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PK workshop; UK PrEP at £17.50 a bottle

CONTENTS

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EDITORIAL

This issue of HTB mainly includes reports from the 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs.

This includes drug interactions with efavirenz with TB drugs and contraceptive implants.

Two other reports look at dolutegravir exposure in breastmilk and a detailed review of antiretroviral PK during pregnancy.

PrEP news in the UK hits a milestone with prices dropping to levels that are broadly affordable for many people. Both Dean Street PrEP Shop and online supplies are selling generic TD/FTC for around £20 for 30 tablets.

Finally, we highlight several reports from other organisations, including an excellent review of HIV criminalisation globally from the HIV Justice Network.

SUPPLEMENTS

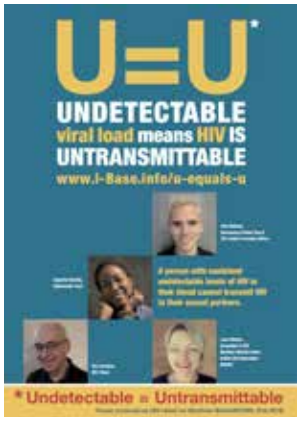
U=U resources for UK clinics: free posters, postcards and factsheets

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.

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

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

14-16 May 2019, Noordwijk, the Netherlands

Introduction

This year, the annual HIV PK Workshop marked its 20th anniversary by returning to the Dutch coastal resort of Noordwijk where the first meetings had been held.

Over the last two decades, these excellent specialist workshops have included first presentations and debates on many topics that have been central to HIV care and optimal use of HIV treatment.

Slides and webcasts are available online:

http://www.infectiousdiseasesonline.com/presentations-20th-international-workshop-clinical-pharmacology-hiv-hepatitis-antiviral-drugs

Two summary talks on research presented at the workshop are available online.

These require an instant sign up at this link:

https://imednet-vironet.talentlms.com

Articles in this issue of HTB are:

- Efavirenz 600 mg exposure appears sufficient with high-dose daily rifapentine
- Drug-drug interactions between efavirenz and levonorgestrel influenced by genetic variants
- Infant dolutegravir exposure through placental and breastmilk transfer
- Antiretroviral pharmacokinetics in pregnancy: update from IMPAACT P1026s

Other highlighted plenary talks include:

Stop measuring ARV levels in plasma! - *Courtney Fletcher*

50% adherence is enough with modern ARVs, right? - *Terrence Blaschke*

Modern ARVs do not develop resistance, do they? - *Jonathan Schapiro*

CRISPR/Cas and gene editing for HIV - *Paula Cannon*

Understanding the key determinants of performance for long-acting formulations - *Andrew Owen*

Efavirenz 600 mg exposure appears sufficient with high-dose daily rifapentine

Polly Clayden, HIV i-Base

Preliminary pharmacokinetic (PK) data support starting efavirenz (EFV)-based ART during TB treatment with high-dose daily rifapentine (RPT). These findings were presented at the 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs.

The Tuberculosis Trials Consortium Study 31 (S31)/AIDS Clinical Trials Group Study A5349 is a phase 3 trial comparing two short-course TB treatment regimens including high dose daily RPT to standard TB treatment.

RPT is a CYP inducer and EFV is a CYP substrate, so there is a potential risk of decreased EFV exposure with co-administration. A secondary objective and sub study of S31/A5349 was to look at the effect of RPT on EFV PK in treatment-naive participants starting EFV-based ART while receiving RPT-based TB treatment.

This sub study included participants starting EFV-based (600mg) ART within the first 9 weeks of TB treatment, randomised to one of two regimens containing daily RPT (1200mg), isoniazid (H), pyrazinamide and either ethambutol or moxifloxacin.

Data were presented for 28 evaluable participants: 25% women, 96% black/African, median age 36 years and mean baseline CD4 count 252 cells/mm^3.

Median EFV concentrations approximately 4 and 8 weeks after starting EFV were: 2.76 (IQR 2.12 to 4.67) mg/L and 2.86 (IQR 2.19 to 4.88) mg/L respectively. EFV concentrations at week 22 (after TB treatment completed) were: 2.86 (IQR 1.93-4.21) mg/L.

