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CONTENTS

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EDITORIAL

This summer edition of HTB includes the first coverage from the IAS conference and Paediatric Workshop held in Paris in July.

Most of these reports focus on ART including the next likely drugs in the ARV pipeline (see the supplements with this issue), but also on remission cases linked to cure research and the results of the Opposites Attract study.

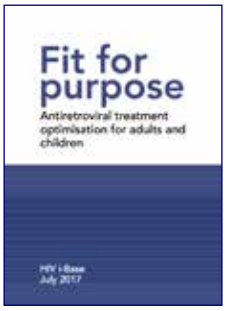
Other ARV news includes the FDA approval of the first generic integrase-based fixed dose combination (FDC) that will significantly change treatment options in countries with access to generic drugs.

And as the controversial PrEP study commissioned by NHS England looks set to enrol the first participants we point out that this is almost three years since the UK PROUD study reported the greatest impact from any HIV prevention study.

Finally, supply issues of vaccines for hepatitis A and B have prompted joint responses from PHE, BHIVA and BASHH, reported here with additional links.

Please also consider helping with our funding appeal to support i-Base for the next year.

Supplements



- **HIV Pipeline Report (2017)**

This annual review of pipeline compounds for the next generation of new drugs was distributed as an HTB supplement in July.

This year we produced a full report and summary version, with a rapid post-IAS update.

- **Fit for Purpose: HIV treatment optimisation for adults and children (2017)**

A comprehensive overview of strategies for treating HIV globally. This includes timelines for new generic drugs and alternative dosing.

Both these publications are available online in electronic format.

i-Base 2017 appeal: we need your help....

This year, the i-Base 2017 appeal was launched to respond to larger changes in our funding.

Your regular support can make a big difference.

We could reach our £100,000 target if:

- 500 people support i-Base with £9.00 a month

and...

- 1000 people support with £4.50 a month.

Please become one of our

subscribers that help.

- i-Base continues to provide all services free, including free community publications for all UK clinics.
- The i-Base website gets more than 400,000 users every month. And last year the i-Base Q&A service answered almost 6,000 individual questions from HIV positive people.

- HIV services are being dramatically cut across the UK, and much of the voluntary sector is vulnerable, including i-Base.

  http://i-base.info/donate

If you would like to help i-Base in other ways, or would like more information about this i-Base appeal, please contact Suzanne Thompson or Simon Collins at HIV i-Base on 020 8616 2210.

Thank you for your help.

CONFERENCE REPORTS

9th IAS Conference on HIV Science

23-26 July 2017, Paris

Introduction

The 9th IAS Conference on HIV Science (IAS 2017) was held from 23–26 July 2017.

As with all IAS conferences, many of the key presentations are available online after the meeting.

All abstracts are also posted online, with full versions of the posters and presentations often also available from the conference website.

http://www.ias2017.org

Webcasts are published to three different webpages:

The main IAS 2017 youtube channel includes most oral abstract presentations and some plenary sessions.

IAS 2017 on youtube.com

Live broadcasts for opening and closing ceremonies, and some press conferences are at this link on the conference website. Currently the link to the closing ceremonies with rapporteur summaries and the community speech is not available.

http://www.ias2017.org/Get-Involved/IAS-2017-Live

Press conferences and other webcasts are online on a different IAS youtube channel.

IAS 2017 press conference webcasts

Articles in this issue are:

- Swaziland nearly halves HIV incidence in five years
- Gay men with undetectable viral load do not transmit HIV: results from Opposites Attract study
- HIV remission news from IAS 2017
- Publications launched at IAS 2017

IAS 2017: ANTIRETROVIRALS

HIV pipeline drugs: IAS 2017 update

Simon Collins, HIV i-Base

Introduction

At each IAS conference, i-Base publishes a review of HIV drugs in development that summarises the most exciting new research over the previous year.

The following article is an update to the 2017 pipeline review. [1]

IAS 2017 was notable for including numerous studies on new drugs, all with generally positive results.

Most of these studies enrolled a low percentage of women enrolled (generally >80% male), who were young (median age around 30 years), largely white (70%+), and in early infection (baseline CD4 <200-350 CD4 in less than 20%). However, research for some investigational compounds (fostemsavir, some monoclonal antibodies) are focused on multidrug resistant HIV.

The results with new compounds generally report non-inferiority to either current standard-of-care or widely-used combinations. When differences were statistically significant, these sometimes related more to the background drugs as to the main study compounds, usually with some reduced side effects.

Several of the studies mentioned below are also reported in more detail later in this issue of HTB.

D/C/F/TAF

This is the first protease inhibitor based fixed dose combination (FDC). It contains darunavir/cobicistat/emtricitabine and tenofovir alafenamide (TAF).

IAS 2017 included interim results from a randomised phase 3 non-inferiority study in over 1100 people on stable boosted-PI plus TDF/FTC who switched to D/C/F/TAF or stayed on their current ART. [2]

The early results showed both groups continued to do very well with no significant differences in terms of viral rebound or side effects, although small improvement in kidney and bone monitoring were linked to the use of TAF in the FDC group.

The main study depends on 48-week results and another phase 3 study is also ongoing.

This compound was submitted to the FDA with a priority review and a decision expected by February 2018 so is likely to be the next HIV drug to be approved and available.

Please see the separate HTB report for full details. [3]

Bictegravir/F/TAF

Bictegravir is a new once-daily integrase inhibitor that does not need boosting and that can be taken with or without food. It is only being developed as part of an FDC with FTC/TAF (B/F/TAF).

