ISSN 1472-4863

hiv treatment bulletin (e)

HTB: 2019 vol 20 no 4

13 March 2019: no 4

CROI 2019: second reports

CONTENTS

Published by HIV i-Base

EDITORIAL

This issue of HTB includes our second set of reports from the recent CROI 2019 conference.

These include reports on pipeline compounds from three new classes – a maturation inhibitor, a capsid inhbitor and first results of a monocolonal antibody PGT121.

Two posters reported that rapid-ART access continues to produce good results in San Francisco and there are additional supportive results for dolutegravir/3TC dual therapy from the GEMINI study.

In a major review, Polly Clayden reports in depth on the current data covering the possible signal of neural tube defects associated with dolutegravir.

Other reports include pharmacokinetic and drug interaction studies including that double-dose levonorgestrel implant does not overcome an interaction with efavirenz, that efavirenz and rifampicin together reduce levels of injectable contraception and that bedaquiline and delamanid can be given together to treat MDR TB.

SUPPLEMENTS

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

Please continue to order these free resources.

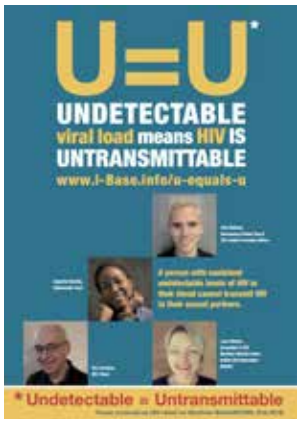
Customise U=U posters for your clinic

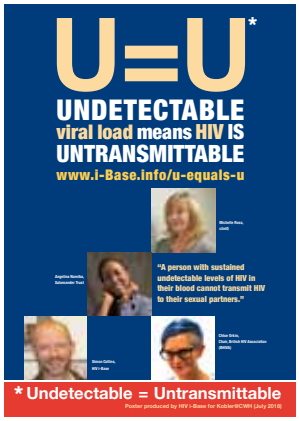
i-Base can customise U=U posters to include pictures of your doctors, nurses, pharmacists, peer advocates or any other staff that would like to help publicise U=U.

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

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.

The meeting had an exciting programme with research that we will report over at least the next three issues of HTB.

CROI is notable for providing same-day or next-day webcasts for most talks and comprehensive online access to abstracts and PDF files for posters.

http://www.croiconference.org

BHIVA have also organised an excellent series of CROI feedback workshops and slides and webcasts from the London meeting are also posted online.

https://www.bhiva.org/BestofCROI2019

This is the second set of HTB reports from the CROI.

- Maturation inhibitor GSK'232 reduces viral load by –1.5 log at day 10
- Capsid inhibitor GS-6297 shows potential for 3-monthly injections
- First phase 1 results from bNAb PGT121 in HIV positive people
- Dolutegravir/3TC dual ART is as effective at lowest viral load cut-off as triple therapy in GEMINI Studies
- Same-day ART in San Francisco: long-term follow-up from Rapid-ART clinic
- Integrase inhibitors and neural tube defects: more data still needed
- Double-dose levonorgestrel implant does not overcome interaction with efavirenz
- Efavirenz and rifampicin together reduce levels of injectable contraception
- Bedaquiline and delamanid safe when given together to treat drug resistant TB
- Isoniazid preventative therapy in HIV positive pregnant women not linked to poor outcomes

CROI 2019: ANTIRETROVIRALS

Maturation inhibitor GSK'232 reduces viral load by –1.5 log at day 10

Simon Collins, HIV i-Base

Results from a 10-day phase 2a dose-finding study for GSK2838232 (GSK'232) – a maturation inhibitor in development at GSK – were presented by Edwin DeJesus from Orlando Immunology Centre.

Maturation inhibitors bind to gag protein to target a late-stage of viral lifecycle and the development of two previous compounds in this class were stopped due to limited activity due to commonly occurring polymorphisms (beviramat) and side effects (BMS-955176).

The new GSK compound has good in vitro potency, minimal protein binding and broad-spectrum activity (including against polymorphisms associated with beviramat).

GSK-232 was given once-daily with cobicistat boosting. Doses in this two-part study were 20 mg, 50 mg, 100 mg and 200 mg - each given with cobicistat 150 mg. The 100 mg dose was run as the first part of this study.

Approximate baseline characteristics of the 33 participants (largely young white men) included mean CD4 and viral load of 540 cells/mm^3 and 58,000 copies/mL (range: 1300 to 363,000).

Mean viral load decline at day 10 was –1.5 log copies/mL in the 200 mg arm and 1.2 log copes/mL on the 50 mg and 100 mg arms, sustained for several days before returning towards baseline over the following 10 days.

Steady state was reached by day 8 and most PK parameters (AUC, Cmax and C trough) showed broadly dose-proportional responses.

Resistance results at days 1 and 11 were available for 28/33 participants. Two participants (one in 50 mg and one in 100 mg arms) had genotypic changes at A364A/W in gag, which phenotypic resistance to GSK'232 detected at day 11 in the 50 mg participant.

Reduced baseline sensitivity to GSK'232 in another participant in the 50 mg arm only produced a viral load reduction of 0.17 log copies/mL.

Tolerability was good with no pattern form mild/moderate side effects or dose relationship, with no serious events and no discontinuations. There were no grade 3/4 lab abnormalities or clinically significant ECG abnormalities.

Reference

DeJesus E et al. A phase IIa study of novel maturation inhibitor GSK2838232 in HIV patients. Conference on Retroviruses and Opportunistic Infections (CROI), 4-7 March 2019, Seattle. Oral abstract 142.

http://www.croiconference.org/sessions/phase-iia-study-novel-maturation-inhibitor-gsk2838232-hiv-patients (abstract)

http://www.croiwebcasts.org/console/player/41311 (webcast)

Capsid inhibitor GS-6297 shows potential for 3-monthly injections

Simon Collins, HIV i-Base

Early results study for a long-acting injection formulation of the capsid inhibitor GS-6297 were presented by Jennifer Sage from Gilead Sciences.

