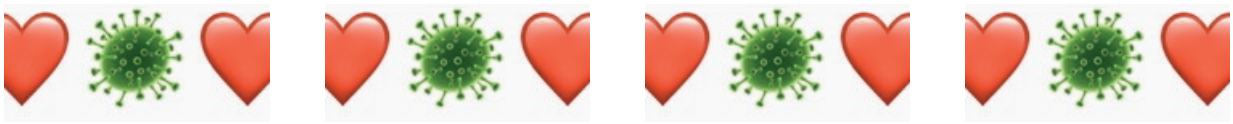
HTB SUPPLEMENT ON COVID-19: Issue 8



COVID-19: HIV and COVID-19 COINFECTION

US study of HIV positive people with COVID-19 reports worse outcomes with comorbidities and having a CD4 <200

Simon Collins, HIV i-Base

A large prospective US study on COVID-19 in people living with HIV has reported worse outcomes associated with multiple comorbidities. It also reports a link to lower CD4 counts that has not been seen in other studies, even when on effective ART. [1]

This study, published on 9 September 2020 in Clinical Infectious Diseases, included 286 participants diagnosed with confirmed COVID-19 between 1 April and 1 July 2020. Cases were submitted by a range of 36 US medical providers from 21 States to a multicentre registry at University of Missouri. Just under half these cases (47%) were from the US South. Three international centres also reported 21 cases. Multivariate analyses were run to determine risk factors for worse outcomes.

The mean age was 51.4 years (SD: 14.4), 26% were female, and 47.5% were African-American and 28% were Hispanic. Most patients (94%) were on ART, 89% had HIV virologic suppression, and mean CD4 counts was 531 cells/mm^3 (SD 340). Five duplicate cases were removed.

Overall, 81% had significant comorbidities including hypertension (46%), obesity (32%), and diabetes (21%).

Within 30 days of confirmed COVID-19, 164 (57%) patients were hospitalised and 47 (16.5%) required ICU admission. Mortality rates were 9.4% (27/286) overall, 16.5% (27/164) among those hospitalised, and 51.5% (24/47) among those admitted to an ICU. The primary composite endpoint of ICU admission, mechanical ventilation or death occurred in 17.5% (50/286) overall and in 30.5% (50/164) of those hospitalised.

Hospitalisation was associated with older age (p<0.01), lower CD4 counts (p<0.01), number of years living with HIV (p<0.01), not being on ART (p=0.04) or being virally suppressed (p=0.02), and high comorbidity burden (p<0.01).

Multivariate analysis showed older age (p=0.02), CD4 count <200 (p=0.05), chronic lung disease (p<0.01), hypertension (p=0.01), and high (3+) comorbidity burden (p=0.05) were significantly associated with severe outcomes.

Based on 47 participants admitted to an ICU and 27 who died, CD4 cell count had a significant effect on survival. Having a CD4 count <200 vs >500 cells/mm^3 was significantly related to both lower ICU-free survival (p=0.04) and overall survival (p=0.05).

Although submission to the registry may have included selection bias, the paper notes that 17/36 clinics included all cases of COVID-19 diagnosis. Other limitations for this study included limited data on steroid use and enrollment in COVID-19 research studies.

The researchers reported that the rates of ICU admission, use of mechanical ventilation, and mortality among HIV positive people with COVID-19 were similar to US general population data. Sensitivity analyses using only US participants did not affect the overall results.

However, this is the largest study to report an association between lower CD4 counts (<200) and worse primary and secondary outcomes from COVID-19, irrespective of viral suppression on ART. These data also disprove an early hypothesis that immune dysfunction might be protective of COVID-19.

An earlier US case-control study reporting a link to lower CD4 count only included 21 HIV positive people. [2]

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Outcomes from COVID-19 in French cohort of 54 HIV positive people on ART

Simon Collins, HIV i-Base

A research letter published in the 1 October 2020 edition of AIDS reported results from a prospective observational study in Paris in HIV positive people who were on ART with generally good CD4 counts. [1]

The study included 54 HIV positive adults (60% men) diagnosed with COVID-19 from 1 March to 30 April 2020.

Median age was 54 years (IQR: 47 to 60) and median CD4 counts was 583 cells/mm^3 (IQR: 474 to 773). All were on ART and nearly all (51/53) had viral load <40 copies/mL.

Over median of 29 days (IQR: 29 to 45 days), all for at least 14 days, 35/54 (65%) developed moderate disease, 14/54 severe (26%) and 5/54 were critical (9%). One person died.

