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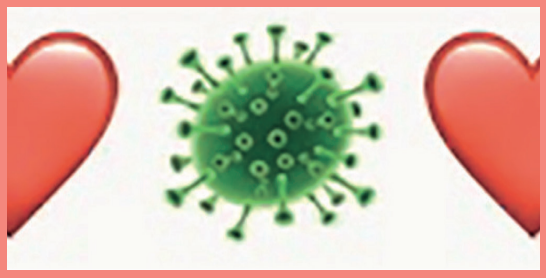
hiv treatment bulletin (e)



R4P reports; COVID variants, vaccines and treatment (24 February 2021)

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Published by HIV i-Base

HTB no.2 (2021): HIV and COVID-19 supplement ISSUE 2

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 is a difficult issue of HTB for having to lead with articles in memory of three friends: Elias Phiri, Dr Joseph Sonnabend and Timothy Ray Brown. Their lives made ours richer and they will be missed.

And as with every issue over the last year, we aimed to minimise coverage of COVID-19 - but the pace of important research means that this is still very much a double issue with HIV news.

HIV prevention news from the R4P 2021 virtual meeting includes the complicated story of the AMP studies using a monoclonal antibody (mAb) for HIV prevention but also another mAb to prevent vertical transmission and review other prevention technologies for use by women.

Other news includes a new 4-in-1 ART for children, and a new study for MDR HIV and a community education programme in Soweto that i-Base partnered.

And for COVID-19, this issue is launched just as all HIV positive people in the UK become eligible for a vaccine and that this can be given at HIV centres.

We cover variants, vaccines and treatment, including the greater pathogenesis of B.1.1.1.7 and the serious under-reporting of COVID-19 in Zambia.

The seven other articles on vaccines include the Novavax and Janssen vaccines that both enrolled HIV positive participants, and new results from both the Sputnik and Oxford vaccines. We celebrate the speed of research in this field and also raise issues of public funding and pricing.

Positive results from treatment trials include the bNAb bamlanivimab as prophylaxis and the IL-6 antagonist tocilizumab in late infection.

More controversially, last month the RECOVERY study reported no benefit from convalescent plasma which might be linked to using low-titre plasma too late in infection, as both the FDA and a recent NEJM paper (Libster et al) remain more optimistic.

In Memory

In memory: Elias Phiri, community HIV and TB advocate

Memory Sachikonye, HIV i-Base

On 27 January 2021, Elias Phiri, a long-standing and much loved community health activist died from COVID-19 after spending almost four weeks in intensive care.

Elias was one of the leading advocates to improve and develop HIV and TB awareness, especially to enable better care for African people living in the UK and Europe. He had an amazing enthusiasm and energy that also made sure than activism celebrated life.

I first met Elias about 15 years ago on a media training course at THT. We then met again when I started working for the UK-CAB in 2008. He was very supportive and always encouraged other HIV advocates - mainly African - to join the UK-CAB. Elias was a dedicated to advocate for HIV and TB causes.

Elias also joined the European AIDS Treatment Group (EATG) when I was co-chair of the membership workgroup. We attended several EATG meetings together and his enthusiasm to support other new members was great. Elias was an inclusive, proactive and effective community leader. He was instrumental in supporting new UK and EU members who joined EATG. He also supported many projects in the Black HIV communities in UK and abroad to include diverse communities.

Hope Mhereza, i-Base Trustee who knew Elias for many said: Elias dedicated his life to advocating and campaigning for access to HIV treatments and access to accurate information. His reputation preceded him: a professional that is compassionate, dedicated, a community campaigner and a pillar of his community. His legacy is testament to his exceptional human qualities. He surely will be missed and is a great loss to the HIV community. One thing that stood out from the hundreds of tributes online is that Elias was “an exceptional leader with a heart for community”.

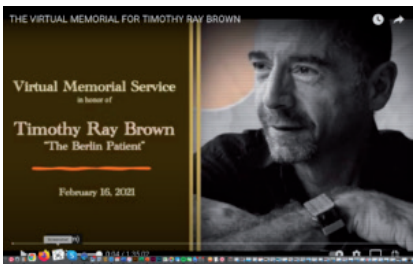
I know I will remember Elias as friend, brother and a great advocate. He touched many lives and his memory and fighting spirit will always live with us. May his family and friends find comfort and remember all his work.

Rest in eternal peace Elias.

Memory Sachikonye, HIV i-Base

Timothy Ray Brown: a virtual memorial

Simon Collins, HIV i-Base



On 16 February 2021, a celebration and virtual memorial was held for Timothy Ray Brown.

This included many community speakers and friends talking about the special impact he had on their lives. This would have been his 14th anniversary of his HIV cure.

This recording is now online:

https://youtu.be/mCYrznU8JI8

This information has also been added to the i-Base in memory page.

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

https://i-base.info/htb/39020

In memory: Dr Joseph Sonnabend, pioneer HIV activist and researcher

Simon Collins, HIV i-Base

It is with great sadness that we report that on 24 January 2021, Dr Joseph Sonnabend, the pioneer activist and research, died after a short illness.

Joseph Sonnabend was one of the most important and high profile HIV doctors in the US who was less known in the UK because his working life was spent in New York. In 2005, he retired to London, where he continued to talk and write about HIV, and where, together with other UK activists, I had a chance to get to know Joe as a friend.

Joe was a highly intelligent and complex man, who above everything else was loved by his patients. Many became close friends and at different times he was the doctor for most of the leading US activists, who credit him now for their surviving long enough to benefit from treatment. He had a daunting reputation for founding key organisations, and a character that, at least in later life, as well as being fiery, was cautious and self-doubting.

Early in his career, Joe was a microbiologist and basic science researcher at the Medical Research Council (MRC) in London where he worked with Alik Isaacs in a lab that discovered interferon. In the late 60s, he moved to New York to continue this research as an assistant professor at Mount Sinai Medical School. He would pointedly and proudly comment on his pre-HIV career as being "actually quite significant, before all this".

For example, he knew and visited Jan Vilček during the early 196s in what was then Soviet Czechoslovakia.

At some point his research position became complicated (many of his relationships were not straight forward) and he became interested in gay men's sexual health. He worked for the NYC health department (moonlighting), volunteered in the mid-70s for the Gay Men's Health ***Project***, and set up a private medical practice in 1978 (where he would run microbiology samples to get the best results for his patients). He could also make his own poppers. As his practice increasingly focussed on HIV, he often didn't invoice patients; he would take their calls at any time, and support their partners, families and friends.

This meant Joe saw some of the first HIV cases long before AIDS or HIV had been reported or named. He was one of the first doctors to report on immunodeficiency and CD4 counts – at the time only recently discovered. His experience as a microbiologist, scientist and doctor who was also a gay man put him in a unique position to respond to HIV and this quickly became his life's work.

Joe was an early champion of peer advocacy and in supporting the active involvement of HIV positive people in their own care. He worked with Michael Callen and Richard Berkowitz to produce an early high-profile sex-positive guide to safer sex in 1983. This was often difficult. As in the UK, the suggestion to use condoms or to limit partners – based on science not morals – was publicly vilified by many in the gay community.

He also gave people hope, by his confidence that some people would survive, even when so many people were dying. One of his principles about infectious diseases – whether HIV or hepatitis B or coronavirus – is the wide range of responses reported by different people. In this he was right – though – like other major scientists – he was controversial for many other issues.

With Mathilde Krim (already an old friend and who also recently died), Joe founded the first private organisation to fund experimental research. This foundation became amfAR. He helped found the community research organisation that became ACRIA and the PWA group in New York that became one of the first buyer's clubs. At different times, he often became separated from organisations, and found it difficult when he thought he had been treated badly. Joe was outspoken over the lack of key research and could be disparaging over the skills of the doctors and researchers who did come forward to work on HIV. This included some of the highest profile public figures and this, perhaps, didn't make for an easy career path.

In his focus on careful management of opportunistic infections, Joe was using cotrimoxazole as prophylaxis for PCP in the early 1980s, long before most doctors were even using this for treatment. This is more than just a historical chance. Treatments for PCP had been discovered years earlier, and this left Joe with a lifelong anger for how long they took to be commonly used for HIV management

"Infections of the immunocompromised host was a distinct sub-speciality of infectious diseases. There were people who knew about that. […] We knew how to prevent infections and how to treat many of them. That experience could have been brought to help people with AIDS in 1981, including prophylaxis for PCP. That information was known in 1977, so why wasn't that translated into practice?"

Joe accumulated significant records from his life and practice. Many of these were donated to the New York Public Library. But many also came back to the UK, where thanks to his friendship with the HIV activist Simon Watney, another 100 archive boxes are now housed at the at the London School of Hygiene and Tropical Medicine.

One box included thank you cards and letters from his patients – and there were hundreds of these – a copy of the New York Native, or POZ magazine, with Joe on the front cover, records from his own family, maybe from 50 years earlier, notes on early medical papers, a letter from the president of amfAR, another from Marc Christian, plus a couple of gas bills. His early diaries recorded those who had died and he had ansaphone tapes with thousands of messages. Joe kept these voices from the past because they carried the evidence that these people were real and that their lives were important.