The protocol specified that at least 80% of participants must have EFV concentrations >1 mg/L at both time points during TB treatment in order to continue enrolment.

The percentage of participants with EFV concentrations >1 mg/L at 4 and 8 weeks after starting EFV were: 25/28 (89%) and 26/28 (93%). At week 22 19/21 (90%) of participants had EFV concentrations >1mg/L.

Median EFV CL/F were: 7.28 (IQR 5.47 to 10.08) and 8.3 (IQR 6.17 to 10.66) L/hr during and post RPT/H respectively.

The GMR of during to post RPT/H EFV CL/F was 0.89 (90% CI 0.64 to 1.23). Median baseline viral load (n=25) was 81,003 copies/mL; 20/23 (87%) participants had undetectable viral load at week 22.

These data provide preliminary support for initiating EFV-containing ART during co-administration of daily high-dose RPT for TB treatment.

This presentation included a summary of ongoing investigations and knowledge gaps in the use of RPT DDI with ART. See Table 1.

Table 1. Gaps in RPT DDI pharmacology

LTBI	Compatible ART	DDI trial status	Results expected	Knowledge gaps
3HP	EFV RAL 400 mg BID DTG	3HP w/ TAF in HV (Yoda) enrolling	Final 2020	3HP + TAF in HIV+
1HP	EFV	ACTG A5372	Initial PK 2020	DTG (what dose?) TAF
TB treatment	Compatible ART	DDI trial status	Results expected	Knowledge gaps
RPT x 17 weeks (S31)	EFV	S31/A5349	Final PK results late 2019	DTG TAF

Key: DDI drug drug interaction; DTG, dolutegravir; EFV, efavirenz; LTBI, latent TB infection; PK, pharmacokinetics; RAL, raltegravir; RPT, rifapentine; TAF, tenofovir alafenamide; 1HP, one month isoniazid/rifapentine; 3HP, three month isoniazid/rifapentine.

Adapted from Swindells and Dooley

Reference

Podany A et al. Efavirenz pharmacokinetics in HIV/TB coinfected persons initiating ART while receiving high dose rifapentine. 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs. 14–16 May 2019, Noordwijk, the Netherlands. Oral abstract 1.

http://regist2.virology-education.com/presentations/2019/20AntiviralPK/07_Podany.pdf (PDF slides)

Drug-drug interactions between efavirenz and levonorgestrel influenced by genetic variants

Polly Clayden, HIV i-Base

CYP2B6 genetic variants influence levonorgestrel (LNG) pharmacokinetics when combined with efavirenz (EFV)-based ART. These findings, from a Ugandan study, were presented at the 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs. [1]

The study investigators from University of Nebraska, Makerere University and University of Liverpool previously described 45–57% lower LNG concentrations in women using the LNG implant (150 mg) plus EFV 600 mg-based ART compared to ART-naive women. [2]

To overcome this interaction, they looked at the effect of doubling the LNG implant dose (300 mg; 2 implants) with EFV-based ART (DoubLNG). [3, 4]

In spite of the dose adjustment, LNG exposure remained 34% lower in the DoubLNG group compared to the same group of ART-naive Ugandan women in the previous study.

The investigators had also identified that CYP2B6 single nucleotide polymorphisms (SNPs) associated with slow EFV metabolism were linked to lower LNG exposure when the standard dose LNG implant was combined with EFV. [5]

To further explore those findings, they investigated potential associations between CYP2B6 metaboliser status and LNG pharmacokinetics (PK) in DoubLNG.

The study included 28 Ugandan women receiving EFV-based ART with undetectable viral load. An LNG implant was placed in each arm at study entry. All women were black African with median age of 33 years and weight 58 kg.

The investigators genotyped three SNPs (CYP2B6 rs3745274 516G→T, CYP2B6 rs28399499 983T→C, CYP2B6 rs4803419 15582C→T) for classification of normal, intermediate, and slow CYP2B6 metaboliser status.

Median LNG concentrations at week 24 for normal, intermediate, and slow metabolisers, were: 534 pg/mL (IQR: 507 to 577), 310.0 pg/mL (IQR: 279 to 346) and 167 pg/mL (IQR: 103 to 301), p= 5.16 x 10^{-5}, β = –0.21. Compared with normal metabolisers, LNG was 42% and 69% lower in intermediate and slow metabolisers respectively.

