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BHIVA: U=U; CROI: bNAbs, DTG paediatrics & cure

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EDITORIAL

Welcome to the fifth issue of HTB this year, where our first report from the BHIVA 2019 spring conference covers the pre-conference workshop on U=U that included a presentation from the campaign founder Bruce Richman.

A key discussion point was the growing consensus that, in the context of good adherence, U=U starts from the first undetectable viral load result. This means there is no longer a need for people to wait for six months before assuming the transmission risk is zero.

Continued reports from CROI cover three topics in depth. These are broadly neutralising antibodies (bNAbs), a paediatric update on dolutegravir and other cure research (excluding the UK remission case we have already reported).

This issue also includes pipeline news that the option for injectable ART moves a step closer with submission of cabotegravir/rilpivirine LA injections to the FDA (EMA to follow shortly) and that the US have already approved dolutegravir/lamivudine as a dual therapy combination (tradename Dovato).

Finally, UK news that a new branch of cliniQ is opening in South London to cover sexual health for trans communities.

SUPPLEMENTS

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

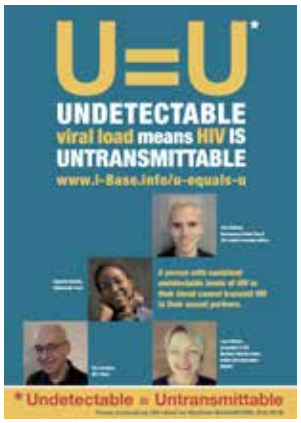
Please continue to order these free resources.

Customise U=U posters for your clinic

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

Personalising these for your clinic is easy and might be an especially nice way to support U=U.

For further information please contact Roy Trevelion at i-Base: roy.trevelion@i-base.org.uk



i-Base 2019 appeal

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

Your help has been inspiring – and we hope this support will continue during 2019. 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

CONFERENCE REPORTS

25th Annual BHIVA Conference (BHIVA 2019)

2 – 5 April 2019, Bournemouth

Introduction

The 25th Annual BHIVA Conference was held this year in Bournemouth and included an impressive programme that covered the diversity of the UK healthcare response to HIV.

Webcasts are already online for all talks from the main programme, including abstract presentations.

This year it is also helpful that most posters are also available to download as PDF files.

https://www.bhiva.org/AnnualConference2019

i-Base reports this year will mainly be short summaries with links to the online resources.

The article in this issue is:

- BHIVA preconference: U=U and HIV and immigration detention

BHIVA preconference: U=U and HIV and immigration detention

Simon Collins, HIV i-Base

This year the conference pre-meeting focused on the importance that BHIVA gives to raising awareness that having an undetectable viral load prevents sexual HIV transmission (U=U). The programme also included an excellent talk on the current care for HIV positive people held in detention centres.

Dr Nadi Gupta from Rotherham NHS Foundation Trust presented results from a BHIVA membership questionnaire in October 2018, that had been prompted by very low awareness of U=U amongst her patients. [1]

The anonymous online survey was answered by 270 doctors with 20% having heard about U=U from colleagues and only three people never having heard of U=U.

Most doctors reported discussing U=U routinely (70%), on diagnosis (70%), when starting ART (55%) or when becoming undetectable (48%) but a small percentage only discussed U=U when asked (3%, n=7) or don't usually discuss it (3%, n=6).

Using direct language when discussing U=U is also important part of U=U but only 37% of doctors in the survey were explicit about U=U having a zero risk. Use of evasive language was still common to describe the risk and these less-direct words actually undermine confidence in U=U: for example, using extremely low (8%), next to zero (21%), virtually impossible (10%) or negligible (11%).

Discussions commonly included reviewing the evidence with their patients in order for the patients to understand the results. However, more than 30% of clinics had no information about U=U in the waiting room.

A majority of doctors (70%) were aware that U=U doesn't cover breastfeeding.

In response to this survey, BHIVA issued a statement supporting U=U (for World AIDS Day on 1 December 2018). [2]

The statement emphasised:

- The importance of using zero risk or no risk in U=U discussion.
- That explaining the data supporting this statement is often important for patients to be convinced.
- Using free U=U resources - such as the posters, post-cards and leaflets produced by i-Base to raise awareness in the clinic. [3]

U=U founder Bruce Richman then talked about the history of U=U as a global campaign. [4]

The chance to have sex without fear has been such a transformative experience that this is needed globally, not just in high-income countries. The scale-up of community mobilisation has seen the campaign endorsed by more than 850 organisations in 97 countries.

An important context that has developed more recently is that having an undetectable viral load should not itself be attached to any moral value. Adopting U=U should always be a personal decision and not a public health initiative.

Examples from the US PEPFAR/USAID-funded Linkages programme included resources for 30 countries. These included the importance of wider access to viral load tests that have a lower threshold of 200 copies/mL.

Two further talks were included in this workshop.

Professor Matthew Wait from the University of Portsmouth gave an overview about how U=U affects HIV and the law in England and Wales. [5]

This focused on implications for reckless transmission and on whether or not HIV positive people need to tell their sexual partners about their HIV status if viral load is undetectable. Prosecution requires proof of transmission, that the intention to transmit was deliberate and that the previously negative partner did not consent to any risk.

The considerable stigma - fueled by transmission cases in the mainstream news media - was highlighted as driving the continued fear of HIV and the related discrimination.

Although not strictly linked to U=U, the final talk by Kat Smithson from National AIDS Trust provided an impressive and comprehensive review of the multiple ongoing concerns about HIV care in immigration detention and removal centres. [6]

During 2017 more than 27,000 people were held in detention centres, just over half of whom were later released back to stay in the UK. There are currently no data on HIV rates in these people but as they disproportionally come from sub-Saharan Africa (20%) or Eastern Europe (20%) rates are likely to be higher than general UK population.

The talk expanded on key issues in the new BHIVA/NAT report on these issues (that is also available online). [7]

- Access to healthcare.
- Stigma and discrimination.
- Detention of vulnerable people.
- Public health.