But his house also included a grand piano that had come back from NY. Although Joe had composed music throughout his life, he had his first debut in June 2018 at the Fitzrovia Chapel, as part of the AIDS Memorial Project, organised by Ash Kotak, which was filled to capacity, and which also made him smile.

Joe was a pretty fiery activist who fought for his patients, but who was also pretty shy and reserved – as you can hear in some of the linked interviews below. He made a huge impact on thousands of HIV positive people and he will be deeply missed.

Selected links

The first two links below are to BBC interviews that include some of his music and the third is a track from the London concert. The Buzzfeed article is a good portrait of his life in London. Joe also gave the final 100-page interview for the ACT-UP New York oral history project and a webcast interview last year in POZ magazine.

BBC Outlook. How I treated New York's first patients. (3 July 2018).
https://www.bbc.co.uk/programmes/p06crn2t

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Ash Kotak. Eulogy for Dr Joseph Sonnabend.
https://medium.com/@ashkotak_64897/eulogy-to-dr-joseph-sonnabend-96e60ac395bb

CONFERENCE REPORTS

R4P virtual conference (2021)

27-28 January and 3-4 February 2021

Introduction

Every two years this international conference brings together a dynamic programme that highlights the most important research on HIV prevention.

The 2021 meeting was organisation by the IAS and held as a virtual meeting.

Some aspects of the virtual meeting worked well - with most talks quickly available online to delegates.

Other aspects of the meeting made this a very difficult meeting to attend. For example, there was no printable programme or PDF version of an abstract book. Posters were difficult to view with no option to download PDF versions. There was no option to directly email researchers with questions.

It is also unclear whether conference materials will be made available to non-delegates after the meeting. Giving the considerable cost and work to put the meeting online, open access after the event should be routine. Or how long the current website will remain active.

https://www.hivr4p.org

Reports in this issue are:

- VRC01 antibody only prevents minority of HIV infections: AMP study results
- Promising data for multipurpose technologies to prevent HIV and pregnancy

VRC01 antibody only prevents minority of HIV infections: AMP study results

Simon Collins, HIV i-Base

Introduction

Some of the most important news from the virtual R4P conference this year included early results from two large HIV transmission studies using a monoclonal antibody (mAb) called VRC01. This antibody, that showed strong cross-clade neutralisation, was identified in 2009 in an HIV positive slow progressor in the US NIH cohort. It was then isolated and manufactured into a treatment in a collaboration involving many leading public health laboratories.

Even though the studies didn't reduce HIV transmission overall, they showed that VRC01 worked in a subset of participants. Results were presented as a late-breaker oral abstract by Lawrence Corey, study co-chair. Further aspects of this research discussed other aspects of this important research in the last roundtable symposium of the meeting. [1, 2]

Between Spring 2016 and Autumn 2018, the two AMP studies (Antibody Mediated Prevention) randomised over 4600 participants (1:1:1) to receive VRC01 (either 10 mg/kg or 30 mg/kg), or to a matched placebo. Infusions were given every two months (total ten per person) with follow-up over two years.

Entry criteria defined risk of HIV as having anal sex without a condom at least once over the previous six months, or having anal sex with two or more partners over six months. Participants had to be between 18 to 50 years old. Exclusion criteria included some pre-existing health complications including BMI >40

AMP 1 (HVTN 704/HPTN 085) enrolled 2699 gay men and transgender women, in the US (n=1381), Peru (n=1131), Brazil (n=151) and Switzerland (n=36). Of these, 899 received 10 mg, 897 received 30 mg, and 903 received placebo. Roughly 90% identified as male, 5% as transgender female, 2% as female, and 1% each as gender queer, gender non-conforming, or transgender male. Just over half were aged 21 to 30 with another 11% aged 18 to 20. Median number of partners in the previous two months was three and STIs were common at baseline (including 13% with syphilis).

AMP 2 (HVTN 703/HPTN 081) enrolled 1924 heterosexual women in run in seven countries in sub-Saharan Africa, mostly in South Africa (n=1019), Zimbabwe (n=434), Malawi (n=180) and Botswana (n=150). Of these, 642 received 10 mg, 645 received 30 mg, and 637 placebo. Median age was 25 (IQR: 22 to 30) with 42% < 25 years old. Condom use was generally low (55% sometimes, 17% never). Median number of partners in the previous two months was 2 (range: 0 to 300) and 17% reported transactional sex. Approximately 25% had a treatable STI at baseline, mostly asymptomatic (16% chlamydia, 7% trichomoniasis, 2% syphilis).

Efficacy results

The efficacy results from AMP studies are based on the primary endpoint of HIV infections after 80 weeks and safety results were based on follow up at week 104. This was the first time a mAb has been used in large HIV prevention studies.

In combined results, 175 people became HIV positive (98 in the AMP-1 and 77 in AMP-2). Neither dose of VRC01, compared to placebo, had any significant impact on reducing HIV transmission. See Table 1.

However, a subgroup of participants were protected by VRC01 - if this virus was sensitive to the antibody. The lack of effect in the study overall, is related to concerns about dosing, formulation and use of mAb monotherapy, some of which were suspected before the studies started.

Table 1: New HIV positive diagnoses (dx) in AMP studies

	Total dx (n)	Placebo	10 mg	30 mg	Est. efficacy (%) (95%CI)	p-value
AMP-1: 704/085) n=2699	98	38	32	28	26.6% (–11.7% to 51.8%)	0.15
AMP-2: (705/081) n=1924	77	29	29	19	8.8% (–45.1% to 42.6%)	0.70
Total pooled (n=4623)	175 (3.7%)	67 (4.3%)	61 (3.9%)	47 (3.0%)	18.1% (–12.2% to 40.2%)	0.21

Dx: diagnoses; CI: Confidence Interval; HT: heterosexual; TGW: transgender women.

Explaining antibody responses

In the AMP studies, a broad panel of potential viruses were categorised by the IC80 values. Three predefined IC80 categories were <1, 1 to 3 and >3 ug/mL In this analysis, the pooled VRC01 arms were approximately 74% less likely to lead to infections against the most sensitive viruses with IC80 <1 ug/mL. compared to placebo. This subgroup reported 9 vs 19 infections in the pooled VRC01 vs placebo arms respectively: prevention efficacy (PE) 75.4 (95%CI: 44.5 to 88.9). No other factors had an impact on efficacy including gender, population, clade, region or dose.

In explaining these results, there are three main characteristics that are needed for a mAb to be effective.

One is that the virus has to be sensitive to the individual mAb. This is a little like a virus being drug resistant for someone using oral PrEP.

When designing the study, researchers tested VRC01 sensitivity in vitro to a global panel of clade B /C viruses and estimated that 60-70% of strains would be sensitive at a target mAb concentration of <10 ug/mL. Note though that this accepted that 30% of viruses would not be sensitive, so that protection would never be as high as with oral PrEP.

If sensitive, the related second issue is to use a dose (or titre) that will give high enough levels of the mAb - a little like testing drug levels with oral PrEP. The VRC01 doses were chosen to inhibit (ie stop) 80% of viral replication - called the IC 80 (Inhibitory Concentration).

In practice, the estimated sensitivity to VRC01 was accurate: 47/64 viruses (73%) from the placebo participants who became HIV positive were sensitive with an IC80 <10 ug/mL. However, the researchers underestimated the in vivo sensitivity and only 30% were sensitive at IC80 level <1 ug/mL, that had also been selected for the studies.

Finally, a third issue relates to using VRC01 as monotherapy. Just as with HIV treatment, a single mAb can be easily overcome in people who become HIV positive. This was known before AMP and was also observd in the results. [3]

Participants who became HIV positive in the active arms developed approximately 2.4 fold greater IC80 compared to those in the placebo arm (p=0.003). Sensitivity to VRC01 (<1 ug/mL) also resulted in lower post-infection viral load in the treatment arms.

The PK limitations of VRC01 meant that mAb levels had peaks and troughs where protection would be more likely early in the dosing schedule but that would wane during the second month. Long-acting formulations - notably VRC01-LS, also have more consistent PK levels throughout.

This validated early concerns raised about the AMP studies about using monotherapy.

Before the AMP studies started it was already known that VRC01 would only cover about 90% of circulating viruses. So maximum efficacy would likely be less than 90%, perhaps significantly so if resistance developed during low concentration of monotherapy. In fact, the protocol was based on VRC01 having perhaps 60% efficacy. So, even before the first participant were enrolled the researchers knew this intervention would be less effective than oral PrEP.

As PrEP became available in different countries during the study it became included as part of the standard of care for study participants. Although few data were presented on this approximately 40% of AMP1 used oral TDF/FTC with no information given for PrEP use in AMP2.

Overall retention was also good with <10% and 5% drop out in AMP1 and AMP2 respectively, This is a important logistical achievement given the intensity of the treatment. It also provides a timely example for responses to COVID-19 that mAb infusions are feasible acceptable to thousands of participants who are not hospitalised, and in a wide range of countries.

