ISSN 1472-4863

hiv treatment bulletin (e)

htb(e): 2018 vol 19 no 15

19 September 2018

CONTENTS

EDITORIAL 2

SUPPLEMENTS 2

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

i-BASE APPEAL 3

- i-Base funding appeal 2018

SPECIAL REPORT 3

- HIV diagnoses in UK drop for third year: among all ages, risk groups, and ethnicities and across most UK regions

CONFERENCE REPORTS 8

22nd International AIDS Conference (AIDS 2018), 23 – 27 July 2018, Amsterdam

- Introduction
- Dolutegravir twice daily is effective and tolerable with rifampicin: 48 week results from the INSPIRING study
- TAF exposures during pregnancy and postpartum appear adequate but more data are needed
- High rate of unintended pregnancy among HIV positive African women on ART

ANTIRETROVIRALS 15

- English court finds in favour of access to generic TDF/FTC
- FDA approves doravirine (Pifeltro) and new FDC with TDF/3TC (Delstrigo) in the US
- FDA update labels for dolutegravir and dolutegravir-based FDCs to reflect potential risk of neural tube defects

ON THE WEB 20

- Alcohol and HIV: new issue of RITA

EDITORIAL

This issue of HTB leads with impressive and optimistic results from the UK HIV surveillance programme coordinated by Public Health England.

In 2017, HIV diagnoses fell for the second year across all key demographic groups, including by gender, sexuality, race, age and geographic region. The report launch was out of step though with current prevention strategies by still emphasising condom use over TasP and PrEP.

We continue with reports from the AIDS 2018 conference. These include twice-daily dolutegravir to overcome interactions with rifampicin, early TAF data in pregnancy and higher rates of unintended pregnancies in African women on ART.

Stop-press ARV news is that generic PrEP can now be used by NHS England. Doravirine has been approved in the US, also in an FDC and FDA label updates for dolutegravir.

Plus On The Web features the new RITA issue on alcohol and HIV.

SUPPLEMENTS

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

i-Base has produced a new series of posters, postcards and leaflets to help raise awareness about U=U in clincs.

This project was developed with the Kobler Centre in London.

As with all i-Base material, these resources are all free to UK clinics. Please order by email or fax. email: subscriptions@i-base.org.uk Fax: 0208 616 1250

Subscriptions

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

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

i-Base 2018 appeal

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.

All help is appreciated.

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

SPECIAL REPORT

HIV diagnoses in UK drop for third year: among all ages, risk groups, and ethnicities and across most UK regions

Simon Collins, HIV i-Base

Preliminary data, press-released by Public Health England (PHE) on 4 September (ahead of the full report due in December), show that HIV diagnoses dropped by 17% in 2017 compared to 2016. [1]

The accompanying press release notes that this is the second year that overall diagnoses have fallen by such a significant amount, although this is technically the third year of reductions. [2]

Crucially, the latest data show a consistent trend for lower numbers of HIV diagnoses across all demographics, and for many groups these have continued for two or three years.

In the last year, figures have reduced for all major risk groups, including gay men, heterosexual men and women, and people who inject drugs. With few exceptions, this trend is also seen across all age groups, for all ethnicities and in all geographic regions of the UK. See Table 1 for selected results.

Overall, HIV diagnoses fell by 17% last year and by 13% the year before, with 4363 people diagnosed during 2017 compared to 6043 in 2015.

These results are remarkable. This is the first time in context of modern ART, that HIV figure dropped so significantly. It is in the context of the lack of impact of HIV prevention

campaigns for the previous 15 years since 2000.

The summary report highlights the reductions in gay men as being a drive behind the size of the reductions. From 2008 to 2014 diagnoses in gay and bisexual men had been increasing every year. Since 2015, diagnoses in London clinics dropped by 44% and outside London by 28%.

As with the reductions reported last year, although driven by the drop in gay and bisexual men in London, it is notable that similar percentage drops occurred across the UK, and in other risk groups.