LNG AUC0-24wks (median) was 34% and 46% lower in intermediate and slow metabolisers compared with normal metabolisers.

At week 24, higher EFV concentrations were associated with lower LNG concentrations, p= 3.37 x 10^{-7} log10, β = –0.56, correlation coefficient –0.8.

Normal metabolisers receiving double dose had similar LNG exposure to historical controls (less than 5% decrease in LNG exposure) but intermediate and slow metabolisers had statistically lower LNG than historical controls: normal to ART- naive p=0.474; intermediate to ART-naive p=0.014; slow to ART-naive p=0.003.

The investigators summarised that in women receiving EFV 600 mg-based ART plus LNG implants double dose (300mg) of LNG in those with normal CYP2B6 metaboliser status result in comparable LNG exposure to standard dose LNG (150mg) in mixed-genotype ART-naive controls. And intermediate and slow CYP2B6 metaboliser status is associated with lower LNG concentrations, irrespective of LNG dose

They suggested that higher EFV exposure results in increased induction of CYP3A41. And that the potential for stratified LNG dosing based on CYP2B6 genotype and EFV dose is worthy of further investigation.

C O M M E N T

This excellent body of work continues to underline the complexities of using hormonal contraception with EFV-based ART.

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Infant dolutegravir exposure through placental and breastmilk transfer

Polly Clayden, HIV i-Base

Dolutegravir (DTG) expected to provide up to four days of additional prophylaxis to breastfed infants following maternal drug cessation. The estimate, based on data from the DolPHIN-1 study, suggests that breastfeeding contributes relatively little to infant plasma DTG exposures.

These findings from a population pharmacokinetic (PK) model, describing infant DTG exposure from residual intrapartum transfer and ongoing breastfeeding, were presented at the 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs.

DolPHIN-1 looked at the PK of DTG in pregnant women and their infants presenting with HIV late in pregnancy (28 to 36 weeks gestation). In this study 28 women from Uganda and South Africa were randomised to receive daily DTG or efavirenz (EFV)-based ART. In comparison to EFV-based standard of care the DTG-based regimen was significantly more likely to achieve maternal viral load <50 copies/mL by day 14 of ART.

The aims of the modelling study were: to develop a population PK model to describe DTG in maternal plasma, umbilical cord, breastmilk as well as in breastfeeding infants following DTG cessation and evaluate potential covariate effects; and to estimate time to DTG protein adjusted IC90 (0.064 mg/L) in breastfed infants.

Infants with recorded date and time of delivery (n=22) were included in the model. DTG dose at birth was simulated based on cord concentrations: 39.9 mg (range: 15.5 to 59.0) or 12.5 mg/kg (range: 5.0 to 19.6).

Predicted median infant half-life (n=21): 38.2 hours (range: 23.0 to 64.1). And predicted median time to PA-IC90 (n=13): 100.2 hours (range: 15.5 to 130.8).

The investigators noted that transplacental and breastmilk transfer of DTG and infant plasma half-life were consistent with results previously reported in the IMPAACT and PANNA studies. And that elimination of DTG in infants was prolonged, likely due to immaturity of metabolic pathways (UGT1A1).

Breastfeeding contributed relatively little to infant DTG exposures and the investigators suggested that breastfeeding alone is unlikely to provide adequate post-exposure prophylaxis. But high transplacental transfer of DTG offers additional infant post-exposure prophylaxis, which decreases with time postpartum.

They concluded that infants whose mothers discontinue DTG in the first week postpartum might have an additional 1–4 days of protection, but those whose mothers discontinue later are unlikely to have additional protection

The group are investigating the impact of prolonged infant exposure to DTG as part of DolPHIN-2.

Polly Clayden is on the trial steering committees of DolPHIN 1 and 2.

Reference

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http://regist2.virology-education.com/presentations/2019/20AntiviralPK/26_Dickinson.pdf (PDF slides)

Antiretroviral pharmacokinetics in pregnancy: update from IMPAACT P1026s

Polly Clayden, HIV i-Base

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1026s looks at antiretrovirals when used alone or with TB medicines.

It is an ongoing, non-randomised opportunistic, phase 4, prospective pharmacokinetic (PK) study of antiretrovirals in HIV positive women during pregnancy and postpartum.