These studies also involved a considerable amount of community involvement and education. This engagement can have positive health effects including increasing participant confidence in this aspect of their health. This is probably what was referred to by participant quoted in various presentations. For example: “Wow, I am so pleased to learn how successful the study has been thus far and I am excited to see what life-changing medicines will come of it” - suggests a disconnect from someone who might have just tested HIV positive.

The congratulatory tone of some of the talks would perhaps have been more appropriate if the study did in fact provide overall protection. Only Michel Nussenzweig, a leading antibody researcher at the Rockefeller University, while acknowledging the logistical achievement, clearly said that the overall results were disappointing, based on issues linked to early modelling and given the knowledge that monotherapy would not suppress infection. [4, 5]

Myron Cohen, the other study co-chair, replied that “at least the train has left the station” - perhaps recognising that the AMP studies were able to use the accumulated 82 kg of VRC01 (a staggering amount of antibody) even though monotherapy with this compound was not going to produce the results that everyone really wanted.

The symposium discussion - recommended to understand many of the details - also commented on the potential for continued treatment to mask HIV infections by suppressing seroconversion (similar to PEP). Also, the general surprise that results were similar for men and women.

The AMP studies were run jointly by the HIV Vaccine Trials Network (HVTN) and the HIV Prevention Trials Network (HPTN).

The American study was run in Brazil, Peru, Switzerland, and the US and the African study was run in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe.

COMMENT

It is important to recognise the lack of overall benefit from the AMP studies - and this doesn’t negate the significant achievement of running large preventions studies against a background of changing research. But it also raises the overlap between ethical and practical questions.

As with other prevention studies, all participants were counselled about HIV risk and given information about how to reduce risks. However, the AMP studies were designed to reduce the risk of HIV transmission and participants joined the studies in the hope that they would not become HIV positive. Therefore, informed consent should also have reflected the possibility of limited protection and that this was an experimental option.

The proof of principle that VRC01 reduced the risk of HIV transmission in a subgroup of participants is also important. It supports future research continuing, using mAbs with greater ptoency and breadth in combinations (including bispecific and trispecific mAbs), that use LS formulations - and ideally only require 6-monthly dosing.

The R4P conference also included results from using VRC07-523LS (a long-acting version of VRC01) to protect infants during breastfeeding, reported below. [6]

In the context of COVID-19, the AMP studies also showed that mAb infusions were an acceptable long-term treatment for thousands of people who were not hospitalised, including in low-income settings.

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Long-acting bNAb is safe and well tolerated and achieves target concentrations in newborns (VRC07-523LS)

Polly Clayden, HIV i-Base

A long-acting broadly neutralising monoclonal antibody (bNAb) VRC07-523LS could achieve target levels in infants for the duration of breastfeeding with three monthly dosing, according to data from IMPAACT 1112, presented at HIVR4P 2021. [1]

Despite the success of antiretroviral therapy, vertical transmission still contributes to the number of new HIV infections each year. One reason for this is transmission among women who acquire HIV during breastfeeding.

A potent bNAb given to HIV-exposed infants has the potential to reduce such transmission.

There could be several advantages to using bNAb in infants:

Exposure is time limited.

Dosing occurs when infants are already in medical care.

Dose volumes are small and easily given subcutaneously.

VRC07-523LS is 5-fold more potent and has a prolonged half-life and a better pharmacokinetic (PK) profile in adults compared to VRC01.

IMPAACT 1112 is an open-label study of VRC07-523LS given to HIV-exposed infants at increased risk of HIV transmission (this group has previously looked at VRC01 in infants [2]).

Non-breastfed infants receive 80 mg subcutaneous (SC) within 72 hours of birth.

Breastfed infants receive 80 mg SC within 72 hours of birth and 100 mg at 12 weeks of age.

The target week 12 plasma level was 10 mcg/mL. Infants are followed for safety, PK and HIV status through week 96.

All infants in the non-breastfed cohort (n=11) were recruited from US sites and those in the breastfed cohort (n=11) from sites in Africa (Zimbabwe or South Africa). All infants received local standard of care infant antiretroviral prophylaxis and received VRC07-523LS dosing within time specified by the protocol (mean 2.5 days for single dose).

Only eight infants in the breast fed cohort received the second dose as the remainder were no longer being breastfed.

Local reactions were rare in the US group but common in the group enrolled in Africa – most were mild and quickly resolved (most severe grade 2). No other adverse events were considered related to study treatment.

PK measurements through week 12 were available for the single dose.

The mean VRC07-523LS levels were: 68.7, 31.1, 16.3 mcg/mL at weeks 4, 8, and 12, respectively. These levels exceeded those previously reported for VRC01 20 mg/kg SC at week 2, 4, and 8. Ongoing growth contributed to the reduction in VRC07-523LS concentration but levels remained over the target of 10 mcg/mL at week 12.

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Promising data for multipurpose technologies to prevent HIV and pregnancy

Polly Clayden, HIV i-Base

Multipurpose technologies for prevention of HIV and pregnancy were the focus of a dedicated session at HIVR4P 2020. This included a antiretroviral and contraceptive vaginal rings as well as a study indicating preference for combined products from heterosexual couples. [1,2 3,4]

Dapivirine and levonorgestrel ring

A combined anti-HIV and contraceptive vaginal ring achieved or exceeded dapivirine and levonorgestrel (DPV/LNG) plasma concentrations sufficient for HIV and pregnancy prevention with cyclic and continuous use. But concentrations in vaginal fluid dropped with periodic removal and it is unclear if HIV prevention efficacy will be maintained although contraceptive efficacy is expected. There was minimal toxicity and no differences in vaginal bleeding profiles between strategies.

The target product is a 90-day extended release vaginal ring – developed by International Partnership of Microbicides (IPM). The study was conducted by the University of Pittsburg.

The ring contains: DPV 200 mg (release rate approximately 440 mcg/day first month then 220 mcg/day) and LNG 320 mg (release rate approximately 120 mcg/day first month then 85 mcg/day).

This was a phase 1 study looking at the feasibility of periodic removal of the ring (which may depend on the rate of local DPV decline). Twenty-five HIV negative women were randomised to continuous vs cyclic (28 days in/2 days out) 90-day use of the ring. They were a median age 36 years, with BMI of 27 and 80% were white.

About a quarter of participants voluntarily removed the ring at least once. About three quarters experienced slippage and 40% full ring expulsion. For some this was a reoccurring issue – the ring is being reformulated to address this with a new clinical trial planned. Overall adherence to protocol was high at about 90%.

With continuous use, median Cmax for DPV 750 pg/mL (IQR 551 to 813) and AUC0–90 50471 pg*d/mL (IQR 44680 to 56279). As expected, in the cyclic group, the plasma concentrations dropped two days after ring removal but plasma DPV remained at target levels associated with previously demonstrated efficacy (25 mg DPV ring now with WHO prequalification).

LNG median Cmax was 1675 pg/mL (IQR 1341 to 2334) and) and AUC0–90 79987 pg*d/mL (IQR 72633 to 93980). Again there was a drop in LNG concentrations in the cyclitic group but this remained in the range associated with contraceptive efficacy.

There was a steep drop in median concentrations for DPV and LNG in vaginal fluid. This was from about 100,000 ng/g to only about 10 ng/g over hours not days for DPV. Although drop in LNG was also pronounced, this is not expected to affect the contraceptive efficacy. But for DPV the implications are currently unknown – it is not clear whether concentrations in vaginal fluid, tissue or plasma are critically important for prevention of HIV.

There were 84 AEs, most were mild (80%) or moderate (29%). There was no difference in genitourinary AEs or grade 2 or higher AEs by arm. There was one grade 4 anaemia in the cyclitic arm judged related to study product in a participant who reported heavy vaginal bleeding. There were no differences in bleeding patterns between arms overall.

Tenofovir and levonorgestrel ring

TFV/LNG and TFV alone vaginal rings were shown to be safe when used by Kenyan women. Pharmacokinetic (PK) characteristics and markers of protection against HIV and pregnancy suggest the potential for clinical efficacy of these rings.

In this phase 2a study, 27 women were randomised 2:2:1 to use vaginal rings: tenofovir (TFV)/LNG (n=11); TFV alone (n=11); and placebo (n=5). Participants were a mean age of 24 (SD 4.7) and enrolled in Kisumu. Median days of ring use was 68 (IQR 36 to 90).

The most common AEs were headache and upper respiratory tract infection. The most common grade 2 AEs were bacterial vaginosis, upper respiratory tract infection and reduction in glomerular filtration rate. These were not judged to be product related.

Nine AEs (8 in TFV/LNG and 1 in TFV arms) were considered to be related to product use – all were related to menstrual bleeding changes and all resolved spontaneously.

TVF concentrations in cervicovaginal fluid (CVF) increased rapidly after insertion and declined on removal. Six hours after insertion TFV concentrations were: 1300 ng/swab in the TFV/LNG arm and 827 ng/swab in the TFV arm. Median steady state concentrations (reached within 24 hours) were: 70,550 ng/swab and 56,572 ng/swab in the respective arms.

TFV plasma concentrations were below quantification throughout period of vaginal ring use.

