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i-Base 2021 appeal

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.

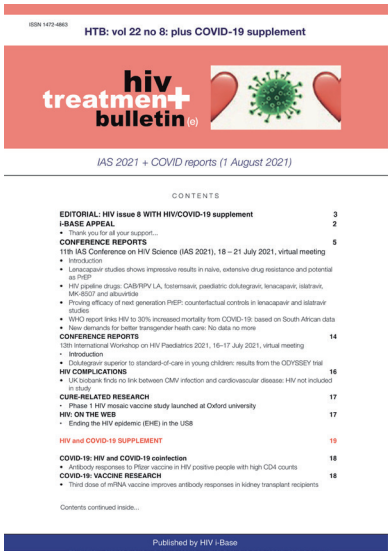
http://i-base.info/i-base-appeal-we-need-your-help

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 issue contains first reports from the IAS 2021 virtual conference and related 13th International Paediatric Workshop held in July.



We review studies presented on some of the most exciting new drugs being developed for treatment and PrEP.

If these study results continue to be so positive, they will enable very different options to taking daily pills.

The reports cover long acting cabotegravir/rilpivirine, fostemsavir, paediatric dolutegravir, lenacapavir, islatravir, MK-8507 and albuvirtide.

We also report a study from the UK Biobank cohort that found no link between CMV and cardiovascular risk, but that didn't adjust for coinfections.

COVID-19 news also continues, with reports on both treatment and vaccines.

This includes several articles on the need for a third vaccine dose.

This includes positive data supporting the urgency of a third dose in some people.

The UK still has to address this important issue, including the implications for HIV positive people, especially with low CD4 counts.

Hopefully, booster dosing should not need to be for all adults, at least not. We include other reports looking at this difficult issue of durability of response, including the the Delta variant.

The discussions are also against the unacceptable situations of such inequality of access to vaccines globally.

CONFERENCE REPORTS

11th IAS Conference on HIV Science (IAS 2021)

18 – 21 July 2021

Introduction

The 11th IAS Conference on HIV Science held from 18 – 21 July 2021 was organised as a virtual meeting, though originally due to be held in Berlin.

These biennial meetings usually include more than 5,000 delegates and alternate with the much larger IAS World AIDS Conferences.

The programme is already online with open access already available for the conference abstracts. This portal includes a search engine that includes URLs for each study.

https://www.ias2021.org/the-programme

The conference format has adapted to a virtual format by reducing the number of oral abstract to three and including plenty of time for live questions and discussion afterwards. This makes it much easier to focus in more depth on the most important studies.

Unfortunately, the open access programme doesn't link to a second stand-alone conference use to host webcasts, posters and other resources.

This second website uses a different portal that restricts access to registered delegates, at least while the conference is running. This website doesn't provide URLs to presentations or abstracts. PDF versions of posters are not currently available, although this might change in the future.

https://conference.ias2021.org

As with all IAS conferences, there are many related workshops before and during the conference, including on paediatric care and cure related research. Access to many of the satellite meetings is restricted to healthcare professionals.

This year the conference has a strong programme including research on PrEP, new HIV drugs for treatment, cure-related research, paediatrics and COVID-19. Many of the session cover healthcare for key populations.

Short rapporteur summaries for key sessions are available as open access at the end of each day.

https://www.ias2021.org/rapporteurs

Early reports in HTB will be added below.

- Lenacapavir studies shows impressive results in naive, extensive drug resistance and potential as PrEP
- HIV pipeline drugs: CAB/RPV LA, fostemsavir, paediatric dolutegravir, lenacapavir, islatravir, MK-8507 and albuvirtide
- Proving efficacy of next generation PrEP: counterfactual controls in lenacapavir and islatravir studies
- WHO report links HIV to 30% increased mortality from COVID-19: based on South African data
- IAS 2021: New demands for better transgender heath care: No data no more

IAS 2021: ANTIRETROVIRALS

IAS 2021: lenacapavir studies show impressive results in naive, extensive drug resistance and potential as PrEP

Simon Collins, HIV i-Base

Three studies at IAS 2021 included new data on the long-acting capsid inihibitor lenacapavir that only requires 6-monthly dosing.

This included two late-breaking abstracts reporting clinical results from the phase 2 CALIBRATE induction/maintenance study in treatment naïve participants and the phase 3 CAPELLA study in treatment experienced participants. [1, 2]

Lenacapavir results in treatment naive

CALIBRATE randomised 182 participants (2:2:2:1) to one of three lenacapavir arms with F/TAF (two using injections with later reduction to two-drug ART at week 28, one using oral lenacavir plus F/TAF throughout) or to a control arm of bictegravir/F/TAF. [1]

Interim pre-specified 16-week results for achieving viral load <50 copies/mL included 92% (48/52), 94% (50/53), 94% (49/52), and 100% (25/25) in the three lenacapavir and control groups respectively.

Baseline characteristics included median age 29 years (range: 19 to 72), 7% women (yes, 7%), 52% black, 45% Hispanic/Latinx,

Median viral load and CD4 count at baseline were 4.3 log copies/mL (IQR: 3.8 to 4.7) with 15% >100,000 c/mL and 437 cells/mm^3 (IQR: 332 to 599), with only two participants <200 cells/mm^3.

At week 16 by ITT analysis, viral load was <50 copies/mL in 94% (147/157) vs 100% (25/25) in the pooled lenacapavir vs control groups respectively. The two cases of virological failure included one participant who did not reach <50 copies/mL at week 28 and one who discontinued the study after two days. Early response rates at week 4 were similar in all groups. The primary endpoint is at week 54.

One participant who had an early viral response at week 2 that rebounded close to 100,000 copies/mL baseline by week 10, developed lenacapavir emergent mutations (capsid Q67H + K70R) associated with a 20-fold loss of sensitivity, together with M184V in RT. Lenacapavir drug levels were consistently within the target range and although viral load was dropping again, treatment was changed to AZT/3TC/TDF plus dolutegravir (an unusual choice) and then became undetectable.

Adverse events were similar across groups (including 11 cases of COVID-19 and 17 cases of syphilis overall) with no drug-related discontinuations or grade 4 side effects.

Injection site reactions (ISRs) were common (40/183) but mostly grade 1 (33/40), with only 1 grade 3 and no grade 4. However, the study reported some nodules lasting for several months that were “palpable but not visible” and these extended from 1 to 4 cms. Two participants discontinued due to grade 1 ISRs with local hardening of the skin.

Laboratory abnormalities included high creatine kinase (n=5 vs 0), mainly explained by recent exercise with no grade 3/4 results judged clinically relevant or leading to discontinuations.

These results support continuing to the dual therapy maintenance therapy switches with extended follow-up to week 80.

Lenacapavir with extensive drug resistance

Clinical results were also presented at IAS 2021 from the phase 2/3 CAPELLA study in 72 highly treatment experienced participants who had HIV multidrug resistance (MDR) to at least three drug classes. [2]

Half the participants were randomised to lenacapavir or placebo for 14 days (before optimising treatment) and half used open label lenacapavir.

The results at IAS 2021 were week 26 from the 36 participants in the randomised section of this study.

Median age was 52 years (range: 23 to 78), 25% were women, 38% were back and 28% Hispanic/Lantinx. Participants had been living with HIV for an estimated median or 24 years (range: 9 to 44 years). Extensive drug resistance to >2 drugs in each class was 99% (NRTIs), 97% (NNRTIs), 81% (PIs) and 69% (INSTIs) at baseline.

Virological results included 81% (n=29/36) of participants reaching an undetectable viral load (<50 copies/mL) and 89% (32/36) <200 copies/mL. There were no missing data, with 7 and 4 participants having viral load >50 and >200 copies/mL, respectively. Although numbers are small, 4/6 participants with no active background drugs also reached <50 copies/mL.

The mean CD4 count increased to 81 cells/mm^3 included increases to >50 cells/mm^3 in the 8/36 participants who had CD4 counts <50 cells/mm^3 at baseline.

