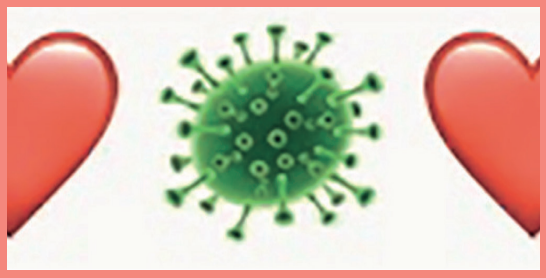
ISSN 1472-4863

HTB: vol 22 no 6: plus COVID-19 supplement

hiv treatment bulletin (e)



Pregnancy, HPV, COVID (1 June 2021)

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Published by HIV i-Base

HTB no.6 (2021): HIV and COVID-19 supplement ISSUE 6

Contents continued ...

i-Base 2021 appeal

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

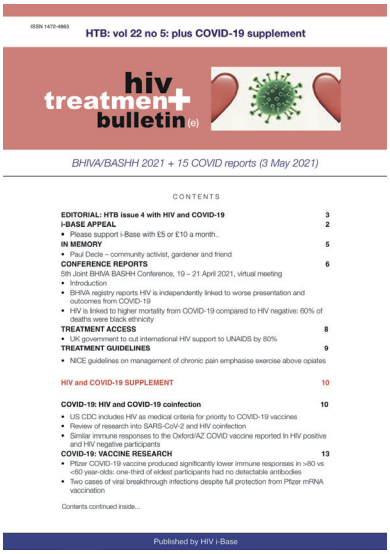
This year we are continuing a funding appeal to help i-Base continue to provide free publications and services during 2020.

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

EDITORIAL

For most of 2021 there has been a move in our COVID-19 reports from potential treatments to the impact of the vaccines, including, this week, the UK approval of the Janssen vaccine.



Effective treatments are still just as desperately needed of course - and treatment research still continues. This issue includes links to a new review of ivermectin.

But the high efficacy of the vaccines has focused management of the pandemic by working towards maximum vaccine coverage, as quickly as possible.

Vaccine efficacy is complex. So far, all authorised vaccines generate both humoral and cellular responses.

Estimates of vaccine efficacy are still mainly based on results from large phase 3 studies. But in this issue we include several reports on people who were not generally included in these studies but who are showing antibody responses limited protection from vaccines.

- People older than 80 (also reported in the previous issue)
- People with severe immune suppression, including people with solid organ transplants.

France has responded by already offers a third vaccine dose (though low CD4 count and HIV are not included) in the hope that this might generate higher antibody titres, similar to approaches with some other vaccines.

But without data we currently do not know whether these concerns will affect HIV positive people who have a very low CD4 count. We report on a small US study showing lower antibody responses followiing the firt dose, but it is response after the second dose that counts. And we need data on a broad range of lower CD4 counts, and in people with detectable viral load, and at higher ages etc etc.

So while limited data showing good vaccine responses in people on ART with a good CD4 count, there is no evidence of protection in the most at risk group, defined by BHIVA as having a CD4 count < 50 cells/mm^3.

As a result, BHIVA helpfully continue to recommend caution to reduce risk of infection in the higherst risk grousp. BHIVA have also formally requested that a low CD4 count should be included in the UK criteria for a third vaccine dose, if this programme is approved, possibly in the Autumn.

On a population level, vaccine programmes also edge towards high enough uptake to reach herd immunity. Estimated targets for herd immunity to control a national epidemic range from 60% to upwards of 85%.

As this issue of HTB went to virtual press, this level in the UK is around 35%. So although 36 million people have received at least once vaccine, generating partial protection, just over 20 million have received two shots. This makes the UK one of the countries with the highest vaccine covers.

Both daily cases and mortality have also dropped but this is still under lock down restrictions. What happens as lock down relaxes in uncertain, especially with the new B.1.617 variants.

Of serious concern, we report cases of COVID -19 in care home residents who have had two vacciines doses, but where vaccination of staff needs to be universal. Although the vaccines still provided population protection, two of these residents progressed to severe COVID-19 and died.

More optimistically, women during pregnancy, also not included in studies (although pregnancy occurred) are showing similar immunogenicity to women who are not pregnant. And more than 10,000 pregnancies have been reported without concern in women who received vaccines.

These perspectives, of course, depend on living in a country that has access to vaccines.

Early access to vaccines almost exclusively went to high-income countries, including the UK and the US, who were able to preorder large supplies. These countries also had sophisticated surveillance programmes that were able to capture the association with extremely rare blot clots.

Most of the rest of the world, including through the international COVAX programme are currently only expecting much lower vaccine coverage during 2021, sometimes only 3% to 20%, with projections that some countries will not achieve herd immunity until 2023.

The historic US administrations support for patent waiver on these vaccines - largely due to activist pressure for global access - will help, but this also needs the transfer of expertise to rapidly be able to produce them.

The block in manufacturing capacity desperately needs generic companies to be included in production - and this includes not only protection from patent restrictions, but also technology transfer and support from originator companies. Vaccines are more complex than antiretrovirals.

CONFERENCE REPORTS

5th joint BHIVA/BASSH conference 2021

19 to 21 April 2021

Introduction

This year the BHIVA spring conference was jointly organised with BASHH and held as a three-day virtual meeting, attended by more than 750 delegates.

As usual, the programme was abstract driven and supported by invited lectures, lunchtime workshops, case studies and more than 180 posters.

The response to COVID-19 was a main theme, including two important oral presentations reporting that HIV was independently associated with more serious outcomes, plus dozens of other studies looking at the impact of both the virus and lock down over the last year.

Access to conference materials, including webcasts and PDF posters originally restricted to delegates, will become open access four weeks after the meeting.

https://bhiva-bashh.org

The abstract book and programme are at this link:

https://www.bhiva.org/AnnualConference2021

The following reports are included this issue of HTB.

- Weight changes on ART and how to lose weight wuccessfuly
- Selected presentations at BHIVA: COVID-19, community involvement and more…

Weight changes on ART and how to lose weight successfully

Simon Collins, HIV i-Base

Several presentations at the BHIVA/BASHH conference looked at the controversial issue of weight gain.

The opening lecture from Dr Anton Pozniak from the Chelsea and Westminster Hospital provided a comprehensive review of the current evidence about weight gain. [1]

The talk was based on weight gain being more complicated than just when HIV drugs cause weight gain.

- Average weight increases with age - and studies need to account for this over the 1-2 years for the research.
- Weight gain needs to account for weight gain in the general population (an epidemic of obesity).
- HIV positive people generally put on weight when they first start ART.
- Some HIV drugs can cause weight gain - but this is usually modest - maybe 1-2 kg over the first 1-2 years.
- Some HIV drugs are linked to limiting weight gain - again, just by a modest amount.
- Individual differences might be related to weight before treatment: ie weight gain might be higher in people who are already heavier when then start ART.
- People in research studies - where we get information about new drugs from - are different to wider HIV population. In general, the majority of people research studies are men but 50% of HIV positive people are women. Most studies are also largely white ethnicity.

This was a good talk including a comprehesive review of different studies but the main evidence of integrase inhibitors and TAF causing weight gain comes from the large randomised ADVANCE study in South Africa. This was a study in a Black African population and more than 50% of participants were women.

If both sex (women) and ethnicity (being black) are linked to higher rates of weight increase reported in ADVANCE, this is likely to explain why it is not reported in evidence reviews of largely white male studies.

HIV treatment needs to be managed individually, so care should focus on individual increases and how to manage these. Although changing drugs has not been successful in studies, maybe these studies were not conducted in the right people?

Diet and exercise

The second of the opening talks for the conference talk was from Maria Halley, a specialist dietician at Imperial College, London. [2]

This focus on the options for management of weight gain, and a summary of this approach is important enough to outline in bullet.

The background to unhealthy weight is complex. In additional to global obesity many social issues are involved in an individual relationship with food: loneliness, psychological issues, anxiety and depression. We live a more sedentary life, taking less exercise and relying on cars. Alcohol use is common and can increase weight and the quality of food and nutrients is low in fast food and high fat and high sugar diets.

Approaches to diet

- Set realistic targets - slow and steady - simple small goals are better - may not even include weight loss targets - for example with the main emphasis to moving to healthier lifestyle.
- Waist circumference is better health predictor than weight or BMI.
- Fad diets DONT WORK - low carb/high carb, crash diets etc -are also difficult to sustain.
- Binge diets - skipping meals - starve then binge - generates guilt, poor self esteem.
- Sometimes it is easy to not realise how much we snack. Starvation diets shift the body's metabolism to store fat - having the opposite effect.
- Generating a fear of fat is especially unhelpful as fats are an essential part of a healthy diet.

The talk emphasised the importance of moving to healthy eating and a more active life.

Useful behaviour changes include:

- Developing a structured eating pattern - three meals no snacks.
- Aim for a balanced diet for nutrients - Mediterranean-based, nuts, pulses, limited red meat.