LNG serum concentrations also showed a quick upsurge after insertion, reaching 400 pg/mL within six hours. Median steady state concentration was 283 pg/mL (threshold for contraceptive effect: 200 pg/mL).

There was high anti-HIV activity in CVF among arms with TFV-containing rings vs placebo. There was also high anti-HSV activity in CVF with TFV-containing rings.

Tenofovir and levonorgestrel ring: CONRAD A15-138

Data from CONRAD A15-138 also suggested that a TFV/LNG vaginal ring was safe, acceptable and delivered high TFV concentrations locally with contraceptive efficacy.

This was a phase I study among HIV negative women, conducted in Norfolk, VA and the Dominican Republic, evaluating the safety, PK, pharmacodynamics (PD), and acceptability of CONRAD's TFV/LNG ring following three months of continuous or interrupted use.

Participants were randomised to 1 of 4 study arms: TFV/LNG or placebo ring worn continuously for approximately 90 days or cyclically for 3 cycles of 28 days of use with 3 days removal then re-insertion. Forty women were randomised and completed all visits.

AEs were mild or moderate – there were no grade 3 or above AEs considered related to study product. There were no significant changes in cervicovaginal epithelium, immune cell populations or soluble immune and inflammatory markers from baseline.

The majority of participants reported either no change in their menstrual cycle or fewer/lighter bleeding days – there were no differences between arms.

Median vaginal fluid TFV concentrations were 546 to 3077 ng/mg throughout 90 days of use. Median TFV-DP tissue concentrations exceeded 1,000 fmol/mg within 72 hours of insertion. High levels remained through five days after removal.

Modelling showed at 1 and 3 months of use, vaginal fluid of women using TFV/LNG rings had significantly greater inhibitory activity against HIV in vitro compared to baseline and to placebo ($p<0.01$).

TFV/LNG ring users had mean serum LNG concentrations exceeding 200 pg/mL within 2 hours of insertion – these levels were not maintained in the cyclitic group.

The microdose of LNG caused changes in cervical mucus (CM), sperm penetration and ovulation compatible with contraceptive efficacy, while inducing acceptable changes in menstrual bleeding patterns.

Preference for combined products in the CUPID study

Heterosexual couples, both individually and jointly, showed high interest in products that combine HIV and pregnancy prevention in the CUPID study, conducted in Uganda and Zimbabwe .

Most research with users of future HIV prevention products has focused on women. The CUPID study looked at preferences for future technologies for pregnancy and HIV prevention and examines relationship-based issues to inform the development and use of these products. It was a multi-methods cross-sectional study started in January 2020.

This study found, of 400 couples (mean age: 26 years women and 31 years men), enrolled through March 2020, nearly all (91%) showed a preference for a dual vs single purpose product.

Benefits indicated included ease of using a 2-in-1 product; women liked to have the ability to present the product as just a contraceptive; and fewer clinic visits. Disadvantages included concerns that combined products might have more side effects; the need to switch methods when pregnancy is desired; and higher volume of drugs in the body.

The majority (73% Zimbabwe and 58% Uganda) of couples selected oral tablets as their ideal formulation, while 27% and 44% in Zimbabwe and Uganda respectively preferred a vaginally-delivered product (ring, insert or film).

Although most participants preferred longer-duration products (2 to 3 months), one-third indicated their ideal product would be monthly and 10% favoured on-demand.

References

All references are to the programme and abstracts for HIV Research for Prevention (HIVR4P) virtual conference.

https://virtual.hivr4p.org/media-452-oa06---multipurpose-prevention-technologies-mpts-for-prevention-of-hiv-and-pregnancy (Webcast - all presentations)

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https://programme.hivr4p.org/Abstract/Abstract/902
2. Mugo N et al. Randomised, placebo-controlled trial of safety, pharmacokinetics, and pharmacodynamics of 90-day intravaginal rings (IVRs) releasing tenofovir (TFV) with and without levonorgestrel (LNG) among women in Western Kenya. Oral abstract OA06.02.
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https://programme.hivr4p.org/Abstract/Abstract/528
4. Minnis A et al. Heterosexual couples' preferences for dual-purpose prevention products for HIV and pregnancy prevention: the CUPID Study (MTN-045) in Uganda and Zimbabwe. Oral abstract OA06.04.
https://programme.hivr4p.org/Abstract/Abstract/676

HIV DRUG RESISTANCE

UK study for people with triple-class drug resistance

Simon Collins, HIV i-Base

A new study designed to overcome multidrug HIV resistance in people whose currently combination is failing to achieve and maintain undetectable viral load.

This is a two-part study. For the first week, participants will be randomised to one of four blinded arms. This will add islatravir, doravirine, both drugs or placebo to their current failing combinations. All participants will then add open-label islatravir and doravirine to optimised background ART for the next 48 weeks.

At the end of the study all participants will have the option to continue to use islatravir/doravirine.

Entry criteria include:

- Adult or adolescent (12 years or older).
- Viral load >500 copies/mL.
- Drug resistance to at least three classes, including to NRTI and NNRTIs.
- Limited alternative ART (based on drug resistance, tolerability/side effects, access or patient acceptability).

Exclusion criteria include genotypic resistance to doravirine or current ART that includes nevirapine, efavirenz or etravirine.

The two sites are the Royal Free Hospital in London and Western General Hospital in Edinburgh.

Importantly, the study will cover expenses, including travel costs for participants from other UK clinics to be able to attend these sites.

For further details please contact research coordinators at either site.

Royal Free:

Tom Fernandez or Johnny Edwards

T: 020 7472 6232 or email: thomasfernandez@nhs.net or jonathan.edwards4@nhs.net

Western General:

Sheila Morris

T: 0131 537 2840 or email: RIDUresearch@nhslothian.scot.nhs.uk

OTHER NEWS

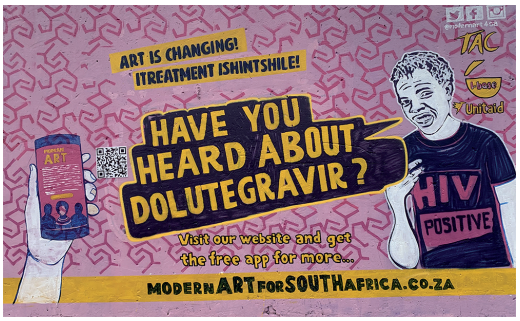
Community murals in Soweto on dolutegravir-based ART: an i-Base collaboration

Nomatter Ndebele, HIV i-Base

South Africa's antiretroviral therapy regimen has been upgraded to include dolutegravir. The Treatment Action Campaign has partnered with i-Base to create awareness about the new regimen in Soweto.

Over a period of fewer than two weeks, 20 bright pink murals began appearing around Soweto and Alexandra townships outside Johannesburg. The murals were positioned in high-visibility locations such as bus stops, community centres, health facilities, schools, taverns and free Wi-Fi hotspots.

The murals were designed by local communication and branding outfit, The Earth is Round. Head designer Karien van der Westhuizen explained that the funky designs were created with a view to modernising the way information about HIV is communicated.



"i-Base asked us to come up with a humanistic and approachable, yet modern look and feel for the Modern ART in South Africa project — something alive and opposite to the dry and sometimes depressing designs we see for materials about HIV," said Van der Westhuizen.

We settled on bright colours and cartoon-like little people, combined with a rough, photocopy-like treatment of pictures of the trainers. This tied in nicely with the activism legacy of Treatment Action Campaign, a central partner in the project.

Pink and yellow became the main colours on the app and website — we hope that it brings a sense of aliveness and optimism, because that is what ART is all about."

In keeping with the theme of all things modern, the murals also feature a QR code which allows people to scan them and download the Modern ART app, which contains the latest information about antiretroviral therapy.

People also can the website or follow the Modern ART social media platforms for instant updates – and the app reminds the user when he or she needs to get more medication.

While South Africa remains under lockdown, the Modern ART project plays a vital role in bringing HIV-related information to the people. There are those who may be reluctant to leave their homes to visit a clinic or hospital and downloading the Modern ART app gives them immediate access to accurate information on their device.

The colourful murals seemed to have the desired effect, with people gathering to take a look. One man commented that the murals were exactly what his community needed.

"You've brought this campaign to the right place… all we hear about is Covid-19 and so many people have forgotten about HIV," he said.

Modern ART collaborated on the murals with local artist Senzo Nhlapho of Senzart911. He said the interaction with onlookers made them realise what an important project this was.

"So many people did not know about the new HIV drug, dolutegravir. When we started creating the murals, people began engaging with us and got to know about the treatment and what it means for people living with HIV.

"The team at Senzart911 are proud to be the first to introduce the drug, using art as a form of communication within townships," said Nhlapho.

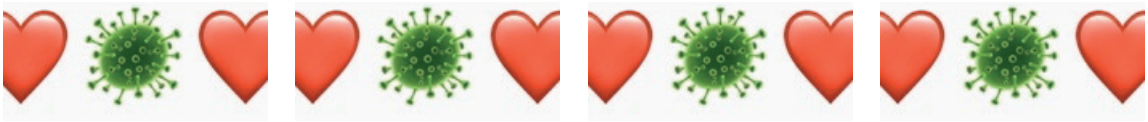
Modern ART will continue spreading these dynamic murals throughout South Africa for the rest of the year.