Participants from Sub Saharan Africa were disproportionally affected compared to the clinic population overall (45% vs 30%), with higher rates of severe disease (13/19 vs 13/35).

By multivariate analysis, age , male gender, ethnic origin from Sub Saharan Africa, and metabolic disorder, were associated with severe or critical forms of COVID-19. Prior CD4 T cell counts did not differ between groups.

COMMENT

The disproportionate impact of ethnicity on COVID-19 infection and outcomes is increasingly reported, including in the US and UK. [2, 3]

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COVID-19: INVESTIGATIONAL TREATMENTS

Tocilizumab fails to meet clinical endpoints in randomised COVACTA study: other studies continue

Simon Collins, HIV i-Base

On 1 September 2020, results from the randomised phase 3 placebo-controlled COVACTA trial were published ahead of peer review, showing no clinical benefit of tocilizumab infusion in adults hospitalised with COVID-19. [1}

Top-line results from this study had already been released in a press release from Roche. [2]

The COVACTA study randomised 452 adults with 438 receiving either tocilizumab (n = 294; 8 mg/kg infusion, maximum 800 mg) vs placebo (n=144) in the modified ITT analysis.

Baseline characteristics were balanced and included approximately 70% men; 60% were white and 14% were black and mean age was about 61 (+/– 14) years.

There was no significant difference in primary endpoint of clinical status at day 28 based on a 7-category ordinal scale in tocilizumab vs placebo groups with odds ratio: 1.19 (95%CI: 0.81 to 1.76), p=0.36.

There was also no significant differences in mortality at day 28: 19.7% vs 19.4% in active vs placebo groups respectively: difference 0.3% (95%CI: –7.6% to +8.2%), p=0.9410.

Time to discharge from hospital was shorter with tocilizumab: median 20 (95%CI: 17 to 27) vs 28 days (95%CI: 20 to NE), p=0.037 but this was not significant due to missing the primary endpoint. Median time in ICU was 5.8 days shorter with tocilizumab (9.8 vs 15.50, nominal p=0.045.

There were no significant important safety results between the two groups.

COMMENT

This is disappointing news as several earlier studies reported positive results. [3, 4, 5]

However, as with many of the dozens of tocilizumab studies currently online ahead of peer review, also mainly reporting positive results for COVID-19, these are generally small, retrospective and often use historical controls.

Other phase 3 studies are still ongoing, including the REMDACTA and EMPACTA trials, and several run by independent investigators, potentially to look at shorter hospital and ICU admissions. Although the CONVICTA study reported no benefit, CORIMUNO-TOCI reported reduced mortality or need for oxygen at day 14 and EMPACTA has reported both reduced mortality and need for intubation.

A recent meta-analyses also supported efficacy, though this might only be in a subset of patients, perhaps before the increase in proinflammatory proteins. [6]

On 27 August 2020, the NIH Panel recommended against the use of anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or an anti-IL-6 monoclonal antibody (siltuximab) for the treatment of COVID-19, except in a clinical trial. [7]

The tocilizumab arm of the UK RECOVERY study is apparently still ongoing. [8]

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COVID-19: TRANSMISSION

COVID-19 reinfection can occur after varying times and with more severe disease

Simon Collins, HIV i-Base

Several cases of reinfection with COVID-19 have now been reported, including several cases that were published this week following peer review. All were supported as reinfection by phylogenetic analysis, some occurred shortly after the first infection, and some reported more serious disease.

The first case, reported in August, was a 33-year-old Hong Kong resident who was diagnosed and hosptialised with COVID-19 in March 2020, and discharged after 17 days. On 15 August, more than 140 days since the first infection, he tested positive a second time while asymptomatic due to travel-related screening (returning to Hong Kong from the UK). Although hospitalised, he remained asymptomitic. Phylogenetic analysis showed that the two viral genomes had different clade/lineages. [1]

A second paper from the group reported that serum neutralising antibody was detected during the first infection but not at presentation of the second. During reinfection, neutralising antibody and high avidity IgG were found within eight days of hospitalisation, but an IgM response was not detected. [2]

A second case, reported on 31 August and just published in Lancet Infectious Diseases, was of a 25 year old man in Nevada who was infected in March, recovered in April and then experienced a second infected in May 2020. Both infections were symptomatic, but the second led to more severe disease requiring hospitalisation and oxygen support. Sequence analysis showed the viruses were unlikely to be linked. [3]

A third case also reported reinfections within a short time. This was a 42 year old man who was diagnosed with symptomatic COVID-19 on 21 March 2020 that resolved with out-patient management within 10 days. He remained healthy for 51 days before developing fever, cough and other symptoms on 24 May that were significantly worse that the first infection. Genetic sequencing of the partial first virus showed distinct differences to the second infection and included a high-confidence variation. [4]

Finally, a fourth case, reported this week in CID, was an 89 year old immunecompromised women treated with B-cell-depleting therapy for Waldenström's macroglobulinemia. She was also diagnosed with SARS-CoV-2 and discharged after five days.