Data from evaluations of tenofovir alafenamide (TAF) 25 mg with PK boosters, cobicistat boosted atazanavir and isoniazid, rifampicin and efavirenz from P1026s were presented at the 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs. There was also a presentation showing a US FDA physiologically-based PK model for rilpivirine that captured changes in exposure in pregnancy.

Tenofovir alafenamide

Plasma exposures to TAF 25 mg with PK boosters did not differ significantly between third trimester and postpartum, although confidence intervals were wide. [1]

When dosed at 25 mg unboosted, a previous IMPAACT 1026s evaluation found that TAF exposures during pregnancy were within the typical range of those in non-pregnant adults but higher than expected postpartum [2, 3]

Seventeen women receiving TAF 25 mg with ritonavir or cobicistat were eligible for the boosted arm and enrolled in the second or third trimester.

PK data were available from 6, 14, and 8 women during the second trimester, third trimester, and postpartum, respectively.

Cobicistat was the booster used by 83% women during the second trimester, 64% during the third trimester and 50% postpartum. The remaining women received ritonavir. The boosted protease inhibitors were darunavir and atazanavir.

Median AUC during the second trimester, third trimester and postpartum was: 133 ng*h/mL (IQR: 128 to 720), 335 ng*h/mL (IQR: 192 to 549) and 507 ng*h/mL (IQR: 221 to 693).

These exposures were comparable to or higher than historical data in adults receiving TAF 10 mg with cobicistat: mean 206.4 ng*h/mL.

Paired data in both second trimester and postpartum were only available in two women, so the investigators limited GMR comparisons to third trimester vs postpartum for this evaluation and await additional data.

GMR for AUC third trimester vs postpartum was: -6% (90% CI: 62 to 133), p=0.74. There were also no significant differences for other PK parameters evaluated (Cmax, CL/F, V/F and T12). But all confidence intervals were wide.

Median TAF plasma AUC was above the 10th percentile cut-off in 66%, 85.7% and 87.5% of women in the second trimester, third trimester and postpartum, respectively. AUC percentile data were similar to those seen in non-pregnant receiving elvitegravir/cobicistat/emtricitabine/TAF 10 mg (E/C/F/TAF).

All but one woman (94.1%) had viral load <50 copies/mL at delivery. Six infants were HIV negative, 7 indeterminate, 3 pending and 1 unknown.

Three congenital anomalies were not considered related to study drug: sacral dimple, Mongolian spot and microcephalia.

Analyses of maternal delivery, cord blood and infant washout samples in IMPAACT 1026s are underway. Data on long-term safety, efficacy and intracellular PK of TAF during pregnancy continue to be needed.

Atazanavir/cobicistat

Pregnant women taking atazanavir in a co-formulation with cobicistat had lower exposure compared to postpartum, and compared to non-pregnant adults. [2]

The PK of atazanavir when co-administered with ritonavir have been described in pregnancy. But atazanavir boosted with cobicistat has not previously been investigated in pregnant women. This study looked at atazanavir exposure boosted with cobicistat (300/150 mg) during pregnancy and postpartum.

Six women were enrolled in the study. Atazanavir PK data were available for 3 women in second trimester, and 5 women in third trimester and postpartum.

The median 24-hour trough concentration at steady state was: 0.16 µg/mL (IQR: 0.14 to 0.22), 0.12 µg/mL (IQR: 0.09 to 0.19) and 0.45 µg/mL (IQR: 0.42 to 0.61) in second trimester, third trimester and postpartum, respectively. Atazanavir trough concentrations in the respective time periods were 80%, 85%, and 44% lower, than previously reported in non-pregnant adults receiving atazanavir/cobicistat.

One woman had a trough concentration below the lower limit of quantitation of the assay (0.047 µg/mL) which occurred in the third trimester.

All other trough concentrations were above the threshold of the historical population EC90 for atazanavir against wild-type HIV (0.014 µg/mL).

The minimum exposure target for atazanavir was the 10th percentile AUCtau in non-pregnant adults receiving once daily atazanavir/ritonavir (28.4 µg*hr/mL). The frequency of participants meeting the target AUCtau was 0/3 in second trimester, 1/5 in third trimester, and 2/5 postpartum.