IAS 2017 included results from two large randomised phase 3 studies, each in more than 600 treatment naive participants.

One study compared B/F/TAF to the FDC dolutegravir/abacavir/3TC and the other to dolutegravir plus separate TDF/FTC. [4, 5]

Both studies reported similar results for the active compared to control groups that fulfilled the criteria for non-inferiority. Small differences in side effects related mainly to the background nukes being used - ie abacavir, TDF or TAF.

This compound was submitted to the US regulatory agency in June 2017 with the EU application expected to follow shortly.

Please see the separate HTB report for full details of both studies. [6]

Doravirine/FTC/TDF

Doravirine is a new once-daily NNRTI that is only being developed in an FDC with generic TDF and 3TC. This will have potential advantages of having a lower price compared to FDCs with fewer generic components but will also only be used in countries where the patent for TDF has either expired or is not enforced.

IAS 2017 included full results from a large randomised international phase 3 study in more than 700 treatment-naive participants comparing doravirine/FTC/TDF to efavirenz/FTC/TDF, with matching placebos. [7]

Full 48-week results reported similar virological results (84% vs 80% with viral load <50 copies/mL in the doravirine vs efavirenz arms) showing non-inferiority compared to efavirenz.

In this case, CNS-related side effects (interrupted sleep, dreams, mood changes) were significantly less with doravirine.

Please see the separate HTB report for full details of this study. [8]

Long-acting injections: cabotegravir/rilpivirine LA

A combined intramuscular injection containing two long-acting formulations has always generated a lot of interest for people wanting an alternating to daily oral ART.

IAS 2017 included longer follow-up – now out to two years – from a smaller early phase 2 study in about 280 treatment-naive participants. [9]

The results are slightly complicated by the study design, which includes a lead-in period using oral versions of both drugs, and the use of two different dosing schedules – every 4 weeks and every 8 weeks – plus a control group using oral cabotegravir plus abacavir/3TC.

In summary, results at week-96 were similar to those previously reported at week-48, with sustained viral suppression and low reports of side effects.

Even though injection site reactions were very common (in >80% of participants with the first dose and 30–40% throughout the study), these were usually mild and resolved within a week. Participants reported higher satisfaction with the injection formulation.

Full details are included in a separate HTB report. [10]

Ibalizumab

Ibalizumab is a monoclonal antibody that blocks HIV entry. It is given as an IV infusion every two or four weeks and has been in development for at least ten years.

IAS 2017 included results from a small phase 2b study in about 110 treatment-experienced participants with drug resistance to at least three other drug classes who used ibalizumab with optimised background therapy.

The study at IAS 2017 wasn't reporting overall results, but that ibalizumab remained similarly sensitive (or active) in people with a diverse range of drug resistance linked to current HIV classes. [11]

MK-8591 (EFdA)

MK-8591– a very interesting NRTI in early stages of development – is notable for a very high potency, a long-half life and the potential for use both as HIV treatment and for HIV prevention.

Oral dosing might be weekly, and PrEP includes the potential for a small removable slow-release implant that would last a year.

Two interesting studies were presented at IAS 2017.

The first, in 30 HIV positive participants, reported mean viral load reductions seven days after a single dose that ranged from approximately –1.2 logs (for the tiny 0.5 mg, 1.0 mg and 2.0 mg groups) to approximately –1.6 logs (for the 10 mg and 30 mg group). [12]

Both plasma and intracellular drug levels were dose-related, with higher doses achieving levels approximately 1 log higher with the half-life in PBMCs ranging from 78 to 128 hours, allowing for a wide range of potential dosing schedules.

For reasons that are unclear, and against the study protocol, one participant did not begin full ART (risking drug resistance by continued monotherapy) although neither viral load nor resistance data were presented for the case.

The second study was for PrEP in 16 macaques randomised to oral MK-8591 or placebo every week for 12 weeks, and were exposed to SIV rectally every week. [13]

All animals receiving the placebo became infected within 1 to 4 challenges compared to none of the MK-8591 animals,

even after 12 challenges with continued follow-up for a further three months. MK-8591 resulted in a 41.5-fold lower risk of infection (95% CI: 7.3 to 237.9) compared to placebo (p< 0.0001).

Mean intracellular trough concentrations of MK-8591-TP at the time of challenge were similar to levels achieved using a once-weekly 10 mg oral dose of 10mg in HIV positive human studies.

Further details of both studies are included in a separate HTB report. [14]

Fostemsavir

Fostemsavir is an attachment inhibitor in phase 3 studies that as a new class of HIV drug might be especially important for people who have multidrug resistance to current ARVs.

Although no new efficacy or safety results were presented at IAS 2017 – the ongoing phase 3 study doesn›t finish until 2020 – two small drug interactions studies were presented as posters.

The first reported increases in levels of methadone or buprenorphine, with a caution for monitoring for signs of sedation, but without a routine need to dose-adjust. [15]

The second poster reported that fostemsavir can be safely taken with a combined oral contraceptive containing norethindrone (1.5 mg) and reduced dose ethinyl estradiol (30 ug). [16]

Elsulfavirine

Finally, a poster was presented on a study in dogs for subcutaneous and intramuscullar injections of the new nanoformulations of investigational NNRTI elsulfavirine or its prodrug (VS-1500A) that is being developed for potential as treatment and prevention in some middle-income countries. [17]

Single injections of both SC and IM formulations of the prodrug maintained therapeutic drug levels for at least four weeks.