Importantly, it also provides practical advice for doctors and other health workers whose patients are involved at any stage of the detention process.

C O M M E N T

Part of the discussions about U=U included the question of how long a person needs to have an undetectable viral load before their partners are protected.

The new consensus seems to be that U=U starts when HIV first becomes undetectable as long as this is in the context of good adherence.

Although initial guidelines (including BHIVA) took a cautious approach and recommended waiting for six-months, there is little data to inform this question. In practice, protection is now commonly taken form the first undetectable viral load result and there is little need to make people wait an additional six months.

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CONFERENCE REPORTS

Conference on Retroviruses and Opportunistic Infections (CROI 2019)

4–7 March, 2019

Introduction

This year the Conference on Retroviruses and Opportunistic Infections (CROI 2019) was held in Seattle from 4–7 March.

This is the third set of reports from the meeting - and more will likely follow in the next issue.

Articles in this issue are.

- bNAbs at CROI: vaccine, prevention, treatment and cure...
- Paediatric dolutegravir update
- Other cure related studies at CROI 2019

bNAb research at CROI 2019: vaccine, prevention, treatment and cure...

Simon Collins, HIV i-Base

Over the last few years the potential role for broadly neutralising monoclonal antibodies (bNAbs) has included research looking at their use for prevention (as PrEP and to prevent vertical transmission), for treatment (based on direct antiviral effect) and as part of a strategy for a cure (by sustaining undetectable viral load off ART).

Historical development

Several studies at CROI focused on bNAbs including an excellent opening plenary lecture by Michel Nussensweig from The Rockefeller University, New York looked at the discovery and development of HIV broadly neutralising antibodies. [1]

This talk included a history of the rapid developments in this field and the implications for developing an HIV vaccine. Although many of the current antibodies are relatively new compounds, it was known for many years that 5-10% of HIV positive people naturally develop broadly neutralising antibodies – although it is only recently that scientists have been able to isolate them in a laboratory. Also, that developing these responses are an unusual process – commonly taking 2-3 years in those who generate them.

The group at Rockefeller and collaborators looked at finding the B-lymphocytes that are producing bNAbs and developed new methods of antibody cloning. Together with other groups they discovered that the range of antibody responses was wider than previously realised and that there were also multiple possible binding sites on the HIV envelope protein (in addition to CD4 binding site). They also realised that HIV bNAbs are highly mutated as a result of multiple repeated interactions between the antibody system and the virus over time – and that a successful HIV vaccine might therefore need to mirror this multiple stage process which has now been achieved in a mouse model. Although this shows proof of concept in a simple constructed immune system this is very different to transfer to the complexity of the human immune system.

Also, although bNAbs are often very expensive (>$100,000), their effectiveness in cancer is highly relevant for HIV: they produce both direct targeting of the disease and the engagement of the immune system, where host immunity then eradicates the cancer.

3BNC117 and 10-1074

Two bNAbs are currently in more advanced development at Rockefeller University: 3BNC117 which targets the CD4 binding site and 10-1074 which targets the base of the V3 loop of the HIV envelope protein. Clinical experience includes results in more than 200 individuals without a signal of serious safety concerns.

The group are focusing on potential for multiple use – including passive protection; a type of PrEP, PEP, as an alternative antiviral treatment to ART in chronic infection and for HIV eradication.

In a macaque study that treated animals with bNAbs three days after infection, the researchers observed a a sustained period of undetectable HIV viral load and that rebounding viraemia as antibody levels faded after 50-100 days was lower than seen with seroconversion. Then, unusually, approximately half the animals (6/13) saw viraemia reduced to undetectable levels again without further bNAb exposure. 4/13 behaved like elite controllers and 3/13 behaved like control animals. [2]

Treating the 6/13 animals with anti CD8 antibodies made them all became viraemic – thought to be similar to a cancer-like response where the antibodies and virus produce complexes that immunised the host, this showed that the viral control appeared to be mediated by CD8 cells.

The potential for bNAb compounds are graded based on breadth and potency but the half-lives of these compounds is also critical, as this determines how frequently the treatments need to be given, and can be extended by modifying the structure of the antibodies (for example using LS mutations).

In human studies, a single injection of either 3BNC117 or 10-1074, individually reduced mean viral load by about 1.5 log copies/mL (range: 0.8 to 2.5) that returned to baseline levels after four weeks, but with selected resistance. However, because each of these compounds uses a different binding site, viruses will not be cross-resistant.

In a phase 1b study combining both antibodies together in nine patients with HIV reservoirs sensitive to both 3BNC117 and 10-1074, extended the time for viral load rebound after stopping ART to approximately 15 weeks after the last treatment. This study involved giving the combined antibody three times and produced three different patterns of response.

In 4/9 participants, viral load rebounded with resistance to the antibody with the shorter half-life (3BNC117), once plasma concentrations fell below 10 ug/mL. In 3/9 participants, viral load only rebounded after both antibodies had dropped to below detection. Finally, 2/9 participants remained undetectable for much longer: one rebounded after a year and the other is still virally suppressed. [3]

Both of these participants were treated within six months of infection, and they have generated strong immune response to nearly every antigen tested both in CD4 and CD8 responses.

Ongoing studies are now using long acting LS versions of these antibodies that, for example for 10-1074-LS, maintain levels above therapeutic cut-off of 10 ug/mL for more than three months using 1 mL subcutaneous dose and considerably longer (well past one year) using 3 mg/kg IV dose.

A UK study using these compounds is currently being planned.

bNAbs as prevention: penile tissue and IV exposure

In an oral abstract, David Garber from US CDC presented results from using a single subcutaneous injection of 10-1074 alone or in combination with 3BNC117 (10 mg each bNAb/kg) in a macaque study using bNAbs as PrEP. [4]

Although current PrEP research has focused on drug concentrations in rectal tissue or female genital tissue there are limited data on exposure via other routes. Although efficacy from penile exposure can be extrapolated from other sexual exposure studies (infections were not reported with good adherence). There are however very limited data on risk from shared drug use/injecting.