This was a phase 1 dose escalation study in 40 HIV negative volunteers.

Capsid inhibitors are potentially active at multiple stages of the viral lifecycle including early uncoating once HIV has infected a CD4 cell and at a late stage when new virus is being reassembled.

GS-6297 is a highly potent molecule that is formulated as a long-acting sub-cutaneous injection.

Forty participants were randomised to one of four single doses: 30 mg, 100 mg, 300 mg and 450 mg with 8 active and 2 placebo recipients in each arm. Three injections were required for the two highest doses.

Approximately 70% of the participants were male and 70% were white. Mean age was about 35 years (range 21 to 44).

Pharmacokinetic results showed prolonged exposure following the single exposure, with drugs levels sustained for over 24 weeks. Drug levels were dose related but similar exposures were seen for the 300 mg and 450 mg groups.

All doses for the 100 mg, 300 mg and 450 mg group remained above the protein adjusted EC95 at week 12 that continued out to week 24 for the 450 mg group.

There were no serious adverse events, mostly grade 1.

In vitro activity data for GS-6207 reporting significantly greater potency compared to current ARVs (including dolutegravir) with activity against resistance to NRTI, NNRTI, PI and integrase inhibitor classes was also presented in a poster. [2]

GS-6297 is already in phase 1 studies in HIV positive people. [3]

References

1. Sage JE et al. Safety and PK of subcutaneous GS-6207, a novel HIV-1 capsid inhibitor. Conference on Retroviruses and Opportunistic Infections (CROI), 4-7 March 2019, Seattle. Oral abstract 141.
   http://www.croiconference.org/sessions/safety-and-pk-subcutaneous-gs-6207-novel-hiv-1-capsid-inhibitor (abstract)
   http://www.croiwebcasts.org/p/2019croi/141 (webcast)
2. Yant SR et al. GS-6207, a potent and selective first-in-class long-acting HIV-1 capsid inhibitor. Conference on Retroviruses and Opportunistic Infections (CROI), 4-7 March 2019, Seattle. Poster 480.
   http://www.croiconference.org/sessions/gs-6207-potent-and-selective-first-class-long-acting-hiv-1-capsid-inhibitor (abstract)
3. ClinicalTrials.gov. Safety, pharmacokinetics, and antiviral activity of GS-6207 administered subcutaneously in HIV-1 infected adults.
   https://clinicaltrials.gov/ct2/show/NCT03739866

First phase 1 results from bNAb PGT121 in HIV positive people

Simon Collins, HIV i-Base

Several studies at CROI provided insight into the potential for broadly neutralising monoclonal antibodies (bNAbs) for both HIV treatment and HIV prevention.

This included results of a randomised double blinded, dose escalation, placebo-controlled trial phase 1 study of PGT121 presented by Kathryn Stephenson from Beth Israel Medical Centre, Boston.

PGT121 is an IgG1 mAb that targets the V3 Env epitope.

The first part of this two-part study was in 20 HIV negative individuals and 15 HIV positive people on ART. Single doses of PGT121 were given at 3, 10, and 30 mg/kg IV infusion or 3 mg/kg subcutaneous injection. The second part gave a single open-label infusion of PGT121 at 30 mg/kg IV in HIV positive participants not on ART with either high viral load (3.3-4.8 log copies/mL, n=9) or low viral load (2-2.6 log copies/mL, n=4).

Safety and tolerability was good in both parts of the study with most participants reporting no local or systemic side effects from the single treatment. The only serious adverse event was a knee operation not related to study medication. Grade 2 events (headache and malaise) were reported in approximately 5% participants.

PGT121 had different pharmacokinetic properties in each of the three groups, with a median half life of 23.5, 19 and 13 hours in the HIV negative, ART and non-ART groups respectively.

In the HIV positive group with high viral load there were five responders and four non-responders with a median viral load reduction at day 7 of –1.7 logs in the responder group (maximum –2.1 log). Viral load then returned to baseline over the next 4-6 weeks with resistance to PGT121 in these 5/5 participants.

However, two participants in the low viral load group had rapid viral load reductions to <40 copies/mL that remained undetectable for the next 6 months. One of these participants rebounded (with PGT121 sensitive virus) at day 168 and the other has remained undetectable at this timepoint. In both these participants, detectable levels of PGT121 fell below the sensitivity of the test (0.7 ug/mL) at day 112.

Immunological assessments so far have failed to find any changes in HIV-specific cellular responses with activity explained by antiretroviral potency of PGT 121.

C O M M E N T

These tentative results give an indication that bNAbs might have the potential to maintained sustained viral suppression off-ART for more than six months in context of very low viral load, albeit using an intervention that is currently too expensive for anything other than a research setting.

It is difficult to understand why bNAbs are being developed using monotherapy studies when the development of resistance in this setting is both predicted and expected.

Reference

Stephenson KE et al. Therapeutic activity of PGT121 monoclonal antibody in HIV-infected adults. Conference on Retroviruses and Opportunistic Infections (CROI), 4-7 March 2019, Seattle. Oral abstract 145.

http://www.croiconference.org/sessions/therapeutic-activity-pgt121-monoclonal-antibody-hiv-infected-adults (abstract)

http://www.croiwebcasts.org/console/player/41314 (webcast)

Dolutegravir/3TC dual ART is as effective at lowest viral load cut-off as triple therapy in GEMINI studies

Simon Collins, HIV i-Base

The phase 3 GEMINI 1 and 2 studies showed that dual therapy (2D) with dolutegravir/3TC was non-inferior to triple therapy (3D) with dolutegravir plus TDF/FTC, based on viral suppression at 48 weeks.