HIV diagnoses dropped by 24% in London, 14% in the Midlands and East England, 12% in the North of England, 21% in the South of England, 20% in Wales and 20% in Scotland. In Northern Ireland, although numbers are relatively low, diagnoses increased by 9% (from 76 to 83).

The changes since 2015 are likely to reflect multifactorial changes in HIV treatment and prevention.

- The move to more frequent routine testing (1-3 monthly, rather than annually) in higher risk groups.
- Easier access to modern sexual health clinics - including walk-in and out-of-hours services.
- Availability of rapid testing, including home testing (for example in the SELPHI study).
- Earlier use of ART, including during primary HIV infection and especially since the START study results in 2015.
- Better and more effective ART, that allow easier adherence, fewer side effects, and quicker and more durable viral suppression.
- Growing acceptance of the impact of having an undetectable viral load on stopping HIV transmission.
- Increasing use of PrEP among gay men at highest risk. This was from the PROUD study but more significantly from buying PrEP online as a result of community awareness campaigns.

Other notable results include:

- Significant reductions in diagnoses in young people, reduced by 32% and 35% for ages 18-24 and 25-34 respectively, comparing over two years from 2015 - 2017.
- 17% reduction in HIV-related deaths in 2017 and 35% reductions compared to 2014.

- 22% reduction in numbers of people diagnosed with a proximal CD4 <350 in 2017 and 39% reduction compared to 2014. This last point is complicated however by the lack of change in the overall percentage of late diagnoses each year. This figure varies by risk group (roughly 31% for gay men, and 50-60% for heterosexual men and women, and when injection drug use is the risk factor). These percentages have not changed.

For detailed breakdowns by gender, age, ethnicity, risk group, geographic region and CD4 count please refer to the full data tables.

Table 1: Selected results on HIV diagnoses, and percentage reductions from previous year (PHE data to end 2017)

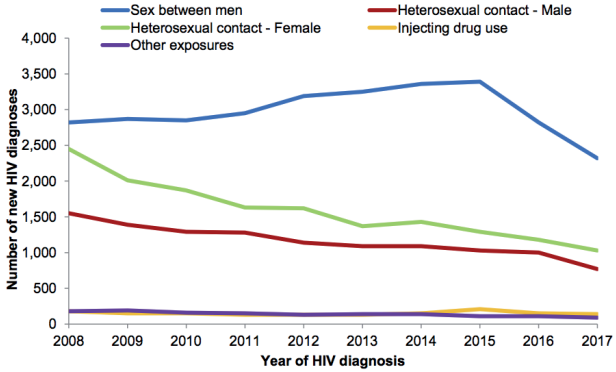
	2014	2015	2016	2017
Total diagnoses	6185	6043 (–3%)	5280 (–13%)	4363 (–17%)
Gay men	3360	3390 (NS)	2820 (–17%)	2330 (–17%)
Heterosexual women	1440	1310 (–10%)	1190 (–10%)	1040 (–13%)
Heterosexual men	1090	1030 (NS)	1000 (NS)	770 (–23%)
PWID	150	210 (+40%)	150 (–29%)	140 (–7%)
16-24 yo	732	734 (NS)	534 (–28%)	502 (–6%)
25-34 yo	2051	2031 (NS)	1616 (–21%)	1326 (–18%)
>65 yo	210	162 (–23%)	190 (+17%)	145 (–24%)
AIDS at diagnosis	281	335 (+19%)	279 (–17%)	230 (–18%)

deaths	650	527 (–19%)	513 (–3%)	428 (–17%)
<350*	5060	4742 (–7%)	3980 (–17%)	3118 (–22%)

* Although numbers for late diagnosis has consistently fallen, the annual percentages of diagnoses that are late is unchanged: ranging from ~31% in gay men, 50-60% in heterosexuals and 50% in people who inject drugs.

NS = no significant change from previous year.

Figure 1. New HIV diagnoses by year of diagnosis and probable exposure route: UK, 2008-2017 *



Adjusted for missing route of exposure

C O M M E N T

The UK surveillance data is an essential project and the team should be congratulated for their consistently impressive work. As a result, the UK has one of the most timely and comprehensive HIV surveillance datasets that has been reporting detailed demographics on HIV incidence for more that 25 years.