Both this exposure risks were used in a macaque study where single or dual bNAbs were used to produce passive immunisation against HIV as PrEP.

Macaques were then challenged with SHIV weekly via penile (prepuce pouch), distal urethra or IV routes.

In six animals given only 10-1074 there was a significant delay to infection compared to 10 placebo control animals, requiring a median of 15.5 (range 5 to 19) vs 2.5 (range 1 to 12) penile challenges, p=0.007).

In the dual bNAb study using IV exposure to SHIV, a median of 5 challenges (range 4 to 9) was needed in five active animals vs only a single challenge (range 1 to 1) in the two control animals, p=0.014.

Neither study reported any differences in viral kinetics between active and control groups after SHIV acquisition, when followed for approximately 11 weeks.

PK results reported breakthough infection linked to clearance levels of the antibodies. Protection in the dual bNAb group was driven by the longer half-life of 10-1074.

Early data on new trispecific bNAb

As discussed above, the limited breadth and potency of even the most promising bNAbs means that resistance can quickly develop if used as monotherapy and is also possible in dual bNAb combinations in people who have reduced sensitivity to one compound at baseline.

Preliminary results were shown for a trispecific bNAb in a joint development by the Vaccine Research Centre at NIAID and Sanofi where a single molecule could interact with three independent envelope regions: the CD4 binding site, MPER and the V1V2 glycan site. [5]

The combination compounds have some of the highest breadth and potencies compared to the global panel of other bNAbs. For example, this includes greater potency compared to VRC01, 10E8 and 3BNC117 and greater breadth compared to PGT121, 3BNC117 and 10-1074 etc with decreased viral escape compared to single bNAbs.

Antiviral activity of up to 3 log copies/mL was reported from an SHIV macaque study (data slides withdrawn from the webcast), with rebound reported when antibody levels fell below the minimum threshold. Human clinical studies are planned for later in 2019.

PGT121: phase 1 results in HIV positive people

Results from a phase 1 study using the bNAb PGT121 study were reported in detail in the last issue of HTB. [6]

In treatment-naive participants, a single infusion of PGT121 produced a median viral load reduction of –1.7 log copies/mL in participants with high baseline viral load, but breakthrough with bNAb resistance also occurred quickly when used as monotherapy.

In two people starting with low baseline viral load (<400 copies/mL) a single infusion dropped viral load to undetectable where it remained, without ART, for at least the next six months. [7]

VRC01 as PrEP in adults and neonates

A preconference workshop talk on was also given by Rosemarie Mason from NIAID on targeted isolation of monoclonal antibodies, including a review on the ongoing international phase 2b VRC01 antibody-mediated prevention (AMP) studies. These are double-blind placebo-controlled studies (with some allowance to use oral PrEP) that are due to have first results later this year. [8]

Elizabeth McFarland from University of Colerado and colleagues presented results from an open-label pharmacokinetic and safety study using the long-acting VRC01-LS sub-cutaneous formulation in 21 HIV-exposed newborns. [9]

Importantly, in this study with sites in the US, Zimbabwe and South Africa, both mothers and babies used ART to minimise risk of transmission.

Pharmacokinetic results showed protection bNAbs levels that were sufficient to cover breastfeeding period with no serious safety concenrs. There have been no HIV transmissions.

C O M M E N T

Research into bNAb includes the expectation that better, more potent compounds will be discovered over time, and that these will have broader coverage. These will in turn increase better bNAb combinations.

As cancer treatment, bNAbs are very expensive (commonly more than £100,000 a course for some indications), though they are significantly cheaper for more common uses (~£5000 for Crohns disease).

Although these compounds are usually high-cost medicines, this depends or both dose and number of people likely to use it, with little transparency for the process that companies use to set a drug price. Ultimately, drug price is an artifact of the political pressure to make treatment accessible.

The risk for developing bNAb resistance once levels fall below 10 ug/mL in the presence of significant viraemia is an important safety concern that should be considered for future studies. Hopefully this risk will be overcome with second-generation long-acting formulations.

Some of the potential limitations for VRC01 monotherapy highlighted in the talk by Michel Nussenweig were known before enrolment of the AMP studies, so results from these PrEP trials are highly awaited.

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Paediatric dolutegravir update

Polly Clayden, HIV i-Base

Dolutegravir (DTG) is currently approved for children and adolescents ages 6 years and above weighing at least 15 kg.

It is currently under investigation in the IMPAACT P1093 and ODYSSEY studies. As well as age cohorts, both studies are looking at World Health Organisation (WHO) weight bands and dosing strategies to support these.

Poster presentations at CROI 2019 included: pharmacokinetic (PK) and DTG dosing by WHO weight band for young children ages 6 months to 6 years with the paediatric 5 mg dispersible tablet; data supporting the use of the adult 50 mg film coated formulation for children 20 to 25kg; real-life data from a clinic in Paris, showing similar safety and efficacy in children and adolescents from 5 years old to over 18; and modelling to help predict dosing in neonates.

Dosing 6 months to 6 years of age: IMPAACT P1093

The paediatric DTG 5mg dispersible tablet (DTG-DT) formulation met target concentrations for children aged 6 months to <6 years, even with moderate intra-participant variability. [1]

DTG-DT is being evaluated in IMPAACT P1093 (NCT01302847), an ongoing phase 1/2 open-label dose-finding study.

Previously reported DTG dosing met target concentrations in children aged 4 weeks to <6 months but needed adjustment in children 6 months to <6 years. [2,3]

The IMPAACT P1093 team showed intensive pharmacokinetic (PK), 4-week safety and efficacy data of higher dosing for DTG-DT for children in the older age group.

Enrolment was stratified into two age cohorts: ≥6 months to <2 years and ≥2 to <6 years. DTG-DT was dosed once daily by WHO weight-band (Table 1).