Limited data were available for the 11 participants who met criteria for resistance testing. Of these, 4/11 developed emerging mutations associated with drug resistance to lenacapavir: M66I (4), Q67H (1), K70N/R/S (1) and N74D (1) although related phenotypic impact was not discussed. Of these, 3/4 later suppressed, one with OBR change and two without. One person without other sensitive drugs who did not become undetectable reported a –1.7 log reduction in viral load. Although no new resistant mutations were reported for other ART, this is likely related to the relatively short follow-up.

Tolerability was good with no study discontinuations and no serious drug-related side effects. Injection site reactions (ISRs) were common (56%; 40/72) but mainly grade 1 (28/40) that resolved in a few days. None were grade 4 and the two grade 3 reactions resolved by days 4 and 8.

All participants have since received a second 6-monthly injection.

Lenacapavir as PrEP

Finally, further results were presented on the potential of lenacapavir as PrEP. [3]

This was a study in 24 female macaques, randomised to one of two doses of a single lanacapavir injection or placebo followed by ten vaginal weekly challenges with SHIV.

The single administration of lenacapavir exceeded the protein adjusted EC95 value (30.2 nM) for at least 10 and 16 weeks (in the 150 mg/kg and 300 mg/kg groups, respectively).

All 8/8 control animals all became infected by week 8 (median of 4 weeks). In contrast, 6/8 animals became viraemic in the 150mg/kg at a median of 14 weeks ($p<0.0001$). However, there were no infections (100% protection) in the 8/8 animals in the 300 mg/kg group, ($p<0.0001$).

This showed similar efficacy to a rectal challenge macaque study reported at CROI 2021. [4]

C O M M E N T

These combined results show exciting potential of very long-acting drugs.

Phase 3 studies are already ongoing for both treatment and PrEP.

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IAS 2021: Update on HIV pipeline drugs: CAB/RPV LA, fostemsavir, paediatric dolutegravir, lenacapavir, islatravir, MK-8507 and albuvirtide

Simon Collins, HIV i-Base

There were exciting results at the IAS 2021 conference on many of the most important compounds currently in phase 2/3 studies as next generation ART.

This included studies for nearly all pipeline compounds or recently approved drugs including long-acting cabotegravir/rilpivirine, fostemsavir, lenacapavir (as treatment and PrEP), islatravir (as treatment and PrEP) and albuvirtide.

- CAB/RPV LA. Several implementation studies and a French study looking at transmitted resistance to both drugs - reporting that 7% of >4000 treatment naive samples showed resistance to rilpivirine.
- Fostemsavir. Two posters on side effects out to 96 weeks and drugs in the background regimen of the BRIGHTE study.
- Paediatric dolutegravir included safety and efficacy from the large international ODYSSEY study in treatment-naive and -experienced children.
- Lenacapavir. Phase 2/3 results in multidrug experienced (CAPELLA) and phase 2 treatment-naïve (CALIBRATE). Also macaque data on PrEP.
- Islatravir/doravirine. 96-week phase 2 safety data on dual ART, including bone and kidney results, and use in renal disease. Plus PK data easily supporting once-monthly oral pill for PrEP and plans to include islatravir in a vaginal ring (combined with a contraceptive).
- GS-8507. Two posters showing no drug interactions with either islatravir or oral contraceptives ,
- Albuvirtide phase 3 results: dual ART with lopinavir

Cabotegravir/rilpivirine long acting injectable combination (CAB/RPV LA)

Although cabotegravir/rilpivirine is already approved in the US and EU, it hasn't been widely used yet in the UK where it is still being evaluated by the NHS.

Week 124 results from the FLAIR study were presented at IAS 2021. This included limited data from not using an oral lead-in dosing for the first month. [1]

Many of the studies at IAS 2021 looked at issue relating to implementation and how health systems adapt to an injectable treatment. [2, 3, 4]

A French study looking at likelihood of baseline resistance to either drug recommended the importance of baseline resistance testing in to detect polymorphisms, transmitted drug resistance and to define HIV-1 subtype. [5]

This was a large drug resistance database (>4200 samples from 2010 to 2020 with both integrase and NNRTI sequences) reported that approximately 7% of treatment-naive people might have transmitted mutations to rilpivirine, especially in people with HIV sub-type A.

There were also several presentations on cabotegravir LA as PrEP.

IAS 2021: fostemsavir

Approval of the gp-120 attachment inhibitor fostemsavir for HIV MDR in the US and EU – in July 2020 and January 2021 respectively. [6, 7]

This was based on 96-week results from the international BRIGHTE study in people with multidrug resistance, reported at IAS in 2019. [8] This includes results in 272 participants in the randomised study and 99 participants using open-label fostemsavir. Further 96-week analyses were presented at IAS 2021 including new analysis of side effects and on the diversity of treatments used in background ART, although this primarily included twice-daily dolutegravir. [9, 10]

As a drug in a new class, supported by results from BRIGHTE, fostemsavir can be a life-saving option for the small percentage of people with MDR HIV.

Paediatric formulations of dolutegravir

New paediatric formulations of dolutegravir were also approved this year which will dramatically improve treatment options for children globally.

Several presentations at IAS 2021 included additional results from large international ODYSSEY study - from an additional cohort of 85 infants and children <14 kg. This included good 36-week efficacy results for younger children but also reported four cases of drug resistance in the main ODYSSEY study in the older age group - showing the importance of access to pipeline ART. [11, 12]

More comprehensive results were also presented at the paediatric workshop held just before IAS. [13]

Safety data from ODYSSEY in the main study was also generally good but included vulnerability of some participants to CNS side effects and mood changes. [14, 15, 16]

IAS 2021: lenacapavir

Lenacapavir is a news capsid inhibitor that is given by injection every six months and that has already been submitted to the FDA as a treatment of extensive drug resistance. [17]

IAS2021 included clinical results from the phase 2/3 CAPELLA study at week 26 from the 36 participants in the randomised section of this study. This is in highly treatment experienced participants who had HIV multidrug resistance (MDR) to at least three drug classes. [18]

The conference also included results from the phase 2 CALIBRATE study in treatment naive participants. [19]

Both studies are covered in details in a separate HTB report. [20]

This also includes a third study using lenacapavir as PrEP showing 96% (p=0.0002) protection against vaginal exposure. [21]

Phase 3 PrEP studies are already ongoing.

Islatravir

Islatravir is an NRTTI (a nucleoside reverse transcriptase translocation inhibitor, a type of NTRI) that is being developed by Merck/MSD for both treatment and prevention. It's incredibly high potency allows long-acting oral formulations that allow once-monthly dosing.

The treatment programme is focused on dual therapy with NNRTIs: either daily dosing with doravirine using or weekly dosing with MK-8507.

Islatravir plus doravirine

IAS 2021 included 96-week results from a phase 2 dose-ranging RCT in treatment naïve participants that started with triple therapy but switched the investigational arm to doravirine plus islatravir dual therapy in participants with undetectable viral load after 24 week. After 60 - 84 weeks the three islatravir arms all changed to the selected 75 mg dose. Throughout these phase the control arm is doravirine/TDF/3TC. [22]

Results from weeks 24 and 48 were previously reported at IAS conferences in 2019 and 2020 and baseline demographic have been reported previously. [23] Viral efficacy results at 96-weeks were presented at Glasgow 2020. [24]

The IAS 2021 results included no new serious drug related events between from 48 to 96 weeks. There were also no new drug-related discontinuations after week 48. There were also no serious side effects that were more common in the combined islatravir vs control groups.

The most common side effects with significant differences between arms through to week 96 was more headaches in the islatravir arms (11% vs 6%) and more diarrhea in the control arm (7% vs 19%). The majority of both these side effects was mild and not related to study drugs.

Week 96 lab abnormalities were generally similar to week 48. Increases in creatine kinase were nearly all related to exercise.

Baseline characteristics for the 121 treatment-naïve participants included mean age 31 years, 93% male. Mean CD4 count was 492 cells/mm^3 (SD: 188) and 22% had viral load >100,000 copies/mL. Race included 76% white and 20% black with approximately half the participants being Hispanic or Latin American. Approximately 40% were treated in sites in North America, 30% in South American and 25% in Europe.