It is therefore unfortunate that the strengths of the data are misrepresented by the narrative in the accompanying report and press release.

The press release issued by PHE continues to refer to condom as the only prevention

option, ignoring the importance of both treatment as prevention and PrEP, which are both significantly more effective than condoms at preventing HIV.

The quote from Professor Noel Gill as Head of the STI and HIV Department at Public Health England, referring only "to consistent and correct condom use" does not reflect the reality of modern HIV prevention strategies.

The press release and summary report – the primary source for mainstream news reports – both show little enthusiasm for the impact of PrEP, despite community estimates that more than 8000 gay men were likely to be using online PrEP by the end of 2017.

Instead the report defers to the ongoing IMPACT study (being coordinated by PHE) as the future indicator for judging PrEP efficacy. The report doesn't acknowledge that many IMPACT study participants are likely to have been previously buying PrEP online. This change in access to PrEP rather than expansion to new PrEP users, by definition, will limit the ability of the IMPACT study to be a marker for the true impact of PrEP HIV incidence since 2017: many people who were already using PrEP are just continuing to use it in the study.

Finally, the report closes with an unhelpful sentence that ignores the scientific consensus that an undetectable viral load prevents HIV transmission. Instead, this PHE document ends with a reference to risk being "very unlikely".

This language is both outdated and unhelpful, and it is out of place in a public report that should be rooted in both the latest evidence and PHE's own otherwise excellent data.

The evidence for U=U is now clear and accepted and like other national and international public health agencies, PHE should now clearly and consistently support this in its publications.

References

1, PHE. Trends in new HIV diagnoses and people receiving HIV-related care in the United Kingdom: data to the end of December 2017. Health Protection Report Volume 12 Number 32. PHE gateway number: 2018392. September 2018.
https://www.gov.uk/government/statistics/hiv-annual-data-tables

2. PHE press release. New HIV diagnoses across the UK fell by 17% in 2017. (04 September 2018)
https://www.gov.uk/government/news/new-hiv-diagnoses-across-the-uk-fell-by-17-per-cent-in-2017

CONFERENCE REPORTS

22nd International AIDS Conference (AIDS 2018)

23 – 27 July 2018, Amsterdam

Introduction

The 22nd International AIDS Conference (AIDS 2018) was held this year from 23–27 July in Amsterdam.

Several thousand studies were presented as oral lectures or exhibited as posters over four days – so all reports touch on a minority of the research and activity – but much of the conference is also available online.

- Abstracts are online using a searchable database for the conference programme. http://programme.aids2018.org
- Clicking on a search result opens a separate window, either for the abstract or the session in which it was presented.
- Slides are available for most oral presentations and plenary lectures.
- Webcasts are available for many oral presentations (using the "video" link in the session window).
- Posters are available for many abstracts (using a PDF download link at the bottom of the abstract window).
- Oral abstracts are also available online and as a PDF supplement to JIAS. https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25148

Reports included in this issue of HTB.

- Dolutegravir twice daily is effective and tolerable with rifampicin: 48 week results from the INSPIRING study
- TAF exposures during pregnancy and postpartum appear adequate but more data are needed
- High rate of unintended pregnancy among HIV positive African women on ART

AIDS 2018: TB COINFECTION

Dolutegravir twice daily is effective and tolerable with rifampicin: 48 week results from the INSPIRING study

Polly Clayden, HIV i-Base

Dolutegravir (DTG) 50 mg twice daily is safe and effective in HIV/TB co-infected adults receiving rifampicin-based TB treatment – according data presented at AIDS 2018. [1]

INSPIRING was a phase 3b, non-comparative, active control, randomised, open-label study in HIV positive ART-naive adults with drug-sensitive TB.

Preliminary week 24 data were presented earlier this year at CROI 2018. [2, 3]

Kelly Dooley from Johns Hopkins University School of Medicine presented the primary week 48 results on behalf of the INSPIRING investigators.