Table 1: DTG dosing by WHO weight band

Weight band (kg)	Revised dose (mg)	Dose range mg/kg	Previous dose (mg)
6 to <10	15	2.50 to 1.50	10
10 to <14	20	2.00 to 1.43	15
14 to <20	25	1.79 to 1.25	15

Participants were either ART-experienced and failing or ART-naive. They received DTG-DT alone or added to stable-failing or empiric initial background regimens. PK sampling was completed between days 5 to 10 under partial fasting conditions .

Based on adult exposures, targets were geometric mean (GM) C24h of 995 (range 697–2260) ng/mL and AUC24h of 46 (range 37–134) mg.h/L.

Ten children were enrolled into each cohort. At baseline, children in the ≥2 to <6 years age cohort (3 girls) were median: age 3.6 years (range 2.1 to 6.0), weight 13 kg (range 9.3 to 17.5), CD4% 25.1 (range 0.3 to 42) and viral load 4.3 log10 copies/mL (range 2.7 to 5.9). Those in the ≥6 months to <2 years age cohort (7 girls) were median: age 1.0 years (range 0.5 to 1.7), weight 7.5 kg (range 6.5 to 9.5), CD4% 31 (range 20 to 49) and viral load 4.1 log10 copies/mL (range 2.5 to 6.1).

For age cohorts of ≥2 to <6 years and ≥6 months to <2 years, the GM (CV%) AUC24h (CV%) was 59.0 (62.2) mg.h/L 70.2 (49.6) mg.h/L and 59.0 (62.2) mg.h/L; Cmax was 5181 (44) ng/mL and 5702 (37.1) ng/mL; and C24h was 791 (105.1) ng/mL and 1094 (70.4) ng/mL, respectively. C24h levels varied from 104 to 4579 ng/mL.

Viral load was <400 copies/mL in 16/20 and <50 copies/mL in 8/20 participants after 4 weeks of treatment. The DTG-DT tablet was well tolerated.

Along with additional PK, long term safety and efficacy data the results will support regulatory approval for DTG in these age groups as well as WHO weight band recommendations.

Dosing for weight band 20 to <25 kg: ODYSSEY

Daily DTG 50mg adult film coated tablet (DTG-FCT) and 30mg DTG-DT (6x5 mg) provide similar and acceptable PK profiles for children 20 to <25 kg. [4]

DTG is also being evaluated for children in the ongoing phase 3 ODYSSEY trial (NCT02259127). Substudies are looking at PK and safety of simplified weight band-based dosing of DTG for children receiving first- and second-line ART.

The EMA recommended dose of 25mg DTG-FCT once daily in children weighing 20 to <30 kg, has previously been shown to lead to lower DTG exposures compared with those seen in adults.

This sub study evaluated PK and safety of 50 mg DTG-FCT and 30 mg DTG-DT in children weighing 20 to <25 kg. DTG-DT have higher bioavailability compared to DTG-FCT in adults (ratio 1.5 to 1.8).

Steady state 24h DTG PK profiles in fasted children taking once-daily 50 mg DTG-FCT or 30 mg DTG-DT were recorded at least 7 days after switch from 25 mg DTG-FCT (main trial dose). DTG plasma concentrations were measured at t=0, 1, 2, 3, 4, 6 and 24h.

Results were compared to those in HIV positive adults receiving 50 mg DTG-FCT once/twice daily, and children 20 to <25 kg receiving 25 mg DTG-FCT once daily.

Fifteen children with a median of approximately 9.5 years of age and enrolled in Zimbabwe and Uganda, were included in the analysis.

The 50 mg DTG-FCT (n=7) and 30 mg DTG-DT (n=8) doses both gave GM Ctrough values comparable to adults receiving 50mg DTG-FCT once-daily and higher than those in children 20 to <25 kg receiving 25 mg DTG-FCT.

GM Cmax with both doses were higher than adult GM values for 50 mg DTG-FCT once and twice daily. GM AUC0-24h for both doses was between values seen in adults taking 50 mg DTG-FCT once daily and 50 mg twice daily.

After median follow-up of 12.9 weeks (IQR: 11.1 to 24.0) and 12.0 weeks (IQR: 6.6 to 18.6) receiving 50 mg DTG-FCT and 30 mg DTG-DT respectively, no children experienced grade 3/4, serious AE or discontinued DTG. Median time on DTG before starting the current dose was 34.8 (range 13.9 to 60.0) weeks.

Provided ongoing longer-term safety is acceptable, the ODYSSEY team suggested that these results support use of either dosing strategy in this weight band.

Adult 50 mg DTG-FCT could offer practical and accessible dosing for children 20 to <25 kg allowing rapid alignment of WHO-preferred ART regimens for adults and children ≥20 kg in low- and middle-income countries, they noted.

Similar safety and efficacy across age groups 5 to 18 years: Necker Hospital, Paris, France

Safety and efficacy of DTG were similar in children and adolescents ages 5–12, 12–18 and 18 years and above in a retrospective analysis conducted at a French paediatric clinic. [5]

The study analysed data from 109 participants, who started DTG-based ART between January 2014 and December 2017: 33, 51 and 25 in the 5–12, 12–18 and ≥18 years groups, respectively.

The primary endpoint was the proportion with viral load <50 copies/mL <3 months after starting DTG, for those with detectable viral load, and remained suppressed until the last follow-up visit for all participants.

At baseline, the majority of participants were ART-experienced (91.7%) and 12 (11%) had previous integrase strand transfer inhibitor (INSTI)-exposure. Four participants had documented INSTI-related mutations: E157Q in two, and N155H in two participants (who received twice-daily DTG).

Only 58.7% of participants had viral load <50 copies/mL for 6 months or more before starting DTG.

After starting DTG, 79.8% of participants achieved sustained virological suppression, with similar rates across the age groups, p=0.22. Duration of follow up was a median of 24 months in the two older groups and 12 months in the 5 to 12 years age group.

With reinforced adherence support, 88.1% achieved undetectable viral load at the last visit, with similar proportions across the groups, p=0.51.

