ISSN 1472-4863

hiv treatment+ bulletin (e)

htb(e): 2018 vol 19 no 10

08 June 2018

CONTENTS

EDITORIAL 3

SUPPLEMENT 4

- Introduction to ART (2018)

TREATMENT ALERT 4

- BHIVA statement on potential safety signal in infants born to women conceiving on dolutegravir
- ViiV Dear Doctor letter

CONFERENCE REPORTS 9

19th International Workshop on Clinical Pharmacology, 22–24 May 2018, Baltimore

- Introduction
- Dolutegravir 50 mg twice daily sufficient with rifampicin but levels reduced significantly with 100 mg once daily
- Vaginal ring reduces efavirenz but not atazanavir exposures
- Dispersible paediatric versions of dolutegravir provide higher bioavailability than immediate release formulations

ANTIRETROVIRALS 16

- EMA approves dolutegravir/rilpivirine (Juluca) in Europe as dual-therapy HIV switch option
- China approves albuvirtide: a once-weekly injectable entry inhibitor

SIDE EFFECTS & COMPLICATIONS 19

- Boosted darunavir is associated with higher cardiovascular risk in D:A:D study, but not atazanavir

TRANSMISSION & PREVENTION **21**
- Broad PrEP access in Australia reduces HIV infections even with reduced condom use by people not on PrEP

CURE RESEARCH **25**
- Online database of current research related to an HIV cure
- Survey on treatment interruptions (ATIs) in cure research

ON THE WEB **26**
- Webcasts on PrEP and women
- Sexual identity and HIV
- Modern ART in Africa: new resources

EDITORIAL

This issue of HTB continues the BHIVA treatment alert from the last issue, with additional documents relating to a potential signal for neural tube defects in babies whose mothers conceived on dolutegravir.

Both the BHIVA statement and the Dear Doctor letter from ViiV emphasise that no concerns have been seen in women who started dolutegravir during pregnancy. They add to similar statements from WHO and the US FDA and NIH. But, until further information becomes available recommendations follow a cautious approach.

We will include a commentary in the next issue looking at what is being done and what needs to be done to better understand this potential risk.

If anything positive can come from this, perhaps the Botswana data will serve as a call for better surveillance of new drugs. This should include well-resourced pregnancy cohorts with systematic collection of timing/infant outcomes and a comparator. After all there are a considerable number of women of childbearing age with HIV in need of ART across the world.

This issue also reviews other important research.

- Our first reports from the recent international PK workshop include postive reports on a paediatric dolutegravir formulation and dosing to overcome drug interactions with rifampicin.
- The dual fixed dose combination of dolutegravir/rilpivirine (Juluca) has received EU approval (and was launched in the UK).
- The D:A:D study reports higher risk of cardiovascular evenets associated with boosted darunavir (but not boosted atazanavir) that might contribute to the UK for adopting the US approach to primarily recommend integrase inhibitors as preferred first-line ART.
- And research on PrEP use in Australia, that has contributed to remarkable reductions in HIV incidence, has been complicted by research and media responses that are still preoccupied with reduced (and hioped for) reductions in condom use.

Finally, we highlight an excellent resource from Richard Jefferys that compiles and maintains a directory of more than 200 cure-related studies. Plus an online activist survey about how to maximise safety when this research includes treatment interruptions.

And On The Web links to new online resources that includes a set of resources from i-Base developed with TAC on modern ART in Africa.

Supplement

Introduction to ART (May 2018)

The 2018 edition of this widely-used booklet is now updated throughout to include latest HIV treatments.

It also integrates changes in treatment guidelines and the wider recognition of treatment as prevention and the U=U campaign.

Subscriptions

To join the email list for HTB please register free online:

http://i-base.info/htb/about/subscribe

i-Base 2018 appeal: we still need your help...

Last year we launched 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 2018. If 1000 people support us with £5 a month we will be on course to meet our shortfall.

HTB is the UK's longest running activist HIV treatment publication - starting as DrFax from 1996-2000 and relaunched as HTB from 2000-2018.

We are the only HIV organisation to provide free booklets to NHS clinics on HIV treatment. All support is appreciated.

http://i-base.info/i-base-appeal-we-need-your-help

TREATMENT ALERT

BHIVA statement on potential safety signal in infants born to women conceiving on dolutegravir

The BHIVA pregnancy guidelines writing group have issued recommendations on DTG use for pregnant women and those of childbearing age.

BHIVA statement (on behalf of the BHIVA HIV in Pregnancy Guidelines Committee) Tuesday 22nd May 2018

A preliminary unscheduled analysis of an ongoing birth surveillance study in Botswana has reported an increased risk of neural tube defects amongst infants of women who become pregnant whilst taking dolutegravir (DTG)-based regimens.

The study reported 4 cases of neural tube defects out of 426 infants born to women who were on DTG-based regimens at the time of conception.

This rate of approx. 0.9% compares to 0.1% of neural tube defects amongst infants born to women taking non DTG-based regimens at the time of conception.

We are awaiting prospective data on 600 women from Botswana and 400 in Brazil who were on DTG-based regimens at conception and have ongoing pregnancies.

Of note there have been no reported neural tube defects in infants born to a further 2000 women in the Botswana study who started DTG during pregnancy, including in first trimester.