Sources:

A version of this article was first published in the Daily Maverick.
https://www.dailymaverick.co.za/article/2021-02-18-modern-art-paints-soweto-bright-pink-to-advertise-the-latest-hiv-drug

More about the murals on our Modern ART YouTube channel:
https://www.youtube.com/watch?v=fafDEPZtWoY

HTB SUPPLEMENT ON COVID-19: Issue 9



COVID-19: HIV and COVID-19 COINFECTION

HIV positive people in the UK now elligible for COVID vaccinations – and to become available at HIV clinics

Simon Collins, HIV i-Base

This week NHS England expanded the priority to receive a COVID-19 vaccination to people who are moderately vulnerable – priority grooup 6 – which includes all HIV positive people. [1]

The NHS has also expanded vaccination options for HIV positive people to now be able to receive COVID-19 vaccines at HIV treatment centres. Similar changes have taken place in Scotland and Wales.

This change was the results of lobbying by the British HIV Association and community organisations to overcome some of the limitations of working exclusively through GP services. [2, 3]

The most important of these were that although being HIV positive qualifies for priority group 6 to access the vaccine, many HIV positive people either do not have a GP, or for reasons of confidentiality, only access HIV care through their HIV centre.

HIV positive people who have not already received their first vaccine, or an NHS letter advising them to book, should contact their GP ti make an appointment, saying that you have a chronic medical condition that qualifies for group 6.

C O M M E N T

i-Base have heard of many cases where people have been missed and mentioning this inequity with you GP should enable you to receive your first shot.

There may be cases where HIV doctors need to contact the GP for HIV positive people in their care who are especially vurlnerable and who have not yet been contacted.

Even though many GP surgeries say to wait for a letter, HIV positive people can contact thier GP to proactivelty request a vaccine now that group 6 is being prioritised on the government website. [3]

People who have not disclosed their HIV status to a GP, or who do not have a GP, should contact their HIV clinic. Access is still being arranged at HIV clinics and this should become easier over the next weeks.

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2. BHIVA, Important Covid risk and vaccine updates. (19 February 2021). https://www.bhiva.org/important-covid-risk-and-vaccine-updates
3. THT. How we improved the COVID vaccine rollout for people living with HIV. (22 February). https://www.tht.org.uk/news/how-we-improved-covid-vaccine-rollout-people-living-hiv

COVID-19: VACCINE RESEARCH

What are the main COVID-19 variants and will they affect vaccines?

Although all viruses change and evolve the new coronavirus variants are especially important because we now have effective vaccines.

By February 2021, several variants have been described - see Table 1.

Although they were first reported in one country most were soon also reported in others. Some of these variants are transmitted more easily and some might affect how well vaccines work. This impact is still being studied. Currently, the most serious is called B.1.351 (initially reported in South Africa). However, all manufacturers are already testing updated versions of their vaccines against these new variants.

Table 1: Key variants and predicted impact on current vaccines

Date reported	Original region	Code name	Mutation	Impact	Comment
March/April 2020	Global	D614G.1	S-protein	Quickly became main global strain.	Increased the replication efficiency and transmissibility. NAbs still recognised
June 2020	Denmark	By November reported in more than 200 mink farms and detected in humans. >1.4 million animals culled.	Seven unique variants in S protein.	Mink-related outbreaks also reported in the Netherlands, Spain, Sweden, Italy and the US.	These are small and largely contained reports. No information on impact on vaccines.
August 2020.	UK (Kent)	B.1.1.7 [also 20I/501Y.V1 And VUI 202012/01 - variant under investigation, year 2020, month 12, variant 01)	N501Y S-protein	Expanded in UK Nov to Jan. >600 cases reported in 33 US states.	Increased transmission. NAbs still recognized by Oxford, Pfizer and Moderna vaccines. Reduces sensitivity to neutralising Abs.
October 2020.	South Africa	B.1.351 (also as 20H/501Y.V2	17 unique mutations in both S and N terminal including K417N, E484K and N501Y).	Already reported in 30 countries including 5 cases in US.	E484K might cause some reduction in NAb but impact is not fully known. Reduced efficacy has been reported to Pfizer, Moderna, Oxford and Novavax vaccines. Reduces sensitivity to neutralising Abs.
January 2021.	Brazil (but detected in travelers to Japan).	P.1 (20J/501Y.V3) Variants of B.1.1.28.	More sequence changes in both S and N terminal including K417N, E484K and N501Y).	Already reported in many countries including Japan, Brazil, Germany and the US.	Not yet known.
January 2021.	California	CAL.20C	ORF1a: I4205V, ORF1b:D1183Y, S: S13I, W152C, L452R.	So far limited to the US.	Impact not yet known.

References and further reading

The following websites are useful resources for updated information about variants.

https://covariants.org/variants

https://nextstrain.org/sars-cov-2

https://www.gisaid.org

A guide to emerging SARS-CoV-2 variants. The Scientist. (26 January 2021).
https://www.the-scientist.com/news-opinion/a-guide-to-emerging-sars-cov-2-variants-6838

Wang Z et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. bioRxiv preprint. DOI:10.1101/2021.01.15.426911. (30 January 2021).
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Novavax: >90% efficacy in UK but 60% in South Africa, hints of lower effect in HIV positive participants

Simon Collins, HIV i-Base

On 28 January 2021, Novavax released preliminary top-line results from two studies using it's NVX-CoV2373 spike protein-based vaccine candidate. [1]

This was at the same time as concern about the B.1.351 variant first started to dominate news in the UK. [1]

The phase 3 study run in the UK enrolled more than 15,000 participants between 18-84 years of age, including 27% over the age of 65. It reported 89.3% efficacy (95% CI: 75.2 to 95.4), based on the first occurrence of PCR-confirmed symptomatic (mild, moderate or severe) COVID-19, at least 7 days after the second study vaccination.

This analysis was based on 62 cases, 56 vs 6 in the placebo vs active group, respectively. Of the 62 cases, 61 were mild or moderate, and 1 was severe (in placebo group). Approximately half the cases were the B.1.1.7 variant and a post hoc analysis calculated 95.6% efficacy against the original COVID-19 strain and 85.6% against B.1.1.7.

Results from a phase 2b study in 4,400 participants in South Africa reported 60% efficacy (95% CI: 19.9 to 80.1) in the 94% of participants who were HIV negative. This was based on 44 cases in 2,536 participants: 29 vs 15 in the placebo vs active groups, respectively. Data available for 27/44 showed 92% to be the B.1.3.5.1 variant.

However, when results from the 148 (6%) of HIV positive participants were added, overall efficacy dropped to 49.4% (95% CI: 6.1 to 72.8). This was due to worse outcomes in the vaccine group: 2.6% vs 5.5% had symptoms in the placebo vs active group. Although these figures are in the wrong direction, the wide confidence intervals means this might not be a real effect.

Importantly. roughly one-third of the 4,400 participants (not included in the analysis) were seropositive at baseline indicating previous COVID-19 infection. This was likely the pre-variant strain, but most infections during the study were with the B.1.351 variant. So although the vaccine provided sginificant although not complete protection against the B.1.351 variant.

Reference

Novavax press statement. Novavax COVID-19 vaccine demonstrates 89.3% efficacy in UK phase 3 trial. (28 January 2021).

https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3

Russian Sputnik vaccine reports 91% efficacy at 21 days after the first dose

Simon Collins, HIV i-Base

On 2 February 2021, early interim phase 3 efficacy result from the Russian recombinant adenovirus-based vaccine, Gam-COVID-Vac (Sputnik V) were published in the Lancet. [1]

This double-blind, placebo-controlled study randomised 21,977 adults between 7 September and 24 November 2020 to either the vaccine (n=16 501) or placebo (n=5476) groups. [2]

The vaccine was developed by the Gamaleya Research Institute in Moscow and the study was run at 25 hospitals in Moscow. The study involves a prime boost vaccination schedule using two vaccinations, three weeks apart. However, the primary endpoint in this interim analysis – called to determine whether sufficient early efficacy could limit the need for further use of a placebo arm during a growing COVID-19 crisis – was confirmed COVID-19 infection 21 days after the first vaccine (ie when the second vaccine was given).

Baseline characteristics included 61% male, 98% Caucasian and 35% were >50 years old.

Based on 16 (0.1%) vs 62 (1.3%) confirmed cases in the active vs placebo groups, the paper reported 91.6% efficacy (95% CI: 85.6 to 95.2).

Tolerability was good with most adverse events reported as grade 1. None of the more erious events (45 vs 23; 0.3 vs 0.4%) were judged to be vaccine related.