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Darunavir/cobicistat/FTC/TAF: 24-week interim results from phase 3 switch study

Simon Collins, HIV i-Base

D/C/F/TAF is the first single pill protease inhibitor based FDC. The formulation includes darunavir, cobicistat, FTC and tenofovir alafenamide.

Planned 24-week interim results from the 48-week phase 3 EMERALD study were presented by Jean-Michel Molina from University of Paris, showing that switching to this FDC maintained undetectable viral load. [1]

This is a 48-week open-label, multicenter, non-inferiority study in 1141 participants who were already on boosted PI-based ART with TDF/FTC. Participants were randomised (2:1) to either switch to D/C/F/TAF (n=763) or continue on current ART (n=378). Enrolment criteria included having viral load <50 copies/mL for at least two months and eGFR that was >50 mL/min. Previous history of viral failure (reported in 15% of participants) was allowed so long as genotypic resistance to darunavir was not documented.

The primary endpoint is cumulative virologic rebound at week 48 (defined as confirmed ≥ 50 copies/mL or premature discontinuations, with last viral load ≥50 copies/mL). Non-inferiority was defined using relatively new criteria of 4% margin for 95% confidence interval.

This was a largely male, white study population with well-controlled HIV infection. Baseline characteristics included age 46 (range 19 to 78); 18% women, 82% men; 75% white, 21% black. Median CD4 count was approximately 630 cells/mm3 (range: 111–1921) with 10% having <350 cells/mm3. Current boosted-PI was darunavir (71%), atazanavir (22%) and lopinavir (8%) and approximately 40% were still on first-line ART.

At week 24, viral load was maintained <50 copies/mL by 96.3% vs 95.5% of the D/C/F/TAF vs control groups respectively (difference 0.8; 95%CI –1.7 to +3.3%). Overall there were similar low rates of virologic failure (0.5% vs 0.8% respectively), with no discontinuations for viral failure and no detected resistance to any study drug.

The most common side effects (nasopharyngitis, upper respiratory tract infection and vitamin D deficiency) were mild and similar in each arm (approximately 7%, 6% and 5% respectively). Grade 3/4 laboratory changes were also not significantly different between groups.

However, small changes in bone mineral density at hip and spine, likely linked to switch from TDF to TAF were significant with small increases in the switch group and small continued loss in the TDF group remaining on current ART.

C O M M E N T

The study is still ongoing and 48-week data are needed to evaluate whether these promising early results are maintained for the primary virological endpoint. This is similarly important for longer-term results about side effects.

A second phase 3 study in treatment-naive participants is also currently ongoing. [2]

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Phase 3 results with bictegravir FDC: a new integrase inhibitor combined with FTC/TAF

Simon Collins, HIV i-Base

Results from two phase 3 treatment-naive studies were presented at IAS 2017 on bictegravir, a new integrase inhibitor that is coformulated in a fixed dose combination (FDC) with FTC/TAF.

Bictegravir has already been submitted to the FDA for regulatory approval in the FDC formulation but it will only be available as a component of the FDC (B/F/TAF) rather than as a single drug.

Both studies showed bictegravir to be very similar in efficacy to dolutegravir with slight differences in the formulations linked to the background NRTIs in the FDCs.

Bictegravir FDC compared to dolutegravir/3TC/abacavir

Joel Gallant from Southwest CARE Center, Santa Fe presented results of a phase 3 study that randomised 629 treatment naive participants to either B/F/TAF or the FDC dolutegravir/3TC/abacavir. [1]

Entry criteria included being HBV negative and B-5701 negative and having eGFR ≥50 mL/min.

Baseline characteristics included median age 32 years (IQR 18 to 71), 90% men: 10% women, 45% Caucasian, 36% black, 20% Hispanic/Latino.

Median CD4 count and viral load was 444 cells/mm^3 (IQR 299 to 608), and 4.5 log copies/mL (IQR 4.0 to 4.9) respectively, with 11% of participants having CD4 <200 cells/mm^3 and 16% with viral load >100,000 copies/mL. Median eGFR was 123 mL/min (IQR 107 to 146).

At week 48, the primary endpoint of viral load <50 copies/mL was reported in 92.4% vs 93.0% participants in the bictegravir vs dolutegravir groups (difference –0.6; 95%CI: –4.8 to +3.6, p=0.78) finding non-inferiority for the bictegravir FDC. Similar responses were seen in sensitivity analyses and for CD4 responses.

Side effects were similar between groups: diarrhoea (13% vs 13%), headache (11% vs 14%), and nausea (10% vs 23%) in the bictegravir vs dolutegravir FDCs respectively. Few people (n=0 vs 4) discontinued due to side effects.

Other side effects were also similar. The mean percentage changes in bone mineral density (BMD) in lumber spine and total hip were –0.83% vs –0.60% (p=0.39) and –0.78% vs. –1.02% (p=0.23) respectively. There were no differences between treatments for eGFR or proteinuria. There were modest increases in all lipids, including HDL, but no differences between groups.

Bictegravir FDC compared to dolutegravir plus FTC/TAF

The second study included 48-week results from a phase 3 study with dolutegravir plus FTC/TAF as background NRTIs, presented as a poster by Paul Sax from Brigham and Women's Hospital, Boston. [2]

This blinded placebo-controlled study randomised 645 treatment-naive participants with eGFR ≥30 mL/min to either B/F/TAF (50/200/25 mg) or dolutegravir (50 mg) plus separate F/TAF (200/25 mg) each with matching placebos. All regimens are once-daily.