In light of these preliminary findings the BHIVA HIV in Pregnancy Guidelines Writing group makes the following recommendations:

- All women wishing to conceive should be started on folic acid 5 mg once-daily regardless of their cART regimen
- All women commencing DTG should have a negative pregnancy test prior to initiation and ongoing method of contraception documented
- We advise a review of all patient records of women aged up to 50 years on DTG with regards to conception plans, documented method of contraception and current pregnancy status
- We recommend that women at risk of pregnancy be contacted by their clinic to discuss the DTG safety report, which should be clearly documented, and the woman seen in person if pregnant

1. For a woman on DTG wishing to conceive

a. We advise switching to an alternative effective cART regimen

b. The best safety data for pregnancy is for efavirenz or atazanavir/r as per BHIVA HIV in Pregnancy Guidelines 2014

2. For a woman on DTG not planning children but of child bearing age

a. We advise a discussion on current method of contraception to be clearly documented

3. For a woman on DTG who becomes or is pregnant

a. We acknowledge the neural tube has closed within four weeks of conception but

the EMA are recommending that women on DTG in the first trimester discontinue DTG. We therefore recommend that women in the first trimester on DTG switch to a regimen on which there is more safety data in pregnancy, such as efavirenz or atazanavir/r as per BHIVA HIV in Pregnancy Guidelines 2014

b. We do not recommend switching off DTG if in the second or third trimesters

c. If the physician/woman choose(s) to switch, use a regimen on which there is more safety data in pregnancy, such as efavirenz or atazanavir/r as per BHIVA HIV in Pregnancy Guidelines 2014

d. Detailed anomaly scans should be performed as per national pregnancy guidelines with no additional scans required

4. For a woman who is pregnant and not yet on cART

a. We advise using recommended cART such as efavirenz or atazanair/r as per BHIVA HIV in Pregnancy Guidelines 2014 (currently being updated and due for release this summer) available on www.bhiva.org/guidelines.aspx

Please note that these findings are very preliminary and advice may change.

For safety data on antiretrovirals please refer to the Antiviral Pregnancy Registry (www.apregistry.com) or seek advice from an expert colleague.

This report highlights the need to continue to prospectively report pregnancies to the National Study of HIV in Pregnancy and Childhood (www.ucl.ac.uk/nshpc) and the antiretroviral Pregnancy Registry (www.apregistry.com).

For further information

European Medicines Agency (EMA)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1

WHO guidance
http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf?ua=1

FDA statement
https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm

US NIH statement and recommendations

https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential

Source

BHIVA. BHIVA statement on Potential Safety Signal in Infants Born to Women Conceiving on Dolutegravir (on behalf of the BHIVA HIV in Pregnancy Guidelines Committee). (22 May 2018).

http://www.bhiva.org/BHIVA-statement-on-Dolutegravir.aspx

ViiV Dear Doctor letter on neural tube defects

ViiV Healthcare UK Ltd,

23rd May 2018 UK/HIV/0036/18

Tivicay▼ (dolutegravir),Triumeq▼(dolutegravir,rilpivirine): neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception

Dear Healthcare Professional

ViiV Healthcare, in agreement with the European Medicines Agency, would like to inform you of the following:

Summary

In an ongoing birth outcome surveillance study, conducted in Botswana, the Tsepamo study, 4 cases of neural tube defects (NTD) have been reported in 426 infants born to women who took dolutegravir as part of combined antiretroviral therapy at the time of conception. This represents an incidence of about 0.9% compared with an expected background rate of about 0.1% in infants born to women taking other antiretroviral medicines at the time of conception.

While this safety signal is being evaluated, the following measures are recommended:

- In women of child bearing potential (WOCBP) pregnancy testing should be performed and pregnancy should be excluded before initiation of treatment.
- WOCBP who are taking dolutegravir should use effective contraception throughout treatment.
- In WOCBP who are actively seeking to become pregnant, it is recommended to avoid dolutegravir.
- In case a woman becomes pregnant while taking dolutegravir and the pregnancy is confirmed in the first trimester, it is recommended to switch to an alternative treatment unless there is no suitable alternative.

Background information

The issue has been identified from a preliminary unscheduled analysis of the ongoing Tsepamo study in Botswana. Further data from this study will be captured during the ongoing surveillance. This information will help to further inform about the safety of dolutegravir during pregnancy.

(dolutegravir,abacavir,lamivudine), Juluca▼

Although there is limited experience with the use of dolutegravir in pregnancy, the currently available data from other sources including Antiretroviral Pregnancy Registry,

clinical trials and post-marketing use has not indicated a similar safety issue. There is only one other report of NTD reported spontaneously from Namibia in which dolutegravir was used a few months prior to conception and during pregnancy.

There are currently no congenital abnormality signals (including NTD) associated with the use of dolutegravir during pregnancy from other data sources. Dolutegravir was tested in a complete package of reproductive toxicology studies, including embryofetal development studies, and no relevant findings were identified.

Neural tube defects occur when the neural tube fails to completely form (between 0 and 28 days after conception), and the spinal cord, brain and related structures do not form properly.

This new finding is being considered in the context of other available data and the product information of TIVICAY/TRIUMEQ/JULUCA will be updated accordingly and further information will be communicated as appropriate.

Call for reporting

Adverse events should be reported. For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK UK Safety Team on 0800 221 441 selecting option 3 or email UK PharmaSafety team (uksafety@gsk.com).

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point

For further information, please contact Deborah on 020 8990 4616 or: deborah.2.whitehouse@viivhealthcare.com.

Debrorah Whitehouse

UK ViiV Healthcare Country Manager

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

The abstract book is not yet online.

Reports included in this issue of HTB.

- Dolutegravir 50 mg twice daily sufficient with rifampicin but levels reduced significantly with 100 mg once daily
- Vaginal ring reduces efavirenz but not atazanavir exposures
- Dispersible paediatric versions of dolutegravir provide higher bioavailability than immediate release formulations

Dolutegravir 50 mg twice daily sufficient with rifampicin but levels reduced significantly with 100 mg once daily

Polly Clayden, HIV i-Base

Dolutegravir 50 mg twice daily achieved sufficient concentrations in the presence of rifampicin in HIV/TB coinfected participants in the NAMSAL trial. But dolutegravir 100 mg once daily dosing with rifampicin reduces C24h by 76% in healthy volunteers. [1, 2]

These findings were presented at the 19th International Workshop on Clinical Pharmacology.