Results for the INSTI-experienced participants with regard to sustained virological suppression and undetectable viral load at the last visit were: 91.7% and 100.0%, respectively.

There was no selection of new RAMs in the RT, protease or integrase gene in 22 participants with virological failure during follow-up.

Only one participant stopped DTG for severe drug-related side effects (dizziness, sleep disturbance).
Three grade 3 laboratory events were considered unrelated to DTG exposure (acute liver enzyme abnormalities, which resolved without stopping DTG).

Neonate dose: in silico prediction

Modelling suggests that appropriate doses for DTG in neonates range between 2 to 4 mg, resulting in plasma exposure comparable to those observed in older infants and children, according to data from the University of Liverpool, UK.

Current studies are investigating dosing in infants aged >4 weeks. Dose optimisation in neonates is complex and physiologically-based pharmacokinetic (PBPK) modelling might help to inform this. The investigators explained that neonates are a vulnerable population and the lack of clinical PK data complicates clinical management.

Rapid development and immature ontogeny mean that direct scaling of existing doses is not usually appropriate for this population. PBPK modelling allows these changes to be represented mathematically, and can support accurate predictions.

Clinical trials in neonates are extremely difficult to conduct and trial design might be de-risked by such dose prediction.

DTG is predominantly metabolised by UGT1A1 and CYP3A4 and the PBPK model was qualified using clinical data from the surrogate substrates raltegravir (UGT1A1) and midazolam (CYP3A4) in neonates. Adult and paediatric DTG clinical data were used for the validation of the model.

A combination of different DTG single and multiple dose strategies were simulated in 100 healthy virtual neonates (0 to 28 days of age) with the aim of achieving plasma exposure comparable to levels observed in paediatric patients: Ctrough 0.90 mg/L and AUC24 46 mg.h/L.

Based on the presented data, the PBPK model predicted that appropriate doses for DTG in neonates range from 2 to 4 mg, resulting in exposure comparable to those observed in paediatric patients.

The investigators suggested that these data can be used to inform neonatal clinical trials to help accelerate dose optimisation in this population.

C O M M E N T

These studies are a useful addition to what we know about DTG in all paediatric populations and will help to inform approval, recommendations and further investigations.

That the 50 mg adult formulation could be used in children weighing 20 to <25 kg in low- and middle-income countries is important. But adult DTG dosing will usually be within a fixed dose formulation with TDF/3TC and the recommendation for children is with ABC/3TC.

As the current recommendation for DTG use with rifampicin-based first-line TB treatment requires twice-daily DTG 50 mg to overcome the drug-drug interaction with this co-treatment, national programmes are likely to procure 50 mg singles for this purpose. So it might be possible to facilitate this paediatric dosing strategy without too many complications.

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Other cure related studies at CROI 2019

Richard Jefferys, TAG

The following reports are taken from a longer article that also includes coverage of the two new cases of HIV remission off ART that we reported in an earlier issue of HTB.

SB-728-T

Outside of the setting of stem cell transplants for cancers, the leading approach to knocking out CCR5 from CD4 T cells has been Sangamo Therapeutics SB-728-T. In clinical trials, CD4 T cells are extracted from individuals with HIV, edited at the CCR5 gene using zinc finger nuclease technology, and then expanded and reinfused. The company was hoping to achieve control of HIV viral load after ART interruption, but so far it hasn't proven possible to modify sufficient numbers of CD4 T cells. Further commercial development for HIV has been abandoned, but some investigator-initiated studies continue.

Pablo Tebas presented new results from a trial of SB-728-T that broadly conformed to previous research. [1]

A total of 14 individuals on ART received a single infusion of modified CD4 T cells, either with or without a preceding dose of cyclophosphamide (intended to deplete existing CD4 T cells and make more room for modified cells). In a slight wrinkle, the delivery of the zinc finger nucleases to the cells was achieved using messenger RNA instead of the adenovirus vector employed in prior studies; the proportion of CD4 T cells successfully edited at the CCR5 gene by the two approaches was similar. The protocol included an ART interruption, and Tebas noted that there was a slight delay in viral load rebound compared to historical controls, but no cases of prolonged containment of HIV.

As observed in prior trials, participants heterozygous for the CCR5Δ32 mutation appeared to respond best. Because these individuals already have one disabled CCR5 gene, the zinc finger nucleases only have to edit one of the two alleles present in each CD4 T cell in order to prevent expression of a functional CCR5 co-receptor. Tebas concluded that more efficient CCR5 modification could potentially lead to more stringent control of HIV off ART, but it appears unlikely that such an outcome can be achieved with SB-728-T.

One variation on the theme of trying to genetically protect CD4 T cells from HIV infection involves focusing on modifying cells capable of recognising and responding to the virus (HIV-specific CD4 T cells). A seminal study by Danny Douek many years ago showed that the virus preferentially infects HIV-specific CD4 T cells, which become dysfunctional and unable to perform their task of coordinating an effective immune response to the virus. [2]

The company American Gene Technologies is pursuing a strategy involving the genetic modification of HIV-specific CD4 T cells, with trials planned soon, and results should shed light on whether this is a better approach than attempting to modify CD4 T cells in bulk. [3]

Taking a bite out of the latent reservoir with CRISPR/Cas9

One of the more intuitively appealing ideas in cure research involves attempting to cut the integrated HIV genome out of the DNA of latently infected cells. In this scenario, gene-editing strategies are targeted against the virus itself rather than a host gene like CCR5. The goal is to perform a sort of genetic surgery, excising HIV genes from infected cells without damaging the cell's genome.

The gene-editing tool CRISPR/Cas9 has emerged as the leading candidate in this research, and some very preliminary results in mouse models have suggested it may have potential. [4] The laboratory of Kamel Khalili at Temple University has pioneered these studies, in tandem with Excision Biotherapeutics, a company Khalili founded to move the approach into the clinic.