- No food are off-limits, just in moderation. It is really important to still enjoy food.
- Drink more water: 1.5-2 litres a day.
- Switch off the TV more, especially when eating.
- Keep a food and mood diary (to understand your relationship with food).
- Look at other coping mechanisms rather eating - for example, walking and other exercise.

In summary, successful outcomes from dieting should not aim for perfection or extremes but steady change using realistic goals. It is important to get help and support from a dietician who can individualise your approach. Peer support helps - it is difficult to do this alone. And it is difficult to do anyway. Change is rarely easy but it is never too late to start.

Finally, a related poster from the Royal Free reported on outcomes for a pilot project integrating a dietician within HIV services, with twice-weekly diet clinics. This led to 84 referrals (from over 3300 HIV positive people) with roughly half of initial meetings being face-to-face and half virtual. Unfortunately one-third in each group missed this appointment and did not attend. [3]

Median age of attendees was 54, 60% male, one-third Black African. Most were diagnosed before 2010 (85%), were undetectable (95%) and had CD4 >400 cells/mm^3 (82%). Most referrals were for help to reduce weight but this also includes diabetes management and IBS. About one-third in each group rescheduled a second appointment.

Longer follow-up is not available, and is complicated by short-term funding.

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Unless stated otherwise, all references are to the programme and abstracts to the 5th Joint BHIVA BASHH Spring Virtual Conference, 19–21 April, 2021.

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Selected presentations at BHIVA: COVID-19, PrEP in the UK, community involvement, and more…

Simon Collins, HIV i-Base

The following review reports on some of the highlights from the 5th Joint BHIVA/BASHH conference, held this year as a virtual meeting.

Major themes included diverse aspects of COVID-19, PrEP and community-related research and also weight gain (reported in a separate article).

For full details of all the studies below, please see the online presentations.

COVID-19 in the UK

A wide range of studies on COVID-19 included the UK response to adapting UK services during lock down, the impact on HIV and sexual health, sexual behavior in response to guidelines and clinical outcomes of COVID-19.

Clinical outcome of COVID-19

Two oral presentations - a BHIVA audit and early PHE data - both reported that HIV was independently associated with small but significant increased risks of worse outcomes from COVID-19. [1, 2]

Also that mortality was disproportionately higher in HIV positive people from black and Asian communities.

The causes are unclear but thought to be related to social factors that are difficult to fully adjust. Both studies were reported in the previous issue of HTB. [3, 4]

BHIVA COVID-19 vaccine guidelines

A review of upcoming changes in BHIVA guidelines included an update on vaccination guidelines focusing on those for COVID-19, currently out for comment. [5]

Produced against the challenge of a continued stream of new data, the panel reviewed limited data in HIV positive people. This included a single case of lack of vaccine response in someone with a very low CD4 count (20 cells/mm^3) and high viral load. The guidelines strongly recommends vaccination for all people living with HIV, with whatever vaccine is offered - and noted the importance of further research to inform current research gaps.

Other talks in this session included a report from CROI and an update by Laura Water and the BHIVA TB guidelines by Clare van Halsema.

Adapting UK health services during lock down

An early response to lock down included a move to virtual consultations, usually by phone, reduced monitoring, especially for people on stable ART and using ART that needed minimal support from laboratory services (including minimal need for resistance and HBV tests).

Some of these changes improved services some of which were previously planned but enabled more easily because of COVID-19.

Many studies reported on moving to virtual from face-to-face consultations and this was reported very positively including in a poster from NHS Grampian. In a survey of 44/48 HIV positive people rated telephone consultations at either 9 or 10 (out of 10). The preference for future consultations included 10/48 wanting face-to-face, 12/48 preferring telephone and 26/48 saying “it depends”. [6]

However, although all 19 staff saw the benefit of telephone consultations, only 35% preferred these.

A study from Newcastle presented an interim analysis of deferred viral load tests during 2020. Of 1110 people registered the previous year, 815 (73%) had a deferred viral load. [7]

Of these, just under half 68 of these had a viral result after the deferral, at a mean of 12 months (range: 8 to 20) since the previous test. Viral load responses were similar in for periods: 96% vs 94% <200 copies/mL and 82% vs 86% <50 copies/mL in previous vs deferral periods, respectively.

In those previously suppressed, 13 (4%) were detectable >200 copies/mL, with 7/13 having had historical periods of unsuppressed viral load in the previous five years.

Although the study in probably not powered for whether these differences were significant these data report include 10% of participants who appear to blip between 50 to 200 copies/mL.

In related study from Buckingham Health Trust reported no serious outcomes in 73 regular clinic attendees from deferred monitoring: one case of detectable viral load rapidly resuppressed and one case of increase in HbA1c was linked to weight gain. [8]

A study from Cardiff reported 45% reduction in visits by young people (aged 18 and younger) to sexual health services from 3278 in 2019 to 1789 in 2020. Although the largest group were aged 18, the services were access by people at all ages, including small numbers aged 13 and 12 and under. Reductions by age ranged from –28% to –50%. [9]

The impact of changes on HIV and sexual health: engaging in care and mental health

Several studies used the challenges of lock down to develop new services, with new approaches to testing, including for people who disengaged from care.

Changes is services for people who were previously homeless and included the chance for health interventions.

A London study reported on using COVID-19 as a time to contact people who were registered at the clinic but who had not attended since 2017, cross referenced to PHE records to check they had not transferred care. A new loss to follow up team (LTFU) identified 255 people plus another 181 who had not visited during the previous 12 months. [10]

This provided a group of 436 people disengaged from care, roughly half of which last had an undetectable viral load, but who were now likely to be off ART. This cohort had median age 46, was 59% male, 41% black African and 39% heterosexual. Only 18% answered the phone number on file.

By contacting people individually, 19 people returned to the clinic with 6/19 still undetectable though earlier visits. Of the 13 new re-engagements, 9/13 were women, with median 72 months (range: 58 to 99) since last visit. The median CD4 count was 279 cells/mm^3 (range: 94 to 574) and all patients are now back on ART.

Every successful link to care is clearly important but one of the questions pointed out the relatively high cost for few cases. The study show that LTFU remains an important problem and that many people are still do not engage with care.

A study from UCL used the temporary housing provided during lock down to provide testing and care for point of care testing for HIV, syphilis, HBV and HCV. [11]

Between May and October 2020, the service testing 1209 people at 66 venues. Approximately 80% were man and 50% were from black or minority ethnic groups. About half were previously sleeping rough. Mean length of homelessness was 2.3 years and about 40% had become homeless in the previous 6 months.

Overall, 35 were HIV positive (3%), with 6 newly diagnosed, 5 coinfected with HCV and 5 had interrupted ART due to problems accessing treatment during COVID-19. All 35 and now engaged with care and receiving peer support.

A study from Somerset NHS trust reported results from prospectively screen for anxiety and depression to look at the impact of COVID-19 on mental health of 160 HIV positive people (74% male). [12]

Based on the PHQ-9 and GAD-7 scores, 47 people (29%) developed a new mental health illness between March and November 2020.

Among the 120 (84 males, 35 females) with no previous mental health history, 19, 3 and 6 developed mild, moderate and severe depression respectively. The results for anxiety were 9, 5 and 5, respectively.

Overall, one third that a diagnosis of depression which was higher during COVID-19 but did not affect HIV treatment outcomes. However, social factors related to higher scores included COVID health concerns, inconsistency on advice for shielding, financial and family concerns and fake news on social media.

A community survey of sexual behavior completed by 918 gay men in London during COVID-19 included mainly cis men (5.4% were tans or non-binary), 82% were white and 20% were HIV positive.

Just under half (approximately 440) reported having casual partners from other households during lock down. This was significantly more likely in those younger than 40 years (vs older than 40), and in those who were HIV positive; both $p<0.01$.

However, nearly 60% of those having casual sex reported reduction risk of COVID-19 by washing/showering, less kissing, more condoms, wearing a mask etc. [13]

A retrospective case note review from a sexual health clinic in east London, reported an increase in cases of syphilis during 2020: 164 compared to 111 in the same period in 2019. Roughly one-third were primary, secondary and early-latent. Early cases were similar during and after lock down. Overall, 85% were self-referrals but 11% had tried to access help via a GP. 80% were male (of which 77% were gay men). The study noted that overall caseload increased after lockdown was relaxed and similar increases are expected now. [14]

Increased reports of domestic violence and other need for support

Researchers from Central North West London reported results from a renewed focus on domestic violence with guidelines for all doctors to routinely ask patients in consultations about whether this was an issue. The project included reminders doctors on a weekly basis and emphasised referral pathways. [15]

Although there were fewer appointments, routine screening improved from an average of 8% (range 0-19%) pre-lockdown to 33% (range 0-56%) post-lockdown.