Participants receiving rifampicin-based TB treatment for at least eight weeks were randomised (3:2) to receive either DTG 50 mg twice daily during and two weeks post-TB treatment, followed by 50 mg once daily; or efavirenz (EFV) 600 mg once daily; both with two NRTIs (tenofovir DF with either FTC or 3TC) for 52 weeks.

The primary endpoint was the proportion of participants in the DTG arm with viral load <50 copies/mL using the modified FDA Snapshot algorithm in the ITT-E population. The study was not powered for non-inferiority.

INSPIRING enrolled 113 participants across 37 sites in low- and middle-income countries; 65 participants were from South Africa. Full enrollment took almost two years.

Participants were randomised to DTG (n=69) or EFV (n=44). Median age was 32.5 years, approximately 60% were men and 67% of African origin. Baseline CD4 was just above 200 cells/mm^3 and viral load just above 5 log copies/mL. The majority had pulmonary TB and the median time from start of TB treatment was approximately 30 days.

The proportions of week 48 responders (ITT-E) were 52/69, 75% (95% CI: 65 to 86%) for DTG and 36/44, 82% (95% CI: 70 to 93%) for EFV.

Non-response in the DTG arm among 11 participants (16%) was mainly due to non-treatment-related discontinuations while suppressed (mostly lost to follow up).

Week 48 median CD4 increase in the DTG arm was 220 cells/mm^3 and 190 cells/mm^3 in the EFV arm. Two participants in the EFV arm discontinued due to AEs.

TB-associated IRIS rates were low (4 in each arm) but people with CD4 counts <50 cells/mm^3 at baseline were excluded from the study.

Median DTG trough concentration during twice-daily dosing with rifampicin was similar to that of once-daily DTG 50 mg without rifampicin. TB treatment success was high, approximately 90% in both arms.

C O M M E N T

The DTG label already recommends twice-daily dosing with rifampicin, based on a previous drug-drug interaction study in HIV negative participants. [4] WHO also recommends this approach. [5]

A recent PK study looking at DTG 100 mg and 50 mg once daily in the presence or absence of rifampicin found that rifampicin reduced DTG C24h by 76% and 85% respectively compared with DTG 50 mg alone. [6]

In this study, the maximum induction of rifampicin was reached at three weeks and drug absorption reached saturation limit in the range of 50–100 mg DTG (rifampicin 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).

Whether DTG 100 mg once daily + rifampicin will be safe and effective in people with HIV/TB coinfection currently is unclear.

The study 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. Dooley K et al. Safety and efficacy of dolutegravir-based ART in TB/HIV co-infected adults at week 48. AIDS 2018. Amsterdam. 23–27 July 2018. Oral abstract TUAB0206.
   http://programme.aids2018.org/Abstract/Abstract/6122 (abstract)
   https://www.youtube.com/watch?v=7XQjSgZKyyY (webcast)
2. Dooley K et al. Safety and efficacy of dolutegravir-based art in TB/HIV coinfected adults at week 24. 25th CROI. Boston. 4–7 March 2018. Oral abstract 33.
   http://www.croiconference.org/sessions/safety-and-efficacy-dolutegravir-based-art-tbhiv-coinfected-adults-week-24 (abstract)
   http://www.croiwebcasts.org/console/player/37073 (webcast)
3. Clayden P. Twice-daily dolutegravir is effective and tolerable with rifampicin. HTB. 14 March 2018.
   http://i-base.info/htb/33644

4. Dooley K et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):21-7.
https://journals.lww.com/jaids/Abstract/2013/01010/Safety,_Tolerability,_and_Pharmacokinetics_of_the.4.aspx
5. WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance – policy brief. (23 July 2018).
http://apps.who.int/iris/bitstream/handle/10665/273632/WHO-CDS-HIV-18.18-eng.pdf
6. 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)

AIDS 2018: PREGNANCY

TAF exposures during pregnancy and postpartum appear adequate but more data are needed

Polly Clayden, HIV i-Base

Plasma tenofovir alafenamide (TAF) exposures during pregnancy were within the typical range of those in non-pregnant adults but higher than expected postpartum when dosed at 25 mg – according to data from IMPAACT P1026s presented at AIDS 2018.