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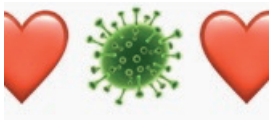
Janssen vaccine reports efficacy after single injection: FDA decision imminent

Simon Collins, HIV i-Base



On 29 January 2021, Johnson & Johnson reported 66% efficacy against moderate to severe COVID-19 after a single dose of the Ad26.COV2.S adenovirus-based vaccine developed by Janssen. The vaccine reduced the risk of severe COVID-19 by 85% and results included efficacy against the B.1.351 variant in South Africa. [1]

On 25 February, the results were published in an FDA briefing report with a planned FDA review the next day, which recommended authorisation in the US. [2, 3]

The phase 3 ENSEMBLE 1 study randomised almost 44,000 participants in eight countries and included 34% aged over 60 years old. Approximately 44% of participants were in the US, 41% in Central and South America (Argentina, Brazil, Chile, Colombia, Mexico, Peru) and 15% in South Africa. Approximately 40% had at least one comorbidities associated with an increased risk for severe COVID-19. This included obesity (28%), type 2 diabetes (7%), hypertension (10%) and HIV (3%).

Efficacy results were based on COVID-19 symptoms 28 days after the injection and were similar in different regions: 72% in the US, 66% in Latin America and 57% in South Africa. Efficacy increased over time with no cases of severe COVID-19 reported seven weeks after infection.

Overall tolerability was good, with grade 3 fever reported in 0.2% of participants and no cases of anaphylactic reactions.

A second study, ENSEMBLE 2, that includes sites in the UK, is also looking at a two-dose schedule with this vaccine.

C O M M E N T

On 26 February 2021, (just after the HTB mailing) the US FDA vaccine advisory panel recommended unanimously that the vaccine should be approved for emergency use authorisation (EUA). [3]

Although recommendations are non-binding, an EUA is expected shortly.

Reference

1. Johnson & Johnson announces single-shot Janssen COVID-19 vaccine candidate met primary endpoints in interim analysis of its phase 3 ENSEMBLE trial. (29 January 2021).
   https://www.jnj.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial
2. FDA Briefing Document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19. (28 February 2021).
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3. J&J press statement. Johnson & Johnson single-shot COVID-19 vaccine candidate unanimously recommended for emergency use authorization by U.S. FDA advisory committee. (26 February 2021).
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Oxford/AZ vaccine might still prevent severe COVID-19 from B.1.351 variant: supports continued used in South Africa

Simon Collins, HIV i-Base

On 7 February 2021, mainstream media publicised the decision in South Africa to suspend use of the Oxford/AstraZenica ChAdOx.1 vaccine in a vaccination programme that was about to start for health workers at high risk of infection.

This was based on low efficacy against the B.1.351 strain (also called the 501Y.V2 variant) that is currently dominant in South Africa. Specifically the vaccine had no impact on reducing mild symptoms of COVID-19 in people at low risk of more serious disease.

The few study details so far released include that the study involved approximately 1,500 volunteers, with median age 31 years, and that mild COVID (defined by at least one symptom) was reported in 19 vs 20 participants in the placebo vs active group respectively. [1]

The timing of the study results was especially difficult because South Africa had just received one million doses of the Oxford/AZ vaccine for to vaccinate health worker.

The announcement also led to widespread confusion in other countries either using or planning to use this vaccine, as in many cases the Oxford/AZ vaccines will be the only current practical option based on lower cost and having easier storage and transport restrictions.

However, the outcome results might have been extremely positive in testing the vaccine in a real world setting, and still could still include an important role for the Oxford/AZ vaccine. This was further explained by Professor Shabir Madhi from Wits University, the principal investigator on the study, in webinar on 9 February organised by the Daily Maverick with 1400 participants. [2]

The webinar presentation, included the following explanation for the results together and implications for continued use of this vaccine in South Africa.

- The study only provided results on mild infection because the study population were generally at low risk. The lack of effect showed that in this population, the Oxford/AZ vaccine neither prevented infection from the B.1.351 variant or prevented low-level symptoms. It did show that the B.1.351 variant is able to evade and overcome the neutralising antibody responses generated by this vaccine.
- However, the Oxford/AZ vaccine is still expected to be very effective against the more serious outcomes of severe COVID-19 in people at high risk. This is because the vaccine still generates cellular immune responses which are likely to protect against severe COVID-19 outcomes including mortality. Although it is too early to have clinical data on outcomes from the Oxford/AZ vaccine in people infected with B.1.351, it produces very similar immune response to those seen against the same variant with the (very similar) Johnson & Johnson (J&J) vaccine. [3]
- In practice, this means the Oxford/AZ vaccine would have no benefit for the expected 75% of health workers who would be expected to have low risk or mild COVID-19. However, it is still hoped to have significant benefit in the 25% of health workers whose other health factors put them at higher risk of severe COVID-19.
- The study results therefore support pausing the proposed vaccine programme in order to prevent 75% of the vaccines being wasted on people who would have no likely benefit.

The webinar also highlighted several important practical points.

1. In settings with limited access to an alternative vaccine, people at high risk of severe COVID-19 should still use the Oxford/AZ vaccine, even against the B.1.351 variant. Protection against severe outcomes is still likely. This is supported by immune responses similar to the J&J vaccine. It supports continued use in South Africa and other countries now. This point was emphasised by panelist Professor Glenda Gray, also an investigator on the J&J study in South Africa.
2. Preventing severe outcomes in people at high risk would also protect the health system in South Africa, which, as in many countries, is severely stressed.
3. Having an initial vaccination with the Oxford/AZ vaccine does not prevent using a different vaccine in the future to boost protection.
4. Other vaccines in development, notably the J&J and Novavax candidates, are close to regulatory submission and have shown activity against the B.1.351 variant.
5. Negotiations for access in South Africa are already underway with J&J which includes data on protection from a single vaccine course.
6. The experience from this recent study should focus vaccine programmes on preventing deaths and in supporting health systems by reducing severe COVID-19. This is more likely to be effective and practical than a focus on achieving herd immunity.
7. WHO also support continued use of the Oxford/AZ vaccine, and will continue to use it in global vaccination programmes, including in counties with B.1.351 and P.1 variants. There are no safety issues from continuing to use this vaccine in all settings. [4]

COMMENT

Although these results were disappointing it could be seen as a stress test for the primary outcome to reduce deaths and to protect health care systems.

It also highlights the difficulty of preventing transmission as a primary goal.

By 8 February 2021, approximately 150 cases of B.1.351 have been reported in the UK, where non-travel-related infections prompted intensive door-to-door testing of more than 80,000 people based on geographic region.

This article will be updated with details of the pre-review publication, when available.

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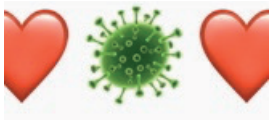
Unprecedented rapid speed of COVID vaccine development

Simon Collins, HIV i-Base



Although HTB mainly includes reports with immediate clinical significance, a paper recently published in Annals of Internal Medicine is interesting for highlighting the unusually rapid development of vaccines against COVID-19.

Hopefully this sets a benchmark for future research.

A literature search, principally of studies listed on ClinicalTrials.gov, traced the likelihood of candidate vaccines for 23 new or emerging viral infections progressing from phase 2 to FDA approval and the associated timelines since 2005.

From 606 trials (involving 220 candidate vaccines and 267,000 participants) the probability of vaccines being approved within 10 years was 10% (95%CI: 2.6 to 16.9) with median time of 4.4 years (95%CI: 6.4 to 13.9). Most vaccines were against H1N1 or H5N1.

The study also concluded that any COVID vaccine developed within 18 months of phase 2 would be unprecedented.

Reference

MacPherson A et al. Probability of success and timelines for the development of vaccines for emerging and reemerged viral infectious diseases. Ann Intern Med. [Epub ahead of print]. doi:10.7326/M20-5350. (24 November 2020).

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https://www.acpjournals.org/doi/abs/10.7326/M20-5350

WHO online vaccine tracker

Simon Collins, HIV i-Base

The WHO website includes a COVID-19 vaccine landscape database available as an Excel file that is updated twice weekly.

The website includes:

- Summary tables of COVID-19 candidates vaccines in clinical and pre-clinical development.
- Tracks the progress of each vaccine from pre-clinical, Phase 1, Phase 2 through to Phase 3 efficacy studies,
- Links to published reports on safety, immunogenicity and efficacy data of the vaccine candidates;
- Main attributes of each candidate vaccine.
- Includes search facility for COVID-19 vaccines by criteria such as vaccine platform, dosage, schedule of vaccination, route of administration, developer, trial phase and clinical endpoints in Phase 3 studies.

References

WHO. The COVID-19 candidate vaccine landscape and tracker.

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

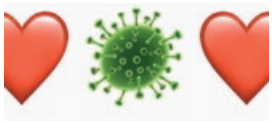
Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process (20 January 2021)

https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_20Jan2021_v2.pdf (PDF)

Vaccine pricing: a BBC guide

Simon Collins, HIV i-Base

Table 1 is compiled from a BBC online article to roughly show the development funding and estimated pricing of COVID-19 vaccines.



Even if these figures are soon out of date, this ball-park guide, includiding for comparisson between manufacturers might still be useful.