Overall, 17 of domestic abuse were reported, with disclosure higher during lock down. Approximately 60% were male (70% gay men), with roughly 50% white and 50% Black. Importantly, for future services, most cases (89%) only disclose after being asked at more than one consultation, with one person only disclosing on the fourth time.

Several studies reported impact of COVID-19 on well-being and the need for support.

An anonymous cross-sectional survey in Brighton was completed by 653 HIV positive people with 385.653 also completed including qualitative free-text responses. Overall, 501 (77%) respondents were more anxious; 464 (72%) were more depressed; and 128 (29%) reported suicidal thoughts during the pandemic. [16]

HIV concerns included 40% worrying about supply of HIV meds, 38% on accessing HIV services and 63% on other health services. Half the respondents felt that more support could have been provided for HIV positive people.

On a more positive note, 80% thought their experience from HIV helped them deal with the difficulties of COVID-19.

Similar resilience was reported by 245 respondents to a anonymous community survey from Positively UK (response rate 43%). Demographics included 60% aged 45 to 64, 68% men, 69% white. [17]

Approximately 50% reported difficulties accessing HIV care during COVID-19 (often due to service closures) and 40% to general health care. Roughly 20% reported adherence difficulties, one third of which were linked to poor mental health.

PrEP access across the UK

PrEP was another key conference theme covering impact of COVID-19 (generally clinics reported maintaining services throughout lock down, though using reduced monitoring), current access across the UK, and reports on broadening access to other groups.

The importance of raising awareness of PrEP in under represented communities appropriately launched the main conference with short positive videos made with the Sophia Forum and Women and PreP. [18]

These clips include confident and positive community advocates talking about the importance of PrEP for women, sex workers, non-binary and transgender people and heterosexual Africans.

Three oral posters covered:

- Baseline demographics for the 25,000 largely white gay men enrolled in PrEP Impact Trial (now ended). [19]
- A community project looking to raise awareness of PrEP in black African heterosexual populations in the UK. [20]
- A focus on improving adherence and supporting people to continue PrEP based on a two-year programme in Scotland. [21]

A retrospective review from Swansea reported continuing the PrEP service from March 2020 that included starting PrEP in 66 new cases (compared to 102 during the same period in 2019). The clinic moved to telephone consultations and manged similar monitoring for STIs and renal function. This poster also reported 11 new HIV diagnoses, which was similar to the previous year. [22]

A lunchtime workshop on Wednesday included a panel of speakers to summarise current access to PrEP across the UK. This is an excellent review of latest access details. Although the webcast is apparently online, the URL was difficult to find. [23]

Community engagement with the BHIVA conference

The BHIVA conference always includes strong community involvement in the programme.

Case study: Angelina Namiba

This year included a case study presented by an HIV positive patient who is also one of the UK's leading treatment advocates. For most of the last two years, with a diagnosis still not fully resolved, Angelina Namiba from the 4M Network of Mentor Mothers presented her own case story. [24]

This included a traumatic and serious mass that was not identified by biopsy or other tests. This included a long period of hospitalisation including several hospital transfers.

It was notable how some aspects of care were difficult to navigate, even for an experienced advocate. The presentation notably moved other doctors involved in the presentation and is highly recommended for community and health workers. [25]

UK-CAB workshop: what keeps me awake at night

The UK-Community Advisory Board (UK-CAB), a network of more than 800 community advocate also organised one of the workshop in the main programme on Monday. [26]

This session included personal perspectives from three leading UK activists: Ant Babajee, Leasuwanna Griffiths and Husseina Hamzaa. These talks covered experiences of the COVID-19 vaccine, HIV and pregnancy, quality of sleep, peer support and issues of mental health and how these issues affect different populations.

There were also many community-led research studies presented as oral and poster presentations, some of which are already reported above.

It is always good to see BHIVA continue working closely with people living with HIV.

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Unless stated otherwise, all references are to the programme and abstracts to the 5th Joint BHIVA BASHH Spring Virtual Conference, 19–21 April, 2021.

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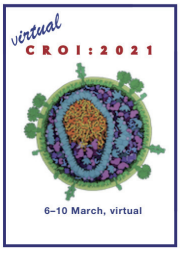
CONFERENCE REPORTS

28th Conference on Retroviruses and Opportunistic Infections (CROI 2021) virtual

6–10 March 2021

Introduction

These reports concludes our coverage from the CROI 2021 virtual conference.



All conference materials are now available as open access documents on the CROI website, including webcasts.

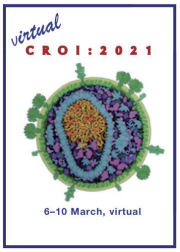
https://www.croiconference.org

Articles in this issue of HTB are:

- No differences in outcomes among women with and without HIV with high-risk pregnancies and COVID-19
- Dolutegravir-based regimens safe and effective in pregnancy and postpartum
- Dolutegravir superior to standard of care in children and adolescents: results from the ODYSSEY trial

No differences in outcomes among women with and without HIV with high-risk pregnancies and COVID-19

Polly Clayden, HIV i-Base



In a cohort of high-risk pregnant women with COVID-19 in South Africa, there were no clinical differences in outcomes between women with HIV (where the majority had undetectable viral load) and without HIV. These data were presented at CROI 2021.

In South Africa, pregnancies are considered high-risk if the woman requires specialist care. Common conditions include: diabetes, hypertensive disorders, obesity, multiple previous Caesarean sections, multiple pregnancies and other indications for preterm delivery.

There are limited data from African countries reporting the outcomes of COVID-19 in pregnancy, particularly for women with high-risk pregnancies and those living with HIV.

This observational study looked at the clinical features, maternal and birth outcomes of COVID-19 high-risk pregnancies. It also assessed whether risk factors for severe disease and adverse COVID-19 differed in pregnant women with and without HIV.

Tygerberg Hospital is a large public referral hospital in Cape Town that manages high-risk pregnancies. Twenty percent of women managed at the hospital are living with HIV and there is a vertical transmission rate of less than 1%. At the start of the COVID-19 epidemic, a dedicated obstetric unit was set up to care for women with suspected and confirmed COVID-19.

The investigators prospectively collected data pregnant from women with COVID-19 attending the high-risk obstetric service, between 1 May 2020 and 31 July 2020. The women were followed until 30 October 2020 to allow for all pregnancies to deliver.

One hundred pregnant women were enrolled, including 28 with HIV, of which, all but one were receiving ART and 19 (73%) had viral load <50 copies/mL.

Overall, the women were a median age of 31 years of age and the women with HIV a median of 34 years. Of note, 75% of the cohort were obese or morbidly obese. Other frequent risk factors were chronic and gestational hypertension, diabetes mellitus and gestational diabetes – these were no different in women with and without HIV.

Most women (81%) were diagnosed with COVID-19 in the 3rd trimester and 50% delivered within two weeks of their diagnosis. The most common presenting symptoms were coughing (77%), dyspnoea (49%) and fever (36%) – again these were no different for women with and without HIV. Forty per cent of women needed supplementary oxygen and 15% were admitted to the ICU.

Almost half (49%) of the women had a Caesarean section – the rate was higher in those with HIV (68%) than those without (42%), p= 0.019. This higher rate was mostly associated with having two or more previous Caesarean sections.

Eight women died of COVID-9, two with and six without HIV. Six died because of respiratory failure and one advanced HIV (and she had stopped taking ART).

When the investigators compared the outcomes for women delivering with COVID-19 to all other pregnant women delivering at the hospital during the study period, maternal deaths were significantly higher among those with COVID-19: 8.8% vs 0.2%, p<0.001. There were no differences across other key obstetric indicators (multiple pregnancies, Caesarean sections, stillbirth or low birth weight infants).

There were 91 live births, 30% delivered before 37 weeks and the rate of low birth weight was 28% – this proportion is similar to the rest of the obstetric population at Tygerberg Hospital. There was one neonatal death from complications related to perinatal asphyxia. Otherwise, neonatal outcomes were good.

C O M M E N T

This is the first study from sub-Saharan Africa to look at the impact of COVID-19 in high-risk pregnant women.

A third of the cohort were living with HIV but there were no differences by HIV status in the mothers or infants.

High BMI, chronic hypertension and diabetes were common in these high-risk pregnancies.

Women were severely ill with COVID-19 and the maternal mortality rate was high. Infant outcomes were no different to background in this population.

Reference

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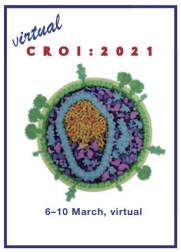
Dolutegravir-based regimens safe and effective in pregnancy and postpartum

Polly Clayden, HIV i-Base

Two presentations at CROI 2021, showed post-partum data from key studies of dolutegravir in pregnancy.



