ISSN 1472-4863

hiv treatment bulletin (e)

HTB: 2018 vol 19 no 9

21 May 2018: no.9

DTG ALERT and BHIVA/BASHH 2018

CONTENTS

Published by HIV i-Base

h-tb

HIV TREATMENT BULLETIN

HTB is published in electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered using the form on the back page or directly online:

http://www.i-Base.info

or by sending an email to: subscriptions@i-Base.org.uk

Editor: Simon Collins

Contributing Editor: Polly Clayden

Medical consultants:

Dr Tristan Barber, Chelsea & Westminster Hosp, London.

Dr Karen Beckerman, Albert Einstein College of Medicine, NYC.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Prof. Diana Gibb, Medical Research Council, London.

Dr Gareth Hardy, PhD.

Prof. Saye Khoo, University of Liverpool Hospital.

Prof. Clive Loveday, ILVC, UK.

Prof. James McIntyre, Chris Hani Baragwanath Hosp. S Africa.

Dr Graeme Moyle, Chelsea & Westminster Hosp, London.

Dr Stefan Mauss, Düsseldorf.

Prof. Caroline Sabin, UCL Medical School, London.

Dr Graham P Taylor, Imperial College, London.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

Dr Edmund Wilkins, Manchester General Hospital, Manchester.

HTB is a not-for-profit community publication. It reviews the most important medical advances related to clinical management of HIV including access to treatment. We compile comments to articles from consultant, author and editorial responses.

We encourage i-Base originated material to be reprinted for community use but copyright remains with HIV i-Base. A credit and link to the author, the HTB issue and the i-Base website is always appreciated. Copyright for other articles remains with the credited source. We thank other organisations for this use and encourage readers to visit the linked websites.

HIV i-Base receives educational grants from charitable trusts, individual donors and pharmaceutical companies. All editorial policies are strictly independent of funding sources.

HIV i-Base, 107 The Maltings,

169 Tower Bridge Road, London, SE1 3LJ.

T: +44 (0) 20 8616 2210. F: +44 (0) 20 8616 1250

http://www.i-Base.info

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

EDITORIAL

This issue of HTB leads with worrying reports of a potential signal of neural tube defects in four women taking dolutegravir at the time of conception. Importantly, there is no signal from dolutegravir use during pregnany.

This news only became available as this HTB issue was being finalised. Further news is expected over the next week and we will add this online, with further comment.

Even if the early reports are not confirmed, this highlights a continued problem with the process for access to new ARVs in low- and middle-income countries (LMICs).

Two further reports in this issue also emphasise the significant gaps in the data from phase 3 studies that limit early use by the global populations most in need of better drugs.

Perhaps the unfortunate findings with dolutegravir will serve as a warning for better surveillance, inclusion of pregnant women in trials etc.

Generally more positive news is included in our further reports from the 4th Joint BHIVA/BASHH Conference held in Edinburgh.

Definitely more positive is the report that the government has backed down on the policy of NHS medical health records being routinely made available to UK immigration services.

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

Potential safety signal for dolutegravir from the time of conception

Polly Clayden, HIV i-Base

On 18 May 2018, the World Health Organisation (WHO) issued a statement following the identification of a potential safety issue with dolutegravir (DTG) related to neural tube defects in infants born to women who were taking DTG at the time of conception.

The safety issue was found at a preliminary unscheduled analysis of the ongoing observational study in Botswana that previously reported reassuring data on DTG started during pregnancy. The analysis revealed four cases of neural tube defects (spina bifida, anencephaly, encephalocele/iniencephaly) out of 426 women who became pregnant while taking DTG.

This rate of approximately 0.9% compares with a 0.1% risk of neural tube defects in infants born to women taking other ARVs at the time of conception.

The originator company ViiV Healthcare will release a Dear Doctor letter next week and BHIVA plan to issue recommendations for women in the UK.

i-Base will provide further commentary on plans to monitor women who have conceived on DTG and are currently pregnant (particularly in Botswana and Brazil) and for better follow up of pregnancies exposed to DTG and other new antiretrovirals.

C O M M E N T

The WHO statement was swiftly followed by others from PEPFAR, FDA, EMA and the Southern African HIV Clinicians Society (SAHCS). [2, 3, 4, 5]

Until there are more data to guide them, the recommendations suggest varying degrees of caution. The WHO statement (in full below) advises:

- **Pregnant women who are taking DTG should not stop their ARV therapy and should speak with their health provider for additional guidance.**
- **Antiretroviral (ARV) therapy for women of childbearing age, including pregnant women should be based on drugs for which adequate efficacy and safety data are available; an efavirenz–based regimen is a safe and effective first-line regimen.**
- **If other first-line ARVs cannot be used in women of childbearing age, DTG may be considered in cases where consistent contraception can be assured.**
- **Programmes should continue strengthening pharmacovigilance including monitoring of birth outcomes.**

PEPFAR encourages countries to continue with their transition to tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD), but states that transition times might be altered to allow for the use of efavirenz-based regimens for certain women. Until further data are available, they recommend that women with HIV who wish to become pregnant should take efavirenz-based regimens.

How this might work in real-life, where a large proportion of people using ART are women of child-bearing potential, a large proportion of pregnancies are unplanned, access to contraception can be inadequate, and fertility rates can be rather high (approaching 6 in Uganda, Zambia and Malawi), remains to be seen.