ANRS-12313 NAMSAL is a 48 week non-inferior multicentre study looking at a dolutegravir (DTG) 50mg once daily vs EFV 400mg once daily containing regimen as first-line treatment in HIV positive adults. The study is ongoing in Cameroon.

DTG is a substrate of UGT1A1 and CYP3A4 and rifampicin (RIF) is a strong inducer of these enzymes. Previous data suggest that giving 50 mg DTG twice daily will overcome DTG/RIF drug-drug interactions.

NAMSAL includes a sub study to assess the steady state pharmacokinetics (PK) and efficacy of twice-daily DTG 50 mg based ART with once-daily RIF 600 mg based TB treatment in HIV/TB coinfected participants.

The investigators collected dried blood spots (DBS) at least 4 weeks after starting ART (steady-state). Antiretroviral DBS concentrations and TB DBS drugs were determined using UPLC-MS/MS (LOQ <10ng/mL and <50 ng/mL, respectively).

DTG C12h was interpreted using a 10-fold protein adjusted IC90 (approx 640 ng/mL) and the inhibitory quotient (C12h/IC90).

Data were presented for eight participants: 23 DBS, weeks 12, 24 and 36.

DTG C12h were: 1,123 ng/mL (IQR 820–1,746); between participant variability 63% and within participant variability 72%.

TB drug concentrations suggested good adherence to TB treatment. At week 48, all participants had viral load <200 copies/mL. Among them, two had viral load >50 copies/mL with DTG C12h <640 ng/mL, corresponding to an inhibitory quotient of 0.1 and 5.

The investigators noted that these results support 24 week interim results from the INSPIRING study which showed DTG twice daily with RIF produced similar concentrations to those for DTG 50 mg once daily in the phase 2/3 trials.

A related presentation showed results from a PK evaluation that investigated the effect

of RIF on the PK of DTG 100mg once daily. The study was conducted to look at whether doubling the DTG dose over 24 hours could offer an easier option than 50mg twice daily to manage the drug interaction.

The study is open label in healthy volunteers receiving DTG 50mg or DTG 100 mg once daily in the presence or absence of RIF 600 mg. Participants were sequentially given: DTG 50 mg for 7 days, DTG 100 mg for 7 days, RIF 600 mg for 14 days, DTG 50 mg + RIF for 7 days, and DTG 100 mg + RIF for 7 days. Four steady-state full PK profiles were evaluated. Fourteen participants completed the study.

Geometric mean ratios (GMR) 50 mg DTG + RIF vs 50 mg DTG, C24h and AUC24h respectively: 0.65 (90% CI 0.55 to 0.75), 0.15 (90% CI 0.13 to 0.17) and 0.44 (90% CI 0.37 to 0.52)

GMR 100mg DTG + RIF vs 100mg DTG, Cmax, C24h and AUC24h respectively: 0.64 (90% CI 0.55 to 0.74), 0.12 (90% CI 0.10 to 0.15) and 0.42 (0.35 to 0.50)

GMR 100mg DTG + RIF vs DTG 50mg, Cmax, C24h and AUC24h respectively: 1.09 (90% CI 0.97 to 1.21), 0.24 (90% CI 0.20 to 0.28) and 0.74 (90% CI 0.64 to 0.86).

The investigators noted that RIF reduced DTG 100 mg once daily C24h by 76% and 50 mg once daily by 85% compared with DTG 50 mg alone.

They also observed that the maximum induction of RIF was reached at three weeks and drug absorption reached saturation limit in the range of 50–100 mg DTG (RIF has no additional effect on the saturation limit of DTG absorption).

DTG C24h remained 2–14 fold above the in vitro protein adjusted IC90 of 64 ng/mL in all participants (but <300 ng/mL in the majority).

C O M M E N T

Whether DTG 100 mg once daily + RIF will be safe and effective in people with HIV/TB coinfection remains unclear from the PK results above.

The investigators (from Imperial College London, St Stephen's Centre, Chelsea and Westminster Hospital and University of Cape Town) are planning follow up in patients. These evaluations will be highly monitored for safety.

References

1.Le M et al. Pharmacokinetic and efficacy of dolutegravir (50 mg BID) containing regimen in association with rifampin in HIV-infected patients using Dried Blood Spot: ANRS-12313 NAMSAL sub-study in Cameroon. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 7.

http://regist2.virology-education.com/presentations/2018/Antiviralpk/23_le.pdf (PDF)

2.Wang X et al. Pharmacokinetics of dolutegravir 100 mg once-daily with rifampicin. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 11.

http://regist2.virology-education.com/presentations/2018/Antiviralpk/22_boffito.pdf (PDF)

Vaginal ring reduces efavirenz but not atazanavir exposures

Polly Clayden, HIV i-Base

The contraceptive vaginal ring (NuvaRing) reduces efavirenz and ritonavir exposures while atazanavir exposure was not significantly different. [1]

Antiretrovirals are known to alter the exposure of hormonal contraceptives. Hormones might also induce or inhibit drug-metabolising enzymes, with potential to affect antiretroviral exposure. Lower exposure has been observed for efavirenz (EFV), ritonavir (RTV, r) and nelfinavir (NFV) when combined with various hormonal contraceptives in some studies – others find no difference in antiretroviral exposure.