Viral load at delivery was <50 copies/mL for all six women. Two of the six infants were HIV negative and four are indeterminate or pending.

The investigators are analysing cobicistat plasma concentrations from this study.

Additional PK, safety and outcome data in a larger cohort are needed before atazanavir/cobicistat can be recommended in pregnant women.

Isoniazid, rifampicin and efavirenz

Low isoniazid concentrations in pregnant and postpartum women treated for TB regardless of efavirenz-based ART co-treatment. [3]

Women in this study received first-line TB treatment in fixed-dose combination tablets according to WHO guidelines. HIV positive women also received efavirenz-based ART. Data were shown for 25 women: 14 African, 6 Thai and 5 other. Eleven women were HIV positive and receiving efavirenz-based ART.

Isoniazid and rifampicin PK data in second trimester, third trimester and postpartum were available for 7, 10 and 7 women in the ART-group and 5, 11 and 8 women in the non-ART-group.

Isoniazid median AUC0-∞ was 7.9, 8.4 and 8.7 ug·h/mL and 6.2, 10.9 and 14.8 ug·h/mL in the second trimester, third trimester and postpartum groups with and without ART respectively. Isoniazid median Cmax was 2.8, 3.3, and 3.0 ug/ml and 3.0, 3.5 and 3.6 ug/mL respectively.

There was no significant difference between the the second trimester, third trimester and postpartum groups. But, isoniazid exposure was much lower than in historical controls (South African non-pregnant adults) across all groups: AUC0-∞ 32.5 ug·h/ml and Cmax 6.5 ug/mL.

Rifampicin median AUC0-∞ was 36.8, 35.8 and 31.2 ug·h/mL and 30.6, 41.4 and 32.7 ug·h/mL respectively. Rifampicin median Cmax was 8.4, 6.1, and 6.6 ug/mL and 4.5, 6.9 and 7.9 ug/mL respectively.

There was no statistical significant difference between the groups and concentrations were similar to the control group.

The investigators are analysing pregnancy outcomes, TB treatment outcomes and safety outcomes. The clinical implication of low isoniazid exposure in pregnant women with TB needs to be assessed.

US FDA physiologically-based pharmacokinetic modelling

FDA physiologically-based pharmacokinetic (PBPK) model for rilpivirine captured changes in exposure in pregnancy. [4]

PBPK modelling might be used to assess the effect of pregnancy on drug PK. To evaluate PBPK predictive performance in pregnant women with HIV, the FDA developed a PBPK model using rilpivirine.

A PBPK model for non-pregnant adults predicted rilpivirine PK within a two-fold error range of the mean observed clinical values.

In pregnant women, the predicted values were within ± 50% of the mean in second (n=30) and third (n=57) trimester clinical values for Cmax, Tmax, AUC, and Cmin.

There is a reduction in rilpivirine exposure in the second and third trimester of pregnancy, clinical data shows 30–40% decrease in both AUC and Cmin. The PBPK model captured these changes, with a predicted decrease in exposure of about 30% for both AUC and Cmin compared with postpartum.

The investigators suggested that this PBPK model for rilpivirine could capture the effects of pregnancy on maternal exposure from 20–38 weeks gestation. The model included changes in plasma binding proteins, CYP3A4 enzyme activity, and glomerular filtration rate resulting in differences in volume of distribution, unbound fraction and clearance between the non-pregnant and pregnant populations.

This group will look at the effects of using laboratory values from the P1026s study to modify the HIV negative pregnant population to represent that of women with HIV. They plan modelling with other antiretrovirals to continue this assessment pregnancy PBPK.

C O M M E N T

Data from P1026s is usually the first publicly presented information on new antiretrovirals in pregnant women.

TAF is not currently recommended during pregnancy due to insufficient data describing its use in this population. This has been a bit of a sticking point for global recommendations. Despite TAF being considered a possible candidate for optimised ART for a while now and until such data are available it will remain stuck.

Both cobicistat-boosted darunavir and elvitegravir are not recommended in pregnancy due to low drug exposure, so these data for atazanavir are unsurprising.