- VESTED (IMPAACT 2010) compared safety and efficacy of dolutegravir (DTG) + emtricitabine (FTC)/tenofovir alafenamide fumarate (TAF) vs DTG + FTC/tenofovir disoproxil fumarate (TDF) vs efavirenz (EFV)/FTC/TDF in women starting ART in pregnancy. Results shown were from enrollment through week 50 postpartum (PP). [1]
- DolPHIN-2 compared safety and efficacy of DTG- vs EFV-based regimens among women starting treatment in the third trimester to in South Africa and Uganda. Final results with follow-up of mothers and infants to 72 weeks PP were shown. [2]

Both studies have previously reported results through delivery [3, 4].

VESTED

ART-naive pregnant women with HIV in 9 countries (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, US and Zimbabwe – the majority from Africa) were randomised 1:1:1 to start open-label DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF at 14–28 weeks' gestation.

Safety outcomes included pairwise comparisons of grade 3 and higher maternal and infant adverse events, infant mortality and infant HIV infection. Efficacy analyses included comparison of maternal viral load <200 copies/mL at week 50 PP between the combined DTG arms and the EFV arm.

Six hundred and forty three women were randomised to DTG + FTC/TAF; DTG + FTC/TDF and EFV/FTC/TDF. At baseline median age was 26.6 years, gestational age 21.9 weeks, viral load 903 copies/mL and CD4 count 466 cells/mm^3. Median baseline BMI was 24.7 – pre-pregnancy BMI was not available.

There were no apparent differences between arms at week 50 PP in the estimated probability of maternal or infant grade 3 and higher adverse events.

Six hundred and seven (94.4%) women and 566 (91.7%) of 617 liveborn infants completed the study. Three quarters of the infants 479/617 (77.6%) were breastfed for a median of 49.9 weeks.

There were 20 infant deaths, of which 15 were within 28 days of delivery. The estimated probability of infant death was higher in the EFV arm (6.9%) compared to DTG + FTC/ TAF (1.0%, p<0.001) and DTG + FTC/TDF (2.0%, p=0.008) arms. In post-hoc analysis, combining still births and infant deaths, this was highest in the EFV arm (8.5%) compared to DTG + FTC/ TAF (4.6%) and DTG + FTC/TDF (7.0%).

Major congenital anomalies occurred in 4 infants: 2 in DTG + FTC/TAF arm (atrial septal defect and talipes equinovarus in the right foot) and 2 in EFV/FTC/TDF arm (duodenal atresia/ileal stenosis and subgaleal cyst).

Either stillbirth (previously reported) or infant death (combined) occurred as follows: 10 in DTG + FTC/TAF, 15 in DTG + FTC/TDF, and 18 in EFV/FTC/TDF arms. Four infants were diagnosed with HIV: 2 in DTG + FTC/TAF, 1 in DTG + FTC/ TDF, and 1 in EFV arm.

Week 50 PP maternal viral load results were available for 573 (89.1%). Another 30 women had results within an extended window (due to covid-19).

Proportions of women with viral load <200 copies/mL were similar in the combined DTG arms (96.3%) and EFV arm (96.4%).

The average weight loss from enrolment through PP was: –0.027 kg/week in DTG + FTC/TAF, –0.050 kg/week in DTG + FTC/TDF, and –0.084 kg/week in EFV/FTC/TDF arms (p<0.001, DTG + FTC/TAF vs EFV/FTC/TDF). There were no statistical differences in obesity rates between arms at week 50 PP – although this was highest in the DTG + FTC/TAF (22.6%) and lowest in the EFV/FTC/TDF (15%) arms.

DOLPHIN-2

In this study, 268 ART-naive pregnant women at 28 weeks' gestation or more (safety cohort) were enrolled and randomised to receive EFV- (n=133) or DTG-based ART (n=135). Of those women, 250 (125 EFV and 125 DTG intention-to-treat cohort) were evaluable for efficacy.

At baseline women had a median age of 28 years, viral load 4.5 $\log_{10}$ copies/mL and CD4 449 cells/mm^3.

Safety outcomes included maternal and/or infant drug related serious adverse events (SAE). Primary efficacy included maternal viral load <50 copies/mL.

At week 72 PP, 21.3% of women experienced one or more SAE: DTG 24.4% vs EFV 18.0%. But only 3% were judged to be drug-related. DTG was well tolerated with a lower frequency of drug-related SAE: DTG 2.2% vs EFV 3.8%.

Among the infants, 56.2% experienced one or more SAE, with 24.8% grade 3 or higher. There were 11 infant deaths: DTG 8 vs EFV 3. None of the SAE were judged to be drug-related. The high frequency of SAE was driven primarily by umbilical hernia and birth marks.

There were 4 infant HIV infections: 3 in utero in the DTG arm and 1 transmission at week 72 PP in the EFV arm. The late transmission was despite optimal maternal suppression (viral load <50 copies/mL) at delivery and serial negative tests in the infant.

At week 72 PP, 116/125 mothers receiving DTG achieved viral load <50 copies/mL with a median time of 4.14 (IQR: 4.00 to 5.14) weeks. This compared to the EFV arm in which 114/125 women achieved suppression at a median of 12.14 (IQR: 10.71 to 13.29) weeks: adjusted HR 1.93 (95% CI: 1.47 to 2.53), p<0.0001.

For time to viral suppression to <1000 copies/mL, these values were DTG 1 week (IQR 1 to 2.86) vs EFV 3.71 weeks (IQR: 3 to 4): adjusted HR 1.83 (95% CI: 1.83 to 2.44), p<0.0001.

There were very few protocol defined failures (failure to achieve <50 copies/mL by week 24 PP or suppression with subsequent rebound – 2 consecutive results with viral load >1000 copies/mL). There was a small difference by arm: DTG 2.4% (n=3) vs EFV 6.4% (n=8).

The mean change in maternal weight from delivery to 72 weeks PP was –1.2 kg, with nonsignificant differences by arm in weight loss: DTG –0.7 kg vs EFV –1.6 kg.

C O M M E N T

These data are reassuring and support WHO and most national recommendations to use DTG-based ART first-line including for pregnant and lactating women.

The HIV transmission to one infant in the DolPHIN-2 EFV arm, detected at week 72, shows the potential for transmission during breastfeeding despite undetectable viral load. The investigators described the infant feeding as exclusive breastfeeding to 6 months and stopped at 12 months. Maternal adherence included a "slight blip at 24 weeks".

It is not clear how much additional evidence is needed before the UK BHIVA pregnancy guidelines change from the recommendation to still use efavirenz/boosted PI-based combinations?

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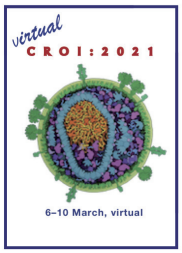
Dolutegravir superior to standard of care in children and adolescents: results from the ODYSSEY trial

Polly Clayden, HIV i-Base

Dolutegravir (DTG)-based treatment outperformed standard of care (SOC) at 96 weeks in first- and second-line regimens in children and adolescents – according to data presented at CROI 2021.



ODYSSEY (PENTA-20) is an international, multi-centre, randomised, non-inferiority trial looking at DTG + 2 NRTIs vs standard-of-care (SOC) in children starting first- or second-line ART.

The data shown was from the main trial including participants aged less than 18 years and weighing at least 14 kg.

The primary outcome was virological or clinical failure. This was defined as: confirmed viral load ≥400c/mL after week 36; insufficient virological response, <1 log drop by week 24 and ART switch for treatment failure; new or recurrent severe WHO stage 3 or WHO stage 4 event and death due to any cause.

Overall, 707 children and adolescents were randomised. The majority (88%) were from African sites: Uganda 47%, Zimbabwe 21%, South Africa 20%, Thailand 9% and Europe 4%. Median age was 12.2 years (range 2.9 to 18) and weight 31 kg (range 14 to 85); 49% were girls and 22% had CD4 <200 cells/mm^3.

In ODYSSEY A, 311 children started first-line ART: 154 DTG and 157 SOC (92% efavirenz [EFV]). NRTI backbones were: abacavir (ABC)/lamivudine (3TC) (78%) and remainder tenofovir disoproxil fumarate (TDF)/3TC or emtricitabine (FTC) (20%).

In ODYSSEY B, 396 started second-line ART: 196 DTG and 200 SOC (72% lopinavir/ritonavir [LPV/r] and 25% atazanavir/ritonavir [ATV/r]). NRTI backbones were: ABC/3TC (55%); TDF/3TC or FTC (26%) or zidovudine (AZT)/3TC (19%). Previous ART exposure was for a median of 5.5 years with 97% receiving NNRTI + 2 NRTIs.

In the total study population, 47 (14%) participants receiving DTG vs 75 (22%) receiving SOC had clinical or virological failure at week 96. Difference –8% (95% CI: –13.5 to –2.6); p=0.004. This difference allowed the investigators to conclude non-inferiority and superiority of DTG.

In ODYSSEY A, 15 (10%) receiving DTG vs 34 (23%) SOC had clinical or virological failure. Difference –12.5% (95% CI: –20.6 to –4.3); p=0.003 (superior). In ODYSSEY B, 32 (17%) receiving DTG vs 41 (21%) SOC had clinical or virological failure. Difference –4.6% (95% CI: –11.8 to 2.7); p=0.22 (non-inferior).