TAF is a prodrug of tenofovir, manufactured by Gilead, the originator company, as part of a fixed dose combination either with or without the pharmacokinetic (PK) booster cobicistat (COBI). TAF is given at a dose of 25 mg unboosted and 10 mg when boosted with 150 mg COBI.

IMPAACT P1026s is an ongoing, non-randomised, open-label, multi-centre, phase 4 study conducted to characterise antiretroviral PK in HIV positive pregnant women. Those eligible to enroll in the TAF arms were receiving the drug as part of routine clinical care at an IMPAACT site. Mark Mirochnick presented findings from this evaluation of TAF administered with or without COBI on behalf of the study group.

The investigators obtained intensive steady state PK profiles of TAF following once-daily dosing of either rilpivirine/emtricitabine/TAF (R/F/TAF) 25/200/25 mg or elvitegravir/COBI/emtricitabine/TAF (E/C/F/TAF) 150/150/200/10 mg during the second and third trimesters and 6–12 weeks postpartum. Maternal plasma and cord blood samples were collected at delivery

Target TAF exposure was assessed relative to the 10th percentile value in non-pregnant adults.

There were 31 participants enrolled in the TAF 25 mg and 27 in the TAF/COBI 10/150 mg arms. All women were from the US. Their median age at delivery was approximately 32 years. Postpartum sampling was performed at a median of approximately 9 weeks.

Plasma TAF exposures during pregnancy and postpartum were in the range of those observed in non-pregnant adults.

TAF exposure with 25 mg was lower during pregnancy compared with postpartum but Professor Mirochnick explained that this difference was driven by higher than expected AUC postpartum. See Table 1.

Table 1: GMR second and third trimesters/postpartum

	GMR (90% CI) second trimester/ postpartum	GMR (90% CI) third trimester/postpartum
TAF 25 mg	n=14	n=25
AUC0-t (ng*hr/mL)	0.57 (0.34 to 0.98)	0.66 (0.54 to 0.82)
TAF/COBI 10/150 mg	n=14	n=22
AUC0-t (ng*hr/mL)	0.79 (0.50 to 1.27)	0.86 (0.66 to 1.12)

The proportion of participants exceeding the TAF target AUC ranged from 84 to 96% without differences during pregnancy and postpartum.

One grade 2 maternal adverse event (probable hepatic steatosis) was considered to be possibly related to study drug.

Congenital anomalies considered possibly related to study drugs included left congenital pseudoarthrosis clavicle in one infant and renal cyst in another.

At the time of analysis 46 infants were HIV negative, 8 indeterminate and 4 pending.

Analyses of all maternal delivery samples, cord blood samples and infant washout samples are not yet complete but TAF was below the limit of quantification (3.95 ng/mL) in all 15 cord blood samples tested to date.

This group are planning to look at intracellular levels of TAF in pregnancy and postpartum.

C O M M E N T

These are the first publicly presented data on TAF in pregnancy.

TAF 25 mg is considered to be a potential component of optimised ART for low- and middle-income countries. But lack of data in populations who are treated in these settings, including pregnant women, has meant that it has not been recommended in WHO guidelines or included in the Essential Medicines List.

Before TAF can be recommended for use in pregnancy additional safety and outcome data from larger numbers of women and their infants (including preconception exposure) as well as intracellular PK data are needed.

Reference

Momper JD et al. Tenofovir alafenamide pharmacokinetics with and without cobicistat in pregnancy. AIDS 2018. Amsterdam. 23–27 July 2018. Oral abstract THAB0302.

http://programme.aids2018.org/Abstract/Abstract/5960 (abstract)

https://www.youtube.com/watch?v=djY2rjG_F-c (webcast)

High rate of unintended pregnancy among HIV positive African women on ART

Polly Clayden, HIV i-Base

Unintended pregnancy is widespread among HIV positive African women and about 90% of these pregnancies are attributed to non-use of effective family planning methods. Long acting reversible contraceptives are acceptable – although under used. These findings from the US-PEPFAR PROMOTE cohort study were presented at AIDS 2018.

