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Darunavir/cobicistat alert & PK reports

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EDITORIAL

This issue of HTB starts with a treatment alert stating that cobicistat boosted darunavir is contraindicated in pregnant women. This is based on significantly reduced plasma levels of darunavir and cobicistat during the second and third trimesters of pregnancy.

Ritonavir-boosted darunavir can still be used during pregnancy and we include the Dear Doctor letter from Janssen.

Our second batch of seven reports from the 19th International Workshop on Clinical Pharmacology in May includes results from a small PK study in which both elvitegravir and cobicistat exposure too were significantly lower during pregnancy. Elvitegravir/cobicistat is also not recommended for pregnant women because of reduced drug levels.

Other reports from this meeting include studies looking at: unbound dolutegravir plasma concentrations in pregnancy and transplacental transfer; bioavailability of the paediatric etravirine dispersible tablet, co-administration of adult and paediatric antiretrovirals with TB medicines; and the frequency efavirenz side effects and drug-drug interations in an African setting.

Other HTB reports in this issue include the news that China just approved albuvirtide, a once-weekly injectable; and promising phase 2b/3 trial data for PRO 140, a once-weekly subcutaneous monoclonal antibody (mAb).

Prevention news includes draft FDA guidance for developing PrEP drugs. Closer to home, the UK PrEP Impact trial has increased the number of participants from 10,000 to 13,000. However, low recruitemnt of women, African people and transgender people has led to halving the number of these previously ring-fenced trial places that are not for gay men.

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TREATMENT ALERT

New contraindication against using darunavir/cobicistat during pregnancy

Simon Collins, HIV i-Base

On 22 June 2018, Janssen issued a Dear Doctor letter (included below) against using darunavir/cobicistat during pregnancy. [1]

This new contraindication is based on significantly reduced plasma levels of darunavir and cobicistat during the second and third trimesters of pregnancy.

Darunavir can still be used during pregnancy, but only when boosted by ritonavir

The new results are from a pharmacokinetic study presented earlier this year in seven HIV positive pregnant women and a more recent FDA update. [2, 3]

Although another recent FDA update to the darunavir/cobicistat in February 2018 cautioned about low darunavir exposure during the third trimester, the new alert goes further in making pregnancy a contraindication. [4]

No HIV transmissions to the baby were reported in these studies, but it is unclear whether transmissions have been reported in other settings.

The coformulation of darunavir/cobicisat is marketed as Rezolsta in the EU and Prezcobix in the US.

The single pill fixed dose combination of darunavir/cobicistat/emtricitabine/TAF is marketed as Symtuza.

References

1. Janssen Dear Doctor letter. Darunavir/cobicistat: Increased risk of treatment failure and increased risk of mother-to-child transmission of HIV infection when darunavir and cobicistat co-administered, due to low exposure values during the second and third trimesters of pregnancy. (22 June 2018).
2. Crauwels HM et al. Pharmacokinetics of total and unbound darunavir in HIV-1–infected pregnant women receiving a darunavir/cobicistat-based regimen. Poster presented at the 8th International Workshop on HIV & Women, 2-3 March 2018, Boston.
3. FDA. Prezcobix pregnancy label update. (05 June 2018). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=94
4. US darunavir label updated: drug interactions and pregnancy. HTB February 2018. http://i-base.info/htb/33410

Direct Healthcare Professional Communication: Prezista (darunavir), Rezolsta ▼ (darunavir/cobicistat) and Symtuza ▼ (darunavir/cobicistat/emtricitabine/tenofovir alafenamide)

Darunavir/cobicistat: Increased risk of treatment failure and increased risk of mother-to-child transmission of HIV infection when darunavir and cobicistat co- administered, due to low exposure values during the second and third trimesters of pregnancy.

Dear Healthcare Professional,

Janssen in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- Therapy with darunavir/cobicistat should not be initiated during pregnancy.
- Women who become pregnant during therapy with darunavir/cobicistat should be switched to an alternative regimen: darunavir/ritonavir may be considered as an alternative.
- This is because pharmacokinetic data showed low exposure values of darunavir and cobicistat during the second and third trimesters of pregnancy.
- Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of mother-to-child transmission of HIV infection. Background The pharmacokinetic data from the Phase 3b study TMC114HIV3015 in 6 pregnant women demonstrated that the mean exposure (AUC) of darunavir boosted with cobicistat was 56% and 50% lower during the 2nd and 3rd trimesters of pregnancy, respectively, compared with 6 to 12 weeks postpartum. Mean darunavir Cmin concentrations were around 90% lower during the 2nd and 3rd trimesters of pregnancy as compared to postpartum. Exposure of cobicistat was 63% and 49% lower during the 2nd and 3rd trimesters of pregnancy, respectively, as compared to postpartum.
- Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the child. Therefore, therapy with darunavir/cobicistat should not be initiated during pregnancy and women who become pregnant during therapy with darunavir/cobicistat should be switched to an alternative regimen.