The investigators reported no significant differences between groups A and B, p=0.16. There were also no significant differences in treatment effect by sex, weight, age, baseline viral load or CD4. The benefit of DTG was apparent at 48 weeks and continued to 144 weeks (difference >9%).

Overall there were 10 WHO stage 3 to 4 events (most were stage 4) in 8 participants in the DTG group and 8 events in 8 participants in the SOC group, p=0.97. There were 5 deaths, 2 in the DTG and 3 in SOC groups.

Similar proportions of participants in DTG and SOC groups had one or more or grade 3 and above SAEs. There were more ART-modifying events in SOC vs DTG groups, p=0.01.

At week 48 and 96 gains in CD4 count and percentage were similar in DTG and SOC. Mean change in total cholesterol favoured DTG at 48 and 96 weeks, p<0.001.

There was a slightly greater increase in weight, height and BMI in DTG than SOC groups: differences 1.0 kg, 0.8 cm and 0.3 kg/m^2 respectively at 96 weeks. These differences were statistically significant and occurred early and stabilised.

C O M M E N T

These findings support WHO guidelines that recommend DTG-based regimens as preferred ART for children weighing at least 14 kg starting first- or second-line ART – which allows some harmonisation with adult treatment programmes.

Results for children weighing less 14 kg will be available mid-2021.

Reference

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http://www.croiwebcasts.org/p/2021croi/croi/174 (webcast)

CANCER AND HIV

High efficacy of HPV vaccine in HIV positive gay men

Simon Collins, HIV i-Base

An open label phase 2 HPV vaccination study in the US reported high efficacy at preventing both low- and high-grade squamous interepithelial lesions (LSIL/HSIL) in HIV positive gay men aged 18 to 26.

The study, reported by Joel Palefsky and colleagues in CID.

Of the 260 men screened at 17 clinic sites, 88/260 (34%) were excluded due to existing HSIL, and 144 were vaccinated with the quadrivalent HPV vaccine (qHPV) active against HPV 6, 11, 16 and 18. Of these, 74% had LSIL at baseline and 77% were either seropositive or DNA positive to at least one strain: 72%, 50%, 45% and 33% to 6, 11, 16 and 18, respectively.

Median age was 23, 60% were African-American and 34% were white; 91% had had at least one sexual partner in the previous 6 months. Median CD4 counts was 594 cells/mm3 (range: 237 to 150) and 91% had viral load <400 copies/mL.

Cytology, high-resolution anoscopy with biopsies of lesions, serology, and HPV testing of the mouth/penis/scrotum/anus/perianus, were performed at screening and months 7, 12 and 24.

No lesions were detected in people naive to each clade, compared to 11.1, 2.2, 4.5, and 2.8 cases/100 person-years in those previously exposed to clades 6, 11, 16 and 18 respectively.

Antibody responses were also not affected by current or nadir CD4 count or by viral load (other than lower titres to HPV18 in those with high viral load at month 7.

This is the first study to report such high prevalence of HSIL in HIV positive young gay men that also tracked incidence of lesions by subtype.

Given the elevated risks of HPV-related cancers in gay men and that this is increased further by HIV infection, these results support broader vaccination for this population. Ideally, this should be at a target age of 11/12 before the risk of sexual exposure to HPV or in catch-up programmes afterwards. In the UK this included making the vaccine available to gay men up to 45 years old.

References

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HPV vaccine does not prevent recurrence of high-grade lesions in HIV positive gay men

Simon Collins, HIV i-Base

The hope that the HPV vaccine might protect against recurrence of high-grade anal intraepithelial neoplasia (HGAIN) in HIV positive gay men was unfortunately not seen in a randomised clinical study from the Netherlands, published ahead of print in the journal AIDS.

HGAIN are precursors to anal cancer and rates of recurrence after treatment are high in this population, often >50% within 12 months.

This double-blind placebo controlled study randomised 126 HIV positive gay men with CD4 counts >350 cells/mm3 and recent successful treatment of HGAIN to quadrivalent HPV (qHPV) vaccine or placebo at 0, 2 and 6 months. Participants were enrolled between March 2014 and June 2017. Median age was 49 (+/–9) years old. The primary endpoint was return of biopsy-proven lesions by high resolution anoscopy (HRA) at 6, 12 and 18 months.

The study reported no differences in cumulative recurrence between the groups: 68% (44/64) vs 61% (38/62) in the active vs placebo groups respectively, p = 0.38. This was despite adequate serological responses to the vaccine.

Of the 78 participants with a recurrent HGAIN, 47%, 24% and 28% recurred at 6, 12 and 18 months respectively. There were no progressions to anal cancer.

In both groups, approximately 40% vs 60% of recurrent HGAIN were with HPV types covered by the vaccine vs other HPV strains.

In multivariate analysis, higher baseline CD4 count was associated with recurrence (aOR=1.30 per 100 cell increase (95%CI: 1.05 to 1.61), p=0.02.

Earlier preliminary results from this study had been presented at specialist medical meetings in 2019 and 2020.

C O M M E N T

Although this vaccine is highly effective in preventing anal HPV infections and related complications in young men it is disappointing that this study did not find a treatment effect.

The lack of effect was seen in all analyses and in all sub groups.

This doesn't mean that the vaccine might not have other benefits, including in reducing the risk of anal cancer linked to HPV strains covered by the vaccines.

Some advocates also think that there might be a longer-term benefit that was not shown in this study and that if available to individuals the vaccine is unlikely to cause harm.

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HIV PREVENTION

HIV bNAbs prevent intravenous exposure to SHIV in macaques as PrEP

Simon Collins, HIV i-Base

Positive results from an animal study using a combination of two HIV broadly neutralising monoclonal antibodies (bNAbs) showed protection against intravenous (IV) exposure to SHIV. [1]

This study is significant because the risk of transmission IV are significantly higher than the highest risks from sexual exposure. Also, because registration PrEP studies have only focused on sexual exposure, leaving little data for people whose risk comes from injecting drug use.

The study, from David Garber and colleagues is published on 5 May 2021 ahead of print in the journal AIDS.

This was a small study with five cytologous macaques treated with a single subcutaneous injection of each bNAbs (10-1074 and 3BNC117) with two untreated animals as controls.

All animals were then exposed intravenously to SHIV each week until viral load was detected.

Animals receiving the bNAbs took a median of 5 viral challenges before becoming infected. This compared to both controls who becomes infected after a single challenge.

PK levels of the bNAbs correlated with infection, with median plasma level of 10-1074 at SHIV breakthrough was 1.1 µg mL^{-1} (range: 0.6 to 1.6 µg mL^{-1}), by which time levels of 3BNC117 were undetectable.

The study concluded that protection was primarily due to 10-1074 and that the results suggest the potential for a long-acting formulation to work as PrEP for people who inject drugs.

C O M M E N T

These results are important given the close correlation for other PrEP drugs between animal and human results, and because these antibodies are available in long-acting formulations that might allow for six-monthly dosing.

These results were first presented at CROI in 2019, together with results showing protection from penile exposure. [2]

This dual combination is also being studies in the UK RIO study for their potential to maintain undetectable viral load during a treatment interruption. [3]

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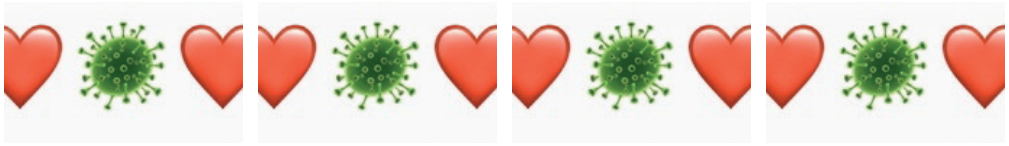
HIV and COVID-19 - bulletin



COVID-19: HIV and COVID-19 coinfection

HIV associated with higher risk of severe COVID-19 in US cohort

Simon Collins, HIV i-Base

A US case-control observational study matched HIV positive and HIV negative samples collected from August to September 2020 looked at incidence and severity of COVID-19. [1]

The study, reported in Lancet HIV, included 1138 samples from 955 people living with HIV and 1118 samples from 1062 people without HIV. The analysis adjusted for age, sex, race or ethnicity, and clinical factors (ie, history of cardiovascular or pulmonary disease, and type 2 diabetes).

Baseline characteristics of the HIV positive group included median age of 54 years (IQR: 46 to 63), median CD4 452 cells/mm^3 (IQR: 249 to 656) and 88% with a viral load of ≤200 copies/mL.

Fewer infections were detected in the HIV positive vs negative groups: 3.7% (95% CI: 2.4 to 5.0) vs 7.4% (5.7 to 9.2). The adjusted odds ratio was 0.50 (95% CI: 0.30 to 0.83).