Baseline characteristics included median age 34 years, 12% women and 31% black. Median CD4 and viral load were 440 cells/mm^3, and VL 4.4 copies/mL respectively with 12% CD4 <200 cells/mm^3 and 19% viral load >5.0 log copies/mL.

At week-48, viral load was <50 copies/mL in 89.4% vs 92.9% of participants in the bictegravir vs dolutegravir arms respectively (difference –3.5%; 95%CI –7.9% to +1.0%, p=0.12), showing noninferiority based on lower margin of –12%.

Side effects again were similar in each group: headache (13% vs 12%) and diarrhoea (12% for both) with few discontinuations (n=5 vs 1) and no serious renal events.

The only other poster about bictegravir was a pharmacokinetic study showing similar drug levels in Japanese compared to Caucasian HIV negative volunteers. [3]

C O M M E N T

Both study results show that bictegravir is very likely to soon be approved in the B/F/TAF formulation.

In high- and middle-income countries where the bictegravir FDC is likely to first be used, access is likely to be dependent on drug pricing, even with the advantage of not requiring B*5701 and HBV testing before use.

In low-income countries with access to generic dolutegravir, the generic FDC will be coformulated with F/TAF rather than abacavir/3TC.

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Doravirine/3TC/TDF compared to efavirenz/FTC/TDF as first-line ART

Simon Collins, HIV i-Base

Doravirine is a new once-daily NNRTI active against many first generation NNRTI resistant mutations, that is being developed by Merck in an FDC coformulated with generic lamivudine (3TC) and TDF.

Results from a randomised phase 3 study comparing the doravirine FDC to efavirenz/FTC/TDF (Atripla) in 728 treatment-naive participants were presented by Kathleen Squires from Thomas Jefferson University Hospital, Philadelphia.

This is an ongoing, double-blind, placebo controlled non-inferiority study defined using a 10% boundary for the 95% confidence interval.

Baseline characteristics included mean age 33 years, 85% male and 48% were white. Approximate mean (+/– SD) baseline CD4 and viral load were 420 (+/– 220) cells/mm^3 and 4.4 (+/– 0.7) log copies/mL respectively with approximately 12% having CD4 count <200 cells/mm^3 and 20% having viral load >5 logs.

At week-48, viral load <50 copies/mL was reported for 84.3% (307/364) vs 80.8% (294/364) of the doravirine vs efavirenz groups respectively, (difference 3.5%, 95%CI [–2.0 to +9.0]). Viral suppression was similar between arms in participants with <100,000 and >100,000 copies/mL (approximately 90% and 80% in each arm) and with baseline CD4 <200 and >200 (approximately 69% vs 83% and 91% vs 90% in the doravirine vs efavirenz groups respectively). However, CD4 increases were similar between groups (+198 vs +188 cells/mm^3; difference +10, 95%CI: –16 to +36).

There were slightly more protocol defined virological failures in the doravirine arm: n=22 (6%) vs n=14 (3%). Of these, 6 vs 4 were non-responders and 16 vs 10 involved viral rebound. Slightly fewer people in the doravirine arm discontinued for other reasons (n=35 vs 50).

Of approximately 24 genotype tests in each arm, n=5 in each group had NRTI resistance and n=6 vs 12 people had NNRTI resistance).

Doravirine was superior to efavirenz based on secondary endpoints CNS and lipid side effects.

For example, dizziness (9% vs 37%, p<0.001), sleep disorders/disturbances (12% vs 25%, p<0.001) and mood changes (4% vs 8%, p=0.03) were all significant. Similarly, fasting lipids included significantly reduced LDL (–1.6 vs +8.7 mg/dL, p<0.0001), cholesterol and triglycerides for the doravirine group but higher HDL increases (+1.9 vs +8.5 mg/dL) in the efavirenz group, and no data presented for HDL:TC ratio.

The timeline for regulatory submission for doravirine in this FDC is unclear but marketing will depend on FDC patents for the generic TDF in different countries.

These results support the doravirine FDC as a more tolerable alternative to efavirenz in treatment-naive participants.

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Continued viral suppression with long-acting cabotegravir/ rilpivirine injections: 96-week LATTE-2 results

Simon Collins, HIV i-Base

Longer follow-up results from using the first coformulated injectable ART were presented from the phase 2b LATTE study. [1]

Following a lead period that included using oral formulations of cabotegravir and rilpivirine, 286 treatment-naive participants were randomised (2:2:1) to either 8-weekly (8W) or 4-weekly (4W) injections, or to oral cabotegravir plus abacavir/3TC.

Approximate baseline characteristics have been previously described and include 92% men, 80% white, CD4 489 cells/mm3 with 18% of participants having viral load >100,000 copies/mL.

The 96-week results presented at IAS 2017 maintained high levels of viral suppression to <50 copies/ mL in 94%, 87% and 84% of participants in the 8W, 4W and oral groups respectively. Viral suppression with both injection schedules were non-inferior to oral dosing: 8W: difference +10.0% (95%CI: –0.6% to +20.5%) and 4W: +3.0% (95%CI: –8.4% to +14.4%). This compared to viral suppression rates at week-48 of 92%, 91% and 89%, respectively. [2]

Viral non-responses were more frequent in the 8W group (n=5 vs 0 vs 1) with only one case of viral failure in each of the 8W and oral arms.

Non-virological discontinuations occurred more frequently in the 4W group, with n=2, n=15 and n=8 in the 8W, 4W and oral groups respectively. The discontinuations in the 4W group included five drug-related causes: rash, QT prolongation, tachycardia, depression and psychosis and five non-drug related events.