ACTG A5316 was designed to characterise plasma hormone exposure when combined with EFV- or ATV/r-based ART. These results were presented at CROI 2018. [2,3]

Compared to the control group, participants in the EFV group had 76–79% lower ENG and 53–57% lower EE over 21 days (all comparisons $p<0.001$). Participants in the ATV/r group had 71–79% higher ENG (all $p<0.001$), but 29– 35% lower EE ($p=0.066$, 0.032 and 0.004 at days 7, 14 and 21, respectively) over 21 days compared to the control group.

A secondary objective of the study was to estimate the effect of etonogestral (ENG) ethinyl estradiol (EE) – 15/120 mcg/day in the combined contraceptive vaginal ring – on the pharmacokinetics (PK) of ATV, RTV and EFV.

Kim Scarsi from the University of Nebraska presented these data at 19th International Workshop on Clinical Pharmacology.

A5316 was an international, multicentre, parallel group, PK evaluation of HIV positive women at least 16 years old. A vaginal ring was inserted at study entry (Day 0) in two groups of participants receiving ART containing EFV 600mg daily or ATV/r 300/100mg daily, both + 2 NRTIs. Participants were on stable ART and had viral load 400 copies/mL or less at screening.

PK sampling for EFV or ATV/r on Day 0 took place pre-ART dose (0h), then 1, 3, 4, 5, and 8 hours post-ART dose, and before vaginal ring placement.

ART PK sampling was repeated on Day 21 before the vaginal ring was removed. EFV, ATV, and RTV were assessed by validated LC/MS/MS methods. Antiretroviral exposure was compared between Day 21 and Day 0 within each group by geometric mean ratio (GMR) with 90% CI.

For the antiretroviral PK analysis, there were 24 evaluable participants in the EFV group and 23 in the ATV/r group.

In the EFV group, Cmin 2.1 (range 0.90 to 13.62) mcg/mL on Day 0 and 1.77 (range BLQ to 12.93) mcg/mL on Day 21: GMR 0.64 (90% CI 0.42 to 0.97); AUC0-24h GMR was 0.87 (90% CI 0.77 to 0.99), both p<0.05.

In the ATV/r group, ATV Cmin 797 (range BLQ to 2731) ng/mL on Day 0 and 599 (range BLQ to 3599) ng/mL on Day 21: GMR 0.70 (90% CI 0.41 to 1.21); AUC0-24h GMR was 0.77 (90% CI 0.57 to 1.03).

Also in the ATV/r group, RTV Cmin 70 (range BLQ to 1042) ng/mL on Day 0 and 51.9 (range BLQ to 917) ng/mL on Day 21: GMR 0.67 (90% CI 0.38 to 1.19); AUC0-24h GMR 0.63 (90% CI 0.45 to 0.89), p<0.05.

The investigators observed moderately lower EFV (13–36%) and RTV (34–41%) concentrations after 21 days of vaginal ring use.

Despite lower RTV exposure, ATV exposure was not statistically different. Median Cmin values remained within the expected range for each antiretroviral on Day 21.

The investigators noted that four participants in each ART group had at least one EFV or ATV measurement below a conservative concentration threshold.

Viral load remained undetectable in 7 of 8 participants; the other increased from <40 copies/mL at entry to 54 copies/mL on Day 21.

Despite lower antiretroviral concentrations, there was still a significant drug-drug interaction with the combined hormonal contraceptive.

References

1. Scarsi K et al. Intraindividual comparison of efavirenz, atazanavir, or ritonavir plasma pharmacokinetics before and during 21-days of vaginally administered hormone contraception. 19th International Workshop on Clinical Pharmacology, 22– 24 May 2018, Baltimore. Oral abstract 10.
http://regist2.virology-education.com/presentations/2018/Antiviralpk/28_scarsi.pdf (PDF)
2. Scarsi K et al. Vaginal contraceptive hormone exposure profoundly altered by EFV- and ATV/r-based ART. 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), 4–7 March 2018, Boston. Oral abstract 141.

Dispersible paediatric versions of dolutegravir provide higher bioavailability than immediate release formulations

Polly Clayden, HIV i-Base

Higher bioavailability was achieved with the paediatric dispersible tablet formulation of dolutegravir but the lower strength immediate release tablet showed similar bioavailability to the adult formulation. [1] There is also higher

dolutegravir bioavailability and equivalent ABC/3TC bioavailability with the dispersible fixed dose combination tablet. [2]

Findings from pharmacokinetic (PK) evaluations of paediatric formulations of dolutegravir (DTG) in HIV negative adults, conducted by the originator manufacturer ViiV Healthcare, were shown at 19th International Workshop on Clinical Pharmacology.

Originator DTG is approved as a 50 mg, immediate release (IR) tablet for adults and adolescents. Lower strength 25mg and 10mg IR have been developed for paediatrics and a 5 mg dispersible tablet (DT) is currently in development.

The company evaluated the PK and safety of the alternative IR and DT vs either the 50 or 25 mg IR tablets, respectively after single-dose to HIV negative adults.

This was a phase 1, 2-part, open label, randomised, crossover study:

- Part 1. Participants randomised to receive 5 tablets of 10 mg IR (A) or one 50mg IR tablet (B, reference) over two dosing periods.

- Part 2. Participants received 5 tablets of 5mg DT as a dispersion and immediately taken (C) or 5 tablets of 5mg DT administered direct to mouth (D), or a 25mg IR tablet (E, reference) over 3 dosing periods.

There was at least seven-days washout between doses. Fourteen participants completed Part 1 and 24 Part 2 of the study.

This evaluation revealed, In Part 1, after 5 X 10mg DTG tablets, geometric mean systemic exposure for AUC(0-inf), Cmax, and AUC(0-t) of DTG were equivalent to that following 1 X 50mg DTG tablet. In Part 2, geometric mean systemic exposure to DTG were approximately 1.5-fold to 1.8-fold higher with treatments C and D than that observed following E.