However, the risk of more severe COVID-19 was higher in the HIV positive group (although confidence intervals were wide). In the 31 vs 70 people with evidence of past infection, the odds of severe COVID-19 were 5.52 times higher in the HIV positive group (95% CI: 1.01 to 64.48). In 3/5 HIV postive people with severe COVID-19, the CD4 count was <200 cells/mm^3 with adj OR >25 and a very wide confidence interval (OR: 25 to 49, 95% CI: 1·41 to 1805·02).

IgG concentrations and antibody titres were also lower in the HIV positive group, although avidity was similar.

An accompanying editorial article highlighted the importance of finding lower immune responses to natural infection in the HIV positive group. Even though the numbers are small with no prospective follow-up, the comment suggests that HIV positive people might be at higher risk of reinfection. [2]

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COVID-19: VACCINE RESEARCH

MHRA authorises Janssen/J&J COVID-19 vaccination in the UK

Simon Collins, HIV i-Base

On 28 May 2021, the UK Medicines and Healthcare products Regulatory Agency (MHRA) authorised use of the Janssen/J&J single-dose (Ad26-COV2.S) vaccine against COVID-19. [1]

This is based on top-line efficacy rates of 67% overall in preventing COVID-19 infection. After two weeks there were 116 vs 348 cases in the active vs placebo arms respectively, out of almost 20,000 people in each arm. The vaccine was 85% effective in preventing severe disease or hospitalisation.

Although the vaccine only needs a single dose ongoing studies are looking at using two doses. The vaccine can be transported and stored for up to three months at regular fridge temperatures (2 to 8 C). It is a DNA-based vaccine delivered using inactivated adenovirus-26.

The UK has apparently reduced the original 30 million doses ordered to 20 million doses although the vaccine will not be available until later in the year.

The European Medicines Agency (EMA) recommended authorisation in the EU in March 2021. [2]

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Reduced antibody responses to mRNA COVID-19 vaccines in HIV positive people with a lower CD4 count

Simon Collins, HIV i-Base

Results from a small prospective study in HIV positive volunteers showed reduced antibody responses following the first dose of an mRNA vaccine against COVID-19 (6 Pfizer and 6 Moderna) to CD4 count. [1]

Although these data are interesting, the important results will be after the second dose, and also to see data from other authorised vaccines.

The 12 volunteers (all men, 11 were white) were recruited between January and March 2021. Median age was 64 years (IQR: 57 to 70). All were on ART ≥ 6 months with HIV viral load <50 copies/mL.

Distribution by CD4 count was 2, 1, 3 and 6 for <200, 200 to 349, 350 to 499 and ≥500 cells/mm^3 respectively.

Although antibody results were all positive (>0.8 U/mL), levels ranged from 2.12 to >250 U/mL

Unfortunately, the specific CD4 counts were not included in this study, reported as a letter to the journal AIDS. It would help to know the far below 200 the two participants with <200 CD4 counts were. Similarly, although beyond the range of the test, it would be useful to know how high antibody levels reached in those with the highest CD4 counts.

There were no significant adverse reactions to the vaccines.

Table 1: Mean antibody levels by CD4 count *

CD4 (cells/mm^3)	N	Ages	Days to antibody test	mean titre (U/mL)	range
<200	2	61, 75	27, 21	2.3	2.1 to 2.5
200 to 349	1	70	15	>250	NA
350 to 499	3	55, 65, 72	19, 20, 27	50.1	4.6 to 128
≥500	6	33 to 68	16 to 28	138.0	44 to >250

* Test sensitivity: range 0.4 to >250 U/mL; positive = >0.8.

C O M M E N T

Although vaccine can also protect from cellular responses, the emphasis on humoral responses in the development of these vaccines suggests caution given the very low and often undetectable responses in people with severely reduced immune function.

This is supported by a recent article in Nature Medicine reporting antibody levels are highly predictive of immune protection. Further data is clearly needed urgently. [2]

This small phase 1/2 study highlights other data that are needed. This includes getting the results from the second vaccine dose. It also includes similar data from other authorised vaccines. These studies need to include a range of low CD4 counts and results in people with detectable viral load to understand the thresholds for concern.

In a similar way the age threshold of +/– 80 years-old could drop lower in general population and might be lower still for HIV positive people. [3]

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   https://i-base.info/htb/40502

France routinely recommends third dose of COVID-19 vaccine for some people with reduced immune function

Simon Collins, HIV i-Base

Numerous studies have now reported that two doses of an mRNA COVID-19 vaccine are insufficient to generate immune responses in some people with reduced immune function.

Based on these results, the French Vaccine Strategy Guidance Council routinely recommends a third dose in people who are severely immunocompromised. [1, 2, 3]

This includes a broad range of situations including:

- Solid organ transplants.

- Recent bone marrow transplants.
- People on dialysis.
- Autoimmune diseases.
- People under strong immunosuppressive treatment (anti-CD20 or anti-metabolites).

The third dose is recommended four weeks after the second dose, or as soon as possible for people who have already exceeded this time.

The guidelines stress the importance of further data in these populations and for medical records to record the third dose.

They recommend that all severely immunocompromised people receive a quantitative anti-S type serology 30 days after administration of the second dose and the third dose. People also need to be rapidly informed that two doses of any vaccine is only likely to provide very limited protection.

Further updates will be posted including on whether a third dose will also be recommended for other groups, including:

- Chronic kidney disease without dialysis.
- Auto-immune diseases using other immuno-suppressive treatments.
- People being treated for cancer.

COMMENT

The 3 May edition of HTB included two studies of suboptimal vaccines responses, one in people older than 80. We used these examples to raise the importance of data on vaccine responses in HIV positive people at low CD4 counts, including under 50 cells/mm^3. [4]

Recent cases have also been reported where anti-CD20 therapies including rituximab have been associated with a lack of humoral responses following recovery from COVID-19 leaving people vulnerable to second infections. [5]

Although data is now needed on whether a third dose generates significantly higher response rates, the high risk of COVID-19 supports this approach.

Some of the studies references in the French guidelines include cases of severe COVID-19 experienced by people more than two weeks after receiving a second vaccine dose. These include ICU admission and mortality.

While France accumulates the first early data, the UK are not currently planning to decide on use of a third dose until the Autumn (not confirmed, but likely).

BHIVA has approached the Department of Health and Social Care (DHSC) to ask that HIV positive people with CD4 <50 cells/mm^3 be included *if such a recommendation is made.*

BHIVA also repeat advice "that people with a low CD4 count and/or other health conditions, should continue to take extra precautions, including working from home where possible, although everyone in this group should have been vaccinated by now". [5]

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US CDC reports 10,000 breakthrough infections after full vaccination: showing success of vaccine programme

Simon Collins, HIV i-Base

On 25 May 2021, the latest issue of MMWR included a review of breakthrough cases of COVID-19 reported up to the ends of April.

The 10,262 cases are a tiny percentage (0.01%) of the more than 100 million people fully vaccinated at the time of the analysis, and were expected given that vaccines are not 100% effective. They were largely mild infections, but not always, and perhaps half were linked to new variants.

Breakthrough infections were defined as occurring more than 14 days after receiving the second dose of an authorised vaccine, confirmed by RNA testing.

Median age was 58 (IQR: 40 to 74) and 63% were women. Approximately 27% were asymptomatic. 995 were hospitalised (not always related to COVID-19). Although 160 people died, this is dramatically lower than without vaccination where the US has reported more than 30 million cases and 600,000 deaths.

The median age of people who died was 82 (IQR: 71 to 89), including 28 (18%) unrelated to COVID-19.

Genomic sequencing was only available for 555 (5%) of cases, of which almost two-thirds (n=356, 64%) were variants of concern, including B.1.1.7 (199; 56%), B.1.429 (88; 25%), B.1.427 (28; 8%), P.1 (28; 8%), and B.1.351 (13; 4%).

The surveillance programme depends on passive reporting so the results are likely an underestimate. Future reports will also only focus on people who are hospitalised.

More than 130 million adults in the US (~40% of adults) have now had two doses.

Reference

CDC. COVID-19 vaccine breakthrough infections reported to CDC — United States, January 1–April 30, 2021. MMWR Morb Mortal Wkly Rep. ePub. 2021 (70). DOI: 10.15585/mmwr.mm7021e3. (25 May 2021).

https://www.cdc.gov/mmwr/volumes/70/wr/mm7021e3.htm

Cases of COVID-19 reported with two deaths in care home residents after full-course vaccination

Simon Collins, HIV i-Base

Several recent studies have reported cases of COVID-19 in residential care homes despite full-course mRNA vaccination, including the B.1.351 variant.

Other studies have also reported significantly lower humoral responses to COVID-19 vaccines in some people with reduced immune function, including those older than 80 years.

A paper published in CID reported an outbreak of the 501.v2 (B.1.351; South African) variant in an elderly nursing home in France. All non-vaccinated residents (5/5) became infected compared to half (13/26) who had been fully vaccinated (two doses) with the Pfizer mRNA vaccine (BNT162b2). COVID-19 was serious in 4/5 and 2/13 of these two groups respectively.