Serious adverse events occurred in 10%, 10% and 13% in the 8W, 4W and oral groups respectively, but none were judged drug-related.

Injection site reactions (ISRs) were common (>80% at day 1 and at ~30 to 40% in injection arms throughout follow-up, occurring slightly more in the 8W group, but 84% overall were mild and 15% were moderate. Most common ISR events were pain (66%), nodules (8%), swelling (6%), and pruritus (6%). Median duration of ISRs was 3 days, with 89% resolving in <7 days. Only two participants (both in the 8W group) discontinued due to ISRs.

Participant satisfaction continued to be highest in the injection arms (99% rating 5 or 6 out of 6 to continue on present dosing, compared to 78% with the oral group).

The 96-week results were also published in the Lancet. [3]

C O M M E N T

Phase 3 studies are currently ongoing using the 4W schedule selected based on week-48 results and all participants have the option to change to this dose after week 96.

Only one phase 3 study will continue to evaluate 8W dosing.

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MK-8591: further compelling early results for both treatment and prevention

Simon Collins, HIV i-Base

Two very interesting early studies were presented at IAS 2017 for the investigational NRTI MK-8591 (EFdA).

This compound in early stages of development is notable for a very high potency, a long-half life and the potential for use both as HIV treatment and for HIV prevention. Oral dosing might be weekly and PrEP includes the potential for a small removable slow-release implant that would last a year.

The first study, presented as a poster, looked at the impact on viral load of a single dose of MK-8591 (30 mg, 10 mg, 2 mg, 1 mg or 0.5 mg) in 30 treatment-naive participants (n=6 for each arm), with the recommendation to start ART after 7-10 days depending on the dose. [1]

Mean viral load reductions at day 7 were dose-related and ranged from approximately –1.2 logs (for the 0.5 mg, 1.0 mg and 2.0 mg groups) to approximately –1.6 logs (for the 10 mg and 30 mg group).

The study also looked at the pharmacokinetics of different doses, especially drug levels in plasma and PBMCs and the impact on plasma and intracellular half-life for potential dosing schedules.

Both plasma and intracellular drug levels were dose-related, with higher doses achieving levels approximately 1 log higher with half-life in PBMCs ranging from 78 to 128 hours, allowing for a wide range of potential dosing schedules.

For reasons that are unclear, and against the study protocol, one participant did not begin full ART (risking drug resistance by continued monotherapy) although neither viral load nor resistance data were presented for the case.

The second study looking at potential for PrEP, presented as a late-breaker oral abstract, reported weekly oral doses of MK-8591 or placebo for three months in 16 macaques who were then exposed to rectal SIV (on day 6 of every weekly cycle) for 12 weeks. [2]

The results were pretty remarkable: all animals receiving the placebo became infected within 1 to 4 challenges compared to none of the MK-8591 active animal, even after 12 challenges and continued follow-up for a further three months. MK-8591 resulted in a 41.5-fold lower risk of infection (95% CI: 7.3 to 237.9) compared to placebo (p< 0.0001).

Mean intracellular trough concentrations of MK-8591-TP at the time of challenge were 4.07 mM (range: 2.26-5.17) and were similar to levels achieved using a once-weekly 10 mg oral dose of 10mg in HIV positive human studies.

Taken together, these studies show that this is a compound to follow closely through the next stages of development.

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Dolutegravir outperforms lopinavir/ritonavir second-line: interim results from the DAWNING study

Polly Clayden, HIV i-Base

Unsurprisingly, dolutegravir (DTG) was superior to lopinavir/ritonavir (LPV/r) in a comparison of DTG-based regimen vs WHO-recommended second-line. These data were presented as a late breaker at IAS 2017.

DAWNING is a non-inferiority, randomised, phase 3b, open label study conducted to evaluate the safety and efficacy of DTG + 2 NRTIs compared with LPV/r + 2 NRTIs in participants failing first-line ART of an NNRTI + 2 NRTIs.

Investigator-selected NRTIs had to include at least one that was fully active based on resistance testing at screening.

Eligible participants were on first-line NNRTI + 2 NRTI for at least six months and failing virologically with no primary resistance to PIs or INSTIs. The primary endpoint was proportion with viral load <50 copies/mL at week 48 (FDA snapshot; 12% non-inferiority margin). DAWNING enrolled from December 2014 to August 2016 and is ongoing.

After two of three pre-planned analyses, the study Independent Data Monitoring Committee (IDMC) conducted an ad hoc

review of week 24 data and large subsets from weeks 36 and 48. They recommended discontinuation of the LPV/r arm due to differences in rates of virologic nonresponse and increasing differences in rates of virologic failure favouring the DTG arm. Participants in the LPV/r could switch to the DTG one.

DAWNING was a multi country study enrolling participants from 13 low- and middle-income countries (LMICs), including 168 from South Africa.

A total of 968 were screened and 624 randomised 1:1 to the two study arms: 11% vs 17% withdrew from the study and 53% vs 52% completed week 52, in the DTG and LPV/r arms respectively.

Participants were a median of 37 years of age, about a third were women, about 40% were of African origin, about half had CD4 count <200 cells/mm^3 and 20% viral load >100,000 copies/mL.

In their second-line regimen across both arms, just over 40% received TDF + 3TC (or FTC) NRTI backbone and a further 40% AZT + 3TC (the remainder received TDF + AZT or ABC + 3TC or other).

At week 24, 82% of participants on DTG vs 69% on LPV/r achieved viral load <50 copies/mL: adjusted difference 13.8% (95% CI: 7.3 to 20.3), p=0.001.