GLS mean ratios of C vs E and D vs E for AUC(0-inf), Cmax, and AUC(0-t) were: 1.62 (90% CI 1.50 to 1.76) and 1.55 (90% CI 1.43 to 1.67), 1.79 (90% CI 1.62 to 1.98) and 1.80 (90% CI 1.63 to 1.99), and 1.63 (90% CI 1.50 to 1.77) and 1.55 (90% CI 1.43 to 1.68), respectively.

The terminal elimination half-lives for all formulations ranged from 15.5 to 16.2 hours.

The investigators noted that 5mg DT is suitable for further use in paediatric clinical trials of DTG.

ViiV Healthcare also produces a fixed dose combination (FDC) immediate release tablet of DTG/abacavir (ABC)/ lamivudine (3TC) approved in the US and the EU for adults and adolescents weighing at least 40 kg.

A lower strength, paediatric, dispersible FDC of DTG/ABC/3TC is currently in development.

As DTG is a metal-binding molecule, the divalent metal concentration in dispersion

media and time lag following dispersion may affect its solubility and potentially bioavailability.

So, the evaluation was designed to look at relative bioavailability of the dispersible FDC compared to non-dispersible tablets of DTG and ABC/ 3TC taken with purified water with varying mineral contents and dispersion times.

This was a phase I, single-centre, single-dose, randomised, open-label, 5-period crossover, relative bioavailability study in HIV negative adults.

Participants received five single dose treatments that included four dispersible FDC tablets each containing ABC 150 mg/DTG 10 mg/3TC 75 mg, with varying mineral content of water (zero or high-mineral content) and dispersion times (immediately or after 30 minutes delay), as well as four non-dispersible tablets containing DTG 10 mg plus one non-dispersible ABC/3TC tablet (reference) under fasted conditions. There was a seven-day washout period between treatments.

After a single dose of dispersible FDC formulation, the relative bioavailability of DTG AUC0-inf and Cmax were 53– 58% and 56–59% higher respectively. But ABC and 3TC were bioequivalent to non-dispersible tablets of DTG plus ABC/3TC.

Neither mineral content of the water nor dispersion time affected the exposures.

Development of the dispersible paediatric FDC tablet is also continuing.

References

1.Parasarmpuria R et al. Comparison of relative bioavailability of Tivicay immediate release and dispersible pediatric tablets to immediate Release Tivicay adult tablets. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Poster abstract 29.

2. Shaik J et al. Effects of low and high mineral content water on the relative bioavailability of a co-formulated Triumeq (abacavir/dolutegravir/lamivudine) dispersible tablet in healthy adults. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Poster abstract 26.

ANTIRETROVIRALS

EMA approves dolutegravir/rilpivirine (Juluca) in Europe as dual-therapy HIV switch option

Simon Collins, HIV i-Base

On 21 May 2018, the oral fixed dose combination (FDC) of dolutegravir/rilpivirine was approved by the EU as a switch option for people stable on ART for more than six months. The indication also includes no history of treatment failure or drug resistance.

The fixed dose combination is notable for only containing two active drugs, and for being an NRTI-free combination.

- Standard adult dose is once pill, once daily.
- Juluca needs to be taken with food (to boost the rilpivirine).
- A drug interaction with the TB medicine rifabutin requires taking an additional daily 25 mg rilpivirine tablet.
- Other drug interactions mean that Juluca should not be taken with the following drugs: dofetilide, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, proton pump inhibitors (including: esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, rabeprazole), St. John's wort, or more than 1 dose of the steroid medicine dexamethasone or dexamethasone sodium phosphate,
- No dose adjustment is needed with mild or moderate kidney damage (defined as CrCl greater than 30mL/min). Increased monitoring is recommended in more severe kidney damage (CrCl less than 30mL/min).
- No dose adjustment is needed with mild or moderate liver damage.

This FDC is a collaboration between ViiV Healthcare (dolutegravir) and Janssen Pharmaceutical (rilpivirine) and is marketed under the brand name Juluca.

Juluca was approved in the US in November 2017.

For further details please see the full prescribing information.

Reference

ViiV press statement, ViiV Healthcare receives EU marketing authorisation for Juluca (dolutegravir/rilpivirine), the first 2-drug regimen, once-daily, single-pill for the treatment of HIV. (21 May 2018).

https://www.viivhealthcare.com/media/

https://www.viivhealthcare.com/media/press-releases/2018/may/viiv-healthcare-receives-eu-marketing-authorisation-for-juluca-dolutegravirrilpivirine-the-first-2-drug-regimen-once-daily-single-pill-for-the-treatment-of-hiv.aspx

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.

C O M M E N T

Although Juluca has been launched in the UK, access will depend on different NHS procedures by the NHS in each country.

- **Scotland. Juluca has been submitted to the SMC with an anticipated reimbursement decision by September/October 2018.**
- **Northern Ireland has similar timing to NHS Scotland – expected September/October 2018.**
- **England. Timing is more difficult to predict based on the timeline of the specialised commissioning process. Expect early 2019.**
- **Wales. Timing still to be confirmed.**

References

1. Frontier Biotech press release. Frontier Biotech receives marketing authorization from China FDA for Aikening (albuvirtide for injection), China's first new drug for the treatment of HIV. (06 June 12018). http://www.frontierbiotech.com/en/news/
2. Collins S. Once-weekly albuvirtide infusion: early results of T-20-like compound. HTB Novemebr 2016. http://i-base.info/htb/31017
3. Wu H et al. Efficacy and safety of long-acting HIV fusion inhibitor albuvirtide in antiretroviral- experienced adults with HIV-1: interim 48-week results from the randomised, controlled, phase 3, non-inferiority TALENT study. Glasgow Congress on HIV Therapy, 23-26 October 2016 (Glasgow 2016). Oral abstract O336. Webcast: https://vimeo.com/189136480
4. Frontier Biotech licenses 3BNC117, a novel broad-spectrum HIV neutralizing antibody. (25 July 2017) https://www.firstwordpharma.com/node/1491015

SIDE EFFECTS & COMPLICATIONS

Boosted darunavir is associated with higher cardiovascular risk in D:A:D study, but not atazanavir

Simon Collins, HIV i-Base

Compared to HIV positive people using other HIV drugs, cumulative use of the boosted protease inhibitor darunavir/ritonavir was associated with an approximately 60% higher rate of developing heart disease over five years, in an analysis from the D:A:D study. Similar results were not found for atazanavir/ritonavir.