A new analysis, presented as a poster at CROI 2019, now also shows no differences between the two arms at viral load <40 copies/mL.

The analysis was based on participants with viral load <40 copies/mL having either a target detected (TD) or target not detected (TND) result.

At the primary 48 week endpoint and at all earlier time points there were no significant differences between the 2D vs 3D arms: 77% vs 73% (adjusted difference: 3.8%, 95% CI –0.6%, 8.2%).

Proportions were similar at all other time points: 34% vs 32% (week 4), 52% vs 49% (week 8), 60% vs 57% (week 12), 59% vs 56% (week 16), 65% vs 63% (weeks 24) and 65% vs 68% (week 36), in the 2D vs 3D arms respectively.

By baseline viral load, there was also no differences between arms in participants starting <100,000 copies/mL but a numerical advantage for the 2D arm when baseline viral load was >100,000 copies/mL (64% vs 52% (difference +12.7% (95%CI: 1.4 to 23.9). See Table 1.

Time to TND was the same for both arms: 29 days with baseline VL <100,000 and 57 days when >100,000 copies/mL.

Table 1. Proportion of participants with VL <40 copies/mL and TND at week 48

Baseline VL (c/mL)	DTG+3TC n (%)	DTG+TDF/FTC n (%)	treatment difference (95%CI)
<100,000	463/576 (80)	446/564 (79)	1.3 (–3.4 to 6.0)
>100,000	90/140 (64)	79/153 (52)	12.7 (1.4 to 23.9)
>250,000	25/51 (49)	20/46 (43)	5.6 (–14.3 to 25.4)
>400,000	5/18 (28)	6/24 (25)	2.8 (–24.2 to 29.8)

Reference

Underwood M et al. HIV replication at <40 c/mL for DTG+3TC vs DTG+TDF/FTC in the GEMINI 1 & 2 studies. CROI, 4-7 March 2019, Poster abstract 490.

http://www.croiconference.org/sessions/hiv-replication (abstract)

Same-day ART in San Francisco: long-term follow-up from Rapid-ART clinic

Simon Collins, HIV i-Base

Offering same-day ART on diagnosis as part of comprehensive care at a specialist HIV clinic in San Francisco reported such significant benefits that it is the standard of care in the city.

Sara Coffey and colleagues presented a retrospective analysis of newly diagnosed individuals referred to Ward 86 Rapid-ART programme from 2013 to 2017. Of these, 98% (216/225) accepted same day ART (4 declined, 3 were not offered and 2 were lost to follow-up). [1]

Baseline characteristics included median age 30 years (range 16-61) with median CD4 count and viral load of 441 (range: 3 to 1905) cells/mm^3 and 37,000 (range: 0 to >10 million) copies/mL respectively.

This was a largely male cohort (7.9% women). Ethnicity was 12% African American, 27% Hispanic and 37% white.

This is also a cohort with complex social factors: 51% reported substance use, 48% had a major mental health diagnosis and 30% were either homeless or had unstable housing.

Median time from the Rapid-ART clinic visit to starting ART start was 0 days (range 0 to 56) achieving undetectable viral load in median of 41 days.

Over a median follow-up of 1.1 years (range 0 to 3.9) 96% participants had at least one viral load <200 copies/mL with 92% undetectable at one year. Viral rebound >200 copies/mL was reported for 14% of participants with 78% of these resuppressing to <200 copies/mL.

These results support the effectiveness from offering same-day ART in the context of a multidisciplinary care package (including case worker support for insurance, housing etc), even in a complex population with high rates of substance use, mental health issues and homelessness.

Early results from the pilot study of this programme in 39 men were first presented at the IAS conference in 2015. [2]

C O M M E N T

A similar model has been developed at some UK clinics including 56 Dean Street which has reported similar rates of high patient acceptability. [3]

All projects work to integrate other social support within this model, but prioritise starting ART which other services become involved.

ART in the San Francisco project is almost exclusions based on integrase-inhibitors which both overcomes concerns which results from drug resistance tests are still ongoing, but also minimises risk of serious side effects.

References
1. Coffey S et al. High rates of virologic suppression after rapid ART start in a safety-net clinic. Conference on Retroviruses and Opportunistic Infections (CROI), 4-7 March 2019, Seattle. Poster abstract 515.
http://www.croiconference.org/sessions/high-rates-virologic-suppression-after-rapid-art-start-safety-net-clinic (abstract and poster)
2. Pilcher C et al. Providing same day, observed ART to newly diagnosed HIV+ outpatients is associated with improved virologic suppression. 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015), 19 – 22 July 2015. Oral abstract WEAB0104.
http://www.abstract-archive.org/Abstract/Share/70312 (abstract)
http://pag.ias2015.org/PAGMaterial/Webcast/2230_13083/webcast.mp4 (webcast)
3. Whitlock G et al. Rapid initiation of antiretroviral treatment in newly diagnosed HIV: experience of a central London clinic. 23rd BHIVA 4-7 April 2017, Liverpool. Oral abstract O14.
https://www.bhiva.org/file/QpTjibLZUaFzD/GaryWhitlock.pdf (PDF)
http://www.bhiva.org/170406GaryWhitlock.aspx (webcast)

CROI 2019: PREGNANCY

Integrase inhibitors and neural tube defects: more data still needed

Polly Clayden, HIV i-Base

Unsurprisingly a number of presentations at CROI 2019 focused on integrase inhibitors and neural tube defects.