The difference was mainly driven by lower rates of virologic non-response in the DTG arm: 12 vs 25%. There were more drug-related adverse events in the LPV/r arm, mainly due to higher rates of gastrointestinal disorders.

Interim data for weeks 36 and 48 were consistent with week 24 in favour of DTG, respectively: 78% (230/293) vs 69% (203/293), adjusted difference 9.8% (95% CI: 2.7 to 16.8); and 81% (199/247) vs 66% (161/245), adjusted difference 15.4% (95% CI: 7.8 to 23.1).

No participant receiving DTG + 2 NRTIs with confirmed virologic withdrawal (3%) developed primary INSTI or NRTI resistance mutations.

C O M M E N T

The big question for LMICs is whether these results can be repeated without resistance testing.

Evidently of 968 people screened (624 randomised) about 30% (7–8% of the total) failed screening due to lack of at least one fully active NRTI.

It will be important to look how many of the participants receiving a TDF + 3TC or FTC backbone received the same in their first-line regimen.

Notably, in a subgroup of analysis by fully active NRTIs, participants with less than two did better than those with two, in both arms: 84 vs 73% and 74 vs 55% <50 copies/mL in the DTG and LPV/r arms respectively.

As low-cost generic DTG-based FDCs come to market next year more countries will be adopting DTG first-line. And as most desirable characteristics for an ART regimen (durability, tolerability, cost etc) favour DTG/TDF/XTC over PI- as well as NNRTI-based regimens, other groups beyond first-line could benefit too.

As well as ART-naive people, those who are suppressed on EFV-based regimens can be switched to DTG-based. But can unsuppressed people on EFV remain on TDF/XTC with DTG? And can those already suppressed on a LPV/r-based regimen also be switched to DTG/TDF/XTC?

The next set of ART optimisation studies plan to look at these questions.

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Reduced-dose darunavir is safe and effective in switch study

Polly Clayden HIV i-Base

A 400/100 mg once-daily darunavir/ritonavir (DRV/r) dose plus two NRTIs maintained virologic efficacy through 48 weeks in participants previously suppressed with DRV/r 800/100 mg. [1]

These data from the ANRS-165 Darulight study were shown at IAS2017.

Darulight was a multicentre, phase 2, single arm, open label study in stable participants with viral load <50 copies/mL who had received DRV/r 800/100 mg for at least 12 months.

Of 100 participants enrolled in the study, 95 were included in the modified intent to treat analysis.

A minimum of 94 participants were needed to detect a difference in success rate from 80% to 90% with 85% power.

Participants were a median age of 43 years and 78% were male. They had received ART for a median of 46 months, and had a median CD4 count of 633 cells/mm3 and duration of viral load <50 copies/mL of 35 months. The majority (76%) received a TDF/FTC backbone and the remainder ABC/3TC.

At 48 weeks 87 of 95 participants had viral load <50 copies/mL: 91.6% (95% CI 84.1 to 96.3), p<0.001. Of the remaining 8 participants: 2 changed DRV dose without virological failure; 6 had viral load >50 copies/mL (2 >200 copies/mL).

The only risk factor for viral load >50 copies/mL was baseline peak viral load >threshold: OR 4.76 (95% CI 1.47 to 15.4), p=0.009.

Nine participants had serious adverse advents, none led to treatment discontinuation.

A pharmacokinetic sub study of Darulight conducted in 15 men found total and unbound blood and seminal plasma exposure of DRV to be not significantly different between both doses, despite 50% dose reduction. [2]

Unexpectedly total blood plasma exposure of ritonavir trended to be higher in 400/100mg once-daily, than in 800/100mg once-daily (p=0.09) due to a change in the inducer/inhibitor balance between DRV and RTV.

C O M M E N T

DRV has long been a candidate for dose optimisation and these data support further investigation.

A DRV/r 400/100 mg switch trial in South Africa is currently enrolling participants, stable on boosted lopinavir-based second-line. [3] And plans for phase 2 and 3 studies in unsuppressed participants are underway.

Fit for Purpose July 2017 gives more details. [4]

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IAS 2017: PREGNANCY

Preliminary results on dolutegravir use in pregnancy are reassuring

Polly Clayden, HIV i-Base

Reports of dolutegravir use in pregnancy from Botswana, Europe and the Antiretroviral Pregnancy Registry to date did not show an increased risk of adverse outcomes compared with other antiretrovirals. [1, 2, 3]

But more data are needed, particularly with dolutegravir exposure before conception, to reach definitive conclusions, according to analyses presented at IAS 2017.

Botswana

The risk of adverse birth outcomes was similar for dolutegravir-based and efavirenz-based ART among women starting treatment in pregnancy in the Tsepamo study.

Botswana introduced dolutegravir-based first-line ART for all adults, including pregnant women, regardless of CD4 count in May 2016.

Since August 2014 the Tsepamo Study has performed ongoing birth surveillance to evaluate the safety of ART in pregnancy.

Conducted at eight government hospitals, the study captured data on over 47,000 births at study sites (approximately 45% of all deliveries in the country). The majority (99%) had documented maternal HIV status; 25% of mothers with known status were HIV positive; 91% were on ART before delivery; and the regimen was recorded for 94% of treated mothers.

In a previous analysis, at two years, maternal ART of efavirenz, tenofovir and emtricitabine from conception was associated with lower risk of adverse birth outcomes compared with other (older) regimens, among infants exposed to ART from conception in Botswana. [4, 5]

This more recent analysis included women who started either efavirenz, tenofovir and emtricitabine (4593 delivered August 2014 to August 2016) or dolutegravir, tenofovir and emtricitabine (845 delivered November 2016 to April 2017) during singleton pregnancy.