At CROI 2019, Tricia Burdo from Temple University debuted the results of a study exploring whether CRISPR/Cas9 could excise latent SIV in the SIV/macaque model of HIV infection. [5]

The cutting machinery of CRISPR/Cas9 is aimed at a target by the inclusion of molecules called guide RNAs (gRNAs), and in this case the researchers created gRNAs capable of recognising three relatively conserved sites in the SIV genome

(two in the long terminal repeats present at either end of the genome, and one in the ***gag*** gene). Burdo noted that the targeting of multiple sites is necessary for both attempting to excise large chunks of the viral genome and avoiding the potential development of resistance (somewhat similar to the rationale for combination ART). The technique produces "very little to no off-target effects," according to Burdo.

The SIV-targeted CRISPR/Cas9 was delivered using an adeno-associated virus serotype nine (AAV9) vector. AAVs are a popular gene therapy delivery vehicle that can carry their payload into a broad range of both dividing and non-dividing cells without apparent safety issues (two AAV-delivered gene therapies have been approved by regulatory agencies).

The study included three macaques, all infected with SIVmac239 and placed on a suppressive ART regimen. In initial experiments, peripheral blood mononuclear cells (PBMC) sampled from the animals were transduced with the AAV9-CRISPR construct, producing evidence of excision of SIV genes between targeted sites.

AAV9-CRISPR was then infused into two of the macaques at a dose of 10^{13}(ten trillion) copies per kilogram, a lengthy process involving the delivery of 100 mL at a rate of 1 mL per minute. Three weeks after the infusion, animals were euthanised and necropsy studies conducted. The third animal served as a control and was also euthanised to facilitate comparisons with the AAV9-CRISPR recipients.

Burdo reported that prior to euthanasia, fragments of the SIV genome that had been cut at targeted sites—referred to as excision products – could be detected in PBMC from the treated animals, as was observed when PBMC were exposed to AAV9-CRISPR in a laboratory dish. Cas9 DNA could also be detected in cells, indicating uptake of the gene-editing tool.

Necropsy studies included a preliminary evaluation of SIV outgrowth from PBMC samples. The PBMC were combined with SIV-susceptible CEM cells and then SIV p27 Gag protein levels were measured over time. SIV replication could be detected in samples from the control but not those from the macaques that received AAV9-CRISPR. However, Burdo emphasised that this assessment did not involve activating the PBMC to induce virus production (as is the case with the standard virus outgrowth assays used in human studies) – those experiments are pending.

Analyses of Cas9 DNA demonstrated widespread distribution in the tissues of the two treated macaques, ranging from around 1-10 thousand copies per million cells in the brain to over 10 million copies per million cells in the spleen and liver (presumably reflecting the presence of multiple copies in some cells). Burdo also showed evidence of SIV excision products in spleen, lung and several lymph nodes (including inguinal, submandibular, bronchial and colonic) from the animals.

The data appear very encouraging, but do not provide information on the magnitude of effect on the latent SIV reservoir (i.e. exactly how much latent SIV was successfully excised or disabled). In response to a question, Burdo reported that future plans include conducting analytical treatment interruptions in macaques treated with AAV9-CRISPR to assess whether viral load rebound is limited or prevented by the intervention.

An issue not covered in the presentation is the potential for the induction of immune responses against Cas9, which has been observed in mouse studies. [6]

Because Cas9 is derived from bacteria, it is treated as foreign by the immune system, and AAV vectors can have an adjuvant effect that seems to promote immune responses against AAV-delivered proteins (this has occurred in studies using AAV to deliver anti-HIV broadly neutralising antibodies). [7] Pre-existing anti-Cas9 immune responses have also been detected in humans due to infection with *Staphylococcus aureus* and *Streptococcus pyogenes*. [8]

In a graph displaying longitudinal viral load measurements in the macaques (on slide #4 in the webcast), it looks as if administration of AAV9-CRISPR may have been temporally associated with a transient increase in SIV viral load – which could be suggestive of immune activation – although there were also viral load fluctuations in other animals. Gaining an understanding of whether AAV9-CRISPR delivery can activate the immune system and lead to the generation (or activation) of anti-Cas9 immune responses will be important prior to initiating human trials.

A theoretical concern that researchers have raised about strategies aiming to excise latent HIV relates to what might occur in cells that have more than one integrated copy of the HIV genome (this phenomenon is thought to be uncommon, but has been reported). [9, 10]

In this situation, it's possible that rather than just removing HIV genes, an excision approach might make cuts in each of the separate integrated virus genomes and thereby remove all of the cell's DNA located between the different HIV integration sites. Damaging the genome of a cell in this way could potentially have untoward effects.

Overall, Burdo's results offer significant encouragement for efforts to translate the approach into human clinical trials. Kamel Khalili and colleagues are now working toward that goal in collaboration with Jeffrey Jacobson, a highly experienced clinical HIV researcher who joined Temple University in 2016.

Attack of the repliclones

The past few years have seen an increasing focus on the role of CD4 T cell proliferation in sustaining the latent HIV reservoir. Evidence has accumulated demonstrating that HIV proviruses can be faithfully copied into the daughter cells of latently infected CD4 T cells when they proliferate—the phenomenon can be discerned by the detection of genetically matching copies of the HIV provirus integrated into the exact same place in the genome of multiple CD4 T cells (the progeny of proliferating CD4 T cells are known as clones). Mathematical modeling suggests CD4 T cell proliferation may be the primary mechanism that allows the latent HIV reservoir to persist, and decline only very slowly over time. [11]

Elias Halvas from the University of Pittsburgh showed at CROI 2019 that CD4 T cell clones containing integrated, intact HIV DNA are a source of low-level HIV viral load that can be detected in some individuals on ART. Essentially, some of these cells can spit out sufficient amounts of HIV RNA to be detectable, even though the virus is not actually replicating (i.e. going on to infect other cells—this is prevented by ART). [12]

Halvas's study involved 10 people who had been referred due to persistent low-level viral load despite ART (HIV RNA >20 copies/mL occurring for at least 6 months). The average time on treatment was 10 years, and viral load ranged from 40 to 356 copies/mL, with a median of 97.5 copies/mL.