This study included 31 residents and 59 staff. The first case was in a 92 year-old resident, with 17 residents testing positive over the next three weeks. Vaccinated residents had received their second vaccine dose from 4 to 26 February,

Only 19/59 staff were fully vaccinated. with 1/19 becoming infected vs 10/40 unvaccinated staff. No staff developed serious COVID-19 symptoms but the outcomes for residents who had received two vaccine doses was more serious.

Although 2/13 cases were asymptomatic, 9/13 developed mild to moderate symptoms and 2/13 2 (15.4%) progressed to severe disease and died, secondary to acute respiratory distress syndrome (ARDS).

A second more optimistic but still cautious study included a retrospective review from 280 care homes in the US reported in a letter to the NEJM. This included more than 18,000 vaccinated (13,000 of which had received both doses) and approximately 4,000 unvaccinated residents.

The incidence of infections declined significantly over time in all groups. Vaccination were mRNA: 80% Pfizer, 20% Moderna.

In those receiving one dose there were 822 incident cases (4.5%) within 0 to 14 days and 250 cases (1.4%) at 15 to 28 days. In those who received both doses there were 130 incident cases (1.0%) within 0 to 14 days and 38 cases (0.3%) after 14 days. Cases also decreased in unvaccinated residents from 173 cases (4.3%) within 0 to 14 days after the first vaccination clinic to 12 cases (0.3%) at more than 42 days after the clinic.

While showing levels of community protection in those who were unvaccinated, the paper showed infections after receiving both doses.

C O M M E N T

These data should inform individual management of risk for care home residents.

They also highlight the continued risk to residents if staff are not vaccinated, including vulnerability to new variants.

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Israeli study reports reduced vaccine efficacy in people with immune suppression until 14 days after the second dose

Simon Collins, HIV i-Base

Although a paper reports lower vaccine efficacy in Israel in people with immune suppression, the results are more optimistic, and increased mortality is more linked to the time points defined in the study. [1]

This is a report on real-world efficacy from a health provider in Israel covering 25% of the population. Of 2.6 million people registered, 900,000 people had received at least one dose of the Pfizer mRNA vaccine. Mean age was 47 years (SD +/–18) and just over half were women.

The study compared rates of infection in the week after vaccination (the reference period) to those occurring from day 7 to 28 (protected period). This seems an unusual decision given that full protection is not assumed until day 14. As a result this directly skews the overall findings.

Efficacy was based on PCR testing in the subgroup of approximately 60,000 and 27,000 participants during the reference and protection periods respectively (roughly 5% and 3% of the whole cohort). In this group, 4514 infections (7.4% of those tested) occurred during the reference period compared to 728 (2.7%) during the protected period. Mean daily incidence rates of 54.8 vs 5.4 per 100,000, respectively.

Overall efficacy was estimated at 90% (95% CI: 79% to 95%). This was 92% (95% CI: 83% to 96%) in ages 16 to 44, 90% (95% CI: 80% to 95%) in those aged 45 to 64, 82% (95% CI: 63% to 92%) in the age groups 65 to 74 and 82% in those aged 75 and above (95% CI: 61% to 91%).

Lower efficacy (71%; 95%CI: 37% to 87%) was reported among immunosuppressed patients, defined by medical history (e.g. immune deficiencies, CKD) and history of medications and procedures (e.g. long term use of corticosteroids). Importantly, vaccine efficacy dropped to 52% (95%CI: –26% to 82%) in immunosuppressed people older than 65, with confidence intervals that crossed 1.0 showing no significant reduction in mortality from the vaccine.

So although overall mortality rates from COVID-19 were low in both groups, most cases were in people older than 75, who showed no reduction from vaccination.

By age, the 39 vs 11 COVID-19 related deaths in the reference vs control periods were 0 vs 3 (0.2%), 1 (0.7%) vs. 8 (2.4%) and 10 (9.0%) vs. 28 (11.7%) in those aged 45 to 64, 65 to 74 and >75, respectively.

Also significant, but not discussion in the paper, most confirmed infections during the “protected” period occurred during days 7 to 14 (see Figure 1 in the paper), when the vaccine is already known to not be fully active. By day 14, daily incidence in all age groups appears to drop by another log to <0.5 per 100,000 (approximately <0.005%).

C O M M E N T

This is a difficult study to report partly because of the defined period for protection.

When looking at overall efficacy rates there is little difference from deciding whether this should be from day 7 or day 14.

However this becomes much more important for the mortality endpoint. The decision to define the protection period from 7 rather than 14 days after the second vaccine underestimates vaccine efficacy at reducing mortality in all groups, including those with immunosuppression.

Similar results were seen in the overall analysis of the Israeli national data. Among elderly patients, out of 63/124 COVID-related deaths recorded at least 7 days after second vaccine dose occurred in days 7 to 14. However, it had only a small (yet significant) effect on VE estimates (98.2% vs. 96.9). [2]

Reference

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Novavax reports 43% efficacy against B.1.351 South African variant but negative impact in HIV positive participants

Simon Collins, HIV i-Base

On 5 May 2021, results from a phase 2/a/b study of the Novavaz NVX-CoV2373 vaccine reported 43% efficacy against the B.1.351 South African variant. Importantly, it also reported the results by HIV status, showing negative results in participants who were HIV positive.

The analysis included 2684 participants who were seronegative for SARS-CoV-2 at baseline and randomised (1:1) to vaccine or placebo injections. Of these, 94% were HIV negative and 6% were HIV positive, with results reported separately by HIV status. Although more than 4,300 participants were originally enrolled, one-third were later found to be seropositive for SARS-CoV-2 at baseline.

This was a generally young population at low risk of COVID-19 (median age 32, with only 4% > 65 years) and the primary endpoint was mild/moderate symptoms (rather than hospitalisation or mortality).

Overall efficacy, seven days after the second dose, was 49.4% (95% CI: 6.1 to 72.8), based on 15 vs 29 cases in the active vs placebo group, respectively. At the time of the study, national incidence of the B.1.351 variant was approximately 93%.

Among the HIV negative group, symptomatic COVID-19 was observed in 11 vs 27 participants in the active vs placebo groups respectively: efficacy 60.1% (95% CI: 19.9 to 80.1)

The corresponding efficacy in HIV positive participants, based on 4 vs 2 cases in active vs placebo groups respectively, was 52.2% (95% CI: –24.8 to +81.7). This showed a negative impact of the vaccine, although the numbers in this subgroup were small.

C O M M E N T

The study discussion notes that these results are preliminary and that the B.1.351 sequencing analysis was post hoc.

Also that the vaccine effects in the HIV positive group represented a relatively small fraction of the trial population and the study was not powered for efficacy results by HIV status.

Reference

Shinde V at al. Efficacy of NVX-CoV2373 covid-19 vaccine against the B.1.351 variant. NEJM. DOI: 10.1056/NEJMoa2103055. (5 May 2021).

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Oxford/AZ vaccine linked to 242 rare bloods clots in the UK: alternative recommended for people younger than 40

Simon Collins, HIV i-Base

On 7 May 2021 the UK Government recommended that adults aged under 40 years old should preferably use alternatives to the Oxford/AZ vaccine against COVID-19. [1]

This was based on a risk:safety analysis by the UK MHRA linked to rare complications of serious blood clots and age. Detailed information on these and other side effects were included in a detailed safety report. [2]

By 28 April 2021, the UK Yellow Card Scheme had received 54139 cards for Pfizer, 160543 for Oxford/AZ, 683 for Moderna and 574 where the vaccine make was not specified. For the two most widely used vaccines, Pfizer and Oxford/AZ, there were approximately 3 to 6 cards per 1000 doses.

These reports included 242 cases of major thromboembolic events (blood clots) with concurrent thrombocytopenia (low platelet counts) following the Oxford/AZ vaccine, of which 49 were fatal.

This was after approximately 22.6 million first doses and 5.9 million second doses.

Demographics included 141 cases in women (32 fatal) and 100 in men (17 fatal). Age of cases ranged from 18 to 93 with number of reports/fatalities by age: 18–39 (55/14), 40–59 (106/22), 60–79 (61/12), 80–99 (6/1) and unknown (14/0). Six fatalities were after the second dose.

Cerebral venous sinus thrombosis was reported in 93 cases (average age 47 years) and 149 had other major thromboembolic events (average age 55 years) with concurrent thrombocytopenia.

The reports also includes all deaths following all recent vaccinations, evaluating likely cause as many of these were in older people with complex comorbidities.

C O M M E N T

Official comments focused these serious reactions being very rare events. Also, that on a population level the risks are lower than those of having a serious outcomes in the event of COVID-19.

This missed the point, from a community perspective, that many of these individuals could have continued to avoid SARA-CoV-2 through continued isolation and other safety measures – and that they engaged in the vaccine programme for personal and community prevention.