References

1. WHO statement on DTG. 18 May 2018. http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf
2. PEPFAR statement on potential safety issue affecting women living with HIV using dolutegravir at the time of conception https://www.pepfar.gov/press/releases/282221.htm
3. EMA press release. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir. 18 May 2018. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1
4. US FDA. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). 18 May 2018. https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm
5. Statement from the Southern African HIV Clinicians Society. 19 May 2018. http://sahivsoc.org/Files/Dtg%20in%20Pregnancy%20Statement_1905.pdf

Potential safety issue affecting women living with HIV using dolutegravir at the time of conception

WHO statement (10 May 2018)

The investigator of an independent NIH-funded study has identified a potential safety issue with the HIV antiretroviral medicine dolutegravir (DTG), and reported it to the World Health Organization (WHO) and ViiV Healthcare. The potential safety issue is related to neural tube defects in infants born to women who were taking DTG at the time of conception.

The issue has been identified from a preliminary unscheduled analysis of an ongoing observational study in Botswana, which has found 4 cases of neural tube defects out of 426 women who became pregnant while taking DTG. This rate of approximately 0.9% compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception.

Information on neural tube defects

The neural tube is the foundation of the spinal cord, brain and the bone and tissues that surround it. Neural tube defects occur when the neural tube fails to completely form; this formation takes place between 0 and 28 days after conception. Neural tube defects may be related to folate deficiency, other medications or family history.

WHO recommends that women take daily supplements of folic acid before conception and during pregnancy to help prevent neural tube defects.

Details on preliminary findings concerning the potential safety issue

Preliminary data from the aforementioned study in Botswana so far seem to suggest that the potential safety issue arises from a woman's exposure to DTG at the time of conception, rather than during pregnancy. From the same study, there is currently no evidence of any infant born with a neural tube defect to a woman who started DTG during her pregnancy.

Surveillance is ongoing for additional pregnant women in Botswana who were exposed to DTG at time of conception. Their deliveries will be monitored closely over the next 9 months (May 2018 – February 2019), and results are expected to be known soon thereafter. These data will provide more information about the safety of DTG for women of childbearing age.

According to manufacturer ViiV Healthcare, DTG was tested in a complete package of reproductive toxicology studies, including embryofetal development studies in rats and rabbits, where dosing occurred during the sensitive window for neural tube defects in these species. There was no evidence of adverse developmental outcomes in these studies.

WHO response

WHO recognizes that dolutegravir (DTG) has established efficacy, tolerability and a high genetic barrier to resistance.

Current WHO Guidelines released in 2016 cautioned that there were insufficient data for using DTG during pregnancy or breastfeeding and recommended efavirenz (EFV) in combination with tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) as the preferred option in pregnancy.

WHO convened an expert guideline development group meeting on 16-18 May 2018 to review all available data on the efficacy and safety data of dolutegravir, including the Botswana data, and will release updated guidance on the role of DTG in first- and second- line HIV treatment in the coming months.

In the interim, WHO advises that countries and ministries follow the existing 2016 WHO Consolidated ARV Guidelines, and consider the following:

- Pregnant women who are taking DTG should not stop their ARV therapy and should speak with their health provider for additional guidance.
- Antiretroviral (ARV) therapy for women of childbearing age, including pregnant women should be based on drugs for which adequate efficacy and safety data are available; an efavirenz–based regimen is a safe and effective first-line regimen.
- If other first-line ARVs cannot be used in women of childbearing age, DTG may be considered in cases where consistent contraception can be assured.
- Programmes should continue strengthening pharmacovigilance including monitoring of birth outcomes.

Next steps

WHO is taking this potential safety issue very seriously and is working closely with all relevant stakeholders including ministries of health, the study investigators, the manufacturer and partner organizations to investigate these preliminary findings.

Regulatory authorities are also reviewing this matter.

WHO will update this data and information at a later date as more information becomes available.

For further information contact: pvsupport@who.int

Source

WHO statement. Potential safety issue affecting women living with HIV using dolutegravir at the time of conception. (10 May 2018).

http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf (PDF)

CONFERENCE REPORTS

Fourth Joint Conference of BHIVA/BASHH (4th BHIVA/BASHH)

17–20 April 2018, Edinburgh

Introduction

This issue of HTB continues our reports from the Fourth Joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH) was held from 17 – 20 April in Edinburgh.

As with previous joint meetings, the programme expanded to include a broader focus on sexual health with almost 1000 delegates and 400 poster presentations.

Materials from the conference, including the programme and abstract book are now online, together with slides for many of the oral presentations. Webcasts from the oral presentations are now also online.

http://www.bhiva.org/AnnualConference2018.aspx

Abstract book (direct link):

http://www.bhiva.org/documents/Conferences/2018Edinburgh/AbstractBook2018.pdf (PDF)

Short summary articles of some of the highlights are included below.

- Low awareness of PEP and PrEP among trans people in London and their partners
- Low awareness of PrEP in BME communities in Leeds but high interest in use
- Younger people living with HIV more likely to have a positive self image
- Zero or negligible risks of HIV, HBV or HCV transmission by biting or spitting
- UK-CAB community representation on guideline panels and research studies

Low awareness of PEP and PrEP among trans people in London and their partners

Simon Collins, HIV i-Base

Results from a survey of trans people and their partners attending a sex-on-premises venue in central London showed low knowledge about both PEP and PrEP in people who were at high risk for HIV. [1]

This study was presented by Aedan Wolton from cliniQ, a sexual health and wellbeing clinic for trans people based at 56 Dean Street in Soho, London. [2]

This was part of a regular service that offered HIV testing and provided information about sexual health including awareness of PEP and PrEP. The venue caters for trans women, members of the cross-dressing/transvestite communities, and their mainly cis-gendered (i.e. not trans) male partners.

Results were presented from 131 responses over a 12-month period. Approximately two-thirds of participants identified as male (including 3% trans men and 17% who identified as cross-dressing or transvestite) and 30% female (nearly all trans women), with 1.5% non-binary.