One individual displayed evidence of ongoing HIV evolution and the development of drug resistance mutations and was considered a case of ART regimen failure, excluding them from further analysis.

Samples from the remaining nine showed the presence of genetically identical HIV RNA at multiple timepoints, and there was no sign of viral evolution or resistance mutations against current ART. The source of the HIV RNA was identified as CD4 T cell clones containing integrated, replication-competent HIV DNA (Halvas has christened them "repliclones"). In four cases the genetic sequence of the HIV RNA could be matched to viruses detected in the quantitative virus outgrowth assay (qVOA).

Halvas concluded that the possibility of production of HIV RNA by infected CD4 T cell clones needs to be borne in mind by clinicians caring for people with HIV, who might otherwise suspect that persistently detectable low-level viral load indicated non-adherence or treatment failure.

As to the implications for HIV cure research, Halvas suggested that repliclones may contribute to rapid viral load rebound after ART interruption (when the HIV RNA they produce is able to start infecting other cells), and he stressed that they will need to be targeted for elimination or suppression. The mechanisms prompting HIV RNA production by the cells are unclear, and need to be elucidated.

Notably, the data indicate that HIV latency can be more dynamic than was initially appreciated. It's now clear that in some CD4 T cell clones containing integrated HIV DNA, the virus is not permanently latent, because there are times when production of HIV RNA is detectable.

In an article by Jon Cohen for ***Science*** that covers the study, John Mellors points out that the data raise questions about the "kick & kill" strategy in HIV cure research. [13]

The rationale for providing a latency-reversing "kick" is that most latently infected cells do not produce HIV RNA and therefore remain invisible to the immune system. Halvas's results demonstrate that at least some latently infected cells do intermittently generate HIV RNA, and don't die off as a result.

One salutary possibility is that researchers developing "kill" strategies may be able to study their efficacy in individuals like those described by Havlas, who already have low-level viral load on ART without the need for administration of any latency-reversing candidate. In theory, an effective "kill" approach should be able to reduce the amount of HIV RNA detected in such cases.

Targeting the latent HIV reservoir with anti-proliferative therapy

The recognition that the HIV reservoir is at least partly sustained by the proliferation of CD4 T cells is rekindling interest in testing the effects of anti-proliferative therapies in the context of cure research.

At the pre-CROI community HIV cure research workshop, Joshua Schiffer from the Fred Hutchinson Cancer Research Center described a small (four person) pilot trial of the anti-proliferative drug mycophenolate mofetil (MMF) being conducted by his research group with funding from amfAR. The rationale is based on the results of mathematical modeling work suggesting that inhibiting CD4 T cell proliferation in people on ART should significantly accelerate the decay of the HIV reservoir. Results are anticipated to be available for CROI 2020. [14]

Links to the video of Joshua Schiffer's talk are on the workshop web page, along with the slides. [15]

Timothy Heinrich from UCSF presented results of an AIDS Clinical Trials Group (ACTG) trial of sirolimus (a drug with potent anti-proliferative activity, also known as rapamycin) in people on suppressive ART. In the 16 participants who completed 20 weeks of dosing, there was a slight but statistically significant 0.16 logs reduction in HIV DNA levels. CD4 T cell expression of the proliferation marker Ki67 was also significantly reduced. [16]

Heinrich noted that rates of sirolimus discontinuation were high, and there were also transient increases in the inflammatory biomarkers IL-6 and sCD14 and the coagulation biomarker D-Dimer. The results appear consistent with the notion that inhibiting CD4 T cell proliferation can affect HIV reservoir size, but additional research is needed to confirm that this was the primary mechanism for the HIV DNA reduction.

One of the pioneers in this area of HIV cure research is Andrea Savarino, who reported many years ago that the gold-based anti-proliferative drug auranofin reduced the SIV reservoir in ART-treated macaques. [17]

Since that time, Savarino and colleagues have collaborated with investigators in Brazil to conduct a small pilot trial involving auranofin (which is a licensed treatment for rheumatoid arthritis). The latest results were presented in a poster at CROI 2019. [18]

The study design is complicated, involving multiple interventions administered to six groups, each with just five participants. The researchers report that auranofin combined with several other agents led to a reduction in HIV DNA, but the contribution of the anti-proliferative effect is unclear. Administration of the drug was not associated with any serious side effects. Given the renewed interest in targeting CD4 T cell proliferation and the uncertain safety profile of some anti-proliferative drugs, additional studies of auranofin may be justified.

Source

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ANTIRETROVIRALS

Dual long-acting cabotegravir/rilpivirine injection submitted to FDA

Simon Collins, HIV i-Base

On 29 April 2019, ViiV Healthcare announced that the long-acting two-drug injection formulation of cabotegravir/rilpivirine has been submitted to the US FDA. [1]

This announcement was expected following the presentation at CROI 2019 last month of the primary endpoint results from the phase 3 FLAIR and ATLAS studies. [2]

These studies reported >90% viral suppression <50 copies/mL at week-48 meeting criteria for non-inferiority compared to three-drug oral therapy.

The press release also notes that submission to the European Medicines Agency (EMA) is expected within the next few months.

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Dolutegravir/3TC dual FDC (Dovato) approved in the US and given positive opinion in the EU

Simon Collins, HIV i-Base

On 8 April 2019, the US FDA approved a new single-pill two-drug fixed dose combination (FDC) of dolutegravir (DTG) plus lamivudine (3TC). [1]

A few weeks later, positive opinion for dolutegravir/lamivudine was also given by the European Medicines Agency, indicating likely approval in the EU. [2]

DTG/3TC is a once-daily combination that can be taken with or without food.

The indication is for treatment-naive adults who do not have drug resistance to either of these two drugs and approval is based on results of the phase 3 GEMINI 1 and 2 studies that were presented at the IAS conference last year. [3, 4]

The approval includes a boxed warning for management of patients coinfected with hepatitis B (HBV). All patients should be tested for HBV before starting DTG/3TC and additional treatment for HBV should be used.