Islatravir plus MK-8507

Islatravir is also being studies in combination with the NNRTI MK-8507 as a weekly oral combination. Viral load reductions of a mean –1.5 log after seven days monotherapy and support once-weekly dosing above 80 mg. [25]

Two PK studies on MK-8507 at IAS 2021 reported no drug interactions with either islatravir or oral contraceptives. [26, 27]

Islatravir as PrEP

At IAS 2021, PK data showed that drug levels using once-monthly oral PrEP remained at protective levels for at least two months after the last dose. Another study included plans to include islatravir in a vaginal ring, combined with a contraceptive. [28, 29]

Two large phase 3 studies are already underway using monthly oral islatravir. [30, 31]

Albuvirtide - fusion inhibitor

Albuviride is an HIV fusion inhibitor that works at an early stage of the HIV lifecycle by blocking attachment to CD4 cells. It was approved in China in June 2018. [32]

It has a similar structure and mechanism to an earlier HIV fusion inhibitor called enfuvirtide (T-20, Fuzeon) that was developed for people who had run out of treatment options.

However, it is still a pipeline drug because phase 3 results have not previously be published. Two US phase 2 studies are listed for use in multidrug resistance together with the bNAb 3BNC117. [33, 34]

A presentation at IAS 2021 presented very limited results from the phase 3 TALENT study. The TALENT study compared a two-drug arm of albuvirtide with lopinavir/r produce similar viral load results to lopinavir/r with two NTRIs. The poster didn't show published results though, just a short oral summary.

The study design was selected when lopinavir/r was still widely used as second-line therapy in China.

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IAS 2021: PrEP

Proving efficacy of next generation PrEP: counterfactual controls in lenacapavir and islatravir studies

Simon Collins, HIV i-Base

A satellite session before IAS 2021 focused on the new research challenge for the next generation of PrEP studies and was organised by the Forum for Collaborative HIV Research. [1]

This included the critical issue of how to prove activity of new compounds given the near 100% efficacy with good adherence of current PrEP. The first randomised studies used either placebo (now unethical due to PrEP being the new standard of care) or active controls (that would need to be too large as non-inferiority studies).

The workshop focused on the FDA decision to accept results using counterfactual placebo arms as options for estimating background HIV incidence in active control studies. This approach has been used to study contraceptive efficacy that used background pregnancy incidence.

For PrEP studies, this can include data on STIs, cross sectional data from HIV recency tests at baseline and historical incidence data. However, for HIV this needs to allow or adjust for temporal trends in testing, ART use and viral suppression etc. [2]

Recency tests give an approximate HIV incidence at baseline from a similar population. However, the tests themselves are not sufficiently sensitive for individual use. Not all recent infections remain recent and some long term infections can wrongly show as recent. Instead, the tests are largely for epidemiological research, use a 12-month sensitivity cut-off to broadly define a recent infection.

The phase 3 PrEP studies using monthly oral islatravir and 6-monthly lenacapavir injections.

Phase 3 studies for these long-acting compounds are already planned using counterfactual placebo controls. [3, 4, 5]

The workshop included presentations and a roundtable discussion from key researchers involved in these studies.

Recency testing has already been widely used in surveillance systems Previously referred to as RITA or STARHS testing), including in the UK for more than a decade.

Dozens of related satellite and symposium meetings looked at the importance of having a choice from different formulations and delivery methods as part of global roll out of current and pipeline PrEP. [6, 7, 8]

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IAS 2021: COVID-19

WHO report links HIV to 30% increased mortality from COVID-19: based on South African data

Simon Collins, HIV i-Base

On 15 July 2021, WHO published a 12-page report linking HIV to a higher risk of mortality in people hospitalised with COVID-19, based on a large international database. [1, 2]

The report was also the first study highlighted in a press conference for the upcoming IAS 2021 conference, due to run from 19 to 21 July, and as such was quickly picked up as headline news.

The results are from an WHO international database looking at outcomes of people hospitalised with COVID-19 submitted to the WHO Clinical Platform. Individual, anonymised data could be submitted using a case report form in various ways, either directly or locally, collecting results at baseline, during hospitalisation and at discharge/death.

This analysis was to describe the demographics, clinical presentation, clinical outcomes, and risk factors among people living with HIV who have been hospitalised for suspected or confirmed COVID-19.

From January 2020 to April 2021, the database collected more than 268,400 cases from 37 countries, with 24 countries including results about HIV.

Of these, 15,522 were HIV positive (9% of 168,649 cases – presumably the total records from the 24 countries with HIV data). The vast majority – more than 96% (14,914/15,522) – were from the WHO African Region, with 94% (14,682/15,522) from South Africa.

Within the HIV positive cohort, the mean age was 45.5 years, 37% (5737/15,442) were male, 91% (8842/9631) were on ART, and 36% (5613/15,522) had severe or critical illness on hospital admission.

Among the severe cases, 89% (5039/5611) were less than 65 years old and 39% (2187/5596) were male. Overall, the mean duration from hospital admission to death or discharge was 9.5 days (SD 13.4, n= 14,776).

Results: increased mortality in South Africa

Overall, 23% (3578/15,463) of the HIV cohort died and HIV infection was independently associated with a higher risk of death (aHR 1.29, 95% CI: 1.23 to 1.35, p<0.0001). This analysis adjusted for age, sex, disease severity and underlying conditions (diabetes, chronic pulmonary disease and malignant neoplasms).

Rates were higher for people with either two (aHR 1.40, 95% CI: 1.37 to 1.43) or three or more underlying conditions (aHR 1.50, 95% CI: 1.44 to 1.56), both p<0.0001.

Other significant risk factors included being >65 or older (aHR 1.82, 95% CI: 1.62 to 2.04), male (aHR 1.21, 95% CI: 1.15 to 1.28), having diabetes (aHR 1.50, 95% CI: 1.39 to 1.62) and hypertension (aHR 1.26, 95% CI: 1.19 to 1.34), all p<0.0001.

However, by geographic region, the link to mortality was not supported in the WHO European Region (aHR 0.59, 95% CI: 0.29 to 1.2) or the WHO Region of the Americas (aHR 0.92, 95% CI: 0.37 to 2.31) and limited data prevented analyses for other regions.

Similarly, excluding South African data resulted in comparing 311 vs 7474 (HIV positive vs negative) no longer showed HIV to be significant (aHR 1.16, 95% CI: 0.90 to 1.51).

At the press conference, IAS President and IAS 2021 International Co-Chair Adeeba Kamarulzaman said: “This study underscores the importance of countries including all people living with HIV in the list of priority populations for national COVID-19 vaccine programmes. The global community must also do much more to bring COVID-19 vaccines to countries around the world with high prevalence of HIV and other diseases. It is unacceptable that as of today, less than 3% of the entire African continent has received a single dose of the vaccine and less than 1.5% have received both doses.” [3]

C O M M E N T

This is an important programme to collect a large international database to look at outcomes for different global populations.

But it is difficult other countries have not contributed and support this programme. Both the report and the related publicity, minimised the limitations from nearly all the HIV data coming from South Africa, even allowing for the fact that this country has the highest HIV prevalence.

The overall conclusion linking HIV to a higher risk of mortality is still important for comparing HIV positive vs negative outcomes.

The limited HIV specific data (only available for 60% cases) also prevented an analysis of HIV related factors including CD4 count, viral load and use of ART.

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IAS 2021: ADVOCACY

New demands for better transgender heath care: No data no more

Simon Collins, HIV i-Base

On 19 July 2021, the first full day of IAS 2021 conference included the launch of a new HIV prevention campaign for better health for transgender people. [1]

The campaign is based on a 24-page manifesto written and informed by trans and gender-diverse (TGD) global activists based on the need for peer-led HIV prevention research with ownership and acceptability in TGD communities. [2, 3]

Demands include:

- Including the full range of the gender spectrum in clinical trials, including trans men.
- That data gender-affirming hormonal therapy (GAHT) is available for all biomedical prevention compounds.
- That research sites are funded to recruit transgender participants and to engage local LGBTQ community, including transgender-led organisations.

The document is published and supported by the US prevention organization AVAC.

Several other sessions at the conference are recommended for their focus on transgender health. [4, 5, 6]

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CONFERENCE REPORTS

13th International Workshop on HIV Paediatrics 2021

Virtual workshop, 16–17 July 2021

This meeting has been an annual fixture from Virology Education since 2009.