Mean age was 46 (range 25 to 75). Ethnicity included 45% white UK, 10% white European, 8% south Asian with 12 other groups reported. Just over half (53%, n=70) reported sex without condoms in the previous 6 months.

Overall, awareness of both PEP and PrEP was low.

Even though PEP has been available for more than a decade, less than one-third of respondents (31%, n=41) had heard of PEP, and only 24% (n=32) knew where to access it.

Awareness of PrEP was even lower, with only one in six respondents (16%, n=21) having heard of PrEP, and 14% (n=18) knowing how to get PrEP.

Even though trans communities have one of the highest rates of HIV, and even with information about PrEP from the health team at cliniQ, only 22% answered that they would be interested in using PrEP if it was available. Only 25 people gave reasons for reluctance to use PrEP, but 80% said this was due to worry about efficacy, 72% because of the cost and 44% because of concerns over drug interactions with hormone treatment.

Additionally, 133 HIV tests were provided, all of which, luckily, were HIV negative. HIV positive results have been reported by the service though, just outside the timeframe of the current analysis. Experience at cliniQ is that people either test HIV negative, or test HIV positive but with very advance late-stage infection. Continued outreach hopes to help with both more routine testing and earlier diagnosis.

In summary, the Trans:mission project showed low awareness of sexual health information in this population, despite high risk of HIV. The low awareness for both PEP and PrEP in trans communities and concerns about use led to the development of two new booklets by cliniQ, also available online. [3, 4]

C O M M E N T

This project showed how to positively engage with trans communities so people can access appropriate health care.

This is especially important as the ongoing PrEP IMPACT study in England has ring-fenced allocations to enrol transgender people. [5]

Consistency and continuity of the service were both key to the success, enabling the same people to build up confidence to engage because the team continue to attend the same venue every month.

Reference

1. Wolton A et al. Trans:mission – a community-led HIV testing initiative for trans people and their partners at a central London sex-on-premises venue. 4th Joint BHIVA/BASHH Conference, 17–20 April 2018, Edinburgh. Oral abstract O29. Published in HIV Medicine, 19 (Suppl. 2), s5–s20. The webcast is 43 minutes into the session webcast. http://www.bhiva.org/180419-Oral-Research-Presentations-Session-4.aspx (webcast)
2. cliniQ – Inclusive trans sexual health & wellbeing. https://cliniq.org.uk
3. cliniQ. A trans woman's guide to the sex club scene: https://cliniq.org.uk/resources/the-hook-up-a-trans-womans-guide-to-the-sex-club-scene
3. cliniQ. A trans guy's guide to the gay sex scene: https://cliniq.org.uk/resources/cruising-a-trans-guys-guide-to-the-gay-sex-scene
4. PrEP IMPACT Trial. https://www.prepimpacttrial.org.uk

Low awareness of PrEP in BME communities in Leeds but high interest in use

Simon Collins, HIV i-Base

A pilot survey of people attending football matches featuring African teams provided confirmation of the expected low awareness of PrEP amongst black and minority ethic (BME) communities in Leeds. The results also reported a high interest in using PrEP if it was available.

The project was a collaboration between Leeds Centre for Sexual Health and BHA Leeds Skyline a community HIV organisation.

Overall, 75 completed surveys (95% from men) were returned from two events (the African Cup of Nations and the refugee football tournament).

Age ranged from 15-74 years old, with the majority (52%) from people aged 15-24. Ethnicity demographics included 77% black African, 8% black British, 4% white British and 11% other. Although 93% were heterosexual, 4% were bisexual and 3% didn't answer this question.

Overall, 81% (61/75) had not heard about PrEP. With further information, however, 60% (45/71) said that they would be interested in taking PrEP if it was provided by the NHS, half of whom said they would not use PrEP unless it was provided free. Also, 45% (34/71) said PrEP would not change their current condom use.

Amongst people who identified as having risk for HIV, everyone said they would take PrEP if provided by the NHS. This included 19% of the group who had a partner from a country considered high risk for HIV, 4% men who had sex with men, 3% who had an HIV positive partner or who paid for sex respectively.

C O M M E N T

Although this was only a small survey, this group was able to reach a population affected by HIV that existing information networks have been unable to reach.

This is important as the ongoing PrEP IMPACT study has ring-fenced places for people who are non gay or bisexual men. [2]

Further outreach is essential if the study is to adequately recruit people from other risk groups.

References

1. Ekong N et al. Awareness of pre-exposure prophylaxis (PrEP) in the black and minority ethnic (BME) community: results of a questionnaire survey. 4th Joint BHIVA/BASHH Conference, 17–20 April 2018, Edinburgh. Oral abstract O29. Published in HIV Medicine, 19 (Suppl. 2), s21–s152. Poster abstract P71.
2. PrEP IMPACT Trial. https://www.prepimpacttrial.org.uk

Younger people living with HIV more likely to have a positive self image

Simon Collins, HIV i-Base

Results from a survey of people living with HIV in the UK who are aged 15-24 included the optimistic results that younger people might be experiencing less stigma than older HIV positive people.

Irina Lut from the Family Planning Association presented results from two cross-sectional UK Stigma survey of people living with HIV. This analysis compared results between young people aged 15 to 24 (n=300) and adults >18 years old (n=1450).

Although there are still important difficulties from being HIV positive, the younger group were twice as likely to have a positive self image compared to adults. Young people consistently and significantly reported more positive feelings and less negative feelings compared to adults living with HIV, and reported significantly less stigma. See Table 1.

However the study also reported that younger people are more likely to avoid seeking health care when needed. Also, in conclusion: "while young people experienced less discrimination, a poor experience was more likely to become a barrier to future care".