The new advice includes circumstances when the risks from COVID-19 are higher in some people under 40 where using the Oxford/AZ is still recommended, especially if supply issues limit access to alternatives.

Anyone who experiences any of the following symptoms four days after vaccination is recommended to promptly seek medical advice.

- **A severe, persistent headache.**
- **Blurred vision.**
- **Shortness of breath.**
- **Chest pain.**
- **Leg swelling.**
- **Persistent stomach/abdominal pain.**
- **Unusual bruising or red/purple pinpoint spots beyond the injection site where the vaccine is given.**
- **Neurological symptoms such as weakness in the legs or seizures.**

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COVID-19 vaccine candidate from GSK and Sanofi to move to phase 3 placebo controlled study

Simon Collins, HIV i-Base

On 17 May 2021, GSK reported selected top-line results from a phase 2 study of a candidate COVID-19 vaccine being developed with Sanofi. This also included plans for a large international phase 3 study. [1]

The press release reported that the two-dose adjuvanted recombinant vaccine generated "95% -100% seroconversion rates" after the second dose. Also that "neutralising antibodies that were "comparable to those generated after natural infection".

The phase 2 study included over 700 participants in the US and Honduras, with half aged 18 to 59 and half aged over 60.

As context, this 95% to 100% is not an efficacy percentage and some currently authorised vaccines generate antibody responses that are much higher than from natural infection.

The upcoming phase 3 study plans to enroll 35,000 volunteers, in a randomised placebo controlled study. This is controversial because all participants in research studies should be offered the current standard of care. Rather than comparing the new vaccine to a placebo, it is more ethical to compare it to one or more vaccines that are already authorised.

It might also be a challenge that many countries will also have already vaccinated people at highest risk, based on age or other comorbidities. This might make enrolment using the current design difficult.

Other studies include whether a lower dose can be used as a booster.

In this partnership, Sanofi provides the recombinant antigen and GSK provides the pandemic adjuvant.

GSK is also working with CureVac on an mRNA COVID vaccine. [2]

References

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COVID-19: TREATMENT

Meta-analysis of 18 ivermectin studies reports evidence in favour of benefit

Simon Collins, HIV i-Base

A new meta analysis on the controversial question of whether ivermectin has a beneficial role in management of COVID-19 this time reports in it's favour. [1]

This is in contrast to a recent randomised study reported in HTB that found no benefit in mild infection. [2]

Other large randomised studies are ongoing but likely to report soon.

References

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COVID-19: TRANSMISSION & PREVENTION

Asymptomatic infection has similar SARS-CoV-2 viral load to mild COVID-19

Simon Collins, HIV i-Base

A lack of correlation between levels of SARS-CoV-2 and symptoms in people with mild COVID-19 was reported in a recent study showing that people with asymptomatic infection do not present lower risks for transmission.

These data are important given the UK recommendation to continue prevention measures as lock down is eased.

The study included PCR results from 39 asymptomatic and 144 symptomatic participants attending a community clinic in South Korea. Overall, median age was approximately 25 years (IQR 21 to 46), 50% were male/female and one-fifth of people diagnosed SARS-CoV-2 positive but without severe symptoms were asymptomatic.

PCR levels in the upper respiratory tract were similar in these two groups, with no significant differences (p>0.99).

However, the study also reported that more than half of these young, mildly symptomatic patients, showed persistent positive upper respiratory RT-PCR results at the follow-up visit two weeks later.

C O M M E N T

A lack of symptoms has never been considered uninfectious as the main difference between SARS-2 and SARS-2 is that transmission occurs in the pre-symptomatic stage.

However, even though SARS-CoV-2 viral load doesn't always correlate with infectiousness, these results are important for recognising potential transmission risk in people who remain asymptomatic throughout infection, and who are therefore less likely to be diagnosed.

However, being PCR positive at two weeks is very common with inpatients – but this does not help knowing if this is a replicant competent virus that can infect others or it just a bit of dead virus.

Reference

Ra SH et al. Upper respiratory viral load in asymptomatic individuals and mildly symptomatic patients with SARS-CoV-2 infection. Thorax 202176:61-63. (1 May 2021).

https://thorax.bmj.com/content/76/1/61 (html)

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COVID-19: PATHOGENESIS

Missed TB diagnoses during COVID-19 outbreaks despite prolonged respiratory symptoms

Simon Collins, HIV i-Base

Three cases of missed TB diagnoses in 2000 in the US state of Washington are reported in an advance print publication of CID. The cases were identified as part of a public heath intervention including interviews and retrospective case note review.

Although some delays were partly due to reluctance to seek care during COVID-19 outbreaks, all three cases included failure to test for TB, even with prolonged respiratory symptoms, and after multiple negative tests for SARS-CoV-2 (13 times in one case).

The cases were three women (in their late teens, fifties and eighties) who were originally from high incidence TB countries. The paper details the timeline for missing TB during outbreaks of COVID-19 and stresses the importance of also considering dual infection.

Reference

Narita M et al. Delayed tuberculosis diagnoses during the COVID-19 pandemic in 2020 — King County Washington. Clinical Infectious Diseases, ciab387, doi: 10.1093/cid/ciab387. (06 May 2021).

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COVID-19: IMMUNOLOGY

Correlation between COVID-19 severity and immune responses after six months

Simon Collins, HIV i-Base

The strength and durability of immune responses after recovery from COVID-19 helps model the future public health risks and can also inform the timing of vaccination.

This study reports the duration of humoral and cellular immunity in 97 participants from three stages: asymptomatic (n=14), symptomatic/non-pneumonic (n=42), and pneumonic (n=41).

Six months after diagnosis, overall anti-SARS-CoV-2 IgG and neutralising antibody (NAb) titers were positive in 66.7% and 86.9%, in the combined non-pneumonic and pneumonic groups respectively. Those with this sustained humoral immunity were more likely to be older, with longer viral shedding and pneumonia - and were also more likely to have a SARC-CoV-2 specific T-cell response.

Reference

Noh JY et al. Longitudinal assessment of anti-SARS-CoV-2 immune responses for six months based on the clinical severity of COVID-19. JID, jiab124, DOI: 10.1093/infdis/jiab124. (4 March 2021).

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Durable antibody responses 9 months after exposure: irrespective of symptoms during infection - but vaccine coverage is needed to reach herd immunity

Simon Collins, HIV i-Base

By April 2020, approximately 7% of the general population in Wuhan, China had antibodies to COVID-19, mostly linked to asymptomatic infection (80%), and 40% developed neutralising antibodies that persisted for at least nine months. [1]

These results, reported in the Lancet, are encouraging but still show that universal vaccination is essential, irrespective of previous infection, in order to reach herd immunity.

This first study on long-term immune responses included more than 9000 residents who were tested at the end of the first lock down in April 2020, with follow up at 3, 6 and 8 months.

An accompanying editorial noted that the high percentage of asymptomatic infections is likely to account for underestimates of incidence at the time and that the study is an important milestone in understanding immunity, providing a much deeper understanding of natural seroconversion. It also describes the public health response as remarkable at a time when testing, tracing, and treatment resources were much less developed. [2]

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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

HIV Prevention Review Meeting 2021

2 June 2021, Virtual (free registration for health workers, researchers and community).

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

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

Workshop On Long-Term Complications Of HIV And SARS-CoV-2

6 – 9 December 2021, virtual

https://www.intmedpress.com/comorbidities

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.

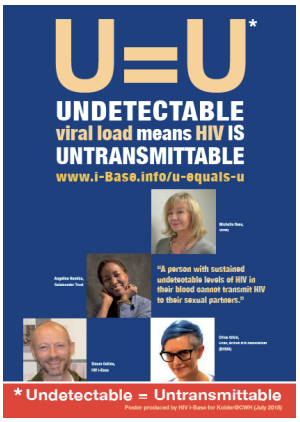
This project was developed with the Kobler Centre in London.

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.

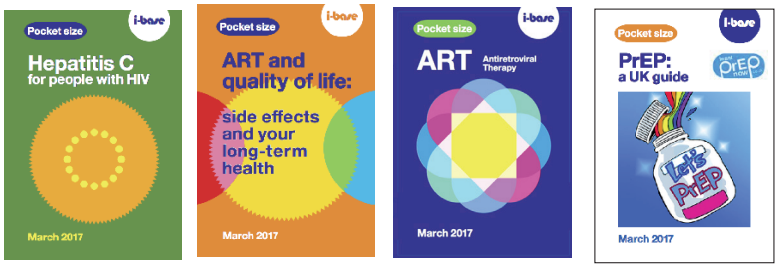
Personalising these for your clinic is cheap and easy and might be an especially nice way to highlight the good news.

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.

Some articles are reproduced from other respected sources. Copyright for these articles remains with the original credited authors and sources. We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We thank them for permission to distribute their work and encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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 is a registered charity no 1081905 and company reg no 3962064. HTB was formerly known as DrFax.

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

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

- **Booklets about HIV treatment**

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