Based upon this information, the product information for PREZISTA (darunavir), REZOLSTA (darunavir and cobicistat) and SYMTUZA (darunavir, cobicistat, emtricitabine, tenofovir alafenamide), will be updated, as recommended by the European Medicines Agency (EMA).

Call for reporting

▼This medicinal product is subject to additional monitoring to support risk management and it is therefore important to report any suspected adverse events.

Please continue to report suspected adverse reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme.

It is easiest and quickest to report adverse drug reactions online via the Yellow Card website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Alternatively, use prepaid Yellow Cards for reporting:

- Write to FREEPOST YELLOW CARD (no other address details necessary)
- Email: yellowcard@mhra.gov.uk
- See the back of the British National Formulary (BNF).
- Telephone the Commission on Human Medicines (CHM) free phone line: 0800 731 6789,
- Download and print a form from the Yellow Card section of the MHRA website.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, product brand name and batch numbers.

Suspected adverse reactions should also be reported to Janssen-Cilag Limited on telephone: 01494 567447, fax: 01494 567799 or by email at: dsafety@its.jnj.com.

Company contact points

If you have further questions or require additional information, please contact: Janssen- Cilag Ltd. Medical Information Department: email: medinfo@its.jnj.com, telephone: 0800 731 8450 or 01494 567 444.

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CONFERENCE REPORTS

19th International Workshop on Clinical Pharmacology

22–24 May 2018, Baltimore

Introduction

The19th International Workshop on Clinical Pharmacology was held from 22–24 May 2018 in Baltimore.

Some materials from the conference, including the programme and slides for many of the oral presentations are posted online.

http://www.infectiousdiseasesonline.com

Programme

http://www.virology-education.com/event/previous/antiviralpk-workshop-2018/program-2/

Presentations

http://www.infectiousdiseasesonline.com/antiviral-pk-2018-presentations

Abstract book is not yet online:

http://www.infectiousdiseasesonline.com/abstract-book

Reports included in this issue of HTB.

- Unbound dolutegravir plasma concentrations unchanged in pregnancy and standard dosing crosses the placenta in placental perfusion model
- Reduced exposure to elvitegravir in pregnancy: results from the PANNA Network
- Etravirine dispersible paediatric tablet has greater bioavailability when dispersed in water compared to swallowed whole

- Rifabutin dosed 2.5 mg/kg daily with lopinavir/r in children achieves comparable exposure to adults
- Boosted darunavir 800/100 mg twice daily might overcome interaction with rifampicin
- No clinically relevant reduction in oral cabotegravir when co-administered with rifabutin
- Efavirenz side effects and other drug-drug interactions are common in Ugandan cohort

Unbound dolutegravir plasma concentrations unchanged in pregnancy and standard dosing crosses the placenta in placental perfusion model

Polly Clayden, HIV i-Base

Dolutegravir (DTG) plasma Cmin is unchanged in the third trimester compared with postpartum. [1] And modelling suggests that 50 mg DTG once daily might also have potential for foetal pre-exposure prophylaxis. [2] These findings from the PANNA Network were shown at the 19th International Workshop on Clinical Pharmacology.

Total DTG plasma exposure is 25–51% lower during pregnancy compared with postpartum. DTG is highly bound to human plasma proteins (>99.3% in vitro) and has a low extraction rate. Changes in the free fraction of a drug are not always proportional to that of the total.

Investigators from the PANNA Network – a European clinical network to investigate the pharmacokinetics (PK) of new antiretrovirals in pregnancy – evaluated unbound DTG plasma concentrations in HIV positive pregnant women in the third trimester and postpartum.

Pregnant women receiving DTG 50mg once daily had intensive steady-state 24-hour PK profiling under fed conditions in the third trimester and 3–7 weeks postpartum. Using these PK-curves, the investigators selected Cmin and Cmax samples for further evaluation of total and unbound DTG concentrations.

Nine women with a median age 30 years (range 21–42) were included in the analysis. Participants received DTG with TDF/FTC (n=4) ABC/3TC (n=4) or DRV/r + TDF (n=1). All participants had viral load <50 copies/mL at delivery. Three left the study before the postpartum visit so only six participants provided both third trimester and postpartum data.

In the third trimester, respective geometric mean (variance, CV%) for total plasma and unbound Cmin were: 710 (102) ug/L and 4.0 (80) ug/L and postpartum 1070 (61) ug/L and 4.2 (70) ug/L.

Geometric mean ratio (GMR) for total and unbound DTG Cmin in third trimester vs postpartum were: 0.72 (90% CI 0.40 to 1.29) and 0.98 (90% CI 0.55 to 1.75).

Third trimester median of the free fraction for Cmin was 0.63% (IQR 0.43 to 0.73) vs 0.33% (IQR 0.28 to 0.70) postpartum, p=NS.

Results for total and unbound Cmax plasma concentrations were in line with those for Cmin. The investigators noted this was due to the observed linear plasma protein binding. They concluded that, despite the small sample size, these findings, and the undetectable viral loads at delivery suggest uncompromised efficacy of DTG 50mg once daily in pregnancy.