Table 1: Responses to stigma survey from adults and young people

Survey Q	Adults (n=1450)	Young people (n=300)	p	Adj OR (95%CI) A vs. YP
Treated differently	441 (30.4%)	15 (5.0%)	<0.001	0.19 (0.099–.037)
Refused or delayed care	243 (16.8%)	9 (3.0%)	<0.001	0.45 (0.195–1.03)
Heard negative comments	120 (8.3%)	16 (5.3%)	<0.001	0.83 (0.45–1.55)
Use of excess barrier protection	202 (13.9%)	27 (9.0%)	<0.001	0.73 (0.45–1.19)
Avoid seeking care	396 (27.3%)	50 (16.7%)	<0.001	1.69 (1.13–2.56)

Ref: Lut I et al, Stigma Survey UK: an intergenerational comparison of stigma and discrimination in non-HIV healthcare settings across the UK . 4th Joint BHIVA/BASHH Conference, 17–20 April 2018, Edinburgh. Poster abstract P127. Published in HIV Medicine, 19 (Suppl. 2), s21–s153.

Zero or negligible risks of HIV, HBV or HCV transmission by biting or spitting

Simon Collins, HIV i-Base

Two related posters presented results from literature searches on the risk of transmission of HIV or viral hepatitis from biting or spitting. These reviews were prompted by recent parliamentary debates on a proposed parliamentary bill that sought to increase penalties for assaults on staff.

The HIV review concluded "there is no risk of transmitting HIV through spitting and only a negligible risk from biting" and that this would be zero too if someone is on ART. Policy to protect emergency workers should be made with this evidence in mind, and balanced with respecting the rights and dignity of people living with HIV.

The hepatitis review concluded "although transmission of HBV and HCV via spitting or biting is biologically plausible, the virulence and risk of this is not established. Only a small number of transmissions of HBV and HCV from spitting or bite injuries have been reported and that the overall risk appears to be very low."

References

1. Cresswell F et al. A systematic review of risk of HIV transmission through biting or spitting: implications for policy . 4th Joint BHIVA/BASHH Conference, 17–20 April 2018, Edinburgh. Poster abstract P66. HIV Medicine, 19 (Suppl. 2), s21–s152.
2. Pintilie H and Brooks G. What is the likelihood of acquiring hepatitis B virus (HBV) or hepatitis C virus (HCV) through biting or spitting? A review of the published literature with particular reference to the emergency services. 4th Joint BHIVA/BASHH Conference, 17–20 April 2018, Edinburgh. Poster abstract P140. HIV Medicine, 19 (Suppl. 2), s21–s152.

UK-CAB community representation on guideline panels and research studies

Simon Collins, HIV i-Base

A useful review of the involvement of HIV positive engagement in health policies and structures was presented at the 4th BNIVA/BASHH conference by Longret Kwardem.

This study reported results from semi-structured interviews with 13 community representatives (7 men, 6 women) in the UK Community Advisory Board (UK-CAB). Participants were sampled to provide diversity of roles, experience and demographics. with advocacy experience ranging from 1.5 to >20 years.

Interviews were carried out by two trained researchers who are also UK-CAB members. The format was similar to a study last year that interviewed health workers on their views and experiences of community reps. [2]

The interviews looked for examples of outcomes from community involvement and these included:

- Community reps wanted to 'make a difference' and their experience correlated with whether they perceived they had made an impact.
- Commonly cited benefits included: changes in trial design – particularly exclusion and inclusion criteria; inclusion in guidelines of overlooked issues; highlighting concerns of specific groups; bringing community perspectives; using community-friendly language; and improvements to clinics.
- Benefits from engaging in this work included: gaining respect and support from HIV professionals; increased learning opportunities; and giving back to their community.
- Reps reported valued UK-CAB support – training, networking, communicating through the forum – and accountability among activists.

However, sustainability for both individual and the CAB was also mentioned as one of the most difficult ongoing challenges, especially when more reps work in a voluntary capacity. Some responses commented that they had to give up work shifts in order to volunteer as reps.

As one comment quoted in the poster made clear: "We can do a lot as a network with little funding but can't do anything with no funding".

Reference

1. Kwardem L et al. What impact do UKCAB representatives on guideline writing committees and academic/clinical research study boards make? 4th Joint BHIVA/BASHH Conference, 17–20 April 2018, Edinburgh. Poster abstract P273. Published in HIV Medicine, 19 (Suppl. 2), s21–s152. http://www.bhiva.org/AnnualConference2018Presentations.aspx
2. Kwardem, L., James R. and Shepherd J. (2017), 'What is the impact of having UK-CAB representatives on guideline writing committees and academic/clinical research study boards?' (Abstract). HIV Medicine, 18, Supp 1, p67.

TREATMENT ACCESS

Phase 3 registrational data is not sufficient for roll-out of new ARVs in low- and middle-income countries

Polly Clayden, HIV i-Base

Phase 3 randomised trials for drug approval in high-income countries do not provide sufficient evidence to support the widespread use of new antiretrovirals in low- and middle-income countries (LMICs), where the majority of people with HIV live.

Once again this issue of missing evidence was highlighted in a paper published ahead of print in AIDS 9 May 2018. The paper summarises discussions from the Third Conference on Antiretroviral Drug Optimisation (CADO 3) that took place at the end of 2017. [1] A summary meeting report is also available on the WHO website. [2]

This meeting focused on optimised second- and third-line ART for adults and the sequencing and recycling of key products: tenofovir pro-drugs (tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), dolutegravir (DTG), and darunavir/ritonavir (DRV/r).