If there is still anyone who missed this: last year, the Botswana Tsepamo study reported neural tube birth defects in 4/596 (0.67%) infants born to women receiving dolutegravir-based ART periconception vs 14/11,300 (0.12%) receiving periconception non-dolutegravir ART. [1]

Further data are still required to confirm or refute this potential safety signal. Although there have been a number of reports from small birth outcome cohorts since the Botswana data was released, these have been insufficient to alter concerns about periconception dolutegravir (or other integrase inhibitor) use. [2]

Reports at CROI included: data from the French National database; rates of neural tube defects in Uganda among HIV positive and negative women; data on raltegravir from its originator company; data from the Antiretroviral Pregnancy Registry; limitations of pharmacovigilance databases; and women's choices in a cohort already receiving dolutegravir following the signal.

French Perinatal Cohort

There was no evidence of a higher birth defect rate among infants exposed to integrase inhibitors (mostly raltegravir) at conception in the French Perinatal Cohort. [3]

The French Perinatal Cohort, which has been running since 1986, collects data prospectively on all pregnant HIV positive women in 90 centres across the country.

There were 8126 pregnancies reported between 2008 and 2017. Of these, 808 pregnancies were exposed to integrase inhibitors: 301 exposed at conception; 183 as part of first-line ART and 324 as part of second-line had started during pregnancy.

Of 301 periconception exposures: 218 were exposed to raltegravir, 41 to dolutegravir, and 42 to elvitegravir. Birth defect rates for integrase inhibitor-exposed infants at conception did not differ significantly from those exposed during pregnancy: 5.8% (18/301) vs 2.7% (both pregnancy exposure groups 5/184 and 9/324), p=0.09.

Matched controls of pregnancies not exposed to integrase inhibitors also had similar rates of birth defects to those exposed to integrase inhibitors.

And rates of preterm birth, still birth and low birth weight were similar between exposure groups.

Uganda

A report from the Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda found neural tube defects to be common but no significant difference between rates in infants born to HIV positive or HIV negative women. [4]

A total of 69,766 births, at four centres, were included in this surveillance. Median maternal age was 25 years, 9.6% were HIV positive with 95.3% receiving ART, the majority efavirenz-based. Only one woman received dolutegravir in this cohort as this was not commonly available in Uganda during the study period (August 2015 to December 2017).

There were 71 neural tube defects (66 in HIV unexposed and 5 exposed infants), giving a prevalence of 10.5 (95% CI 8.3 to 13.3) vs 7.4 (95% CI 3.2 to 17.4) per 10,000 live births in HIV unexposed and exposed infants respectively: aOR 0.91 (95% CI 0.3 to 2.4), p=0.858.

The authors noted that these findings are similar to the current estimates for Africa.

Raltegravir

Prospectively collected pregnancy outcome data on raltegravir by the originator company Merck did not suggest an association between exposure in the periconception period and neural tube defects. [5]

As of 31 May 2018, collected 803 prospective reports of which 443 (55%) were first trimester exposures; 295/443 were periconception exposures. There were no neural tube defects reported among this group.

There was one retrospective report of myelomeningocele among life births following periconception exposure to raltegravir.

Antiretroviral Pregnancy Registry

Too few integrase inhibitor exposed pregnancies have been reported to the Antiretroviral Pregnancy Registry (APR) to date to draw definitive conclusions about a potential association between dolutegravir and neural tube defects. [6]

The majority of reports to the APR and from US and Europe.

Through 31July 2018 there were 1,193 live births with an integrase exposure at any time during pregnancy, of which 604 had ongoing exposure at conception, including 174 dolutegravir, 186 elvitegravir, and 244 raltegravir live birth outcomes. There were no neural tube defects among prospective cases for any integrase inhibitor.

There were 7 neural tube defects plus 2 encephalocele cases reported to the registry retrospectively for which the denominator is unknown. Five were associated with periconception exposure to dolutegravir (4 Botswana and 1 US) and 4 raltegravir (2 periconception exposures, 1 second trimester and one unknown; 3 US and 1 UK).

Limitations of pharmacovigilance databases

An analysis of reports of neural tube defects to four pharmacovigilance databases found many limitations. [7] Most notably lack of a clear denominator, reporting is not systematic, there is overlap in reports for multiple drugs used in ART, duplicate cases are difficult to identify, and results differ between databases.

The analysis included reports to: 1. Food and Drug Administration FAERS database (USA) 2. World Health Organisation VigiAccess (WHO) 3. European EudraVigilance (EU) 4. UK Medicines Health Regulatory Authority (MHRA).

This revealed, out of a total of 165 neural tube cases (262 reactions) across the databases, after de-duplication, 44 remained.

Neural tube defects were reported for all drugs except bictegravir (but this is the newest drug with the smallest database). The numbers of reported neural tube cases with dolutegravir exposure were similar in the FDA and WHO databases, but no cases were reported to EU and UK MHRA.

As ART includes multiple drugs, neural tube defects could be reported for multiple drugs and by multiple sources for the same person; for example, for a single case in the FAERs database, there were 40 neural tube defect reports for the same woman who received 7 different drugs

Given widespread use and anticipated use of several new antiretrovirals worldwide, ongoing prospective follow up of pregnant women and birth surveillance studies such as Tsepamo are critical. And pregnant women should be enrolled in phase 3 trials where regulations allow, the authors wrote.

Women's choice in Uganda

A report from a clinic in Kamala, following the introduction of dolutegravir in 2017, described choices among women of reproductive potential already receiving dolutegravir-based ART after the safety signal in May 2018. [8]

Of 510 women identified, 21% opted to be switched from dolutegravir (90% to efavirenz) and 79% to remain on dolutegravir. But, only 40% of these women chose effective contraceptives methods and 60% opted for condoms only/ no contraceptive method.

Factors associated with switching off DTG were younger age and not using effective contraception. The authors noted that although women made informed decisions with most opting to stay on dolutegravir, effective contraception uptake was low.

C O M M E N T

Also at CROI 2019, Lynne Mofenson from Elizabeth Glaser Pediatric AIDS Foundation, gave an excellent update on antiretrovirals and birth defects. [9] It is worth watching the webcast.