The PANNA group also evaluated a pregnancy physiologically-based pharmacokinetic (p-PBPK) model which can help to assess maternal and foetal drug exposure.

In order to simulate foetal exposure, using this model, the investigators evaluated placental DTG transfer via ex vivo dual-side placental perfusion experiments. They then integrated the data into the p-PBPK model and simulated maternal and foetal DTG exposure in third trimester of pregnancy.

They established the p-PBPK model using a PBPK model for DTG exposure in healthy volunteers (performance was verified against clinical PK data from several DTG dosing regimens). Then the physiological parameters were modified to take into account maternal physiological changes during pregnancy. Ex vivo dual side placental perfusion experiments were performed using healthy term human placentas.

The model was used to simulate maternal and foetal exposure after maternal dosing and simulations were compared with available third trimester clinical PK data from PANNA and IMPAACT 1026s.

The simulations suggested that 50mg dolutegravir once daily would result in a maternal C24h of 0.98 mg/L, which is in line with the clinical PK data: C24h 0.7mg/L and 0.93mg/L, PANNA and IMPAACT respectively.

The simulations also suggested that 50 mg DTG once daily crosses the placenta in vivo and ex vivo and might have potential for foetal pre-exposure prophylaxis.

C O M M E N T

These findings add to the data to suggest that, although there is a signal for risk with pre-conception exposure, DTG appears to be a good option for use in later stages of pregnancy.

References
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2. Freriksen J et al. Assessment of maternal and fetal dolutegravir exposure by integrating ex vivo placental perfusion data and physiologically-based pharmacokinetic modeling. 19th International Workshop on Clinical Pharmacology, 22–24 May 2018, Baltimore. Oral abstract 14.
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Reduced exposure to elvitegravir in pregnancy: results from the PANNA Network

Polly Clayden, HIV i-Base

Preliminary data from a small pharmacokinetic (PK) study suggests exposure to elvitegravir is lower during the third trimester of pregnancy than postpartum. [1]

These results are in line with those from IMPAACT and support caution for its initial use in pregnancy. [2, 3, 4]

PANNA is an open-label, multi-centre, observational, phase 4 study in HIV positive pregnant women recruited in HIV treatment centres in Europe. The findings were presented at the 19th International Workshop on Clinical Pharmacology

Participants receiving elvitegravir/cobicistat 150/150mg + 2 NRTIs (86% TDF/FTC) once daily during pregnancy had intensive steady-state 24-hour PK-profiling in the third trimester and 5–7 weeks postpartum. Optional cord and matching maternal blood samples were taken at delivery. Seven participants with a median age of 32 years (range 25–40) years were included in the analysis.

Geometric mean ratios of PK parameters during the third trimester/postpartum were: 0.67 h*mg/L (90% CI 0.47 to 0.96) for AUC0-24; 0.79 mg/L (90% CI 0.61 to 1.02) for Cmax; 0.35 mg/L (90% CI 0.0.16 to 0.76) for Ctrough.

Five out of seven participants had a sub-therapeutic Ctrough in the third trimester, one out of six postpartum. The median cord/maternal elvitegravir plasma concentration ratio (n=4) was 0.87 mg/L (range 0.3 to 1.2) – indicating substantial foetal exposure around delivery.

During pregnancy 71% of the participants had sub-therapeutic Ctrough versus 17% postpartum.

The investigators noted that cobicistat exposure was 56% lower during pregnancy, which might have led to less boosting, increased elvitegravir clearance and, in turn, lower exposure.

Approaching delivery 6/7 (86%) participants had viral load <50 copies/mL; one participant had a viral load of 6363 copies/mL six weeks before delivery.

There were no serious adverse events or birth defects in this small study and all infants were HIV negative.

C O M M E N T

These PK results are similar to those presented previously by the IMPAACT Network, based on which, US DHHS perinatal guidelines do not recommend elvitegravir/cobicistat for initial use in pregnancy.

The upcoming BHIVA guidelines will recommend that elvitegravir/cobicistat may be continued with close monitoring if a woman receiving it with undetectable viral load becomes pregnant but not do recommend starting in pregnancy.

References
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Etravirine dispersible paediatric tablet has greater bioavailability when dispersed in water compared to swallowed whole

Polly Clayden, HIV i-Base

Etravirine (ETR) oral clearance in young children who swallowed the dispersible paediatric formulation was half that achieved with the tablet dispersed in water, according to results from IMPAACT P1090.

This finding in HIV positive children ages 1–6 years was presented at the 19th International Workshop on Clinical Pharmacology

The population pharmacokinetics (PK) of ETR have previously been described in adults, adolescents, and children 6 years and above but not in younger populations.

This study aimed to characterise the population PK and pharmacokinetic/pharmacodynamic (PK/PD) relationships of ETR in HIV positive children ages 1 to <6 years.