Importantly, the analysis adjusted for other factors linked to cardiovascular risk and were independent of dyslipidaemia. The study was authored by Lene Ryom and colleagues and published online in Lancet HIV. [1]

The D:A:D study is a large prospective cohort study designed to look for serious non-AIDS events including cardiovascular risk of HIV drugs. The current analysis included data from 35,711 HIV positive people with follow-up data from 2009 (approximately 70% of the original D:A:D cohort) to look at the currently used protease inhibitors atazanavir and darunavir. Cardiovascular disease (CVD) was defined as myocardial infarction, stroke, sudden cardiac death, or use of invasive cardiovascular procedures, including coronary bypass, coronary angioplasty, and carotid endarterectomy.

D:A:D is drawn from 11 cohorts mainly in Europe, but also Australia and the USA. Baseline demographics include median age 44 (IQR: 38 to 51), 74% male and 48% white (43% ethnicity unknown). Median CD4 count was 501 cells/mm^3 (IQR: 360 to 689), more than 85% were ART-experienced and 76% were virologically suppressed. Traditional cardiovascular risk factors were common: 40% had dyslipidaemia, 39% were current smokers (23% previous), 10% had hypertension, 5% had diabetes, and 1% had previous CVD.

At baseline, exposure to atazanavir/ritonavir and daraunavir/ritonavir was 18% and 4% respectively, increasing to 26% and 22%, respectively, at the time of the last study visit.

During a median 6.96 years of follow-up (IQR 6.28 to 7.08), 1157 people developed CVD, with an overall incidence rate of 5.34 events per 1000 person-years (95% CI: 5.03 to 5.65).

The most common CVD events were angioplasty (n=459), type 1 myocardial infarction (n=454), stroke (n=379) and bypass (n=93), with multiple events possible for one individual on the day the CVD event was registered.

The CVD impact of darunavir/ritonavir was cumulative with longer duration of use. The event rate (95%CI) was 4.91 (4.59 to 5.23) in individuals who had not used to ritonavir-boosted darunavir compared to 13.67 (8.51 to 18.82) for people who used darunavir/ritonavir for more than six years.

This produced an adjusted incidence rate ratio (IRR) of 1.59 (95% CI: 1.33 to 1.91) per five years of exposure to darunavir/ritonavir. This compared to a non-significant IRR of 1.03 per 5 years 0.90 to 1.18) with atazanavir/ritonavir.

This association was supported in several sensitivity analyses.

The analysis also calculated the number needed to treat with darunavir/ritonavir to produce one case of harm (NNTH), stratified by the underlying estimated 5 year CVD risk (using the online D:A:D calculator [2]). This produced an NNTH of 15 (95% CI: 13 to 17) for those at high risk and 533 (95% CI: 314 to 706) for those at low risk (defined at >10% and <1% risk over five years, respectively).

Although D:A:D doesn't collect details on drug dosing similar associations with darunavir/ritonavir were seen in both people using first-line ART and those with previous history of viral failure (when the higher dose of darunavir does would be more likely to be used.

C O M M E N T

As with all observational studies, these results include a caution that they only show association rather than a causative link.

However, the magnitude of the association with darunavir/ritonavir is similar to that previous reported for earlier protease inhibitors indinavir and lopinavir/ritonavir, in earlier D:A:D analysis. The lack of association with atazanavir/ritonavir supports this being a drug-specific rather than class effect.

The low number needed to treat to harm for people with high CVD risk (15 people would need to be treated with darunavir/ritonavir for five years to produce one related CVD event), suggest baseline CVD risk is an important factor before considering darunavir/ritonavir.

This further supports the decision by US guidelines to only recommend integrase inhibitor based combinations for first-line ART. [3]

Editorial commentary by Padraig McGettrick and Paddy Mallon in the same issue of Lancet HIV, stressed that higher rates of cardiovascular disease in HIV positive people compared to the general population are generally underestimated and the importance of the association observed in D:A:D not being driven by traditional CVD risk factors. [4] It also noted that other research groups, including MACS, have associated cumulative

use of darunavir/ritonavir (> 4 years) with surrogates for subclinical CVD. [5]

References

1. Ryon L et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV (2018). DOI: 10.1016/S2352-3018(18)30043-2. (03 May 2018). https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30043-2/abstract
2. D:A:D online risk calculators. https://www.chip.dk/Tools-Standards/Clinical-risk-scores
3. DHHS guidelines for the use of antiretroviral agents in adults and adolescents living with HIV (May 2018). https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0
4. McGettrick PMC and Mallon P. HIV and cardiovascular disease: defining the unmeasured risk. Lancet HIV (2018), DOI: 10.1016/S2352-3018(18)30061-4. (03 May 2018). https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30061-4/abstract
5. Thomas GP et al. Associations between antiretroviral use and subclinical coronary atherosclerosis. AIDS. 2016; 30: 2477–2486 https://journals.lww.com/aidsonline/fulltext/2016/10230/Associations_between_antiretroviral_use_and.9.aspx https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5173385

PREVENTION & TRANSMISSION

Broad PrEP access in Australia reduces HIV infections even with reduced condom use by people not on PrEP

Simon Collins, HIV i-Base

Results from sexual health behavioural surveys of gay men in Melbourne and Sydney report that broad and rapid access to PrEP during 2017 was associated with dramatic reductions in new HIV infections on a state level. This was despite less frequent and less consistent condoms use, including by men who were not directly using PrEP.