More than 90% of global reproductive health need is in sub-Saharan Africa: women of reproductive potential make up more than 60% of people with HIV and several countries have over 60% unmet need for modern family planning methods.

Over 85% of unintended pregnancies are linked to non-use of effective family planning methods, defined as: injectable, oral, interuterine device (IUD), levonorgestrel-releasing implant or tubal ligation.

The most common reasons for not using effective family planning include infrequent sex, safety/side effects, postpartum/breastfeeding, partner opposition and access. These deficits could undermine global goals of improving women's health.

PROMOTE is an extension to the completed PROMISE trial. HIV positive women, receiving ART, and their children are recruited from the eight highest enrolling sites in Malawi, South Africa, Uganda, and Zimbabwe. Follow up is until 2021 – the findings presented were from baseline data among women enrolled between December 2016 to June 2017. The study used standardised questionnaires to collect demographic and reproductive health data.

There was a very high frequency of unintended pregnancies in this cohort. Among 1,985 women included in the analysis, 49.9% overall reported that their last pregnancy was not intended. This proportion ranged from 28.7% in Kampala, Uganda to 81.9% in Durban, South Africa (p<0.001).

Injectables were the commonest method of contraception (40.6%) – especially at the South African sites (56.1%) – followed by condoms (19.3%) and implants (15.7%). Zimbabwe was different from the other countries with oral contraceptives being the most common (44.1%), followed by injectables (21.2%).

Overall 79.9% of sexually active women reported using effective family planning methods. But only 18.8% reported using long acting reversible contraceptive methods (LARC: implants or IUD).

In multivariate analysis, women with no formal employment (p = 0.008), those receiving ART (p=0.001), and those with a viral load >1000 copies/mL (p=0.003) were less likely to report LARC use. Age, marital status, desiring more children, clinic travel time, and household electricity were not associated with contraceptive choice.

Adjusted RR estimates for baseline correlates showed women who desired another child, aRR.0.92 (95% CI 0.87 to 0.99), p=0.017; those who had no sex in the last three months, aRR 0.81 (95% CI 0.76 to 0.87), p<0.001; and those who had not completed primary education, aRR 0.92 (95% CI 0.85 to 0.99), p=0.03, were less likely to use effective family planning. But women with viral load <1000 copies/mL were more likely to use this, aRR 1.10 (95% CI 1.02 to 1.19), p=0.013.

Unintended pregnancy, marital status, no formal income, clinic travel time and household electricity were not associated with use of effective family planning.

Estimates for LARC use showed women with no formal income, aRR 0.66 (95% CI 0.48 to 0.91), p=0.011, were less likely to use it. But women with electricity in the household, aRR 1.33 (95% CI 1.01 to 1.76), p=0.04, and those with viral load <1000 copies/mL, aRR 1.64 (95% CI 1.20 to 2.23), p=0.002, were more likely to do so.

Unintended pregnancy, desire for another child, no sex in the last three months, marital status, completion of primary education and clinic travel time, were not associated with LARC use.

Future planned cohort analyses from PROMOTE include incidence and correlates of unintended pregnancy through 18 months follow up and an evaluation of interactions

between ART (efavirenz in particular) and hormonal contraception and risk of unintended pregnancies.

C O M M E N T

These data are sobering, particularly with the recent spotlight on the potential elevated risk of neural tube defects with preconception dolutegravir exposure and guidance recommending women use reliable and effective contraception with dolutegravir-based ART.

Reference

Aizire J et al. High frequency of unintended pregnancy and predictors of contraceptive choice among HIV-infected African women on life-long antiretroviral therapy (ART). The US-PEPFAR PROMOTE Cohort Study. AIDS 2018. Amsterdam. 23–27 July 2018. Oral abstract THAB0301.

http://programme.aids2018.org/Abstract/Abstract/7362 (abstract)

https://www.youtube.com/watch?v=djY2rjG_F-c (webcast)

ANTIRETROVIRALS

English court finds in favour of access to generic TDF/FTC

Simon Collins, HIV i-Base

On 19 September 2018, the English High Court issued a judgment over the challenge by four generic manufacturers to Gilead's application to extend the patent on TDF/FTC. [1]

This case was previously referred to the European courts reported in October 2017. [2, 3]

The details of the judgment are very difficult to understand, but the outcome appears to be that the NHS England are now legally able to buy generic TDF/FTC.