IMPAACT P1090 is a phase 1/2, multicentre, open-label study designed to evaluate the PK, optimal dose, safety, and tolerability of ETR in treatment-experienced children ages 1 to <6 years.

Participants received ETR with at least two other active antiretrovirals, one of which was a ritonavir-boosted protease inhibitor (PI/r). The study evaluated weight-based and weight-band based ETR doses.

A 12-hour intensive PK was performed two weeks after starting ETR and sparse samples were collected through week 48. Twenty-five children were included.

Children receiving ETR showed considerable inter-individual variability – similar to adults. Apparent oral clearance was 50% lower in children who swallowed the tablet whole versus dispersed in water. Weight and age were not significant predictors in the model. Although country and use of PI/r approached significance over-parameterisation of the model precluded their inclusion in the final model.

PK parameters were not associated with viral load at week 24.

The investigators suggested that this model can aid in comparisons of ETR PK parameters and dose selection in this younger population versus those previously reported for adults, adolescents, and children over 6 years.

Reference

Ibrahim M et al. Population pharmacokinetics/pharmacodynamics of etravirine in HIV-positive children ages 1-<6 years. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 20.

http://regist2.virology-education.com/presentations/2018/Antiviralpk/34_Ibrahim.pdf (PDF)

Rifabutin dosed 2.5 mg/kg daily with lopinavir/r in children achieves comparable exposure to adults

Polly Clayden, HIV i-Base

These findings from an interim analysis of a pharmacokinetic (PK) study conducted in coinfected Nigerian children were presented at the 19th International Workshop on Clinical Pharmacology.

Treatment options are lacking for HIV/TB coinfected children needing protease inhibitor (PI)-based ART. Rifabutin (RBT) is the preferred rifamycins for adults receiving PIs.

Only one previous study looked at RBT PK in children on PIs. It was stopped early after two of six children developed grade 4 neutropenia.

The Nigerian study evaluated PK of RBT in children aged 3–15 years receiving lopinavir/ritonavir (LPV/r)-based ART and RBT 2.5 mg/kg daily-containing TB treatment over 48 weeks. Intensive 24-hour PK sampling was performed at 2, 4, and 8 weeks after starting RBT.

At interim analysis, 8 children (75% male), median age 13.5 years (IQR 12.8–14.3) and weight 28.5 kg (IQR 24.1–32.1) had 20 PK visits.

The median RBT AUC0-24 was 4.77 ug*h/mL (IQR 3.84-6.75). Three participants had an AUC0-24 less than 3.2 ug*h/mL at week 2; but all were above 3.8 ug*h/mL (comparator: adults receiving RBT 300 mg daily without ART) at the 4 and 8 week visits.

Serious adverse events were uncommon: of 407 follow-up laboratory results, grade 3 and 4 abnormalities were reported in 11 (3%) and 2 (0.5%) cases, respectively.

Grade 3 neutropenia occurred on 3 occasions, and resolved without stopping RBT in all cases. Anaemia was the most common adverse event. No discontinuations due to ART or TB treatment were reported.

The investigators reported that the children are doing well clinically with six of seven achieving viral load suppression to less than 1000 copies/mL and resolution of TB symptoms at six months.

Enrollment into this study (n=15) is now complete and an additional study is now underway in young children aged 12–36 months.

Reference

Rawizza H et al. Rifabutin PK and safety among HIV/TB coinfected children receiving lopinavir.19th International Workshop on Clinical Pharmacology, 22–24 May 2018, Baltimore. Oral abstract 13.

http://regist2.virology-education.com/presentations/2018/Antiviralpk/30_rawizza.pdf (PDF)

No clinically relevant reduction in oral cabotegravir when co-administered with rifabutin

Polly Clayden, HIV i-Base

Rifabutin (RBT) can be given with oral cabotegravir (CAB) without dose adjustment, according to data presented at the 19th International Workshop on Clinical Pharmacology. A modest decrease in plasma CAB following long-acting (LA) administration with RBT is expected.

CAB is in development as a LA injectable formulation with an oral CAB 30 mg lead-in for treatment and prevention of HIV.

Significant interaction between oral CAB and rifampicin (RIF) limits their use together. RBT is chemically similar to RIF but considered a weaker inducer of UGTs and CYP3A. CAB is metabolised primarily by UGT1A1, with minor contribution by UGT1A9.

This study evaluated the effect of RBT on the pharmacokinetics (PK) of oral CAB in HIV negative participants. It was phase I, single-centre, open label, two period, fixed-sequence, drug interaction study conducted by the originator manufacturer ViiV Healthcare.

Fifteen male participants with a median age of 44 years and weight of 84 kg received oral CAB 30mg once daily for 14 days and then co-administered with RBT 300mg once daily for 14 days. Twelve participants completed as planned. Serial PK sampling was performed on days 14 and 28.