There is also a caution for women to avoid dolutegravir during conception and in early pregnancy due to a risk of neural tube defects.

Dolutegravir/3TC is manufactured by ViiV Healthcare and is marketed with the tradename Dovato.

For full details see the full product characteristics. [5]

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OTHER NEWS

King's launches transgender sexual health service with cliniQ

Kings College press release

On 29 March 2019, King's College Hospital in Camberwell announced that it is launching the first sexual health service in south London for trans people.

The walk-in clinic, which will run every Tuesday from 4pm to 7pm at the Caldecot Centre at King's College Hospital, will open at the end of April 2019.

In partnership with cliniQ, the new service will offer a range of health and wellbeing initiatives to meet the needs of trans people. Services include STI testing and treatment; contraception; counselling; acupuncture; cervical screening; hormone testing, hormone injection and advice; sexual assault support; hate crime support; housing advice; and the PrEP Impact Trial.

The service will be jointly delivered by trained King's and cliniQ staff and will include a counsellor; a support worker; a nurse; a doctor; and an acupuncturist. The team will provide care and support at the clinic and will work with other relevant services such as primary care, mental health services and social services.

In addition to clinical and support services, King's will be developing and delivering a range of training materials for healthcare professionals to raise awareness, knowledge and skills in relation to trans health.

Dr Michael Brady, Consultant in Sexual Health and HIV at King's College Hospital and National Advisor for LGBT Health at NHS England said, "On Trans Visibility Day (31 March), I am very proud to announce the new service that we will deliver in partnership with cliniQ. Although the focus of our service will be on sexual health, we recognise that trans and non-binary people are disproportionally affected by health inequalities and a range of potential physical, psychological and social problems. As such we will adopt a holistic approach combining health and wellbeing services to help improve mental health, self-esteem and reducing isolation. A holistic approach to trans health also plays a key part in reducing vulnerability to HIV acquisition."

Michelle Ross, cliniQ Co-founder and Director of Holistic Wellbeing Services added, "I am excited and immensely proud to announce that cliniQ in partnership with King's College Hospital will be delivering and developing the very first sexual health and holistic wellbeing services in South London for trans, non-binary and gender diverse people. cliniQ have a substantial background of over seven years providing sexual health, HIV and holistic wellbeing services for trans communities, and we have convened five national ground-breaking conferences with international speakers from; San Francisco, Mexico City and TGEU Berlin. cliniQ's focus is on improving the provision of health and wellbeing services in the UK for trans, non-binary and gender diverse people and enhancing their dignity in accessing services."

Cllr Ed Davie, Lambeth Cabinet Member for Health, said: "This new service is something we're very proud to deliver alongside King's and the Health Innovation Network. I'm certain that it will make a positive difference to the lives of trans people in Lambeth and across South London, providing a whole range of health support in a safe, comfortable environment. This will increase learning and awareness, both for health professionals in the issues that trans people face, and also for trans men and women around sexual health and wellbeing, helping us reduce inequality and ensure that everyone can access the support that is right for them. From our black mental health commission to leading the Do It London HIV campaign, Lambeth Council has a proud record of working with our minority communities to improve health and I'm very pleased this new trans clinic builds on this offer."

The new service is funded by the London Boroughs of Lambeth, Southwark and Lewisham and the Health Innovation Network (South London).

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Source

Kings College Press Release. King's launches transgender sexual health service. (29 March 2019).
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FUTURE MEETINGS

Conference listing 2019

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

20th International Workshop on Clinical Pharmacology of HIV, Hepatitis & Other Antiviral Drugs

14 – 16 May 2019, Noordwijk, The Netherlands

www.virology-education.com

17th European Meeting on HIV & Hepatitis

22 – 24 May 2019, Rome

www.virology-education.com

Viruses, vaccines and eradication conference 2019

Thursday 6 June 2019, London

http://www.vveconference.com

11th International Workshop on HIV Pediatrics

20 – 21 July 2019, Mexico City

www.virology-education.com

HIV & HBV Cure Forum

20 – 21 July 2019, Mexico City

https://www.iasociety.org/HIV-Programmes/Programmes/Towards-an-HIV-Cure/Events/2019-HIV-HBV-Cure-Forum?

International Workshop on HIV & Transgender People

July 2019, Mexico City, date TBC

www.virology-education.com

10th IAS Conference on HIV Science

21 – 24 July 2019, Mexico City

www.ias2019.org

4th European Workshop on Healthy Living with HIV

13 – 14 September 2019. Barcelona

www.virology-education.com

21st Intl Workshop on Comorbidities and Adverse Drug Reactions in HIV

5 – 6 November 2019, Basel, Switzerland

https://www.intmedpress.com

10th International Workshop on HIV & Aging

10 - 11 October 2019 | New York, NY, USA

www.virology-education.com

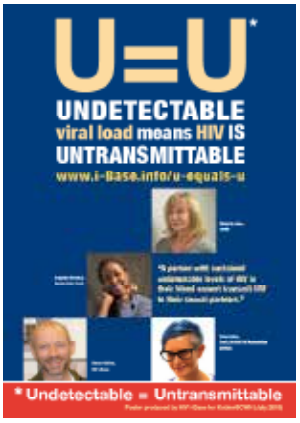
17th European AIDS Conference

6 – 9 November 2019, Basel

www.eacsociety.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website



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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

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

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

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

Pocket guides

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

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

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

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

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

This project was developed with the Kobler Centre in London.

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

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

email: subscriptions@i-base.org.uk

Fax: 0208 616 1250

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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http://www.i-Base.info

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HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

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(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.
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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**

ART in pictures: HIV treatment explained *(June 2017): 32-page A4 booklet* **quantity** _____

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

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

Introduction to ART *(September 2016): 48-page A5 booklet*

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 HIV, pregnancy and women's health *(April 2019): 52-page A5 booklet* **quantity** _____

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

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