Key missing evidence is typically for pregnant women, people with HIV/TB coinfection and people who have not had resistance testing before starting ART. "We need to work in partnership with originator companies to design and perform these studies earlier, so that results can support rapid expansion of new treatments in LMICs" the authors write.

- For DTG, results from new clinical trials to evaluate the transition from efavirenz (EFV)-based to DTG-based regimens are needed to ensure safety and efficacy for the nearly nine million people on NNRTI based ART in LMICs who have either detectable or unknown viral loads.
- More evidence is needed on the use of TAF in pregnant women (in this case, considerably more evidence) and people with HIV-TB coinfection taking rifampicin-based treatment to support widespread use of the new TAF/3TC/DTG combination in LMICs.
- Data from randomised phase 3 GEMINI trials of DTG/3TC will be available in 2018, but the overall disadvantages of this approach appear to outweigh the advantages for people with HIV in the setting of LMICs.
- For new drugs, there is substantial additional research required to evaluate an antiretroviral for widespread use in LMICs. This should be important for new antiretrovirals in development.

CADO3 participants looked at the growing body of programme data on the safety of DTG in first-line – particularly from Botswana and Brazil – and agreed that these data support further expansion of a DTG regimen as a preferred first-line option. But they also agreed that a robust research programme to provide the remaining missing evidence to support its widespread use, as well as careful collection and analysis of programme data, were essential in parallel to countries' transition.

The strategy of universally switching people who are currently stable an EFV-based regimen and DTG's role in second-line was still debatable.

Participants judged EFV 400 mg to be the alternative first-line option for people who cannot tolerate DTG or for countries where it cannot be accessed because of cost and patent protection.

They did not support the use of two-drug regimens for adults based on the trial data currently available. As ever, recent and ongoing studies of two-drug regimens do not consider the usual important populations who will be treated in LMICs: pregnant women, people with TB and HBV co-infections, people diagnosed in advanced HIV infection; and populations with no or limited access to viral load and/or resistance testing.

Many of the two-drug investigations are switching studies. In real-life such strategies would require both widespread use of viral load testing as well as the procurement of two products – there would be many programmatic challenges.

The role of DTG in people who previously failed NNRTI-based regimens and whether or not TDF and TAF could be recycled were defined as key priorities. Following the DAWNING results there was much discussion at CADO3 on whether these results could be duplicated in a public health setting with no genotyping. Trials to answer this question, and whether DTG will perform similarly to a protease inhibitor in the context of NRTI resistance – as in the EARNEST, SELECT and SECOND-LINE studies – or will need to be combined with different NRTIs were judged by the participants to be essential.

Dose optimisation studies on use of low dose DRV/r in second-line for people who either failed first-line or were stable on another second-line regimen was also considered to be a priority.

Long acting drugs (oral, injection or implants) and nanoformulations were judged high-priority in the longer term. But, once again, in order for these or any pipeline products to be usable in LMICs, studies will need to include pregnant and women of child-bearing age, adolescents, people coinfected with TB and on treatment, and other co-morbidities.

Table 1: CADO 3 prioritised optimised products

Short-term 1–2 years	Medium-term 2–5 years	Long-term 5+ years
TDF/XTC/DTG	TAF/XTC	Long-acting formulations (entry inhibitors and INSTIs).
TDF/3TC/EFV400	TAF/XTC/DTG	Maturation and capsid inhibitors.
DRV/r 400/50 mg	New DRV/r formulations*	bNAbs.

*Low dose standard formulation (400/100 mg) or standard dose nanoformulation (800/100 mg).

And any investigations should consider the circumstances in which these products are likely to be given, such as no or limited viral load monitoring nor access to other tests, highly trained experts or laboratories.

CADO 3 defined a prioritised portfolio of new adult ARV products. See table 1. This product portfolio will be updated on a regular basis, like the PADO list, as new information is made available on existing products or on new products.

Other lower priority products might be considered if data suggests superiority to existing products.

References

1. Vitoria et al. The transition to dolutegravir and other new antiretrovirals in low- and middle- income countries – what are the issues? AIDS, Publish ahead of print 9 May 2018. DOI: 10.1097/QAD.0000000000001845
   https://journals.lww.com/aidsonline/Abstract/publishahead/The_transition_to_dolutegravir_and_other_new.97225.aspx
2. WHO. Third conference on antiretroviral drug optimisation (CADO 3): summary meeting report, 29 November to 1 December 2017, Rosebank Crowne Plaza, Johannesburg, South Africa.
   http://apps.who.int/iris/bitstream/handle/10665/272291/WHO-CDS-HIV-18.6-eng.pdf (PDF)

Generic manufacturers from South Africa and South Korea join Medicine Patent Pool (MPP)

Simon Collins, HIV i-Base

On 2 May 2018, the Medicines Patent Pool (MPP) announced that five new generic manufacturers will sign sublicensing agreements with the organisation.

This includes the first companies from South Africa (Adcock Ingram) and from South Korea (Celltrion), along with Langhua Pharma from China, and Mangalam Drugs & Organics and Arene Lifesciences from India.

These new companies were signed to produce formulations of dolutegravir, which is now recommended by WHO as an alternative first-line option.

Generic versions of DTG manufactured under MPP sublicences will soon reach people with HIV living in low- and middle-income countries (LMICs). The US FDA has already granted tentative approval Cipla's dolutegravir and Mylan's fixed dose combination of dolutegravir/lamivudine/TDF (TLD), as well as a combination of dolutegravir/emtricitabine/TAF.

There are now 25 companies working with the MPP to manufacture low-cost, quality-assured treatments for developing countries. In total, the MPP's generic manufacturing network is managing 130 development projects to manufacture, register and deliver 13 antiretrovirals, as well as hepatitis C and tuberculosis treatments.