Comparing CAB + RBT to CAB alone, the GLS mean ratios were: AUC0–24, Cmax, and Ctrough were 0.79 ug*h/mL (90% CI 0.74 to 0.83), 0.83 ug/mL (90% CI 0.76 to 0.90) and 0.74 ug/mL (90% CI 0.70 to 0.78), respectively.

RBT increased CAB oral clearance by 27% following repeat dose co-administration and reduced AUC0–24, Cmax, and Ctrough by 21%, 17% and 26% respectively.

Eleven participants reported 24 adverse events – most were grade 1 and occurred during CAB + RBT co-administration.

The investigators concluded that a 27% increase in clearance does not preclude co-administration of RBT + CAB LA. Simulations will inform strategies for LA regimens and alternative dosing schedules with RBT.

Reference

Ford S et al. Rifabutin (RBT) decreases cabotegravir (CAB) exposure following oral co-administration. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 12.

http://regist2.virology-education.com/presentations/2018/Antiviralpk/29_patel.pdf (PDF)

Boosted darunavir 800/100 mg twice daily might overcome interaction with rifampicin

Polly Clayden, HIV i-Base

Modelling study suggests darunavir/ritonavir twice 800/100 mg daily might be sufficient to overcome the interaction with rifampicin in HIV positive people co-infected with TB, according to data presented at the 19th International Workshop on Clinical Pharmacology.

Co-administration of rifampicin (RIF) and boosted darunavir (DRV) is contra-indicated due to significant pharmacokinetic (PK) interactions that can reduce the efficacy of DRV.

This study aimed to look at the effects of RIF on the PK of ritonavir (RTV)-boosted DRV (DRV/r) and strategies to overcome the interaction.

The investigators implemented in vitro results in physiologically-based pharmacokinetic (PBPK) models to identify DRV regimens with the highest likelihood of successful clinical outcomes.

In vitro inhibition studies confirmed the potent inhibition of RTV of the metabolism of DRV (IC50 RTV: 14 nM), which was counteracted by the induction observed following RIF treatment (IC50 RTV: 46 nM).

Simulated DRV/r PK parameters accurately predicted values previously seen in clinical studies for DRV Cmax, AUC24h, and Ctrough of DRV/r 800/100 mg once daily.

Addition of 600 mg RIF resulted in a significant decrease of DRV Cmax, AUC24h, and Ctrough in the various simulated regimens: DRV/r 800/100 mg once daily, 1600/200 mg once daily DRV/r and 800/100 mg twice daily.

The study generated a framework of in vitro data aimed at supporting the development of accurate PBPK models for predicting the PK of DRV/r as well as to predict potential drug-drug interaction following co-administration of RIF.

Based on these findings, the investigators suggested changing the DRV/r regimen from 800/100 mg once daily to 800/100 mg twice daily as the most promising regimen to counter the interaction of RIF 600 mg once daily in HIV positive people co-infected with TB.

Reference

Jacobs S et al. Predicted pharmacokinetic interactions of rifampicin with ritonavir-boosted darunavir. 19th International Workshop on Clinical Pharmacology. Poster abstract 37.

Efavirenz side effects and other drug-drug interactions are common in Ugandan cohort

Polly Clayden, HIV i-Base

Drug-drug interactions and side effects, associated with currently-used first-line ART, are under-reported and managed in Uganda, according to findings presented at the 19th International Workshop on Clinical Pharmacology. [1]

Investigators from Makerere University and University of Liverpool are conducting an ongoing longitudinal study in adult outpatients taking current ART at three clinics in central Uganda.

In the study, trained pharmacy technicians take medication histories, including side effects. Drug-drug interaction (DDI) screening and side effect assessment is undertaken by pharmacists and clinicians using standardised tools.

The study enrolled 868 participants and this analysis described an initial 416 taking first-line regimens.

Most (72%) participants receiving first-line were on an efavirenz (EFV)-based regimen; 287 (69%) were women; median age was 35 years and time on ART was 36 months.

Of the 416 on first-line ART, 25.5% had at least one clinically significant DDI. People with clinically significant DDIs were more likely to report an adverse event: OR 1.86 (95% CI 1.16 to 2.98), p=0.0059. EFV was associated with reporting adverse events: OR 1.84 (95% CI 1.15 to 2.98), p=0.007. But EFV was not associated with DDIs: OR 0.76 (95% CI 0.46 to 1.27), p=0.265.

Of 252 total adverse events, 72.6% were probably or possibly related to EFV. Symptoms lasted for a median of 22 months (IQR 9–35.3). Of 123 evaluable reports, 83.7% of persistent nervous system/psychiatric disorder adverse events were not recorded in clinical notes.

Among 149 participants taking antimicrobials (antimalarials, antibiotics, antifungals, antivirals) 40.3% had a clinically significant DDI. These affected 14.4% of the 416 participants on first-line ART – accounting for approximately 40% of all clinically significant DDIs.

Of 37 women on first-line line ART who reported using hormonal contraceptives, nine experienced a DDI that put them at significant risk of contraceptive failure.