Then, 59 days from the first symptoms, two days after a second course of chemotherapy, she was diagnosed with SARS-CoV-2 for a second time. Unfortunately this became progressively severe and the patient died after two weeks. Phylogenetic analysis of the two strains showed differences in ten nucleoside positions that was more likely to be from a second infection rather than developing from prolonged shedding. [5]

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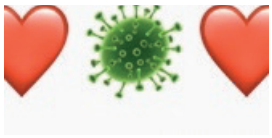
Transmission from children to family members in US childcare setting

Simon Collins, HIV i-Base



A report in the 11 September edition of the US CDC MMWR included cases of onward transmission from 13 children under 10 years old attending three childcare facilities in Salt Lake City.

These reports were from retrospective reviews of transmission patterns from three outbreaks from 1 April to 10 July 2020. Of the 12 children who acquired COVID-19 in a facility, transfer was documented to at least 12 (26%) of 46 nonfacility contacts.

Overall, 184 people, including 110 (60%) children had a link to one of the three facilities. Among these, 31/184 confirmed COVID-19 cases occurred; 13 (42%) in children (all mild and without symptoms) and 18 in adults.

Median age of the adults and children was 30 years (range: 19 to 78 years) and 7 (range: 0.2–16 years), respectively.

Of the 46 non-facility contacts for the 12 children, 12 developed COVID-19 (seven confirmed and five probable). These included six mothers and three siblings.

The study notes that testing criteria for adults included having symptoms that could have underestimated transmission cases and that criteria for testing also changed during the study period, but also that uncertainty about the source case in one of the facilities, that some of those associated cases might have come from outside.

The study noted that although COVID-19 symptoms were mild in the children, this still led to likely transmission to adults, including to parents and possibly to teachers..

Reference

Lopez AS et al. Transmission Dynamics of COVID-19 Outbreaks Associated with Child Care Facilities — Salt Lake City, Utah, April–July 2020. US CDC MMWR, ePub. DOI:10.15585/mmwr.mm6937e3. (11 September 2020).

https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e3.htm

COVID-19: GUIDELINES

BHIVA update guidance for HIV care during second wave of COVID-19

BHIVA.org

BHIVA is updating guidance for HIV clinics as NHS organisations are now having to reinstate plans to manage the epidemic because of the rising number of COVID-19 cases.

1. We advise that the time between routine monitoring (blood & urine tests) of HIV patients should not be longer than 12 months.
2. Services should do all they can to support people to come to clinic for check-ups. This includes explaining and discussing any risks of not doing so. It also includes reassuring them about COVID infection control measures and offering alternatives where possible. These could include blood tests and monitoring by a GP, using existing community services, such as an HIV community nurse, or liaising with other clinics and hospital services.
3. Where it is not possible to undertake the usual monitoring, ART should still be prescribed in all but exceptional cases. Patients should be advised that, without monitoring, there is a risk of a reaction to medication. This risk is low but could include changes in the liver and kidney and/or an increase in viral load. These could increase the risk of serious illness (including death), the development of resistance to HIV medication so that it does not work effectively, and so a risk of passing HIV on to sexual partners. However, for nearly everyone, the risk of interrupting medication is far greater than less frequent monitoring. The longer that HIV has been undetectable though, the less likely it is to rebound. In the same way, the longer someone has been well on a medication the less likely that any new problems will occur. These discussions on the risks of reduced monitoring, should be clearly recorded in the patient's notes.
4. Where there is pressure on staffing and other parts of HIV clinical services due to COVID-19, we repeat our previous advice that the services (a)-(f) listed below must be maintained.
   (a) Blood/urine tests must be provided so that all patients can be monitored at least once a year. Urgent testing must also be available including, for example, where there are new symptoms or concern that the level of the HIV virus in the blood is rising, or for patients with advanced HIV.
   (b) Care for people newly diagnosed with HIV, starting antiretroviral drugs (ART) according to BHIVA guidelines.
   (c) Changing ART medication, when this change means that the patient must be regularly checked for any reaction to the new drugs.
   (d) Monitoring and providing advice to women with HIV during pregnancy.
   (e) Specialist services for people with HIV who also have TB, cancer or other health issues that should be treated urgently.
   (f) Monitoring of mental health, alcohol or drug issues and domestic abuse, referring patients for the right support where necessary.