Last year it was postponed to November but this year it returned to its usual slot and was held as a premeeting to IAS 2021.

It is the only HIV meeting devoted to research in prevention and treatment for infants, children and adolescents. As with most HIV meetings the focus this year is also on the COVID-19 pandemic. Highlights from the meeting include:

- Latest findings from the ODYSSEY trial – a randomised comparison of dolutegravir-based ART vs standard of care – including late-breaking results for the 3 to 14 kg weight band
- An update from WHO on what is new in paediatric HIV treatment and prevention and updated recommendations from 2021 WHO guidelines.
- Latest 2021 UNAIDS data on paediatric HIV, which also describes the effects of COVID-19 on HIV treatment and care in 2020.
- Long-acting HIV prevention for adolescents, looking at cabotegravir-LA and other drugs and strategies under investigation such as broadly neutralising antibodies and new long-acting ARVs islatravir and lenacapavir
- New approaches to accelerate and optimise the study of new drugs for HIV and coinfections in pregnancy – feedback from the WHO/IMPAACT ARV in Pregnancy workshop discussions over the past year
- Review of what is known about COVID-19 in African children
- Progress – and lack of progress – with dolutegravir transition in children

Presentations and webcasts (provided speaker's consent) will be available on the website soon after the meeting:

https://academicmedicaleducation.com/hiv-pediatrics-2021

Early HTB reports will be posted and linked below.

- Dolutegravir superior to standard-of-care in young children: results from the ODYSSEY trial

Dolutegravir superior to standard-of-care in young children: results from the ODYSSEY trial

Polly Clayden, HIV i-Base

Dolutegravir (DTG)-based ART was superior to standard-of-care in children weighing 3 to 14 kg, starting first- or second-line treatment. These 96 week results from the younger cohort of the ODYSSEY trial were presented at the 13th International Workshop on HIV Paediatrics 2021. [1]

ODYSSEY, a multi-country randomised trial, showed superior efficacy for DTG plus two NRTIs vs standard-of-care in 707 children and adolescents weighing 14 kg or more (median age 12 years), starting first- or second-line ART. These results were presented earlier this year at CROI 2021. [2]

Late breaking results, shown at the workshop, were for an additional cohort of 85 younger children weighing less than 14 kg, who completed 96 weeks follow-up on 28 June 2021.

The children were randomised: 42 to DTG and 43 to standard-of-care (Uganda 43, Zimbabwe 22, South Africa 20).

Their median age was 1.4 years (IQR 0.6 to 2.0); 23 were 3 to <6 kg, 40 were 6 to <10 kg and 22 were 10 to <14 kg. Seventy two children started first-line and 13 started second-line ART; 74% in the standard-of-care arm received boosted lopinavir.

Median follow-up was 120 (IQR 97 to 132) weeks; 5 (6%) children were lost to follow-up.

The investigators performed three analyses to estimate the difference in the probability of clinical/virological failure by 96 weeks between DTG-based ART and standard-of-care in children weighing <14 kg:

- Stand-alone analysis, using data only from children <14 kg
- Pooled analysis, assuming the treatment difference is identical in children <14 kg and >14 kg, and combining the two data sets (they allocated a weight of approximately 90% to data from children >14 kg)
- Bayesian analysis, using information from the 707 children as a prior distribution and clinical opinion to determine how much weight is given to the that (based on interviews with paediatricians they assigned a weight of 78% to data from the older children)

There were 11 children in the DTG arm with virological or clinical failure by 96 weeks (26%) vs 21 (49%) in standard-of-care; 8 (19%) vs 16 (37%) failures were virological. Of 6 deaths, 2 (5%) were in the DTG and 4 (9%) in the standard-of-care arms.

The investigators found that there was less probability of failing in the DTG vs standard-of-care arm, p=0.05.

For the difference in proportion with virological or clinical failure by 96 weeks <14 kg, the Bayesian analysis gave an 11% difference in favour of DTG: -0.106 (95% CI -0.192 to -0.020). The other analyses also favoured DTG vs standard-of-care: stand-alone -0.196 (95% CI -0.379 to -0.005) and pooled -0.094 (95% CI -0.146 to -0.038). Test of heterogeneity of treatment effect between ≥14kg and <14kg: p=0.24.

At 96 weeks, 76% of children in the DTG arm had viral load <50 copies/mL compared with 50% in standard-of-care, p=0.02. The corresponding proportions with cut-off <400 copies/mL were 91% vs. 71%, p=0.03.

At 48 weeks, these proportions were 44% and 49% for <50 copies/mL, p=0.69. And 74% vs 69% for <400 copies/mL, p=0.69.

There were a total of 34 serious adverse events: 15 (11 children) in the DTG arm vs 19 (11 children) in standard of care, p=0.92. This included the 2 vs 4 deaths. And 36 (19 children) had grade 3 and above adverse events in DTG vs 34 (21 children) in standard-of-care, p=0.79. There were 2 ART-modifying events in the standard-of-care arm: 1 raised liver enzymes and 1 vomiting.

At 96 weeks there was a significant difference in mean change in total cholesterol (mg/dL) from baseline in children <14 kg also favoring DTG: -26 (95% CI -42 to -9), p=0.003.

Presenting author, Pauline Amuge from Uganda, noted that these results support WHO guidelines and roll-out of DTG-based regimens for younger children starting first- or second-line ART and she added: “procurement of dispersible DTG for children <20 kg should be expedited”.

C O M M E N T

These results provide good evidence for rapid global rollout of DTG for children aged four weeks and above using the new dispersible 10 mg tablets. [3]

Following this ODYSSEY late breaker, WHO released a statement. [4] This applauded the results and emphasised the grim reality that children living with HIV still continue to be left behind by the global HIV response.

In 2020, only 54% of the 1.7 million children living with HIV received ART compared to 74% of adults. Among WHO focus countries, only 40% of children (or 74% of children receiving ART) achieved viral suppression.

WHO has recommended DTG-based ART for all infants and children since 2018 and provided dosing recommendations for those over four weeks old and weighing more than 3 kg in July 2020.

New WHO 2021 consolidated guidelines on HIV [5] and the newly released policy brief on transitioning to the 2021 optimal formulary for antiretroviral drugs for children [6] give further guidance on how to transition to DTG-containing regimens as well as how to best dose it when co-treatment for TB is needed.

Two generic formulations of DTG 10 mg dispersible tablets have been tentatively approved by the US FDA. [3] The cost for children in low- and middle-income countries where these are available is $4.50 for a 90-tablet bottle.

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HIV COMPLICATIONS

UK biobank finds no link between CMV infection and cardiovascular disease: HIV not included in study

Simon Collins, HIV i-Base

An analysis from the large national UK Biobank has reported no association between CMV infection and the risk of cardiovascular disease.

These results are important because of the concern that the immune activation linked to CMV might have serious long term consequences.

Although the study did not report outcomes in people who are HIV positive, the results are important because CMV is more common in HIV positive people and is especially high in gay men.

The analysis included 8,531 participants from the UK Biobank study, recruited from 2006 to 2010. It included 626 cases of cardiovascular disease (CVD) and 529 cases of stroke over a mean follow-up time of 10.2 years.

In adjusted analyses, the hazard ratio for CVD by CMV status was 1.01 (95% CI: 0.86 to 1.20) and for stroke was 0.96 (95% CI: 0.68 to 1.36).

However, this was a largely white population and the study recommended "further research within understudied populations, such as those of non-white ethnicity".

C O M M E N T

Although these results are positive, they were not able to adjust for likely duration of CMV infection or CMV viral load.

The study also didn't study the role of coinfections, including with HIV and HCV, and it was underpowered to detect small changes in CVD risk.

These analyses should be possible given the overall biobank included more than 500,000 samples.

Reference

Hamilton EM et al. Human cytomegalovirus and risk of incident cardiovascular disease in UK Biobank. JID, jiab364, doi: 10.1093/infdis/jiab364. (19 July 2021).

CURE-RELATED RESEARCH

Phase 1 HIV mosaic vacci ne study launched at Oxford university

Simon Collins, HIV i-Base

On 5 July 2021, researchers at Oxford University published a press release for the launch of a phase 1 study of an HIV vaccine.