NHS Scotland have been using generic TDF/FTC since November 2017. [3]

C O M M E N T

Access to generic TDF/FTC will dramatically change earlier cost-effectiveness analyses that have so far restricted access to PrEP across the UK.

NHS England need to rapidly respond to this judgment in order to expand access to PrEP.

The only phrases that are easy to understand in the 12 page document are "in a nutshell" (though not the following sentence) and a reference to Gilead trying to "get a second bite of the cherry".

It does conclude that as tenofovir DF was approved in 2002, less than five years after filing the first patent, the company didn't suffer from any regulatory delay.

The final sentence appears to suggesting that perhaps the original patent for the dual formulation of TDF/FTC wasn't justified: "Gilead made no invention in devising the combination which warranted the grant of a patent, let alone an SPC".

A legal interpretation of this sentence would be interesting.

Currently, PrEP is only available in England at clinics that are participating in the open label IMPACT study. The demand for PrEP meant than many of these sites enrolled within months and are now closed to new participants. [4]

References

1. England and Wales High Court (Patents Court) Approved Decisions. Teva UK Ltd & Ors v Gilead Sciences Neutral, second judgement. Citation Number: [2018] EWHC 2416 (Pat).
   http://www.bailii.org/cgi-bin/format.cgi?doc=/ew/cases/EWHC/Patents/2018/2416.html
2. England and Wales High Court (Patents Court) Decisions. Teva UK Ltd & Ors v Gilead Sciences Inc [2017] EWHC 13 (Pat) (13 January 2017).
   http://www.bailii.org/ew/cases/EWHC/Patents/2017/13.html
3. Generic PrEP in France and Scotland challenges access across the UK. HTB October 2018.
   http://i-base.info/htb/32501
4. Update on the PrEP IMPACT Study. HTB, January 2018.
   http://i-base.info/htb/33315

FDA approves doravirine (Pifeltro) and new FDC with TDF/3TC (Delstrigo) in the US

Simon Collins, HIV i-Base

On 30 August 2018, the US FDA approved doravirine as a separate formulation for use with ART and in a fixed dose combination (FDA) with generic tenofovir DF and lamivudine (3TC). [1]

Doravirine is a once daily NNRTI that was initially developed as MK-1439. The standard adult dose is 100 mg once-daily, with or without food.

Approval is based on results from two large international randomised phase 3 studies in treatment-naive participants with control arms using darunavir (in DRIVE-FORWARD) and efavirenz (in DRIVE-AHEAD).

Each study reported primary endpoint results of viral suppression <50 copies/mL at 48 weeks in 84% vs approximately 81% (doravirine vs control respectively), with 95% confidence intervals that confirmed non-inferiority.

Although discontinuation rates were low in all study arms, tolerability advantages favoured doravirine from fewer darunavir/ritonavir-associated or efavirenz-associated side effects.

Doravirine is contraindicated with drugs that are strong cytochrome P450 CYP3A enzyme inducers, because of the potential to reduce doravirine levels.

These drugs include, but are not limited to, the following:

- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin.
- Androgen receptor inhibitor: enzalutamide
- Antimycobacterials: rifampin, rifapentine.
- Mitotane
- St. John's wort (Hypericum perforatum)

Doravirine is marketed in the US with the trade name Pifeltro and the doravirine/TDF/3TC FDC is marketed as Delstrigo. Both formulations were developed by Merck (MSD).

C O M M E N T

The submission for EU approval is already underway, with the CHMP opinion due by 20 September and final decision expected late November.

Although most treatment guidelines now recommend integrase inhibitor-based first line

treatment, drug-pricing is also increasingly important.

Doravirine has a better tolerability profile compared to efavirenz (which is still widely used despite the guidelines).