As well as providing a tour de force of what is known (and not known) about antiretrovirals and birth defects in pregnancy, she looked at when we can expect more data on the dolutegravir signal.

By the end of March this year there will be data available on at least 1400 dolutegravir periconception exposures in the Tsepamo study.

Citing recent modelling by Schomaker et al, if there are no more defects after 1400 exposures, the confidence interval overlaps with the lower limit of non-dolutegravir exposed prevalence and the findings can be refuted. If there is 1 new defect, 2000 exposures will be needed, and with 2 new defects, 2500 exposures will be before the confidence intervals overlap.

Outside of Tsepamo, there are limited sources of data, usually from high income countries and small cohorts. Together the main ones (APR, Brazil, UK/Ireland) provide about 600 exposures but from countries with lower background rates of neural tube defects than seen in Africa and that usually use folate supplementation.

She also warned of the unreliability of pharmacovigilance databases – something we have grumbled about for some time. [10]

So, by the middle of this year we should have more data from Tsepamo hopefully combined with other good quality observational data – these data will be reviewed by the WHO guidelines group in July.

In the meantime, she pointed out that the risk of neural tube defects is still relatively small 1 in 1000 in general population with a potential increase to 7 in 1000 with periconception dolutegravir.

As do several of the presentations above, once again she called for data in pregnancy to be prospectively and systematically collected for new antiretrovirals.

Polly Clayden is a co-author of the study looking at pharmacovigilance databases (Abstract 746).

References

All references are to the programme and abstracts of the Conference on Retroviruses and Opportunistic infections (CROI) 2019, Seattle, 4–7 March 2019, unless otherwise stated.

1. Clayden P. No additional neural tube defects among a further 170 preconception dolutegravir exposures in Botswana: Tsepamo study (July 2018). HTB. 3 August 2018. http://i-base.info/htb/34673
2. Clayden P. No additional neural tube defects with preconception dolutegravir: data from three birth outcome cohorts. HTB. 13 November 2018. http://i-base.info/htb/35301
3. Sibiude J et al. No increase in birth defects in infants exposed to integrase inhibitors at conception. Poster abstract 744. http://www.croiconference.org/sessions/no-increase-birth-defects-infants-exposed-integrase-inhibitors-conception (abstract) http://www.croiconference.org/sites/default/files/posters-2019/1430_Sibiude_0744.pdf (poster)
4. Barlow-Mosha L et al. Neural tube defects, HIV, and antiretrovirals: birth-defect surveillance in Uganda. Poster abstract 743. http://www.croiconference.org/sessions/neural-tube-defects-hiv-and-antiretrovirals-birth-defect-surveillance-uganda (abstract) http://www.croiconference.org/sites/default/files/posters-2019/1430_BarlowMosha_0743.pdf (poster)
5. Hala H et al. Evaluation of neural tube defects after exposure to raltegravir during pregnancy. Poster abstract 745. http://www.croiconference.org/sessions/evaluation-neural-tube-defects-after-exposure-raltegravir-during-pregnancy (abstract) http://www.croiconference.org/sites/default/files/posters-2019/1430_Shamsuddin_0745.pdf (poster)
6. Albano JD et al. InSTI exposure and neural tube defects: data from Antiretroviral Pregnancy Registry. Poster abstract 747. http://www.croiconference.org/sessions/insti-exposure-and-neural-tube-defects-data-antiretroviral-pregnancy-registry (abstract) http://www.croiconference.org/sites/default/files/posters-2019/1430_Mofenson_0747.pdf (poster)
7. Hill A et al. Reports of neural tube defects for 8 arts, in FDA, WHO, EMA, and UK safety databases. Poster abstract 746. http://www.croiconference.org/sessions/reports-neuraltube-defects-8-arts-fda-who-ema-and-uk-safety-databases (abstract) http://www.croiconference.org/sites/default/files/posters-2019/1430_Hill_0746.pdf (poster)
8. Arnold AS et al. Ugandan clinic experience following potential teratogenicity alert for dolutegravir. Poster abstract 748. http://www.croiconference.org/sessions/ugandan-clinic-experience-following-potential-teratogenicity-alert-dolutegravir (abstract) http://www.croiconference.org/sites/default/files/posters-2019/1430_Arnold_0748.pdf (poster)
9. Mofensen L. Update on antiretroviral drugs and birth defects. Oral abstract 59. http://www.croiconference.org/sessions/update-antiretroviral-drugs-and-birth-defects (abstract) http://www.croiwebcasts.org/p/2019croi/59 (webcast)
10. Clayden P. Dolutegravir preconception signal: time is up for shoddy surveillance. HTB. 11 July 2018. http://i-base.info/htb/34459

CROI 2019: DRUG INTERACTIONS

Double-dose levonorgestrel implant does not completely overcome interaction with efavirenz

Polly Clayden, HIV i-Base

Using two levonorgestrel (LNG) implants does not fully overcome the drug-drug interaction with efavirenz (EFV) – according to findings from a pharmacokinetic (PK) evaluation of double-dose LNG in Ugandan women receiving EFV-based ART. [1]

Kim Scarsi presented these data at CROI 2019 on behalf of investigators from University of Nebraska Medical Center; Infectious Disease Institute, Kampala; Northwestern University, Chicago; and University of Liverpool.

LNG is primarily metabolised in the liver by cytochrome P450 (CYP) 3A4. EFV decreases progestin exposure through induction of cytochrome P450.

LNG subdermal implants can be left in place for up to 5 years and are a highly effective form of contraception with less than 1% risk of unintended pregnancy.