The study, by Martin Holt from the University of New South Wales and colleagues was published in Lancet HIV on 6 June, together with a press release, that unfortunately largely focused on reduced use of condoms. [1, 2]

Between January 2013 and March 2017, the impressive annual cross-sectional Gay Community Periodic Surveys (GCPS) – that have been running for 20 years with results published online [3] – were completed by 27,011 gay men in Melbourne and

Sydney (>13,000 in each city). Of these, the majority (16,827) reported condomless anal sex with a casual partner during the previous six months (acronymed CAIC in the paper) and were included in this analysis. Sex with casual partners has been previously reported as high risk for gay men in Australia, due to common use of serosorting as a risk reduction strategy.

Surveys were distributed online and at social venues and used seven types of sexual activity to categorise HIV risk.

Baseline demographics included mean age 36 (SD: 12) years with 91% self-identifying as gay (with half having a predominantly gay social network). Ethnicity was 64% white, 11% Asian, 12% other and 3% Aboriginal/Torres Strait Islander. Full- or part-time employment was reported by 80%: 56% had a university degree, 20% a trade certificate and 17% completed year 12 schooling. Number of partners in previous 6 months ranged from 44% reporting 0-5 partners to 19% reporting >20 partners. Just over one-third (36%) reported condomless sex with a casual partner (CAIC). Group sex was reported by 17%, ChemSex (crystal meth) by 14% and an STI in the previous 12 months by 23%.

Over time the cohort became slightly younger, increasingly used the online survey, with particpiants more likely to test if HIV negative (76% within previous 12 months) and were more likely to be on ART with undetectable viral load if HIV positive (77% in 2013 and 94% in 2017).

Over the four year period, recent use of PrEP increased dramatically from 2% in 2013 to 24% in 2017 (from 44/2324 to 783/3290 men). As expected, the proportion of men on PrEP who reported not always using condoms also increased - from 1% (26/2692) in 2013 to 16% (652/4018) in 2017. Similarly, consistent condom use also dropped, from 46% (1360 /2692) to 31% (1229/4018). All men on PrEP reported not always using condoms.

There were no significant differences in the percentage of HIV negative men in the overall survey who were not on PrEP but had condomless sex with casual partners. This was reported by 30% in 2013, 31% in 2016 and 29% in 2017, with no significant 5-year trend (p=0.52 and 0.37, for insertive vs receptive categories, respectively).

Within this group (ie using this subgroup as a denominator), the percentage of men not using condoms increased from 30% in 2013 to 36% in 2016 and 39% in 2017. However the overall percentage of men broadly using safe sex remained steady at around 70% (whether from use of PrEP, condoms or having positive partners with undetectable viral load).

From 2016 to 2917, HIV diagnoses in gay men had the steepest drops recorded in these states - by 16% in Victoria (Melbourne) and 11% in New South Wales (Sydney). This was likely related to the increaseing proportion of men using PrEP or ART, from 16% in 2013 to 44% in 2017 (aOR:1.53, 95%CI: 1.46 to 1.60; p=0.0001).

This led the researchers to comment: "This suggests that rapidly increasing PrEP use was effective in preventing new HIV infections and catalysed or built upon improvements in HIV testing and treatment (which had not previously resulted in large reductions in new diagnoses). The rapid increase in PrEP use seems to have outweighed the rapid decrease in condom use in this early phase of PrEP implementation".

There are also several important limitations with the study that should caution against interpreting the low use of condoms on a population level.

As an observational study, the observations about use of PrEP and condoms and reduced HIV incidence are associations rather than proven links. Also, the cross-sectional nature of the surveys means that individual behaviour is not tracked or reported over time. The categorisation using any risk might also overestimate individual risk, for example, where single or limited events were taken as representative consistent risk.

A linked editorial article, from Nittaya Phanuphak and Praphan Phanuphak from the Thai Red Cross Research Centre in Bangkok, comments that the proven benefits of PrEP show the urgency of engaging with communities that are not currently accessing PrEP: "Messages must be clear to destigmatise condomless anal intercourse with casual partners and to make people feel welcome to access HIV testing and antiretroviral-based prevention, whether this be post-exposure prophylaxis, PrEP, or ART to achieve undetectable viral load". [4]

First details on the reduced HIV incidence in Australia were also presented earlier this year at CROI. [5]

C O M M E N T

Importantly, the authors recognise that the rapid increase in PrEP use outweighed the impact of reduced condom use. It is important to accept that the trends for reduced condom use are likely to continue as men gain greater confidence from PrEP.

The emphais placed on reduced condom use was quickly rebutted by Australian community organisations. [6]

Unfortunately, Sarah Boseley's report in the Guardian chose to also focus on reduced condom use, as if reporting from the press release rather than reading the research paper and accompanying editorial. [7] It is both ignorant and misplaced for Boseley to report lower condom use as "complacency" over HIV. It is also wrong for Holt et al to be driving prejudice against PrEP, which are not supported by the reductions in HIV that are noted in the paper.

Consistent condom use is no longer a requirement for reducing HIV incidence in

settings where PrEP is widely available, with associated frequent routine HIV testing, and where there is prompt access to effective ART.