Table 1: Comparative vaccine funding and pricing (December 2020)

Company	Total funding (£ bn)	~ % govt	$ per dose *	# doses pre-ordered (bn)
AstraZeneca	8.19	15% (1.5 bn)	$4-8	3.29
Curevac	1.25	65% (800 m)	$12+	0.41
J&J	0.78	40% (350 m)	$10+	1.27
Moderna	1.90	>95% (1.9 bn)	$25 - 35	0.78
Novavax	1.90	65% (1.2 bn)	$16+	1.38
Pfizer	2.25	15% (350 m)	$18-19	1.28
Sanofi/GSK	0.57	<5% (30 m)	$10 - 21	1.23
Sanofi/Translate	0.30	0		
SinoVac	1.62	0	$13 - 30	0.26
Sputnik	NA	NA	$10+	0.34

* Estimates and subject to trade pricing

Source

BBC business news. Covid vaccines: Will drug companies make bumper profits? (18 December 2020).

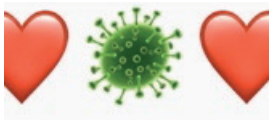
https://www.bbc.co.uk/news/business-55170756

COVID-19: INVESTIGATIONAL DRUGS

Tocilizimab effectively reduces COVID-19 related deaths and hospitalisation time: additive benefit with dexamethasone

Simon Collins, HIV i-Base

On 11 February 2021, the latest results from the UK RECOVERY study reported significant benefits from the IL-6 antagonist tocilizumab. These were in addition to those provided by dexamethasone showing the importance of combination therapy as a principal in the effective management of COVID-19. [1, 2]



Tocilizumab, a monoclonal antibody commonly used to treat arthritis, significantly reduced mortality in people hospitalised with severe COVID-19. Other benefits included significantly reduced the time in hospital before discharge and the need for oxygen.

The RECOVERY study is a randomised, open-label multi-arm platform study that has now enrolled more than 36,000 participants at 178 active sites. Since March 2020 various treatment arms have been stopped and added with some participants having dual randomisations. The initial randomisation originally included dexamethasone, hydroxychloroquine, lopinavir/r or azithromycin (with later options including colchicine or aspirin). However, participants with clinical progression up to 21 days after the initial randomisation (including oxygen saturation <92% or receiving oxygen therapy, and CRP >75 mg/L), were able to undergo a second randomisation that included to options that included tocilizumab (or convalescent plasma or REGN-COV2) – or to standard of care. All randomised options also depended on availability at the study site. [3]

Between 23 April 2020 and 24 January 2021, 4116 adults were randomised to tocilizumab (n=2022) or standard of care (n=2094). This represented 19% of the 21,550 participants in the 131 sites taking part in the tocilizumb study. Tocilizumab IV infusion varied by body weight (from 400 mg to 800 mg) with the option of a second infusion within 12-24 hours if there was no immediate improvement.

At baseline, 14% participants were receiving invasive mechanical ventilation, 41% receiving non-invasive respiratory support, and 45% only received oxygen. Dexamethasone or another systemic steroid was widely used by 82% (and 97% since announcement of dexamethasone benefit).

For the primary endpoint of all-cause mortality within 28 days of randomisation (to tocilizumab), available for 92% of participants, there were 596 (29%) vs 694 (33%) deaths in the tocilizumab vs standard of care groups respectively. The absolute difference of 4% produced a rate ratio of 0.86 (95%CI: 0.77 to 0.96), p=0.007 and NNT of 25 (Number Needed to Treat to prevent one death).

Among those not receiving invasive mechanical ventilation at baseline, tocilizumab significantly reduced the composite endpoint of progression to ventilation or death: 33% vs 38%: RR 0.85 (95%CI: 0.78 to 0.93), p=0·0005.

The three serious tocilizumab-related AEs (otitis externa, Staphylococcus aureus bacteraemia and lung abscess) all resolved with standard treatment.

The discussion notes the benefits of tocilizumab in the recent REMAP-CAP study but also that contradictory results were reported in smaller studies. Overall mortality from eight studies, including RECOVERY, results in a 13% proportional reduction in 28-day mortality (death rate ratio 0.87, 95% CI: 0.79 to 0.96), p=0·005. These benefits are in addition to those from dexamethasone which for most participants in RECOVERY was standard of care when requiring oxygen.

Benefits were seen in all patient subgroups, including by COVID-19 severity at baseline.

However, in a prespecified analysis, tocilizumab had no impact on future use of non-invasive or mechanical oxygen, or in stopping invasive oxygen in those using this at baseline.

Although this analysis was not directly addressed in the paper, the press release from RECOVERY stated that in participants with significant inflammation, the additive benefits of tocilizumab plus dexamethasone reduced mortality by one-third for those using simple oxygen and by half for those on mechanical ventilation.

These dramatic reductions are in a subset of the most severely ill participants and are not reflected in the overall mortality which was 29% vs 33% in the tocilizumab vs standard of care groups respectively.

Full results are expected in early March after >99% of participants will have reached the 28-day endpoint.

COMMENT

Positive results are always good news and the size of RECOVERY and it's randomised design supports the immediate access to tocilizumab in the UK that was announced last month after the results of the REMAP-CAP study. REMAP-CAP was able to report significant benefits from a much smaller study.

Although the benefits from these results will have a huge impact on future standards of care, this is thanks to the many thousands of participants in the RECOVERY who were not lucky enough to be randomised to an active arm. So far, direct interventions in the this study have only reduced mortality for about 200 participants, questioning whether closer monitoring and/or more sensitive stop/go thresholds might stop non-performing arms earlier.

Last month the convalescent plasma arm of RECOVERY was stopped due to lack of benefit. The limited results in the press release reported 1873 deaths among 10,406 randomised participants: 18% in both the active and control arms, with a risk ratio of 1.04 (95%CI: 0.95 to 1.14), p=0.34. The pre-review paper has not yet been posted for this arm of RECOVERY. [4]

Reference

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   https://www.recoverytrial.net
4. RECOVERY press release. RECOVERY trial closes recruitment to convalescent plasma treatment for patients hospitalised with COVID-19. (15 January 2021).
   https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19

Bamlanivimab (LY-CoV555) prophylaxis prevents COVID-19 in care homes: results of BLAZE-2 study

Simon Collins, HIV i-Base

On 21 January 2021, new results reported that a monoclonal antibody called banlanivumab reduced the risk of COVID-19 symptoms when used either before infection or shortly afterwards.

This was a phase 3 study in both residents and staff in long-term care homes. The limited results were reported in a company press release, included significant benefits when used as primary prophylaxis. It also included benefits in a smaller study group who were already positive for coronavirus when the study started.

The BLAZE-2 study randomised 965 participants who were negative for SARS-CoV-2 (299 residents and 666 staff) to either a single infusion of 4,200 mg of bamlanivimab or to placebo control. A second randomised cohort included 132 participants who tested positive at baseline (41 residents and 91 staff) and who were also randomised to either bamlanivimab or placebo to look at potential use as treatment.

Based on eight weeks of follow-up in all participants, bamlanivimab significantly reduced the primary endpoint risk of COVID-19 symptoms (odds ratio 0.43, p=0.00021), with a great reduction in risk for residents (odds ratio 0.20; p=0.00026).

Overall, there were 16 deaths, all among residents, but only 8/16 were linked to COVID-19: 4 in the prevention study and 4 in the treatment study, all in the control groups.

Further details were not included, other than to report that results for all key secondary endpoints also reached statistical significance in both the overall and resident populations.

C O M M E N T

These results show the potential role of monoclonal antibodies for management of COVID-19.

They also show the importance of use before exposure or early in infection.

In October 2020, a phase 3 study in advanced COVID-19 was stopped early by the study DSMB for having no benefit in late-stage infection. [2, 3]

References

1. Eli Lilly press release. Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. (21 January 2021).
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2. HTB. Monoclonal antibody stopped in ACTIV-3 study: bamlanivimab shows lack of benefit in people hospitalised with COVID-19. HTB (11 November 2020).
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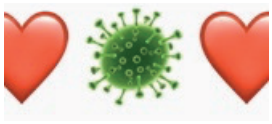
US FDA specifies high antibody titre for convalescent plasma and to only use in early COVID-19

Simon Collins, HIV i-Base



On 4 February 2021, the US FDA updated guidelines for using convalescent plasma (CP) as an investigational treatment for COVID-19. [1, 2]

These are important for now specifying that donor plasma needs to have high levels of neutralising antibodies and that the potential treatment should only be used in early infection.