The MPP was founded and is funded by Unitaid.

Reference

MPP press statement. The Medicines Patent Pool adds new suppliers from South Africa and South Korea to its growing generic manufacturing network. (02 May 2018)

https://medicinespatentpool.org/mpp-media-post/the-medicines-patent-pool-adds-new-suppliers-from-south-africa-and-south-korea-to-its-growing-generic-manufacturing-network/

WHO releases first list for essential diagnostics

Simon Collins, HIV i-Base

On 15 May 2018 the WHO published its first Essential Diagnostics List. This included the tests needed to identify the most common conditions and a number of global priority diseases.

Currently many people are unable to access essential tests leading to inappropriate or no treatment, including for HIV and tuberculosis.

The new WHO resource aims to complement the WHO Essential Medicines List that has been in use for four decades.

The Essential Diagnostics List specifies the test type and intended use, and whether it's appropriate for primary healthcare. When available, the document links to WHO Guidelines or publications and to prequalified products.

The list include 113 products, 58 tests of which are for a wide range of common conditions. The remaining 55 are for detection, diagnosis and monitoring of priority diseases including HIV, syphilis, tuberculosis, malaria, hepatitis B and C and human papillomavirus.

This includes 3rd and 4th generation HIV tests, viral load, CD4 and cryptococcal antigen (for advanced HIV).

The list will be updated annually and is also expected to expand to include neglected tropical diseases and antimicrobial resistance.

Reference

WHO. World Health Organization Model List of Essential In Vitro Diagnostics First edition (2018)

http://www.who.int/medical_devices/diagnostics/WHO_EDL_2018.pdf (PDF)

See also the WHO press release:

http://www.who.int/news-room/detail/15-05-2018-first-ever-who-list-of-essential-diagnostic-tests-to-improve-diagnosis-and-treatment-outcomes

PREGNANCY

Dolutegravir in pregnancy: early data reassuring but ongoing surveillance is still essential

Polly Clayden, HIV i-Base

A recent systematic review of dolutegravir (DTG) in HIV positive pregnant women did not show evidence for increased risks of stillbirth, preterm birth, small for gestational age or congenital anomalies, compared to historical control studies of antiretroviral-treated pregnant women.

Although these results are reassuring, the authors of the review, published in the Journal of Virus Eradication, April 2018, stress that continued pharmacovigilance is essential as up to 15 million people could be receiving antiretroviral treatment with DTG over the next five years and among these a substantial proportion will be women of child-bearing potential.

In many countries with large HIV epidemics, unplanned pregnancies are common and access to both contraceptive services and antenatal clinic facilities may be limited.

The authors included six databases in this analysis, with a total of 1200 pregnant women. The percentage of pregnant women taking DTG with adverse birth outcomes and congenital abnormalities was similar to results from historical control studies of HIV positive women.

But, there was significant heterogeneity across the six databases: percentage of infants with congenital anomalies ranged from 0.0% in Botswana (0/116 infants) to 13.3% in IMPAACT P1026s (2/15 infants).

The authors also noted that there are insufficient data yet recorded for mothers treated with DTG pre-conception.

COMMENT

None of the studies included in this analysis was a randomised clinical trial comparing outcomes for women taking DTG compared with other antiretrovirals in pregnancy.

A number of randomised trials of DTG have been conducted over the past five years, but (as usual) pregnant women have been excluded.

There are also no robust systems in place to collect and review observational data broadly across countries and settings.

Several investigator-led studies now are underway but results will not be available until 2019–2020.

It is hard to think of new ways to say that pregnant women should be included earlier in clinical trials of investigational drugs. Currently decisions about the safety and efficacy of new antiretrovirals in pregnancy are informed by non-randomised studies and observational cohorts, which could be prone to bias.

In the case of DTG, its rapid introduction to countries with many women of child bearing potential, is thus informed.

Reference

Hill A et al. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. Journal of Virus Eradication. April 2018.

http://viruseradication.com/journal-details/Safety_and_pharmacokinetics_of_dolutegravir_in_HIV-positive_pregnant_women:_a_systematic_review/

PAEDIATRIC CARE

FDA guidance for developing paediatric ARVs: online for comment

Polly Clayden, HIV i-Base

The US Food and Drug Administration (FDA) has published draft guidance on the development of products for treatment of HIV in paediatrics (birth to younger than 17 years of age).

The guidance includes recommendations for sponsors on when to start paediatric formulation development and begin paediatric studies to evaluate new antiretrovirals for the treatment of HIV.

The draft recommendations are summarised as follows:

- As dosing recommendations for antiretrovirals have consistently been the same for adults and adolescents (12–17 years old), sponsors should include adolescents in phase 3 trials, or should conduct a separate adolescent study in parallel with the adult phase 3 trials.
- Paediatric formulation development should begin as soon as the adult dose is selected – based on results from the phase 2 trial(s).
- For infants and children age 4 weeks to less than 12 years, sponsors should enrol cohorts within clinical studies in parallel rather than in sequence, unless a drug has a specific safety or drug disposition factor that requires a different approach. Sponsors can use pharmacokinetic (PK) modelling using the adult and adolescent data for initial dose selection to start parallel enrolment of cohorts across the different weight bands.
- Cohort enrolment and dose selection during the clinical studies in infants and children should be based on weight rather than age. The selected weight-bands should align with those predefined by the WHO.
- Approval of a new paediatric formulation (eg granules instead of solution), when safety and PK in children have already been studied using a previously approved formulation, may be supported by a bioavailability/bioequivalence study in adults that show that bioavailability of the two formulations is comparable. If it is not comparable, one or more of the following may be needed to support approval: dose adjustments, scientific rationale to support the difference in bioavailability, or an additional trial. Alternatively, additional work for the development of different formulations might be needed.
- FDA encourages sponsors to have early discussions with WHO, NGOs, FDA and others on their development plans for paediatrics to meet the needs of infants, children and adolescents with HIV eg selection of formulation, strengths and dosage of a drug.