Services should also be able to review patients who are at greater risk because of health problems from other conditions that could lead to complications with COVID-19, or problems affecting the management of their HIV, for example the virus being detected in their blood or their CD4 being low, suggesting that their immune system is weaker. This could include 'check in & chat' services being offered by staff who are self-isolating from COVID-19.

6. All clinics should make sure that up to date information is available for patients.
7. We recommend all services ensure patients, and their GPs, know about the guidance to offer pneumococcal and annual influenza vaccinations.
8. We encourage all services to ask patients about, and record COVID history in their medical notes:
   (a) Confirmed COVID-19 cases.
   (b) Suspected COVID-19 cases.
   (c) Positive COVID tests.
   (d) Examples of harm related to COVID-19 or service changes secondary to COVID-19.

Reference

BHIVA. '2nd COVID peak' guidance for HIV clinics - plain English version. (8 October 2020).

https://www.bhiva.org/BHIVA-2nd-COVID-peak-guidance-for-HIV-clinics

COVID-19: PAEDIATRICS

COVID-19 deaths in children and people <21 years old in the US

Simon Collins, HIV i-Base

Although children have lower risks from COVID-19, serious cases have been reported and a new paper reviews associated deaths in the US from February to July 2020.

This included 121 SARS-CoV-2–associated deaths: 12 (10%) were infants and 85 (70%) were aged 10–20 years. Hispanic, non-Hispanic Black and non-Hispanic American Indian/ Alaskan Native persons accounted for a disproportionate number of deaths (78%) and 33% of deaths occurred outside of a hospital.

Of these, 30 (25%) were previously healthy, 91 (75%) had at least one underlying medical conditions, and 54 (45%) had two or more. The most frequently reported medical conditions were chronic lung disease, including asthma (28%), obesity (27%), neurologic and developmental conditions (22%), and cardiovascular conditions (18%).

People under 21 make up 26% of the US population, and although cases might be under-reported in this paper, this was 0.08% of the 190,000 overall COVID-19-related deaths during the same period.

Reference

Bixler D et al. SARS-CoV-2–associated Deaths among persons aged <21 years — United States, February 12–July 31, 2020. MMWR Morb Mortal Wkly Rep. ePub: 15 September 2020. DOI: 10.15585/mmwr.mm6937e4

https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e4.htm

COVID-10: DIAGNOSTICS

IDSA guidelines on serologic testing for SARS-CoV-2

Simon Collins, HIV i-Base

These US guidelines include eight recommendations on circumstances when use or not of different serologic tests might be considered for determining current or past SARS-CoV-2 infection.

The guidelines are produced by the Infectious Diseases Society of America (IDSA) and are based on comprehensive evidence reviews. However, the quality of evidence for the final recommendations is also noted as only being low to moderate.

Reference

Hanson KE et al. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19:Serologic Testing. Clinical Infectious Diseases, ciaa1343. DOI: 10.1093/cid/ciaa1343. (12 September 2020).

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1343/5904785

COVID-19: OTHER NEWS

Long COVID: Mild infection with sustained complications

Simon Collins, HIV i-Base

Although most COVID-19 studies focus on people hospitalised with severe infection, complications have also been associated with mild infection.

So while many infections have symptoms that resolve within 1-2 weeks, up to 10% of cases might take more than four weeks and include symptoms that fall short of needing to be hospitalised but by reducing daily activities, challenge the category of being mild.

This was the subject of a BMJ editorial written from experience of a longer mild infection. [1]

Common symptoms still include fatigue and shortness of breath that limit exercise, even in people who were fit before infection and the article stresses the need to measure recovery and time to recovery in greater detail for all stages than just by mortality and time to discharge from hospital.

This is also relevant for the longer recovery times that are already recognised as a complication from more severe stages of COVID-19.

Several UK support groups report having >12,000 members.