The HIV-CORE 0052 study will enroll 13 HIV negative participants who are not at high risk of catching HIV.

It will use a mosaic vaccine called HIVconsvX that targets different sections of the virus. The vaccines will use two doses, four weeks apart.

Phase 1 studies look for whether the experimental vaccine is safe and whether it generates immune responses. This

study will not produce results on whether the vaccine is effective.

Results are expected by April 2022.

The study is funded by the EU as part of the European Aids Vaccine Initiative (EAVI2020). Similar studies are planned in other countries, including in Europe, Africa and the US.

Reference
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HIV: ON THE WEB

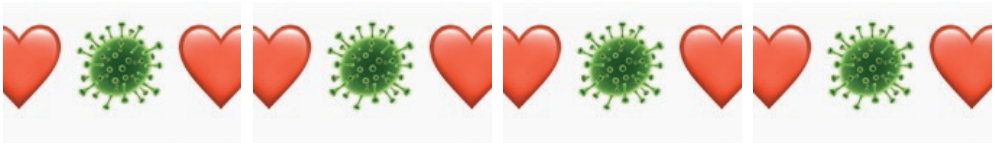
Ending the HIV epidemic (EHE) in the US

Talks and research presented at a virtual conference in April 2021.

The diverse programme for how this wealthy country approaches long-term goals to end the HIV epidemic includes the overlap of HIV and COVID-19. This includes the importance of how social conditions overlap medical concerns.

https://isc3i.isgmh.northwestern.edu/2021-national-ehe-meeting

HIV and COVID-19 - bulletin



COVID-19: HIV and COVID-19 coinfection

Antibody responses to Pfizer vaccine in HIV positive people with high CD4 counts

Simon Collins, HIV i-Base

A small cohort of 12 HIV positive people had similar immune responses to the Pfizer BNT162b2 vaccine as 17 HIV negative people.

The study included 12 HIV positive people (7 women, 5 men) and 17 HIV negative controls (7 women, 10 men) with blood samples taken 7 to 17 days after the second vaccine dose.

Baseline characteristics of the HIV group included median CD4 count or 913 cells/mm^3 (range: 649 to 1678) with undetectable viral load <50 copies/mL (n=9) or very low level viraemia <100 copies/mL (n=3).

There was no significant difference between antibody titers in the positive vs negative groups (median 8.84 vs 9.49 respectively, p=0.07. There were also no differences between the groups for responses to any common variants or in the breadth of T-cell responses.

C O M M E N T

These data are useful but ideally should have been published earlier – and the phase 3 studies should also have also enrolled larger groups of HIV positive people and others at higher risk.

The HIV positive group all had very high CD4 counts on ART when so-called "normal" responses would be expected.

It is important for all vaccines to report responses that include a wider range of low CD4 counts and higher levels of viral load.

Reference

Woldemeskel BA et al. The BNT162b2 mRNA vaccine elicits robust humoral and cellular immune responses in people living with HIV. ciab648, doi: 10.1093/cid/ciab648. (22 July 2021).

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COVID-19: VACCINE RESEARCH

Third dose of mRNA vaccine improves antibody responses in kidney transplant recipients

Simon Collins, HIV i-Base

On 23 July 2021, a research letter in JAMA reported that a third vaccine effectively increase antibody response in 49% of kidney transplant recipients who had no or minimal antibody levels after the second dose.

Results were from University Hospital Strasbourg, following the early French recommendation to use a third vaccine

The included 159 kidney transplant recipients. The median age was 57 years (IQR: 49 to 66), 61% were men, and the median time from transplantation was 5.3 years (IQR, 1.9 to 11.1).

The definition of suboptimal response was IgG antibody levels > 50 arbitrary units/mL

At baseline (median 51 days, IQR: 48 to 59), 64/159 participants had antibody levels between 6.8 to 49.0 AU/mL and 95/159 had antibody levels below the test sensitivity limit (test range: <6.8 to 80,000 AU/mL).

After the third dose, measured after a median 28 days (IQR: 27 to 33 days), 78/159 (49%) had levels >50 AU/mL (median 586; IQR: 197.2 to 1920.1 AU/mL).

In multivariate analysis, only baseline antibody levels and use of triple immunosuppressant therapy (tacrolimus + MMF/MPA + steroids) were significant predictors of responding >50 AU/mL (p=0.001 and p=0.006 respectively).

Importantly, 27% of people with baseline responses <6.8 AU/mL responded to >50 AU/mL (compared to 81% of those who started at 6.8 to 49.9 AU/mL).

C O M M E N T

These results support offering a third vaccine dose to previous non-responders, similar to other studies reported last month in the July issue of HTB. [2, 3]

They also show the urgency of finding alternative strategies for half of the group that still remain highly vulnerable to SARS-CoV-2.

Generating a response from those who started below the limit of detection perhaps suggests a fourth dose, perhaps with a different vaccine, might be important to study.

The UK has not yet published detailed plans for a potential third dose in September, but the rough details suggested this would not prioritise people based on previous antibody response.

The UK also apparently has no mechanism for people to access a third dose - and this should be urgently reviewed based on identifying non responders in the most vulnerable groups. This include those older than 80, people on immune suppressing treatment (for cancer or in transplant recipients), and HIV positive people with CD4 counts <50 cells/mm^3.

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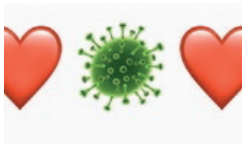
US CDC recommend third vaccine dose in some patients

Simon Collins, HIV i-Base



At a meeting on 22 July 2021 of the Advisory Committee on Immunization Practices (ACIP), a presentation from the US CDC recommended a third dose for some people who are immunocompromised. [1]

An excellent slide set compiling the available evidence is also available online. [2]

Based on 2013 data, the CDC estimates this group to be approximately 2.7% of the US adult population (roughly 5 to 6 million people).

This includes:

- Solid tumour and hematologic malignancies.
- Receipt of solid-organ or hematopoietic stem cell transplant.
- Severe primary immunodeficiencies.
- People living with HIV.
- Treatment with immunosuppressive medications. These include cancer drugs, TNF blockers, certain biologic agents (eg rituximab), and high-dose corticosteroids.

This is not proposing a third dose to the whole population.

Currently, many people who have received two doses assume protection when this might not be the case. These people are more likely to have breakthrough infections.

- 44% of hospitalised breakthrough cases in the US are immunocompromised people.
- 40% of hospitalised breakthrough cases in Israel are immunocompromised people.

The recommendations are similar to earlier guidelines in France, Israel and the UK. [3, 4, 5]

The US FDA with also apparently need to either approval this off-label use or approve the third vaccine.

Pfizer announced plans to apply for an indication for three doses in July 2021. [6]

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Pfizer plans for third dose: questions over population need?

Simon Collins, HIV i-Base

One of the key emerging issues has been over the need for a third vaccine dose.

Accumulating reports, show the benefit of a third vaccine in some vulnerable populations that fail to generate optimal antibody responses after two shots. [1, 2, 3]

This is easy to support. It is in line with national vaccine programmes to ensure protection in people at highest risk of severe COVID-19.

But this is different to the proposal for universal use of a booster dose on a population level. Offering vaccines to all adults in rich countries, not only delays first course programmes to the rest of the world but involves the commercial conflict of large profits for manufacturers.

Over the last month, Pfizer has reported plans to apply to the FDA for coverage of a third dose, though anecdotal rather in a formal press release. This would extend the indication from a two dose to a three dose schedule. [4]

The evidence to support this need is limited, largely based on waning antibody protection and reports from the vaccine programme in Israel. A pre-review analysis from the original phase 3 study also reported that after six months, protection against symptomatic infection dropped from 96% to 84%. [5]

But this is for symptomatic infection and doesn't report reduced efficacy against hospitalisation. This paper, not yet peer reviewed, says further follow-up to two years is needed before knowing whether a third booster dose is needed.

So far the US CDC and FDA have announced that there is currently no need for a universal third dose. [6]While data on the safety on a third dose would help individuals who didn't generate immune responses to two vaccines, the clinical need for the third dose is likely to be more complicated than waning antibody levels, especially if the proposed booster doses have not been developed to produce strong protection against variants.