The FDA invites the submission of either electronic or written comments on the draft guidance by 13 July 2018, before it begins work on the final version.

C O M M E N T

These recommendations are excellent – notably the alignment with WHO requirements and parallel rather than sequential cohorts.

Reference

Pediatric HIV infection: drug development for treatment. Guidance for industry. 14 May 2018.

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm607416.pdf (PDF)_

COMPLICATIONS

US Study tracks kidney transplant results from HIV positive donors

Simon Collins, HIV i-Base

On 8 May 2018, the US NIH issued a press release to highlight the start of a new transplant study to HIV positive recipients that includes using HIV positive donor organs. [1, 2]

The HOPE in Action Multicenter Kidney Study is an open label study of 160 kidney transplants at 16 transplant centres. All transplant recipients will be HIV positive and half will be paired with HIV positive donors and half with HIV negative donors as a control group.

This is not a blinded study and all participants will know the HIV status of the organ donor.

This is the first US study to study HIV positive donors transplants and is only made possible after the HOPE (HIV Organ Policy Equity) Act of 2013 removed the previous ban on HIV positive donors (even if all parties consented).

Further details are included in the clinical trials register, while strangely lists the study to include 360 participants. [3]

References

1. NIH Press release. NIH Clinical Trial to Track Outcomes of Kidney Transplantation from HIV-Positive Donors to HIV-Positive Recipients. (08 May 2018).
   https://www.hiv.gov/blog/nih-clinical-trial-track-outcomes-kidney-transplantation-hiv-positive-donors-hiv-positive
2. NIH grants. HOPE in Action: A clinical trial of HIV-to-HIV deceased donor kidney transplantation.
   http://grantome.com/grant/NIH/U01-AI134591-01
3. ClinicalTrials.gov listing. HOPE in Action prospective multicenter, clinical trial of deceased HIVD+ kidney transplants for HIV+ recipients. NCT03500315.
   https://clinicaltrials.gov/ct2/show/NCT03500315

OTHER NEWS

Campaign forces Government U-turn on sharing NHS data with immigration service

Simon Collins, HIV i-Base

On 9 May the UK government announced that it would suspend NHS Digital (responsible for collecting patient data) from routinely sharing individual patient data with UK immigration services. This reversal by the government is a significant success for public health. [1, 2]

The decision was made during a parliamentary debate on the Data Protection Bill, by accepting an amendment tabled by Dr Sarah Wollaston MP, Chair of the Health and Social Care Committee.

Organisations leading the campaign against this policy since 2014 include the National AIDS Trust (NAT), BHIVA, BMA, Doctors of the World (UK) and Liberty.

In an NAT press release, Deborah Gold, Chief Executive said: "We are delighted that at last this shameful sharing of confidential patient information with the Home Office is to end. Not only did it breach every bit of guidance on confidentiality within the NHS, it also deterred people from essential healthcare putting both individual and public health at risk".

The change in the memorandum of understanding that previously required the NHS to data share confidential records takes immediate effect. However, data-sharing will still be allowed in cases where Home Office are considering deportation due to a serious crime (further details were not provided).

According to an earlier report, Department of Health figures for 2016 showed the Home Office requested medical records for 8127 patients, leading to 5,854 people being traced by immigration enforcement. [3]

C O M M E N T

The successful campaign to overturn government policy is a significant achievement. Further background was reported in an article in the previous issue of HTB. [4]

The policy has been a community activist focus for many years and was highlighted again at the recent BHIVA conference.

In the panel discussion after an excellent presentation on disparity of health care experienced by refugee and migrant populations faced by migrants in the UK, Yusef Asad, Directory of Strategy at NAT, included a case of immigration officials waiting at the hospital for a mother to give birth, so that both the mother and baby could be immediately arrested. Other examples included the common reports of women avoiding maternity care and giving birth at home due to fear of the immigration service. [5]

It is vitally important that sexual health services continue to be free, including for HIV, and that access should not be undermined by hostile government policies.

References

1, NAT press statement. NHS Digital to end data sharing with the Home Office on immigration offences. (09 May 2018).
https://www.nat.org.uk/press-release/nhs-digital-end-data-sharing-home-office-immigration-offences
2. Doctors of the World statement. Government will halt NHS datasharing with home office except for serious crime. (09 May 2018).
https://www.doctorsoftheworld.org.uk/news/government-will-halt-nhs-data-sharing-with-home-office-except-for-serious-crime
3. The Guardian. NHS hands over patient records to Home Office for immigration crackdown.
https://www.theguardian.com/uk-news/2017/jan/24/nhs-hands-over-patient-records-to-home-office-for-immigration-crackdown
4. Trevelion R. Continued demands to stop NHS Digital linking medical records to deportation service. HTB 01 May 2018.
http://i-base.info/htb/34026
5. Asad Y. Refugees, migrants and healthcare access: key issues in the response to HIV, STIs and TB. BHIVA invited lecture 4. 4th Joint BHIVA/BASHH, 17-20 April 2018, Edinburgh.
http://www.bhiva.org/documents/Conferences/2018Edinburgh/Presentations/180420/YusefAzad.pdf (PDF)
http://www.bhiva.org/180420-BHIVA-BASHH-Invited-Lecture-4.aspx (webcast)

St Stephen's AIDS Trust to close after 30 years of HIV research

Simon Collins, HIV i-Base

On 9 May 2018, several short announcements about the ongoing PrEP IMPACT study, reported that St Stephen's AIDS Trust (SSAT) and the linked St Stephen's Clinical Research (SSCR) unit are planning to close.