The FDA indication is only for people who are treatment naive. However, in vitro, doravirine retains sensitivity to common NNRTI resistance mutations (K103N, Y181C, G190A, E101K, E138K, and K103N/Y181C), with a profile that suggests limited cross-resistance to rilpivirine and etravirine. In vivo, doravirine selects for distinct mutations (V106A and F227L) that remain sensitive to rilpivirine and efavirenz (with possible increased sensitivity to the NRTI MK-8591).

Several studies in treatment-experienced participants are ongoing, but only as switch options in people with current viral suppression.

Doravirine is also included in an FDC with 3TC plus the investigational NRTI EFdA (MK-8591), with phase 2 results expected in mid-2019. [2]

The DRIVE-AHEAD study is now published as an open-access paper in CID. [3]

References

1. Merck (MSD) press release. FDA approves Merck's Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate), a once-daily fixed-dose combination tablet as a complete regimen and Pifeltrotm (doravirine), an NNRTI, both for the treatment of HIV-1 in appropriate patients. (30 August 2018).
   https://www.mrknewsroom.com
   https://www.mrknewsroom.com/news-release/research-and-development-news/fda-approves-mercks-delstrigo-doravirine-lamivudine-tenof
2. ClinicalTrials.gov. MK-8591 with doravirine and lamivudine in participants infected with HIV type 1 (MK-8591-011) (DRIVE2Simplify). NCT03272347.
   https://clinicaltrials.gov/ct2/show/NCT03272347
3. Orkin C et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with HIV–1 infection: week 48 results of the DRIVE-AHEAD trial. Clinical Infectious Diseases, ciy540. (August 2018)
   https://doi.org/10.1093/cid/ciy540.

FDA update labels for dolutegravir and dolutegravir-based FDCs to reflect potential risk of neural tube defects

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On 6 September 2018, the US FDA approved revisions to the dolutegravir (Tivicay), abacavir/dolutegravir/lamivudine (Triumeq) and dolutegravir/rilpivirine (Juluca) labels to include information on the risk of neural tube defects.

These changes include:

- Pregnancy testing before starting dolutegravir in adolescent and adult women of childbearing potential.
- Advise pregnant adolescents and adults of the potential risk to the embryo exposed to dolutegravir from the time of conception through the first trimester of pregnancy.
- If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on dolutegravir, if possible, switch to an alternative regimen.
- Advise adolescents and adults of childbearing potential to consistently use effective contraception.
- Register patients who become pregnant to the Antiretroviral Pregnancy Registry (APR).
- Weight gain was also added to the postmarketing experience subsection for each label.

The updated label is available at drugs@fda (listed by trade name).

Link

Updated dolutegravir label (Tivicay).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204790s016s018lbl.pdf (PDF)

ON THE WEB

Alcohol and HIV: new issue of RITA

The new issue of Research Initiative Treatment Action (RITA) is now online.

http://centerforaids.org/pdfs/rita0818.pdf (PDF)

The issue includes an interview with HIV/alcohol expert Jeffrey Samet that suggests what HIV doctors should say about drinking, how to screen for alcohol use disorder, and how to approach treatment.

It includes four review articles.

1. Alcohol use prevalence in HIV populations.
2. How to screen for alcohol use.
3. The clinical impact of alcohol use in people with HIV.
4. Treatment options for alcohol misuse.

Highlights include:

- Alcohol misuse prevalence ranges from 20% to 40% in HIV populations and usually exceeds estimates in the general population.
- Incidence of problem drinking appears to be rising in adolescents and young adults with HIV.
- Current safe alcohol thresholds may be set too high.
- All adolescents and adults with HIV should be screened for alcohol misuse, yet only 1 in 6 adults with HIV talks to their doctor about alcohol.
- Alcohol misuse can disrupt every step of the HIV care continuum.
- Alcohol attacks several organs and systems already made more vulnerable by HIV, including the heart, bones, liver, brain, and immune system.
- Three FDA-licensed drugs for alcohol misuse are old, and little research assesses new therapies in people with HIV.