Also, current data, including from the UK, show current vaccines are currently effective at reducing hospitalisation against the Delta variant, even if transmission and mild symptoms still occur. [7]

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2. Third vaccine dose increases immune response to 68% in French transplant recipients. HTB (July 2021).
   https://i-base.info/htb/40812
3. Third COVID-19 vaccine dose in US cohort of people on immune-suppressing treatment: safety and ethical issues. HTB (1 July 2021).
   https://i-base.info/htb/40843
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https://i-base.info/htb/41034

Efficacy of Pfizer and Oxford/AZ vaccines against Delta variant in the UK

Simon Collins, HIV i-Base

Two papers from Public Health England (PHE), one ahead of peer review, have reported likely efficacy of the Pfizer and Oxford vaccines against the Delta variant.

The first, published in the NEJM, reported modestly reduced efficacy against symptomatic infection with both vaccines against Delta compared to Alpha variants. The absolute reductions were greater after a single dose which was slightly mitigated following the second dose.

The second paper, not yet peer-reviewed reported similar efficacy against hospitalisation to both variants.

However, this analysis was based on only 166 hospitalisations out of 14,019 symptomatic cases with Delta and may be underpowered to show differences.

Both studies report slightly higher absolute efficacy with the Pfizer compared to the Oxford vaccine.

Another recent paper reported lower sensitivity of both Oxford and Pfizer vaccines to the Delta variant with efficacy after two doses estimated at 60% and 88%, respectively. [3]

Table 1: Vaccine efficacy % (95%CI) against symptomatic infection (Lopez-Bernal et al.)

	Delta variant	Alpha
Single dose (both Pfizer and Oxford)	30.7% (25.2 to 35.7)	48.7% (5.5 to 51.7)
Two doses (Pfizer)	88.0% (85.3 to 90.1)	93.7% (91.6 to 95.3)
Two doses (Oxford)	67.0% (61.3 to 71.8)	74.5% (68.4 to 79.4)

Table 2: Vaccine efficacy % (95%CI) against hospitalisation (Stowe et al.)

	Delta variant	Alpha
Single dose (Pfizer)	94% (46 to 99)	83% (62 to 93)
Two doses (Pfizer)	96% (86 to 99)	95% (78 to 99)
Single dose (Oxford)	71% (51 to 83)	76% (61 to 75)
Two doses (Oxford)	92% (75 to 97)	86% (53 to 96)

References
1. Lopez Bernal J et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. NEJM. DOI: 10.1056/NEJMoa2108891. (21 July 2021).
https://www.nejm.org/doi/full/10.1056/NEJMoa2108891

2. Stowe J et al. Vaccines highly effective against hospitalisation from Delta variant. PHE, pre-review access. (14 June 2021). https://www.gov.uk/government/news/vaccines-highly-effective-against-hospitalisation-from-delta-variant
3. Planas D et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. doi: 10.1038/s41586-021-03777-9. (29 June 2021). https://www.nature.com/articles/s41586-021-03777-9

Results from Novavax phase 3 study in the UK

Simon Collins, HIV i-Base

On 30 June 2021, result from the UK sites in the Novavax phase 3 study were published in the NEJM.

This was a randomised, placebo controlled study in over 15,000 participants who received two doses (21 days apart) of NVX-CoV2373 or placebo. The primary endpoint was confirmed COVID-19 occurring at least seven days after the second dose.

Baseline demographics included: 28% >65 years and 45% had coexisting illnesses.

There were 10 vs 96 infections in the active vs placebo groups respectively, showing efficacy of 89.7% (95% CI: 80.2 to 94.6). All 5 cases or severe infection were in the placebo group.

A post hoc analysis reported 86.3% (95% CI: 71.3 to 93.5) against the B.1.1.7 (or alpha) variant and 96.4% (95% CI: 73.8 to 99.5) against non-B.1.1.7 variants.

Serious adverse events were low and similar in the two groups.

C O M M E N T

It is always essential for phase 3 results to be published, though the interpretation of the results is complicated as the Alpha variant is no longer dominant in the UK.

PHE have recently published two studies (one not yet peer reviewed) reporting modest reductions in efficacy of both Pfizer and Oxford vaccines against the Delta compared to Alpha variants. [2, 3]

Reference
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WHO approves Chinese vaccines for emergency use

Simon Collins, HIV i-Base

On 1 June 2020, the WHO approved the Chinese CoronaVac (Sinovac) vaccine against COVID-19. [1]

This was based on limited research that included 51% efficacy against symptomatic infection and 100% efficacy at preventing hospitalisation and death.

Phase 3 studies are currently ongoing in Brazil, Chile, Indonesia, and Turkey and results from a large prospective national vaccine programme in Chile were just published in the NEJM. [2]

This is the second Chinese vaccine to be given WHO emergency use approval. On 7 May 2020, the WHO approved the Sinopharm vaccine developed by the Beijing Institute of Biological Products. [3]

Both vaccines have already been widely used in low-income countries. However, WHO approval means they can be included in the international COVAX programme.

Both vaccines use inactivated virus.

The WHO have also approved vaccines by Pfizer, AstraZeneca, Johnson & Johnson, Moderna and the Serum Institute of India (CoviShield). [4]

References
1. WHO validates Sinovac COVID-19 vaccine for emergency use and issues interim policy recommendations. (1 June 2021). https://www.who.int/news/item/01-06-2021-who-validates-sinovac-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations
2. Jara A et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. NEJM. DOI: 10.1056/NEJMoa2107715. (7 July 2021). https://www.nejm.org/doi/full/10.1056/NEJMoa2107715
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Efficacy of Chinese CoronaVac vaccine in Chile national programme

Simon Collins, HIV i-Base

Although the Chinese CoronaVac vaccine is already widely used in many middle- and low-income countries and is approved by the WHO, phase 3 results have not been published.

However the results of a prospective observational study of this vaccines in more than 10 million people in the Chile vaccine programme from February to May 2021 are reported in the NEJM. [1]

Vaccine effectiveness in more than 4 million people who had received two doses included 65% at preventing symptomatic COVID-19, 87% at preventing hospitalisation and 86% at preventing deaths. Similar efficacy was reported for older people (>60 years), see Table 1.

The study didn't include details of likely background prevalence of variants.

Table 1: Efficacy rates following two doses of CoronaVac in Chile

Prevented event	Overall efficacy (95%CI)	Efficacy in >60 years
COVID-19	65.9% (65.2 to 66.6)	66.6% (65.4 to 67.8)
Hospitalisation	87.5% (6.7 to 88.2)	85.3% (84.3 to 86.3)
ICU admission	90.3% (89.1 to 91.4)	89.2% (87.6 to 90.6)
Mortality	86.3% (84.5 to 87.9)	86.5% (84.6 to 88.1)

C O M M E N T

Similar results from an interim analysis of the phase 3 study conducted in Turkey were also just reported in the Lancet. [2]

References
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Other selected vaccine studies

Simon Collins, HIV i-Base

The following short summaries and links cover other important vaccine papers.

Breakthrough infections corelate with levels of neutralising antibodies

This paper reports 39/1497 breakthrough infections in fully vaccinated heath workers in Israel were lower compared to unvaccinated controls (ratio: 0.36; 95%CI: 0.16 to 0.78). Most had mild/moderate symptoms but 19% lasted >6 weeks. The inverse correlation with levels of neutralising antibodies suggests these levels might be a valid marker of therapeutic vaccine efficacy.

Ref: Bergwerk M et al. Covid-19 breakthrough infections in vaccinated health care workers. NEJM. DOI: 10.1056/NEJMoa2109072. (28 July 2021).

https://www.nejm.org/doi/full/10.1056/NEJMoa2109072

Vaccine efficacy reduced against Delta virus

Being fully vaccinated still significantly reduces risk of symptomatic infection and hospitalisation from the Delta variant. However, the lower potency might be clinically more significant in vulnerable groups who generates lower levels of neutralising antibodies.