This is very disappointing news as SSAT/SSCR is one of the most established UK HIV research units, working closely with the Chelsea and Westminster Hospital and the Kobler Centre, Europe's largest HIV clinic. The charity has been a leading centre of independent academic research for more than 30 years and has been a clinical site involved in the development of every new HIV drug.

Limited details have been released about the reasons for the closure, although recent changes in leadership suggest that the organisation was experiencing financial difficulties. The operating loss for 2015/16 was relatively small given the size of the project, employing approximately 50 staff.

Management for the ongoing PrEP study will transfer to the Chelsea and Westminster Hospital NHS Foundation Trust on 1 June, according to statements from both BHIVA and the IMPACT study. This will not affect the daily running of the study. [1, 2]

The implications for other ongoing research have not been reported and the SSAT website does not yet include a formal statement of news on the planned closure. [3]

References

1. PrEP IMPACT Trial website. Update - Closure of St Stephen's AIDS Trust, (10 May 2018).
https://www.prepimpacttrial.org.uk/update-closure-of-ssat
2. BHIVA announcement to members. St Stephen's AIDS Trust (SSAT) and St Stephen's Clinical Research (SSCR).(09 May 2018).
3. SSAT website.
http://www.ssat.org.uk/index.html

ON THE WEB

New online animation of HIV lifecycle

Simon Collins, HIV i-Base

A new six-minute, easy to watch, animation of the HIV lifecycle is now online, produced by Janet Iwasa from the University of Utah. [1]

Together with a narrative, the film presents details that are not usually included in simplified summaries.

- After entry into the cell, the capsid travels towards the nucleus using a network of micro tubules as a highway system.
- Reverse transcriptase is shown as largely being active within the capsid, rather than in the cytoplasm. (Whether the capsid dissolves before or at the time of integration into the nucleus has been a controversial issue at previous CROI meetings, with work in the UK by Greg Towers and colleagues suggesting it is a late event and the nucleotides to enable reverse transcription are imported into the capsid through pores. [2, 3]
- That multiple RTs work simultaneously to create the double-strand DNA copy of the HIV RNA genome.
- Multiple outcomes for new viral RNA after leaving the nucleus.
- Details of the budding of new virions from the cells using a lattice of multiple gag proteins and recruitment of numerous other proteins, including final ESCRT-III proteins.
- That protease is only apparently active in chopping and reassembling new viral particles after the virion has budded from the cell.
- Similarly, the new capsid is also shown as only forming after budding of the new virions, as a final process of becoming newly mature virus, ready to repeat the cycle with new CD4 host cells.

This animation was first previewed at CROI 2018 as part of the young investigator pre-meeting. which includes a useful discussion. [4]

Further animations are planned to show the impact of different classes of ART.

References

1. Iwasa J. The HIV lifecycle. Online animation. http://scienceofhiv.org/wp/?page_id=20
2. Jacques DA et al. HIV-1 uses dynamic capsid pores to import nucleotides and fuel encapsidated DNA synthesis. Nature volume 536, pages 349–353 (18 August 2016). doi:10.1038/nature19098. http://www.nature.com/articles/nature19098
3. Mamed JI et al. Early cytoplasmic uncoating is necessary for infectivity of HIV-1.CROI 2017, 13–16 February 2017, Seattle. Oral abstract 15. http://www.croiconference.org/sessions/early-cytoplasmic-uncoating-necessary-infectivity-hiv-1 (abstract) http://www.croiwebcasts.org/console/player/33354 (webcast)
4. Iwasa J. Seeing HIV: animating the HIV lifecycle. Program committee workshop for new investigators and trainees. CROI 2018 Abstract 14. http://www.croiwebcasts.org/console/player/37002 (webcast)

FUTURE MEETINGS

Conference listing 2018/19

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

International Workshop on Clinical Pharmacology of Antiviral Therapy 2018

22–24 May 2018, Washington

www.virology-education.com

12th INTEREST

29 May – 1 June 2018, Kigali

interestworkshop.org

10th HIV Paediatrics Workshop

20 – 21 July 2018, Amsterdam

www.virology-education.com

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 (Dec 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 online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK.

http://i-base.info/order

21 May 2018 • **Vol 19 No 9**

Fax-back orders and subscriptions

107 The Maltings,169 Tower Bridge Road, London, SE1 3LJ
Tel: +44 (0) 20 8616 2210 Fax: +44 (0) 20 8616 1250

Please use this form to amend subscription details for HIV Treatment Bulletin and to order single or bulk copies of publications. Publications are available free, but please contact i-Base if you would like to make a donation.

Name _____ **Position** _____

Organisation _____

Address _____

_____

Telephone _____ **Fax** _____

e-mail _____

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

- **HIV Treatment Bulletin (HTB) every two months** ☐ **by e-mail**

- **Pocket leaflets** - *A7 small concertina-folded leaflets (2017)*

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

- **Booklets about HIV treatment**

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

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

UK Guide To PrEP *(November 2016): 24-page A5 booklet* **quantity** _____

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

HIV and quality of life: guide to 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 *(Jan 2018): 24-page A5 booklet* **quantity** _____

- **Other resources**

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

Phoneline *posters (A4)* **quantity** _____

Please fax this form back, post to the above address, or email a request to HIV i-Base:

020 8616 1250 (fax) subscriptions@i-Base.org.uk