Prescribers were only aware of 3.5% of clinically significant DDIs (n=144). DDI checks provided new information in 56.1% of cases (n=214); prescribers changed participant management in 53.1% of cases (n=309); DDI checks saved time in 68% of cases (n=200) and added benefit in 72% (n=200).

C O M M E N T

The study investigators note that, compared to currently used first-line antiretrovirals, roll-out of newer ones with lower potential for DDIs and adverse events – such as dolutegravir (DTG) – might reduce the risk of contraceptive failure, antimicrobial treatment failure and microbial resistance as well as significant morbidity due to adverse drug reactions.

They suggest that people experiencing or at high risk of clinically significant DDIs or side effects should be prioritised for switching to DTG.

This analysis was conducted before the safety signal for neural tube defects with DTG was announced. It is an important reminder of some of the reasons why the drug was prioritised in the first place as part of an optimal ART regimen – including persistent central nervous system adverse events with EFV (often not picked up by providers) and lack of interaction between DTG and hormonal contraception.

These issues, alongside that of NNRTI resistance, need to be considered in order to make more nuanced recommendations for DTG than "no women less than 50 years old". After all, women of reproductive age are frequently not pregnant or wish to have (more) children. The emphasis should be on filling the massive unmet need for contraception for HIV positive women in low- and middle-income countries.

We reported an earlier analysis from this study in which the authors pointed out that putting up with EFV side effects in low- vs high-income countries – where people switch more routinely – is exaggerated by a genetic polymorphism (G516T in CYP P450 2B6) that significantly increases drug levels of EFV (by reducing clearance rates) being more common in African compared with Caucasian populations. [2]

References

1. Seden K et al. Medication safety issues associated with currently used first-line antiretroviral regimens in Uganda. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 9.
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ANTIRETROVIRALS

China approves albuvirtide: a once-weekly injectable entry inhibitor

Simon Collins, HIV i-Base

On 6 June 2018, without news from the US FDA, a press release from Frontier Biotech announced the approval of a new HIV drug in China that is given by once-weekly injection. [1]

This is a rare example of an HIV treatment not being first approved in either the US or Europe.

Albuvitide is an HIV fusion inhibitor that works at an early stage of the HIV lifecycle by blocking attachment to CD4 cells. It has a similar structure and mechanism to an earlier HIV fusion inhibitor called enfuvirtide (T-20, Fuzeon) that was developed for people who had run out of treatment options.

Enfuvirtide was approved in 2003 but has been very rarely for the last ten years used because later drugs have become more effective and have an easier safety profile than the twice-daily subcutaneous injections it required.

Although there is little information about the results of the completed phase 3 studies that would have contributed to approval by the Chinese FDA, early results were presented at a UK conference in 2016. [2, 3]

These reported good efficacy compared to the second-line treatment option that is currently available in China, an older protease inhibitor lopinavir/r. HIV positive people in China do not have access to integrase inhibitors that are now routinely recommended as first-line treatment in the US and Europe, and that also overcome drug resistance to many other widely used HIV drugs.

From a safety persepective, albuvirtide was also not associated with the injection site reactions that limited the use of enfuvirtide.

Unfortunately the press release on approval in China still only refers to interim results from these studies.

Albuvirtide injection are marketed by Frontier Biotech with the trade name Aikening. There are plans to extend access outside of China, although further details have not been publicised.

In July 2017, the company announced a licensing agreement with with Rockerfeller University in the US to coformulated albuvirtide with the broad neuralising monoclonal antibody 3BNC117.

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Single dose PRO140 mAb reduces viral load by 0.5 log copies/ mL in in people with multidrug resistance

Mark Mascolini, NATAP.org

PRO 140, a once-weekly subcutaneous monoclonal antibody (mAb), lowered viral loads by a half-log or more in two thirds of phase 2b/3 trial participants after an initial injection in combination with a failing antiretroviral regimen. [1]

An extension study is testing longer-term response to PRO 140 in people using it with other antiretrovirals.

A humanised IgG4 mAb being developed by CytoDyn, PRO 140 inhibits HIV replication by blocking viral entry into CD4 cells that use the CCR5 coreceptor. [2]

In a previously reported trial, 9 of 9 participants who took PRO 140 monotherapy for a week then added an optimised background regimen attained an undetectable viral load at week 25 despite initial resistance to multiple antiretrovirals. [3]

In cell studies PRO 140 inhibited virus resistant to many antiretrovirals including the CCR5 antagonist maraviroc.

The new double-blind placebo-controlled study aimed to assess the efficacy, safety, and tolerability of PRO 140 added to a failing regimen for 1 week before a switch to an optimised background regimen for 24 weeks. [1]

Researchers set the primary efficacy endpoint as a 0.5 $\log_{10}$ (about 3-fold) or greater drop in viral load at the end of the 1-week double-blind period.