"Sera from convalescent patients collected up to 12 months post symptoms were 4 fold less potent against variant Delta, relative to variant Alpha (B.1.1.7). Sera from individuals having received one dose of Pfizer or AstraZeneca vaccines barely inhibited variant Delta. Administration of two doses generated a neutralising response in 95% of individuals, with titers 3 to 5 fold lower against Delta than Alpha."

Ref: Planas D et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. doi: 10.1038/s41586-021-03777-9. (29 June 2021).

https://www.nature.com/articles/s41586-021-03777-9

Antibody responses and likely duration of protection

Complex study comparing antibody responses from seven phase 3 vaccine and convalescent cohort studies that estimate neutralisation levels and model duration of protection. Correlates early efficacy with durability to estimate importance and timing of booster doses.

Ref: Khoury DS et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nature Medicine 27:1205–1211. (17 May 2021).

https://www.nature.com/articles/s41591-021-01377-8

Data review from mixing vaccines

A review article in Nature for results from five studies that have used mixed vaccine strategies.

"…a least 16 vaccines have been approved for use in one or more countries, and mix-and-match studies so far have been small, so more extensive trials and long-term monitoring for side effects are sorely needed."

Ref: Lewis D. Mix-and-match COVID vaccines: the case is growing, but questions remain. Nature 595, 344-345. (1 July 2021).

https://www.nature.com/articles/d41586-021-01805-2

Vaccines generate long-term immune responses

"Our studies demonstrate that SARS-CoV-2 mRNA-based vaccination of humans induces a persistent germinal centre B cell response, which enables the generation of robust humoral immunity."

"…In this study, we show SARS-CoV-2 mRNA vaccine-induced germinal centre B cells are maintained at or near peak frequencies for at least 12 weeks after secondary immunisation."

Reference

Turner JS et al. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre. Nature. (28 June 2021).

https://www.nature.com/articles/s41586-021-03738-2

Data on Sputnik V vaccine

A review of accumulated evidence from the Russian Spuknik V vaccine, which is so far neither EMA nor WHO approved. Sputnik V uses two different adenoviruses, for the first and second dose (rAd26 and rAd5, respectively).

Sputnik has already been used in some country vaccine programmes including Russia, Argentina, Hungary, Iran and Brazil and it is also being manufactured in South Korea, Argentina and India.

Other studies are still ongoing, including in the UK.

Reference
Mounting evidence suggests Sputnik COVID vaccine is safe and effective.
https://www.nature.com/articles/d41586-021-01813-2

High antibody responses following two vaccines dose in UK study: similar responses in all groups

Significant differences in antibody levels following a single dose were reported, including by age, comorbidity and use of immunosuppressive therapy.

However, these difference largely resolved in all groups following a second dose, with antibody titres above the minimum target of 250 U/mL observed for nearly all people across all ages, demographics, and clinical groups.

The main group still reporting significantly lower responses (approximately 80% protected) were people with a history of haematological cancer. Antibody titres were also lower in people on immunosuppressive therapy. The study included 9 HIV positive people, but without CD4 details.

The study included 8,517 vaccinated participants (median age 65 years [IQR: 58, 71]). Approximately 60% used the Oxford vaccine and 40% Pfizer.

References

Shrotri M et al. Spike-antibody responses following first and second doses of ChAdOx1 and BNT162b2 vaccines by age, gender, and clinical factors - a prospective community cohort study (Virus Watch). Medrxiv pre-print, 2021.05.12.21257102v2. (15 May 2021).
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COVID-19: TREATMENT

NHS supports selected use of inhaled budesonide for COVID-19 in people at risk of severe events

Simon Collins, HIV i-Base

Interim results from a randomised open-label UK study using the inhaled steroid budesonide reported faster recovery and reduced hospitalisation in people with mild COVID-19 at higher risk of progression,

The Principle Study is a multicenter, open-label, multi-arm, adaptive platform trial that randomised 4663 participants to inhaled budesonide (800 ug twice daily for 14 days), or standard of care. Entry criteria included being with 65 years or older, or 50 years and older with comorbidities. Participants were enrolled from November 2020 to March 2021 and needed to be unwell for less than 14 days with suspected COVID-19.

Co-primary endpoints were time to first self-reported recovery, and hospitalisation/death related to COVID-19, both over 28 days.

Overall, 2617/4663 participants (56%) tested SARS-CoV-2 positive and contributed data: 751 budesonide, 1028 usual care and 643 to other interventions.

Time to first self-reported recovery was shorter in the budesonide group compared to usual care (HR 1.208, 95% BCI: 1.076 to 1.356). Estimated benefit of 3.0 days (95% BCI: 1.1 to 5.4).

Among those with 28 days follow up, there was no significant benefit in reduced COVID-19 related hospitalisations or mortality: 59/692 (8.5%) vs 100/968 (10.3%). The estimated percentage benefit was 2.1% (95% BCI: –0.7% to 4.8%).

More than 80% of participants reported taking budesonide for more than a week.

A second UK study also reported benefits from inhaled steroid budesonide with results published in Lancet Respiratory Medicine. [2]

The STOIC study was an open-label, parallel-group phase 2 that randomised 146 adults within seven days of symptoms to inhaled budesonide (800 ug twice daily until symptoms resolved), or standard of care.

Median age was 45 years (range: 19 to 79) with no significant differences in baseline characteristics between groups. Just over half were women, 93% were white and most people had only one comorbidity. The median duration of symptoms before randomisation was 3 days (IQR: 2 to 4) with median recovery after 7 days (IQR: 5 to 11). Budesonide was taken for a median of 7 days (IQR: 4 to 10).

Budesonide was associated with significantly reduced primary outcome of the need for an urgent care (often hospitalised): reported in 1/69 (1%) vs 10/70 (14%) participants, respectively; (difference 0.131, 95%CI: 0.043 to 0.218; p=0·004). Results were similar in the ITT analysis.

Clinical recovery was 1 day shorter: median 7 v 8 days log-rank test p=0·007.

Fewer participants reported fever or use of anti-fever medication (p=0.025) or reported persistent symptoms at days 14 and 28 (p=0·003).

However, oxygen saturations (p=0.943) and SARS-CoV-2 viral load (p=0.554), measured by cycle threshold, were not different between the groups.

There were no serious side effects with only five (7%) participants reporting self-limiting adverse events.

This produced a number needed to treat (NNT) of 8 to prevent one serious hospitalisation.

The study was also stopped early after a DSMB recommendation that further enrolment would not change the outcome.

COMMENT

The results from the PRINCIPLE study were also reported in a press release from NHS England with recommendation to consider use based on meeting all the following eligibility criteria.

- **Symptomatic, with onset within 14 days.**
- **PCR-confirmed COVID-19 within the past 14 days.**
- **Age 65 years and over or 50 years with a long-term significant comorbidity.**

For more details, including dosing and important exclusion criteria and contraindications please see full statement. [3]

This document also noted the positive results from the published phase 2 STOIC trial.

It is unfortunate that a placebo steroid was not available or used especially given the reliance on self-reported recovery, but without significant differences in viral load.

References

1. Yu L-M et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. MedRxiv pre-print. 10.1101/2021.04.10.21254672. (12 April 2021).
https://www.medrxiv.org/content/10.1101/2021.04.10.21254672v1
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3. NHS UK. Interim Position Statement: Inhaled budesonide for adults (50 years and over) with COVID-19. (12 April 2021).
https://www.england.nhs.uk/coronavirus/publication/interim-position-statement-inhaled-budesonide-for-adults-50-years-and-over-with-covid-19
https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/04/C1253-interim-position-statement-inhaled-budesonide-for-adults.pdf (PDF)

Reviews of ivermectin for COVID-19: evidence from RCTs is still needed

Simon Collins, HIV i-Base

The delayed timeline for global access to vaccinations still leaves an urgent gap for treatments that could reduce the risk of hospitalisation with COVID-19.

Although the antiparasitic drug ivermectin has the profile of being cheap and affordable, the limited evidence of efficacy, often from poorly designed studies with low quality of evidence (QoE) has produced conflicting results.

Two recently published meta-analyses also come to different conclusions.