Outcomes included combined endpoints of any adverse outcome (stillbirth, preterm birth <37 weeks, small for gestational age (<10th percentile weight-for-gestational age), or neonatal death (<28 days) and severe adverse outcomes (stillbirth, neonatal death, very preterm birth [<32 weeks] and very small for gestational age (<3rd percentile weight-for-gestational age). Results were adjusted for maternal age, educational attainment and gravida.

Women were similar across treatment groups: median age 28, approximately 10% had no primary education, about half delivered at a tertiary facility, for about a quarter it was the first child but 12% already had four or more. They presented at ANC at a median gestational age of 17 weeks, 6% had a history of preterm delivery and 3% of stillbirth. About a third were diagnosed before pregnancy, median ART initiation was at 20-week gestation and median CD4 count above 400 cells/mm3. But women that started on dolutegravir had fewer days between ANC presentation and ART start: median 11 vs 23 days. And they had fewer CD4 results in pregnancy: 17 vs 45%.

The analysis found no significant differences in total and severe adverse birth outcomes, preterm, very preterm birth, small for gestational age, very small for gestational age, stillbirth, and neonatal death. Adjusted risk ratios (aRR) for dolutegravir-based regimens with efavirenz-based regimens as reference were respectively (for the above outcomes): aRR 1.0 (95% CI 0.9 to 1.1), aRR 1.0 (95% CI 0.8 to 1.2), aRR 1.0 (95% CI 0.8 to 1.1, aRR 1.2 (95% CI 0.8 to 1.7), aRR 1.0 (95% CI 0.9 to 1.2), aRR 0.9 (95% CI 0.7 to 1.2), aRR 0.9 (95% CI 0.6 to 1.5), and aRR 1.0 (95% CI 0.5 to 1.9).

Of 512 first-trimester ART exposures (116 dolutegravir and 396 efavirenz), there was one major congenital abnormality: skeletal dysplasia in an efavirenz-exposed infant.

Presenting author Rebecca Zash concluded that these preliminary data are reassuring but not the whole story. Birth outcomes with dolutegravir exposure from conception still need to be evaluated.

European Pregnancy and Paediatric HIV Cohort Collaboration

Data from European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) were presented at the 9th International Workshop on HIV Paediatrics (as an oral presentation) as well as IAS 2017. [6] Although this is the largest European study to date, small numbers preclude firm conclusions from EPPICC regarding safety of dolutegravir in pregnancy.

EPPICC analyses prospectively collect individual patient data (ie with antiretroviral exposure data collected before pregnancy outcome is known) from observational studies of HIV positive pregnant women and their infants in Europe. This study included women with any prenatal exposure to dolutegravir reported by September 2016.

Of 101 pregnancies, 16 were ongoing at the time of analysis and one was lost to follow up. Of 84 pregnancies with outcomes: 81 live births (83 newborns, two twin pregnancies), one spontaneous abortion, one induced abortion, and one stillbirth, were included in the analysis.

At conception women were a median of 33.1 years, 85% were already diagnosed, and 60% were already on ART. Of the women, 10% were vertically infected, 11% had advanced HIV, 43% had CD4 count 350 cells/mm³ or less in pregnancy, and 9% were HCV coinfected.

Of the total pregnancies, 58 (57.4%) had first trimester earliest dolutegravir exposure, 24 (23.8%) second trimester, 18 (17.8%) third trimester and one unknown.

The spontaneous abortion and induced abortion (personal decision, no foetal abnormality) occurred in pregnancies with first trimester exposure (both conceived on dolutegravir), and the stillbirth in a pregnancy with second trimester exposure.

Among 80 infants (79 pregnancies singleton live birth and one stillbirth), 16.7% had low birth weight and 18.7% were small for gestational age.

Abnormalities were reported in 4 of 81 live born/still born infants (no defect in the still born infant): 4.9% (95% CI 1.4 to 12.2). See Table 1.

Notably, there was no pattern of defects and only infants I and 2 would be classified according to EUROCAT definitions.

Table 1: Congenital abnormalities dolutegravir exposure in EPPICC

Infant	Abnormality	Earliest exposure	Sex	Maternal details	Other ARVs	Country
1	Patent foramen ovale	Conception	Male	Black African, aged 38 at delivery	3TC, ABC	Italy
2	Bilateral hexadactyly of hands (father has same defect). Hypospadias	Week 3	Male	White, aged 40 at delivery	3TC/ABC, FTC/TDF in first trimester	Italy
3	Ankyloglossia (tongue tie)	Week 12	Male	White, vertically infected, aged 31 at delivery	DRV/r, ATV/r, RAL, TDF in first trimester	Italy
4	Hyperpigmentation on back	Week 14	Male	Black African, aged 34 at delivery	3TC, ABC	Switzerland

Table 2: Congenital abnormalities dolutegravir exposure in APR

Infant	Abnormality	Earliest exposure	Sex	Maternal details	Other ARVs
1	Bilateral polydactyly post-axial to both hands	First trimester	Male	Black, aged 26 years at conception	DRV/r in first trimester
2	Polydactyly on the ulnar side and syndactyly on the second, third and forth fingers	First trimester	Male	Black, aged 22 years at conception	FTC/TDF in first trimester
3	Hypoglossia hypodactylia syndrome	Second/third trimester	Female	Black, aged 31 years at conception	DRV/r, FTC/TDF in second trimester, AZT in third trimester
4	Down's syndrome	Second/third trimester	Female	Hispanic, aged 38 years at conception	ABC/3TC in second trimester

Claire Thorne, who presented the data stressed that the European women receiving dolutegravir in this cohort represented a high-risk group including older mothers, those with advanced HIV, treatment experienced and HCV coinfected.