Professor Scarsi's group previously found 45–57% lower LNG exposure in women using the implant at standard dose (150mg) with EFV-based ART compared to ART-naive women. [2, 3]

In that earlier study, 3 of 20 women (15%) had an unintended pregnancy within 48 weeks of combined LNG-EFV use. LNG concentrations were ≤303 pg/mL in the 3 women at the visit before pregnancy; 18 (90%) women had any LNG concentration ≤303 pg/mL during the study.

The aim of the study presented was to see if the LNG-EFV interaction could be overcome with double-dose LNG (300 mg) implants over 48 weeks in women receiving EFV-based ART, compared with historical controls.

It was an open label, sparse-sampling PK study. Women receiving EFV 600 mg based ART, with undetectable viral load, had LNG implants placed sub-dermally in each upper arm (DoubLNG group; n=28). All participants were also given a copper IUD as an additional form of contraception.

Historical controls were ART-naive Ugandan women (n=17) who received a standard-dose LNG implant.

Sampling was performed pre-implant and at weeks 1, 4, 12, 24, 36, and 48. There were optional study visits for 4 weeks after week 48 to assess endogenous progesterone as an indicator of ovarian activity (threshold 3 or 4 ng/mL).

All women were black African. The DoubLNG group was a median age of 33 years and median weight of 58 kg; the control group was 29 years and 69 kg.

At week 48, LNG concentrations were 373 pg/mL (319 to 540) in the DoubLNG group vs 651 pg/mL (469 to 879) in the control group: GMR 0.66 (90% CI 0.61 to 0.72), p=0.003. This reduction in exposure was similar weeks 1 through 48.

Despite the double-dose of LNG implants, concentrations remained 33–44% lower in women receiving EFV-based ART plus LNG vs ART-naive women on standard dose LNG.

More women in the DoubLNG group vs the control group had any LNG value ≤303 pg/mL: 13 (46%) vs 3 (18%), respectively, p=0.06. About 90% were below this threshold in the earlier study.

Approximately 20–25% of participants in the DoubLNG group (n=24) had endogenous serum progesterone levels reflecting ovulation vs 10–15% expected to have ovulation in the first year of LNG use, based on historical data.

C O M M E N T

The reduction in concentrations was smaller with the double-dose compared with the standard dose used in the earlier study: 34 vs 57%. But although it increased exposure a bit, doubling the dose of LNG implants did not fully overcome the interaction with EFV.

Professor Scarsi described this as a "surprising finding" and explained that the contraceptive effectiveness of this approach remains uncertain. She remarked that these results may have complicated the challenges around providing contraception for women on EFV-based ART.

References

1. Scarsi K et al. Double-dose levonorgestrel implant does not fully overcome interaction with efavirenz. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 51.
http://www.croiconference.org/sessions/double-dose-levonorgestrel-implant-does-not-fully-overcome-interaction-efavirenz (abstract)
http://www.croiwebcasts.org/p/2019croi/51 (webcast)

2. Clayden P. Unintended pregnancies with levonorgestrel implant due to drug interactions with efavirenz-based ART. HTB. 24 March 2015. http://i-base.info/htb/28063
3. Scarsi K et al. Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: a three-arm pharmacokinetic evaluation over 48 weeks. Clin Infect Dis. Volume 62, Issue 6. 15 March 2016. https://academic.oup.com/cid/article/62/6/675/2462703

Efavirenz and rifampicin together reduce levels of injectable contraception

Polly Clayden, HIV i-Base

Women with HIV receiving depot medroxyprogesterone acetate (DMPA), with efavirenz (EFV)-based ART and rifampicin (RIF)-based TB treatment, had lower MPA plasma levels compared with women not receiving the two drugs.

These findings from ACTG A5338 were presented by Rosie Mnqibisa from the Enhancing Care Initiative, Durban, South Africa, on behalf of the study group.

Effective contraception is vital for young women with HIV-associated TB. Unintended pregnancy in this population is linked to increased maternal and infant disease and death.

RIF and EFV both induce CYP3A4 leading to lower progestin exposure and, in turn, reduced hormonal contraceptive effectiveness. DMPA is a contraceptive method that is given as an intramuscular injection and commonly used in low- and middle-income countries. The effect on the pharmacokinetics (PK) and safety of using DMPA with both EFV and RIF has not been previously investigated.

ACTG A5338 was a multicentre, single arm, PK study among women in sub Saharan Africa, stable on EFV-based ART and RIF-based TB treatment. It was conducted to estimate optimal dosing frequency of DMPA for women with HIV and TB receiving EFV and RIF and to look at whether standard 150 mg DMPA would be adequate to suppress ovulation through 12 weeks in this population.

Target serum MPA concentration was >0.1 ng/mL. Concentrations were determined pre-dose and 2, 4, 6, 8, 10 and 12 weeks after DMPA injection and progesterone levels measured from week 2 onwards. The primary outcome was the proportion of women with subtherapeutic MPA levels at week 12. MPA PK parameters were compared to historical controls.

A total of 42 women from Botswana, Zimbabwe, Kenya and South Africa were included in this PK analysis. All women were black African; at baseline they were a median of 32 years old and 54 kg; 86% had viral load <400 copies/mL.

All women had MPA levels above <0.1 ng/mL at week 8. At week 10, 1 woman had levels that fell below this target. By week 12, 5 (11.9%) women had MPA levels <0.1 ng/mL (95% CI 4.2 to 26.8).

Apparent clearance was higher in study population vs controls: 19,680 vs 12,117 respectively, p=0.004. Median AUC over 12 weeks was lower: 7.63 vs 12.38 ng*week/mL respectively, p=0.004.

Progesterone levels were below 1ng/mL through week 12 for all women; no ovulation occurred.

There were no grade 3 or higher adverse effects attributed to DMPA. There were no reported pregnancies.

The investigators suggested that shortening the DMPA dosing interval for women receiving EFV and RIF, most likely to every 8–10 weeks, seems prudent.