Roman and colleagues reported on outcomes from ten RCTs with 1173 participants, adjusting for risk of bias. Half the studies used standard of care as controls and half used placebo. [1]

Ivermectin did not reduce all-cause mortality (RR 0.37, 95%CI: 0.12 to 1.13, very low QoE) or length of hospital stay (median 0.72 days, 95%CI: –0.86 to 2.29, very low QoE).

Adverse events, severe events and viral clearance were similar between ivermectin and controls (all outcomes: low QoE). Although all-cause mortality was reduced in three RCTs with a high risk of bias, the authors concluded that ivermectin is not a viable option to treat COVID-19.

A second meta-analysis includes more studies and has a more positive results, but still defers to the need for results from large randomised studies, together with an accompanying editorial. [2, 3]

This paper was based on results from using ivermectin in 24 RCTs with 3328 participants, including studies in the first review above.

In the 11 RCTs of moderate/severe infection, there was a 56% reduction in mortality (RR 0.44, 95%CI 0.25 to 0.77), p=0.004. There was also reduced mortality: 35/1064 (3%) vs 93/1063 (9%) with reduced time to recovery (–1.58 days, 95% CI: –2.8 to –0.35, p=0.01). Also, reduced time in hospital (–4.27 days, 95% CI: –8.6 to –0.06, p=0.05).

However, many of these studies were not peer-reviewed and used a wide range of doses.

Ivermectin was also associated with reduced inflammatory markers (C-Reactive Protein, d-dimer and ferritin) and faster viral clearance by PCR.

Viral clearance was related to both the dose of ivermectin and how the length of treatment.

C O M M E N T S

An important complication, and a caution to any positive results – carefully explained in the paper from Andrew Hill – is that pharmacokinetic studies have shown that drug levels achieved with highest tolerable dosing remain too low to have a direct therapeutic effect reported in in vitro studies. Without PK support for a potential mechanism it is difficult to see how ivermectin could work.

Both studies, and an editorial comment that accompanied the paper from HIll et al, if that evidence from adequately powered RCTs is still needed before ivermectin can be recommended. [3]

Unfortunately, the last two published RCTs did not report a benefit. This included a Columbian study that randomised 476 adults with PCR-confirmed mild COVID-19 disease to either ivermectin (300 μg/kg) or placebo for five days, given as an oral solution. [4]

There were no significant differences in the time to resolving symptoms between the two groups: 10 vs 12 days; HR: 1.07 (95CI: 0.87 to 1.32), p=0.53, with symptoms resolving in 82% and 79% in the active vs placebo groups respectively.

A second study from Argentina randomised 501 participants (1:1) to ivermectin or placebo in a staggered dose, according to weight, for 2 days. There was no significant difference on the primary endpoint of hospitalisation: 14/250 (5.6%) vs 21/251 (8.4%) in ivermectin vs placebo (OR: 0.65; 95% CI: 0.32 to 1.31), p=0.227. [5]

The UK Principle RCT still includes ivermectin. [6]

STOP PRESS: Shortly after this HTB article was published, one of the positive RCTs (by Elgazzar et al) was withdrawn due to serious irregularities in the data set. [7] Removing the 90% benefit reported by this study will significantly affect the results of the meta-analyses report above.

Hill et al are already reanalysing the data used for all the studies in their review, which included another study that is also being questioned. This will take several weeks, but it will also make it much more difficult to see any benefit from ivermectin.

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   https://www.theguardian.com/science/2021/jul/16/huge-study-supporting-ivermectin-as-covid-treatment-withdrawn-over-ethical-concerns

RCT shows no impact of azithromycin in reducing symptoms of mild COVID-19

Simon Collins, HIV i-Base

The lack of impact from a single dose antibiotic at improving COVID symptoms is likely to surprise few people, but the results from the RCT are published in JAMA.

Between March 2020 to May 2021, this US out-patient study randomized 263 outpatients (2:1) to a single oral 1.2 g dose of azithromycin (n=171) or matching placebo (n=92).

Among outpatients with SARS-CoV-2 infection, treatment with a single dose of oral azithromycin compared with placebo did not result in a greater likelihood of being free of symptoms at day 14.

And by day 21, more participants in the azithromycin group had been hospitalised compared with the placebo group: 5 vs 0 (difference +4%; 95% CI: −1% to 9%; p=0.16), although the difference was not significant.

Reference

Oldenburg CE et al. Effect of oral azithromycin vs placebo on COVID-19 symptoms in outpatients with SARS-CoV-2 infection: A randomized clinical trial. JAMA. doi:10.1001/jama.2021.11517. (16 July 2021).

https://jamanetwork.com/journals/jama/fullarticle/2782166

COVID-19: PATHOGENESIS

Variation in ACE2 levels are not related to outcomes from COVID-19

Simon Collins, HIV i-Base

A paper published in JID looking at ACE2 receptor levels, used by SARS-CoV-2 to establish infection, was not related to outcome of infection.

The study reported no significant differences in the levels of ACE2 receptor levels related to age or sex from 58 samples from lung tissue. There was no link between variation in levels and levels of SARS-CoV-2 or in the outcomes from COVID-19.

This meant that other factors are the likely cause of this higher risks of COVID-19 in older people and in men.

Reference

Li K et al. Inter-subject variation in ACE2 protein expression in human airway epithelia and its relationship to SARS-CoV-2 infection. JID. jiab383, doi: 10.1093/infdis/jiab383. (21 July 2021).

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

Virology Education meeting and workshops

Several VE workshops are highlighted below but 35 meetings are planned for 2021:

https://www.virology-education.com

29th International Workshop on HIV Drug Resistance and Treatment Strategies

Virtual - four 120-minute sessions

6 September 2021, 18h00 – 20h00 SAST (UTC/GMT +2 hours)

13 September 2021, 18h00 – 20h00 SAST (UTC/GMT +2 hours)

20 September 2021, 18h00 – 20h00 SAST (UTC/GMT +2 hours)

27 September 2021, 18h00 – 20h00 SAST (UTC/GMT +2 hours)

https://www.hivresistance.co.za

12th International Workshop on HIV & Aging

23 – 24 September 2021. Virtual

https://www.virology-education.com

IDWeek 2021

29 September – 3 October 2021, Virtual

www.idweek.org

18th European AIDS Conference (EACS 2021)

27 – 30 October 2021, Hybrid - virtual and in London

https://eacs-conference2021.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

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

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

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

Pocket guides

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

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

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

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

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

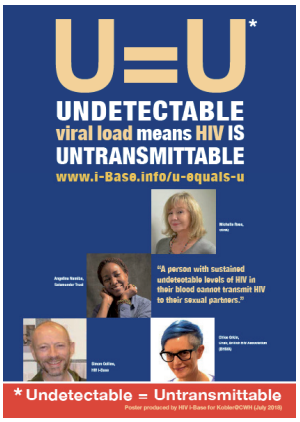
This project was developed with the Kobler Centre in London.

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

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

email: subscriptions@i-base.org.uk

Customise U=U posters for your clinic



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

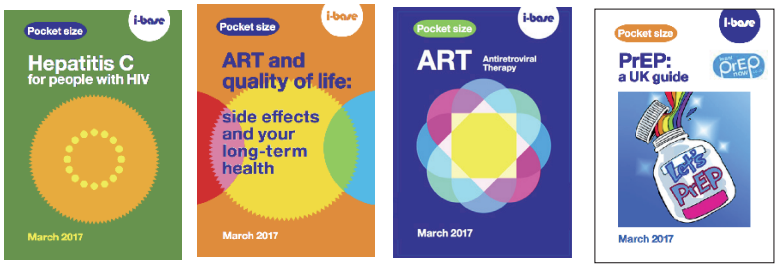
Personalising these for your clinic is cheap and easy and might be an especially nice way to highlight the good news.

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

roy.trevelion@i-Base.org.uk

Order publications and subscribe online

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



h-tb

HIV TREATMENT BULLETIN

HTB is published in electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered using the form on the back page or directly from the i-Base website:

http://www.i-Base.info

by sending an email to: subscriptions@i-Base.org.uk

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

HIV i-Base receives unconditional educational grants from charitable trusts, individual donors and pharmaceutical companies. All editorial policies are strictly independent of funding sources.

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http://www.i-Base.info

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☐ I would like to make a donation to i-Base - *Please see inside back page*

- **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**

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

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