References
1. Alwan NA. What exactly is mild covid-19? BMJ (28 July 2020). https://blogs.bmj.com/bmj/2020/07/28/nisreen-a-alwan-what-exactly-is-mild-covid-19/
2. Long COVID website. https://www.longcovid.org
3. Body Politic website. https://www.wearebodypolitic.com/covid19

Review paper highlights substandard COVID-19 research in both peer-review journals and pre-review websites

Simon Collins, HIV i-Base

A review of medical publications on COVID-19 has highlighted the number of substandard studies that have either been published in peer-reviewed journals or that are getting wider circulation ahead of peer-review on the medRXiv and bioRxiv websites (currently with more than 8000 papers), which have fewer quality checks.

The review, in the Journal of Medical Ethics, also notes the many registered COVID-19 studies - more than 1220 on clinicaltrial.gov by 7 May 2020 - and that these are largely and rightly driven by the urgency of finding effective options for treatment and prevention.

However, the paper is also concerned about the risk of honest errors as well as misconduct. By the end of July 2020, 33 papers (19 published and 14 preprints) have been retracted, withdrawn, or raised serious doubts, including two in the Lancet and New England Journal of Medicine. Most of these papers (19/33) came from Asia, with 11/19 coming from China. Reasons for the change included data falsification, methodological concerns, and concerns about interpretation of data and conclusions, as well as authorship and research participant privacy issues

The paper argues that the rush to publish results is straining the integrity of research and publications and that this has implications for patients, clinicians, and potentially government policy.

C O M M E N T

The caution for any articles published ahead of peer-review is important. Many of the older papers posted on MedRxiv and BioRxiv might also have outdated results and might never be published.

It is good that both sites update listings when papers are published following peer review. It is also positive that many subscription journals are publishing COVID-19 research as open-access articles.

Reference

Bramstedt K et al. The carnage of substandard research during the COVID-19 pandemic: a call for quality. Journal: Journal of Medical Ethics. DOI:10.1136/medethics-2020-106494. (1 October 2020).
https://jme.bmj.com/lookup/doi/10.1136/medethics-2020-106494

COVID-19: FUTURE 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 now virtual including those that were rescheduled in the hope that COVID-19 restrictions would be relaxed.

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

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

International Workshop on HIV Paediatrics 2020

16 – 17 November 2020. NOW VIRTUAL

www.virology-education.com

26th Annual BHIVA Conference (BHIVA 2020)

22–24 November 2020 (rescheduled from April). NOW VIRTUAL

www.bhiva.org

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

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

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

HIV Research for Prevention (HIV R4P 2020)

27 – 28 January and 3 - 4 February 2021, Cape Town (reshedulled from October 2020). NOW VIRTUAL

https://www.hivr4p.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

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

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

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

Pocket guides

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

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

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

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

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

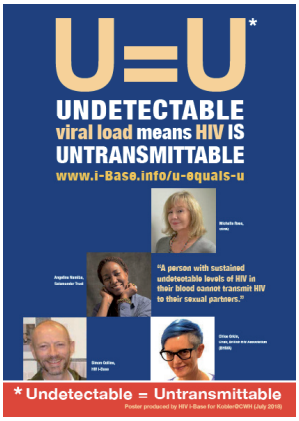
This project was developed with the Kobler Centre in London.

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

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

email: subscriptions@i-base.org.uk

Customise U=U posters for your clinic



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

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

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

roy.trevelion@i-Base.org.uk

Order publications and subscribe online

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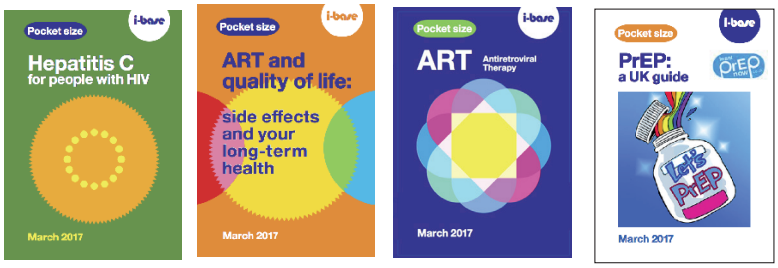

h-tb

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http://www.i-Base.info

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Editor: Simon Collins

Contributing Editor: Polly Clayden

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HIV i-Base, 107 The Maltings,169 Tower Bridge Road, London, SE1 3LJ. T: +44 (0) 20 8616 2210. F: +44 (0) 20 8616 1250

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

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

- **Booklets about HIV treatment**

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

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

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

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

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

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

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

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

- **Other resources**

U=U resources:

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

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

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

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

subscriptions@i-Base.org.uk