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HIV PREVENTION

Two pints of lager and a packet of PrEP please: London price for HIV PrEP drops to £17.50

Simon Collins, HIV i-Base

The PrEP shop at 56 Dean Street clinic in central London has recently announced new prices for PrEP that are lower than many online suppliers. [1]

Their price for six bottles of PrEP is now £105.00 (£17.50 for 30 tablets). Three bottles now are £60 (£20 a bottle) and a single bottle is £30.

These are prices for NHS patients who are also able to get all related tests and monitoring free. This is *not* an internet-based service so you need to be able to visit this clinic.

C O M M E N T

This is the single most important step in broadening uptake to PrEP in England.

For the last ten years the i-Base response to wider PrEP uptake has been that the price needs to be equivalent to a couple of drinks and a packet of condoms. This just about gets us there, certainly for people using on-demand dosing - at least based on London drink prices.

The dramatically lower price from bulk purchasing actually shows how little it would cost to make PrEP now wider available free on the NHS. The cost of drugs are actually likely to now be lower than the cost of monitoring — which the NHS already provides free.

There is no longer any ethical or practical reason for NHS England to not provide PrEP free for all who need it.

This information is included in the i-Base guide to PrEP and two new updated pocket leaflets including PrEP for Women. [2, 3, 4]

Printed leaflets and booklets are available free for all NHS clinics. [5]

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Activists challenge block to generic PrEP and current US price of TDF/FTC

Simon Collins, HIV i-Base

Over the last month the price of TDF/FTC PrEP in the US, where this combination is still under patent, was the focus of several widely reported developments.

Firstly, on 14 May 2019, a coalition of US HIV activists, working under the umbrella organisation PrEP4all, filed a class action lawsuit over delayed access to generic versions of TDF/FTC. [1, 2]

Secondly, the US House Oversight and Reform Committee convened a hearing to examine the high pricing of Truvada.

These proceedings are available in full online and include testimonies from prominant HIV activists, researchers involved in PrEP research and representatives from Gilead.

In the week before these events, Gilead had issued a press release announcing that the company would donate up to 2.4 million bottles of Truvada as part of a ten year programme to broaden access to PrEP for people in the US without medical insurance. [4]

Currently, a bottle of 30 tablets of TDF/FTC is priced at approximately $2000. Based on generic prices for PrEP the manufacturing cost for Truvada is likely to be less than 1% of this price charged.

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   http://makemedicinesaffordable.org/en/truvada-for-prep-gilead-grilled-at-us-congressional-hearing
4. Gilead Sciences to provide free Truvada for PrEP to support US initiative to end the HIV epidemic – donation provides up to 2.4 million free bottles annually to uninsured Americans at risk for HIV. (09 May 2019).
   https://www.gilead.com/news-and-press/press-room/press-releases/2019/5/gilead-sciences-to-provide-free-truvada-for-prep-to-support-us-initiative-to-end-the-hiv-epidemic

TUBERCULOSIS

FDA advisory committee votes favorably on use of pretomanid with bedaquiline and linezolid for drug-resistant TB

TB Alliance press release

On 6 June 2019, the U.S. Food and Drug Administration (FDA) Antimicrobial Drugs Advisory Committee voted (14 yes, 4 no, 0 abstain) that there is substantial evidence of the effectiveness and sufficient evidence of the safety of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug-resistant (XDR) or treatment-intolerant or non-responsive multidrug-resistant (MDR) tuberculosis.

Pretomanid, an investigational anti-TB drug, is the subject of a New Drug Application (NDA) currently under Priority Review by the FDA and a Marketing Authorization Application under review by the European Medicines Agency. It has been developed by TB Alliance, a non-profit drug developer, as part of an all-oral combination therapy known as the BPaL regimen (comprised of bedaquiline, pretomanid and linezolid).

The committee's vote was based on safety and efficacy data from 19 clinical studies, including an interim analysis of the pivotal phase 3 Nix-TB trial of subjects with XDR-TB or MDR-TB who were treatment-intolerant or non-responsive. A modified intent-to-treat analysis of Nix-TB data included in the regulatory submission indicated that treatment with the BPaL regimen resulted in a favorable outcome in 90 percent of patients after six months of treatment and six months of post-treatment follow-up.

The advisory committee's non-binding vote is taken into consideration by the FDA as part of its evaluation of the NDA. The Prescription Drug User Fee Act (PDUFA) action date for an FDA decision is in August 2019.