Participants had to have CCR5-using HIV, a viral load at or above 400 copies/mL at screening for the trial, and documented resistance to at least 1 drug in three antiretroviral classes or to drugs in at least two classes and with limited treatment options. The trial excluded people with no viable treatment options except PRO 140. Investigators randomised participants 1-to-1 in a double-blind fashion to PRO 140 or placebo plus the ongoing failing regimen for 1 week. Among 25 people randomised to PRO 140, 14 (56%) completed the treatment phase of the study; among 27 people randomised to placebo, 14 (52%) completed the treatment phase.

Of 52 trial participants, 38 (73%) were men, 27 (52%) were white, 24 (46%) were black, and 1 was Asian. Median age was 53.5 years. Participants had taken an average 11 antiretrovirals, and their HIV had documented resistance to an average 9 drugs. At baseline, median and mean viral load were 2814 and 21,104 copies/mL respectively, with median and mean CD4 counts at 247 and 298 cells/mm^3.

Two thirds of trial participants randomised to PRO 140 versus one quarter randomised to placebo had at least a 0.5 log viral load drop after one week, a significant difference (64% versus 23%, p=0.0032). Through week 25, CD4 counts rose by a mean 84 cells/mm^3 (median 64 cells). The researchers detected no anti-PRO 140 antibodies during the study.

No one stopped study drugs because of adverse events and no toxicity pattern emerged. Seven of 52 participants (13.5%) had 1 or more treatment-related adverse events. Injection site reactions affected fewer than 10% of participants; all such reactions were mild and all resolved.

At the time of this presentation, 35 people enrolled in an extension study that prolongs access to PRO 140 when the treating physician believes the mAb is essential to building a suppressive regimen.

People should be able to self-inject PRO 140 subcutaneously once weekly. The FDA designated PRO 140 a Fast Track drug candidate. Ibalizumab, a licensed mAb, blocks HIV entry to CD4 cells by binding to the CD4 receptor. The annual wholesale cost of ibalizumab is US $118,000. [4]

C O M M E N T

The study is registered at clinicaltrials.gov. [5] The slides from the conference presentation are also helpfully posted after this original article on NATAP.org.

It is unclear why the loss to follow-up rate was so high in this study. Although 0.5 log is relatively modest, this can be sufficient to support a new combination in people who have other active drugs. Previous studies with PRO 140 have reported greater antiviral activity with continued dosing.

A second phase 2b/3 study - not recruiting - is looking at maintenance therapy with PRO 140 monotherapy (without other ART) as a switch option in 300 people who have sustained undetectable viral load on their current ART. [6]

PRO 140 is given as a 350 mg weekly sub-cutaneous injection that can be self-administered at home.

Source

Mascolini M. Single shot of PRO 140 mAb cuts HIV load in two thirds on failing ART. (11 June 2018).
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PREVENTION & TRANSMISSION

New FDA guidance for developing PrEP drugs

Simon Collins, HIV i-Base

The US Food and Drug Administration (FDA) has produced draft guidance for developing new treatment as HIV PrEP.

The guidance provides general nonclinical and clinical recommendations specific to the development of systemic drugs to prevent HIV. It has a focus on long acting products.

It addresses the FDA's current thinking regarding the overall development programme and clinical trial designs, and include three options.

1. Oral HIV drugs that are subsequently developed as oral PrEP.
2. Oral HIV drugs that are reformulated as a long-acting drug product or other delivery system for PrEP.
3. New investigational drugs.

The deadline for comments is 13 August 2018.

Links

HIV-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis.

https://www.federalregister.gov/documents/2018/06/14/2018-12761/guidance-human-immunodeficiency-virus-1-infection-developing-systemic-drug-products-for-pre-exposure

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610623.pdf (PDF)

UK PrEP IMPACT trial announces 3000 new places for gay men but low uptake by women, African and transgender people

Simon Collins, HIV i-Base

The UK PrEP impact trial has increased the number of people of trial places from 10,000 to 13,000 people. This means that clinics that were previously closed to recruitment might now have new places available.

This news was announced in the June 2018 update from the trial management board. [1]

The increase is needied to more accurately estimate the likely long term needs of a routinely commissioned PrEP programme. The increase in trial size will require resource commitments from commissioners and local authority and NHS England commissioners have supported the principle of an increase in the trial size.

Other information in the update included:

- More than 7000 people are currently enrolled
- The previous goal of keeping 2000 places for people form groups other than gay men is being reduced to 1000 places. This is freeing 1000 more places for gay men, who have so far generated the highest interest and demand.
- As of 17 May, of the 139 clinics participating in the trial, 138 are open to recruitment for gay and bisexual men. All bar one of the London clinics also remained open to recruitment.
- The study management will now be run by the Chelsea and Westminster NHS Foundation Trust. this should not impact on the supply of PrEP drug to current participants or delays in enrolling new participants as this was all being managed locally by individual clinics.
- Community involvement has included workshops to publicise the study.
- Preparation for future commissioning arrangements is also being considered.

The next meeting of the Board will take in July. A further update on progress will be shared after that meeting.