CP was one of the first proposed treatments for COVID-19, supported by the FDA in March 2020 and by expanded donor programmes in both the US and UK. [3]

However, even when US access was further supported by an Emergency Use Authorisation in August 2020, there were no criteria linked to the donated plasma. By this time, more than 70,000 people had received CP treatment. [4]

It is unclear whether the large UK RECOVERY study that recently reported no benefit from using convalescent plasma, included minimum titres for the CP arm. [5, 6]

C O M M E N T

There has always been good plausibility for benefit from CP based on use to treat respiratory and other infections. However, the early studies in COVID-19 reported mixed results, often with no evaluation of the donated plasma. [7]

This led to an i-Base review in October 2020 to include the comment that "this suggests that any benefit will need both early use and high antibody titres in the donated plasma, and that ongoing studies should review their design to improve the likelihood of more positive outcomes". [8]

References

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4. FDA Issues Emergency Use Authorization for convalescent plasma as potential promising COVID–19 treatment, another achievement in administration's fight against pandemic. (23 August 2020).
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6. No benefit from convalescent plasma in UK RECOVERY study: limited results restrict implications for COVID-19. (13 February 2021).
   https://i-base.info/htb/39928
7. Convalescent plasma therapy for COVID-19. HTB (1 June 2020).
   https://i-base.info/htb/38022
8. Convalescent plasma: randomised controlled study finds no benefit in moderate stage COVID-19. HTB (11 November 2020).
   https://i-base.info/htb/39247

No benefit from convalescent plasma in UK RECOVERY study: limited results restrict implications for COVID-19

Simon Collins, HIV i-Base

On 15 January 2021, the UK RECOVERY study reported top-line results showing no benefit from using convalescent plasma as a treatment for COVID-19. Also, that further enrollment to this arm was stopped based on a recommendation from the Data Monitoring Committee (DMC) the day before. [1]

However, only three days earlier, the investigators had issued a statement that "strongly encouraged continuing recruitment" for low risk participant - based on the DMC review a week earlier. The suggests that either significant changes occurred during one week or a disconnect between the investigators and the DMC. [2]

Now, more than a month later, no further details have been released and the pre-review paper is still not published. Also, although the press statement refers to the protocol for the RECOVERY study being available online, the only reference to convalescent plasma is a listing as a new treatment (in May 2020). [3]

The press release reported 1873 deaths among 10,406 participants. There was no difference in the primary endpoint of 28-day mortality with 18% mortality in each arm: risk ratio 1.04 (95%CI: 0.95 to 1.14), p=0.34.

No details were given on the participants, time to treatment, antibody titre, numbers included in the analysis or how many were still in follow-up.

Dosing information from the trial register includes that a single unit of convalescent plasma (275 mls +/– 75 mls IV) was given on day one (as soon as possible after randomisation) and another on day two (with a minimum of 12 hour interval between the first and second units). [4]

As background, although early studies reported conflicting results from using convalescent plasma, [5] several larger studies highlighted the importance of perhaps only using high-titre plasma in early infection.

In August 2020, a large open label US expanded access programme with more than 35,000 participants reported reductions in both 7- and 30-day mortality with early use (within 3 days vs >4 days after diagnosis) and greater IgG antibody levels in the transfused plasma. In this study, 52% of participants were in ICU and 27% were on mechanical ventilation. [6]

Shortly after, in October 2020, a large randomised study (PLACID) reported no benefit from convalescent plasma, but included the possibility that using a high-titre plasma earlier in infection might be more effective. [7]

More recently, a study published in January in the NEJM reported that early use of high-titre convalescent plasma was associated with a 48% reduction in the risk of developing severe respiratory disease. [8]

This double-blind, placebo-controlled study randomised 160 participants at high risk of progression due to age and/or comorbidities at multiple sites in Argentina. The primary endpoint was defined as developing a respiratory rate ≥30 breaths per minute, oxygen saturation <93% on ambient air, or both.

The primary endpoint was reached in 16% vs 31% participants (n=13 vs 25) in the active vs placebo arms respectively: relative risk 0.52 (95%CI: 0.29 to 0.94), p=0.03). This study used a single 250 mL infusion with an IgG titer greater than 1:1000 against SARS-CoV-2 spike (S) protein.

C O M M E N T

The results from the high-profile study received minimal press coverage, certainly compared to results with other repurposed drugs.

As well as these results being disappointing, the drip-release of study results complicates use of the results in clinical practice or ongoing studies - and a paper in CID last July criticised the RECOVERY study for doing this previously. [9]

In this case, however, further details are particularly important to understand whether the RECOVERY study adapted their design to only use high-titre plasma in early infection - also recently recommended by the US FDA. [10]

If not, then in addition to potentially contributing to poor outcomes for the participants, it might be premature to conclude that the question of using convalescent plasma has been answered.

References

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    https://www.fda.gov/media/141477/download (PDF letter)

COVID-19: PATHOGENESIS

High rates of undocumented COVID-19 mortality in Zambia without testing challenges suggestion that Africa has been spared

Simon Collins, HIV i-Base

A paper published ahead of peer-review reported significant levels of COVID-19 in post mortum testing of people who died in Lusaka, Zambia.

The results show that COVID-19 is a serious cause of death, including in children.

Between June to September 2020, the study enrolled 372 people who had recently died and whose bodies were in the mortuary of the University Teaching Hospital (UTH) in Lusaka, Zambia.

COVID-19 was detected in 70/364 (19%) of those with PCR results.

The median age for the COVID-19 deaths was 48 years (IQR: 36 to 72; range: <1 to 105) and 70% were male. However, 75% of deaths were <60 years old and 7/70 (10%) were children. Three of the children were <1, two were 1 to 3 years and two were teenagers. Symptoms recorded in the children were predominantly GI gastrointestinal symptoms (nausea, vomiting, diarrhea or abdominal pains).

Most COVID-19 deaths (51/70, 73%) occurred in the community and none had been previously tested for COVID-19.

Of the 19/70 deaths that occurred in hospital, 6/19 had been tested for COVID-19 during admission.

Of the 52/70 with information recorded on their symptoms, 44/52 included common COVID-19 symptoms (cough, fever, shortness of breath), but only 5/44 had been tested for COVID-19.

The five most common recorded co-morbidities were: tuberculosis (31%); hypertension (27%); HIV (23%); alcohol use (17%); and diabetes (13%).

The paper has since been accepted for publication in the BMJ.

C O M M E N T

These results represented approximately 10% of 3676 deaths registered over this period.

The paper explains that due to the high number of deaths, enrollment was limited to weekdays during working hours, and that, for example, every fifth death was registered during July and every third death in August, with a daily cap of five deaths per day in both cases.

The paper comments that the high percentage of dealths in the community, where the was no COVID-19 tested was contributing to a significant underestimations of COVID-19 in Zambia. This is compounded by rarity of testing in people hospitalised, even with common symptoms of COVID-19.

The authors comment that if similar findings occur in other countries in Africa, noting that Zambia is hardly the poorest country, then the idea that COVID-19 spared the continent is clearly challenged by these results.

Reference

Mwananyanda L et al. COVID-19 deaths detected in a systematic post-mortem surveillance study in Africa. Pre-peer reviews. MedRxiv. 10.1101/2020.12.22.20248327. (24 December 2021)

https://www.medrxiv.org/content/10.1101/2020.12.22.20248327v1

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

Community HIV Cure Research Workshop 2021

Virtual - just before and after CROI

4 and 5 March 2021 (before) and 16 March 2021 (after).

All sessions are at the same time: 5pm (UK), 12 noon (US Eastern)

https://bit.ly/3p7Efh8 (Please register in advance)

https://fb.me/e/1YZlGAFwE (FaceBook event page)

Conference on Retroviruses and Opportunistic Infections (CROI 2021)

Virtual, 6 – 10 March 2021

https://www.croiconference.org

COVID-19 Clinical Forum (one of a series)

Virtual (to cover research presented at CROI)

23 March 2021 at 20:00 CET / 15:00 EDT

11th International Workshop on HIV & Women

26 – 28 April 2021, virtual

https://www.virology-education.com

International Workshop on HIV and Transgender People 2021

17 July 2021. virtual.

https://www.virology-education.com

11th IAS Conference on HIV Science (IAS 2021)

18 – 21 July 2021, Hybrid - virtual and in Berlin

https://www.ias2021.org

12th International Workshop on HIV & Aging

23 – 24 September 2021, virtuaal

https://www.virology-education.com

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.

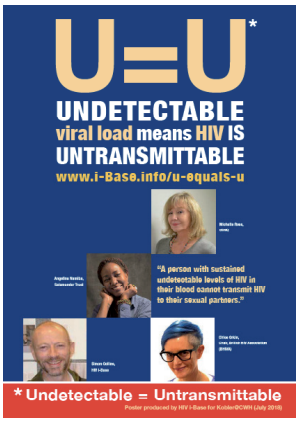
This project was developed with the Kobler Centre in London.

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.

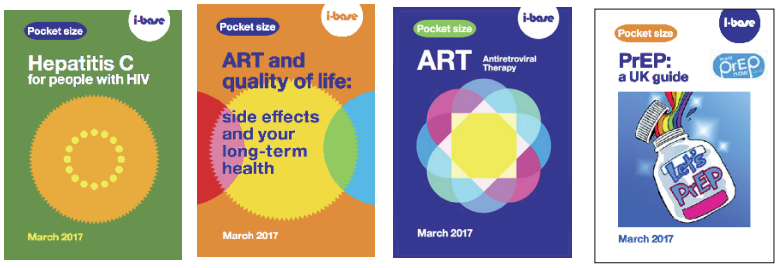
Personalising these for your clinic is cheap and easy and might be an especially nice way to highlight the good news.

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

Editor: Simon Collins

Contributing Editor: Polly Clayden

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

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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HIV i-Base

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Pocket HCV coinfection	**quantity** _____	**Pocket PrEP**	**quantity** _____
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- **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** _____

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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** _____

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- **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** _____

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