Reference

Mngqibisa R et al. Potential concern for timing of DMPA injection among women treated for HIV and TB. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 78.

http://www.croiconference.org/sessions/potential-concern-timing-dmpa-injection-among-women-treated-hiv-and-tb (abstract)

http://www.croiwebcasts.org/p/2019croi/78 (webcast)

CROI 2019: TB COINFECTION

Bedaquiline and delamanid safe when given together to treat drug resistant TB

Polly Clayden, HIV i-Base

QT interval prolongation effects of bedaquiline (BDQ) and delamanid (DLM) given together were no more than additive in a study looking at cardiac safety of the combined use of these drugs in people with multidrug resistant (MDR)-TB.

Data from the ACTG A5343 (DELIBERATE) trial were presented at CROI 2019.

BDQ and DLM are the first drugs from two new classes approved for TB in over 40 years. Both are recommended by WHO for treatment of MDR-TB by WHO.

Both drugs' metabolites prolong the QT interval. Peak QT effects are at 16–18 weeks for BDQ and 8 weeks for DLM. The cardiac safety of these drugs given together as part of a regimen to treat MDR-TB has not been previously studied.

DELIBERATE was a phase 2, randomised, open-label, three arm pharmacokinetic and safety trial. Adults with MDR-TB, receiving multidrug background treatment (MBT), were randomised 1:1:1 to receive BDQ, DLM or both (BDQ + DLM) for 24 weeks.

The primary objective was to compare mean change from baseline in QTcF (in ms; averaged over weeks 8–24) when BDQ and DLM are given together to the mean change when each drug is given alone.

People with QTcF >450ms or CD4 count <100 cells/mm3 were excluded. Clofazamine was not permitted and moxifloxacin was switched to levofloxacin. HIV positive participants received dolutegravir-based ART.

Three electrocardiograms (ECG) were performed at baseline, every two weeks for 24 weeks, then week 28.

A core laboratory blinded to treatment arm calculated QTcF. The study defined grade 3 QTcF prolongation as >500ms or >480ms with increase from baseline >60ms. Grade 4 was life-threatening dysrhythmia.

Sites were in South Africa and Peru. Gary Maartens from the University of Cape Town presented these findings on behalf of the DELIBERATE investigators.

Eighty-four participants were enrolled. Most (75%) were men, median age was 35 years and 37% were HIV positive.

Mean baseline QTcF and standard deviations in the BDQ, DLM and BDQ + DLM arms were respectively: 398 (24), 4004 (19) and 391 (14).

Of 74 participants with QTc data, mean change in QTcF from baseline in the respective arms was: 11.9 (95% CI 7.4 to 16.5), 8.6 (95% CI 4.0 to 13.2) and 20.7 (95% CI 16.1 to 25.4).

There were no Grade 3 or 4 QT interval prolongation events.

The investigators concluded that the combined effect on the QTcF interval of co-administration of BDQ and DLM is clinically modest and no more than additive.

C O M M E N T

The investigators also noted the caveat that this was a carefully-screened population not receiving other DR-TB drugs that have significant QT prolongation effects (clofazamine and moxifloxacin).

Reference

Dooley KE et al. QT effects of bedaquiline, delamanid or both in MDR-TB patients: The Deliberate trial. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 84LB.

http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial (abstract)

http://www.croiwebcasts.org/console/player/41181 (webcast)

Isoniazid preventative therapy in HIV positive pregnant women not linked to poor outcomes

Polly Clayden, HIV i-Base

Isoniazid preventative therapy (IPT) during pregnancy was not associated with a higher rate of adverse maternal or infant outcomes compared to not starting IPT in pregnancy. These findings from the Tshepiso study from South Africa were presented at CROI 2019. [1]

Pregnancy and HIV both increase the risk of TB disease and, in turn, poor maternal and infant outcomes. IMPAACT P1078/TB Apprise, presented at CROI 2018, found that starting IPT in HIV positive pregnant women increased risk of such outcomes compared with starting after delivery – raising questions on the safety of IPT in this population. [2]

Tshepiso was a prospective observational study looking at maternal and infant outcomes among HIV positive women with and without active TB disease conducted in 2014 in Soweto, South Africa from January 2011 through July 2014. Women were enrolled in pregnancy and followed for a year after delivery.

Nicola Salazar-Austin from John Hopkins University School of Medicine presented data on behalf of the study investigators.

The study enrolled 155 HIV positive women without TB disease. The analysis includes 151 women with known pregnancy outcomes; 69 (46%) started IPT during pregnancy.

At enrollment women were a median of 29 years and had CD4 count of approximately 370 cells/mm^3 across both groups. Women in the IPT group were enrolled at a median of 28 weeks' gestation vs 32 weeks in the no IPT group, p=0.01.

At delivery, 66% and 78% of women were receiving ART (84% EFV-based) in the IPT and no IPT groups respectively. The remainder received AZT monotherapy with or without single dose nevirapine (in accordance with guidelines at the time the study was conducted), or no ART.

Of the 69 women starting IPT during pregnancy, the majority started in the second (48%) or third (49%) trimester. The median duration of IPT was 3 months.

Median gestational age at delivery was 39 weeks in both groups.

There was one case of maternal TB in the no IPT group and no infant TB cases.

Respective rates of preterm deliveries, fetal demise (spontaneous abortion and still birth), low birth weight and congenital anomalies in the IPT vs no IPT groups were: 10% vs 22%; 1% vs 1%; 9% vs 12%; and 2% vs 2%.

A composite of the four outcomes showed more adverse outcomes in the no IPT group: 15% vs 27%; p=0.09.

IPT in pregnancy was not associated with a higher rate of poor maternal or infant outcomes in this cohort after controlling for CD4, viral load, ART maternal age, BMI and anaemia. aOR for adverse outcome with no IPT in pregnancy: 2.79 (95% CI: 1.13 to 7.39).