For further information on the trial please visit the trial website. [2]

Reference

1. UK PrEP IMPACT trial update (June 2018) https://www.england.nhs.uk/commissioning/spec-services/npc-crg/blood-and-infection-group-f/f03/prep-trial-updates/#january
2. https://www.prepimpacttrial.org.uk

ON THE WEB

Online resources:

RITA issue on lung health

The latest issue of the community journal Research Action Treatment Initiative (RITA!) is on lung cancer in people with HIV.

http://www.centerforaids.org/pdfs/rita0618.pdf (PDF)

The review articles discuss:

- Changes in lung cancer prevalence, incidence, and age at diagnosis in people with HIV.
- The three big risk factors: smoking, low CD4 count and prior lung infection.
- When to screen people with HIV for lung cancer.
- Disparities between people with HIV and the general population in lung cancer treatment and mortality.

The doctor-oriented interview features Keith Sigel, who has led research on this topic.

Cure research: open access publications

Positively Aware: Cure issue - Summer 2018

https://www.positivelyaware.com/issues/summer-2018

Long running US community publication from Chicago's Test Positive (TPAN+) feature scure research in their summer issue.

Contents include:

- Can your body be reprogrammed to control HIV?
- Fantastic journey - where HIV travels.
- The reservoir - where HIV hides
- Community cure resources
- The new poster boys
- The team player: focus on researcher Steven Deeks
- The mapmaker: Sarah Pillal
- The community watchdog: Lynda Dee

AIDS Research and Human Retroviruses: HIV cure issue

https://home.liebertpub.com/publications/aids-research-and-human-retroviruses/2

Peer review journal with free online issue.

Contents include:

- Managing expectations of an HIV cure: what should we expect?
- HIV cure research crowdsourcing: an author response
- Eradication of HIV from tissue reservoirs: challenges for the cure
- Timothy Ray Brown's continuing activism toward curing HIV
- Harnessing novel imaging approaches to guide HIV prevention and cure discoveries
- Therapeutic vaccine against HIV, viral variability, cytotoxic T lymphocyte epitopes, and genetics of patients
- Low levels of endothelial progenitor cells and their association with systemic inflammation and monocyte activation in older HIV-positve men
- Malnutrition in HIV-positive children is an indicator of severe disease with an impaired response to antiretroviral therapy
- If we build it, will they come? perceptions of HIV cure-related research by people living with HIV in four US cities
- "We need to deploy them very thoughtfully and carefully": perceptions of analytical treatment interruptions in HIV cure research in the US
- What would an HIV cure mean to you? qualitative analysis from a crowdsourcing contest in Guangzhou, China
- In vitro transduction and target-mutagenesis efficiency of HIV-1 pol gene targeting zfn and crispr/cas9 delivered by various plasmids and/or vectors: toward an HIV cure
- Proteomic profiling of a primary CD4+ T cell model of HIV-1 latency identifies proteins whose differential expression correlates with reactivation of latent HIV-1
- Immunogenicity of AGS-004 dendritic cell therapy in patients treated during acute HIV infection
- Now the spleen is an HIV-1 sanctuary during combined ART

US community call for coalition for long-term survivors

https://www.tpan.com/reunion-project

A new report from the US community organisation The Reunion Project on HIV Long-Term Survivors Awareness Day (#HLTSAD) calling for a national coalition of survivors of HIV to advance the needs of survivors in four key areas: research, programs, community building, and advocacy.

The report states that, "A strong coalition of survivors with a single voice and clear message is desperately needed to advance the needs of survivors, as we continue to battle the long-term effects of medications, isolation, post-traumatic stress disorder, stigma, aging, and co-morbidities, to name a few."

FUTURE MEETINGS

Conference listing 2018/19

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

10th HIV Paediatrics Workshop

20 – 21 July 2018, Amsterdam

www.virology-education.com

HIV Cure Research with the Community workshop

21 July 2018, Amsterdam

www.iasociety.org/HIV-Programmes/Programmes/Towards-an-HIV-Cure

22nd International AIDS Conference (AIDS 2018)

23 – 27 July 2018, Amsterdam

www.aids2018.org

International Workshop on HIV & Ageing

13 –14 September 2018, New York, USA.

www.virology-education.com

Australasian HIV&AIDS Conference 2018

24 – 26 September 2018, Sidney

www.hivaidsconference.com.au

HIV Glasgow 2018

28 – 31 October 2018, Glasgow

www.hivglasgow.org

26th Conference on Retroviruses and Opportunistic Infections (CROI 2019)

4–7 March 2018, Seattle

www.croiconference.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 (December 2017)
- Guide to HIV, pregnancy & women's health (December 2015)

New pocket guides

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

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

We hope these are especially useful as low literacy resources.

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.

Order publications and subscribe by post, fax or online

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http://i-base.info/order

h-tb

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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** _____

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HIV Treatment 'Passports' - Booklets for patients to record their own medical history **quantity** _____

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