Source

TB Alliance. FDA Advisory Committee votes favorably on the question of the effectiveness and safety of pretomanid in combination with bedaquiline and linezolid for treatment of highly drug-resistant forms of tuberculosis. (06 June 2019).

https://www.tballiance.org/news/fda-advisory-committee-votes-favorably-question-effectiveness-and-safety-pretomanid-combination

Other links

TB medicine pretomanid enters regulatory review process in the United States.

https://www.tballiance.org/news/pretomanid-enters-FDA-review

TB Alliance and Mylan announce global collaboration to commercialise investigational drug pretomanid as part of two regimens to treat tuberculosis.

https://www.tballiance.org/news/tb-alliance-and-mylan-announce-global-collaboration-commercialize-investigational-drug

Antimicrobial Drugs Advisory Committee meeting announcement.

https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-6-2019-antimicrobial-drugs-advisory-committee-meeting-announcement-06062019-06062019

ON THE WEB

HIV criminalisation: report from HIV Justice Network

On 29 May 2019 the HIV Justice Network published a progress report of achievements and challenges in global advocacy against HIV criminalisation from October 2015 to December 2018.

This includes clear evidence that the growing, global movement against HIV criminalisation has resulted in more advocacy successes than ever before.

However, the number of unjust HIV criminalisation cases and HIV-related criminal laws across the world continue to increase, requiring more attention, co-ordinated advocacy, and funding.

The report is published on behalf of the network HIV Justuce Worldwide.

Although the full report is currently only available in English, a four-page executive summary is available now in English, French, Russian and Spanish. The full report will be translated into these languages and made available later this summer.

Download links

Advancing HIV Justice 3: Growing the global movement against HIV criminalisation

http://www.hivjustice.net/advancing3

http://www.hivjustice.net/wp-content/uploads/2019/05/AHJ3-Full-Report-English-Final.pdf (PDF)

Venezuela: report on health and humanitarian emergency

ICASO and ACCSI

Venezuela faces a complex humanitarian emergency that is expanding and cascading throughout the Latin American region and around the globe.

New research report from ICASO and ACCSI reveal that health, economic, security and social wellbeing projections are far worse than previously estimated.

http://www.icaso.org

http://accsi.org.ve

This is an update to the first report published in November 2017:Triple Threat: Resurging epidemics, a broken health system and global indifference to Venezuela's crisis.

The new update highlights the most important milestones throughout 2018 and the beginning of 2019 with respect to HIV, malaria and tuberculosis in Venezuela. The results are sobering:

- Venezuela has some of the highest numbers of undernourished people in the region (3.7 million or 11.7% of its population).
- More than 3.5 million people have fled Venezuela, in search of food, health care, work and protection.
- Venezuela was responsible for 53% of all malaria cases and 80% of all malaria deaths in Latin America and the Caribbean in 2017.
- There has been a 24% increase in the number of new HIV infections between 2010 and 2016. Viral load suppression is at 7%.
- A total of 10,185 (31.8 per 100,000 population) new and relapse TB cases were recorded in 2017, up 41% from 2014.

Additionally, the rapid deterioration of the living conditions of the Venezuelan population requires realistic, concrete and immediate responses. Any delay in making and implementing decisions to address this deterioration translates into increasing rates of morbidity and mortality.

Triple Threat calls for the urgent streamlining of plans to prevent the further loss of life and human dignity among people living with HIV and affected by TB, malaria, and other health conditions. Failure to do so not only affects Venezuela; left unchecked, these resurgent epidemics threaten global health security.

For further information, please contact Mary Ann Torres.

www.icaso.org
maryannt@icaso.org
Skype: maryannicaso; Twitter: @icaso

FUTURE MEETINGS

Conference listing 2019

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

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

Customise U=U posters for your clinic

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

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

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

roy.trevelion@i-Base.org.uk

Order publications and subscribe online

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

h-tb

HIV TREATMENT BULLETIN

HTB is published in electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered using the form on the back page or directly from the i-Base website:
http://www.i-Base.info
by sending an email to: subscriptions@i-Base.org.uk
Editor: Simon Collins
Contributing Editor: Polly Clayden

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

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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

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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

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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:

subscriptions@i-Base.org.uk