The investigators noted that although this study had well-characterised exposures and outcomes, this was a secondary analysis with a small sample size. As well as this, IPT use was not randomised so the study could not rule out unmeasured confounders and control for all relevant factors.

But these results might provide some reassurance that IPT can be used safely in the second and third trimesters of pregnancy in HIV positive women in high burden settings.

More research is needed to look at the safety of alternative TB preventative therapy, such as 3HP and 1HP, for HIV positive pregnant women in high burden settings, given their high risk of TB disease and poor maternal and infant outcomes.

Reference

1. Salazar-Austin N et al. IPT and pregnancy outcomes in HIV-positive women: the Tshepiso cohort. CROI 2019. Seattle. 4–7 March 2019. Oral abstract 77.
http://www.croiconference.org/sessions/ipt-and-pregnancy-outcomes-hiv-positive-women-tshepiso-cohort (abstract)
http://www.croiwebcasts.org/p/2019croi/77 (webcast)
2. Clayden P. Isoniazid preventive TB therapy in pregnancy and postpartum: recommendations now need to be re-evaluated. HTB 16 April 2018. http://i-base.info/htb/33851

ANTIRETROVIRALS

Dear Doctor letter: Increased risk of treatment failure and increased risk of mother-to-child transmission of HIV infection dues to lower exposure of elvitegravir and cobicistat during the second and third trimesters of pregnancy

Gilead Dear Doctor letter

On 26 March 2019, Gilead, in agreement with the European Medicines Agency (EMA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued a Dear Doctor letter on use of elvitegravir/ cobicistat during pregnancy.

The summary of this letter included:

- Therapy with elvitegravir/cobicistat should not be initiated during pregnancy.
- Women who become pregnant during therapy with elvitegravir/cobicistat should be switched to an alternative regimen.
- This is because pharmcokinetic data showed lower exposures of cobicistat and elvitegravir during the second and third trimesters of pregnancy.
- Lower elvitegravir exposures may be associated with an increased risk of treatment failure and an increased risk of mother-to-child transmission of HIV infection.

C O M M E N T

Lower exposure to elvitegravir and cobicistat was reported last year and included not starting pregnant women on these drugs. [2, 3]

Switching from elvitegravir/cobicistat for women who conceive while taking these as part of their ART regimen is recommended in the 2018 BHIVA guidelines. [4] As is starting elvitegravir/cobicistat-based ART in women who plan to become pregnant.

References
1. Gilead Dear Doctor letter. HIV/UK/19-03/CI/1223. (26 March 2019).
2. Clayden P. Reduced exposure to elvitegravir in pregnancy: results from the PANNA Network http://i-base.info/htb/34358
3. Momper JD et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS. 13 November 2018. https://journals.lww.com/aidsonline/Citation/2018/11130/Elvitegravir_cobicistat_pharmacokinetics_in.8.aspx
4. British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018. https://www.bhiva.org/file/5bfd30be95deb/BHIVA-guidelines-for-the-management-of-HIV-in-pregnancy.pdf (PDF)

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

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

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

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 (November 2016)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (Dec 2017)
- Guide to HIV, pregnancy & women's health (December 2015)

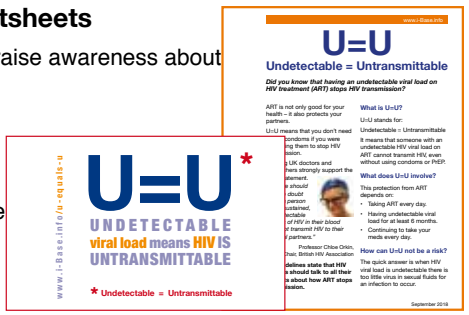
Pocket guides

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.

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.

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

http://www.i-Base.info

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

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.

However, any donation that your organisation can make towards our costs is greatly appreciated.

STANDING ORDER DONATION **THANK YOU FOR YOUR SUPPORT**

Title: _____ First Name _____ Surname _____

Address _____

_____

_____ Postcode _____

Email _____ @ _____

Telephone (s) _____ _____ _____

Please pay HIV I-Base £ _____ each month until further notice

Please debit my account number _____

Name of account (holder) _____ Bank sort code _____/_____/_____

Starting on _____/_____/_____ (DD/MM/YY)

Signature _____ Date _____/_____/_____ (DD/MM/YY)

To: Manager: (Bank name, branch and address)

_____

_____

Please complete the above and return to: HIV i-Base, 107 Maltings Place,169 Tower Bridge Road, London, SE1 3LJ

(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA.
Sort Code: 60-12-14. Account Number: 28007042)

ONE-OFF DONATION

I do not wish to make a regular donation at this time but enclose a one-off cheque in the sum of £ _____ .

GIVE AS YOU EARN

If your employer operates a Give-As-You-Earn scheme please consider giving to i-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit www.giveasyouearn.org

REFUNDS FROM THE TAX MAN

From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

However you chose to donate to i-Base,
we would like to thank you very much for your support.

REG IN ENGLAND WALES WITH LIMITED LIABILITY REG NO 3962064 CHARITY REG 1081905

107 Maltings Place,169 Tower Bridge Road, London, SE1 3LJ
T: +44 (0) 20 7407 8488

Orders and subscriptions

Please use this form to amend subscription details for HIV Treatment Bulletin and to order single or bulk copies of publications. All publications are free, but donations are always appreciated - please see the form on the previous page.

Name _____ **Position** _____

Organisation _____

Address _____

_____

Telephone _____ **Fax** _____

e-mail _____

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

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

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

- **Booklets about HIV treatment**

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 *(November 2016): 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 *(November 2015): 52-page A5 booklet* **quantity** _____

Guide to changing treatment: what if viral load rebounds *(Nov 2017): 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:

subscriptions@i-Base.org.uk