In many ways, the reduced use of condoms is a helpful marker that people already feel sex is safer, especially when supported by data reporting reduced HIV incidence. After decades of sex being associated with risk, this is a healthy change.

Clearly, unless an HIV negative person knows that their partners are on ART, the lowest risk for individuals not on PrEP, is to continue to use condoms. This will be more protective than relying on protection from lower levels of HIV on a population levels.

However, the public health concerns discussed in the paper from reduced condom use are probably more important if PrEP use drops again the future, as reestablishing condom use might then become important again.

These results show the possibility of both having CAIC and, if not eating it, then at least remaining HIV negative.

Given the larger population in the UK, and rapid uptake of PrEP in Scotland and Wales, the PrEP IMPACT Study will need to enrol more than 10,000 people if it is to match the promise of its name.

References

1. Holt M et al. Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney Australia: results of repeated behavioural surveillance in 2013–17. Lancet HIV (2018). Published online 06 June 2018. doi: 10.1016/ S2352-301830072-9.
   https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30072-9/abstract
2. Lancet HIV press release. Rapid uptake of PrEP may contribute to a general decline in condom use among gay and bisexual men. (6 June 2018).
3. Gay Community Periodic Survey. Reports available online.
   https://csrh.arts.unsw.edu.au/research/publications/gcps
4. Phanuphak N and Phanuphak P. Time to focus more on condomless anal sex in non-PrEP users. Editorial commentary, Lancet HIV (2018). Published online 06 June 2018. doi: 10.1016/ S2352-3018(18)30100-0.
   https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(18)30100-0/abstract
5. Grulich A et al. Rapid reduction in HIV diagnoses after targeted PrEP implementation in New South Wales, Australia. CROI 2018, Boston. Oral abstract 88.
   www.croiconference.org/sessions/rapid-reduction-hiv-diagnoses-after-targeted-prep-implementation-nsw-australia (abstract)
   www.croiwebcasts.org/console/player/37190 (webcast)
6. ACON press statement. Statement from ACON And AFAO CEOs In response to reports on PrEP and condom usage. (06 June 2018).
   https://www.aconhealth.org.au/statement_from_acon_and_afao_ceos_in_response_to_reports_on_prep_and_condom_usage
7. Bosely S. Rapid rise in anti-HIV PrEP pills linked to drop in condom use, The Guardian (06 June 2018).
   https://www.theguardian.com/society/2018/jun/06/rapid-rise-in-anti-hiv-prep-pills-linked-to-drop-in-condom-use

CURE RESEARCH

Online database of current research related to an HIV cure

Richard Jefferys, TAG

An impressive comprehensive compilation of more than 200 ongoing clinical studies looking at aspects of HIV cure research.

Each study is categorised by the type of intervention with hyperlinks to the relevant online trial registry for further details.

This resource is regularly updated and can also be downloaded as a PDF document.

Source

TAG. Research towards a cure trials.

http://www.treatmentactiongroup.org/cure/trials

http://www.treatmentactiongroup.org/sites/default/files/Research_toward_a_cure_May_15_2018_final.pdf (PDF)

Survey on treatment interruptions (ATIs) in cure research

Simon Collins, HIV i-Base

A new online community survey is looking to collect community views about antiretroviral treatment interruptions (ATIs) in cure-related research.

The increasing focus on finding an HIV cure – and the related goal of HIV remission without ART – has highlighted the importance of participant safety in studies that ask people to stop HIV treatment.

As treatment interruptions are no longer recommended in treatment guidelines, the importance of understanding both risk and benefits becomes an essential aspect of informed consent for such studies.

This online survey is collecting views on the different approaches to ATIs and additional information is included as part of the survey. Estimated time to complete the survey is 15-45 minutes.

This project is being run by the US community organisation Treatment Action Group (TAG).

Link to survey:

https://goo.gl/forms/kSLjrZuowBrPJVNh2

Please share this information with any networks or individuals that may be interested.

The deadline for responses is Friday 22 June, 2018.

Source: TAG. Community recommendations for clinical research involving antiretroviral treatment interruptions (ATIs) in adults. (31 May 2018).

https://goo.gl/forms/kSLjrZuowBrPJVNh2

ON THE WEB

Webcasts on PrEP and women

Webcasts are now online from the 8th Workshop on HIV and Women.

http://www.infectiousdiseasesonline.com/hiv-women-2018-webcasts

The programme included a strong focus on PrEP in women that at particularly interesting.

- PrEP and women, current evidence - Lynne Mofenson
- PrEP and women, what's in the pipeline - Craig Hendrix
- Debate: Should PrEP be offered for women, Pro - Ellen Cooper
- Debate: Should PrEP be offered for women, Con - Audrey Pettifor
- Debate: Should PrEP be offered for women, community pro - Teresia Otieno
- Debate: Should PrEP be offered for women, community con - Fungai Murau

Sexual identity and HIV

STOPAIDS

A new factsheet from the campaign group STOPAIDS.

This highlights the intersectional forms of discrimination, abuse and violence based on sexual orientation and gender identity diminish the ability of lesbian, gay, bisexual, transgender and intersex (LGBTI) individuals to realise their human rights, including their right to health care.

https://stopaids.org.uk/resources/sexual-orientation-gender-identity-and-hiv/

https://stopaids.org.uk/wp/wp-content/uploads/2018/05/STOPAIDS-factsheet-SOGI-V3-onlineversion.pdf (PDF)

Modern ART in Africa: new resources

i-Base has helped produce new resources about changes to modern HIV treatment (ART).

This involved working with the Treatment Action Campaign in South Africa and other treatment advocates.

We hope that you will adapt them for your own country.

i-Base is happy to help you to adapt them for your local community.

Modern ART for Africa - full details and download links.

http://i-base.info/modern-art-for-africa/