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry (APR) analysis of birth defects includes the largest number of prenatal exposures to dolutegravir to date – presented as a poster at IAS and online in the APR interim report through January 2017. [7]

APR data did not demonstrate an increased risk of congenital anomalies with dolutegravir use above the expected population rate of defects: 2.72 to 4.17 per 100 live births. But this finding was also limited by sample size.

APR is an international (although largely US), registry that monitors prenatal antiretroviral drug exposures to detect potential increases in the risk of birth defects.

Clinicians register pregnant women with prenatal exposure to any antiretroviral before the pregnancy outcome is known, report data on exposure throughout pregnancy and provide birth outcome data. Registration is voluntary and confidential. The APR produces twice-yearly reports.

Antiretroviral exposure is classified by earliest trimester. When at least 200 exposures to a specific drug have been reported, APR can calculate birth defect prevalence and compare it to internal and external comparator groups.

The external comparators are two population-based surveillance systems: Metropolitan Atlanta Congenital Defects Program (MACDP) and Texas Birth Defects Registry (TBDR). Internal comparators include exposure to other drugs and in second and third trimesters. APR has 80% power to detect doubling of risk and type 1 error rate for doubling of risk for overall birth defects with 200 exposures.

As of 31 January 2016, 142 pregnancies with exposure to dolutegravir were prospectively reported to the APR: 88 with earliest exposure first trimester, and 54 second/third trimesters.

At enrolment, 56 (39.4%) women had a CD4 count $\geq$500 cells/mm^3, 48 (33.8%) 200–499 cells/mm^3, 31 (21.8%) < 200 cells/mm^3 and results were missing for 7 (4.9%). Mothers were a median of 29 years old. The majority, 126, were from the US.

Of 142 pregnancies, 128 (90.1%) resulted in live births (74 with first and 54 with second/third trimester exposure), 3 (2.1%) resulted in induced abortions (all with first trimester exposure), and 11 (7.7%) resulted in spontaneous abortions (all with first trimester exposure). No stillbirths were reported.

Four birth defects were reported among 133 live births (77 with first and 56 second/third trimester exposure). See Table 2.
Among 119 live births without defect other adverse birth outcomes included: 13 preterm <37 weeks of gestation (8 with first and 5 second/third trimester exposure); 14 low birth weight <2500 grams (9 with first and 5 second/third trimester exposure); 5 very low birth weight <1500 grams (3 with first and 2 second/third trimester exposure).

At the time of analysis, the APR had not reached the 200 first trimester exposures needed to estimate overall prevalence of birth defects. APR's "Rule of 3" (once three or more prospective similar organ system defects have been recorded, these cases will be flagged for immediate review) is being followed for polydactyly.

The APR authors noted hand anomalies are among the most common birth defects identified in infants: approximately 10% of birth defects; 15% of all upper extremity anomalies involve polydactyly.

Risk factors are African origin, male sex, birth order, increased maternal age and maternal smoking.

C O M M E N T

Global rollout of dolutegravir has been hampered by lack of safety data in pregnancy (as well as with TB co-treatment). So these reports are welcome and reassuring but each one emphasised the need for more preconception dolutegravir exposures.

It should be possible to do a pooled analysis of these data – for the APR/EPPICC the analysis would need to de-duplicate any EPPICC cases reported to APR.

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Low dose efavirenz can be used during pregnancy

Polly Clayden, HIV i-Base

Results from a pharmacokinetic (PK) study of 400 mg efavirenz (EFV400) during pregnancy, showed lower drug concentrations in the third trimester, compared with post-partum, but these were within adequate ranges described elsewhere. The findings were presented as a late breaker poster at IAS 2017. [1]

WHO guidelines recommend EFV400 as alternative first-line drug, with a disclaimer that no data exist on its use at this dose during the third trimester of pregnancy.

This study investigated the PK, efficacy and CYP2B6 pharmacogenetics of EFV400 in HIV positive women during third trimester (TT) and post-partum (PP). The aim was to provide data to support the removal of the WHO disclaimer to allow wider EFV400 first-line use.

It was an open-label, multicentre study conducted in UK and Uganda in women receiving tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and EFV 600 mg with an undetectable viral load (<50 cells/mm^3), who switched to TDF/FTC/EFV400.

The investigators evaluated weekly therapeutic drug monitoring (TDM) 10–14 hours post dose, steady-state PK profiles during TT and PP, safety, virologic efficacy and polymorphisms in CYP2B6 (516C>T and 938T>C).

The primary endpoint was the comparison of EFV Ctrough TT vs PP using geometric mean ratios (GMR). A sample size of 25 provided at least 80% power to detect a 20% decrease in Ctrough during TT vs PP.

The study enrolled 25 women of African origin: baseline median age and CD4 were 29 years (range 18 to 41) and 561 cells/mm^3 (range 152 to 882), respectively. All women had baseline viral load <50 copies/mL at enrolment and remained undetectable throughout the study (there were only two viral load blips, both confirmed <50 copies/mL, when repeated).

All of the infants were HIV uninfected. No women were excluded because of low EFV400 TDM results (<800 ng/mL in >3 consecutive visits).

GMR (TT/PP) of EFV400 Cmax, AUC, and C24trough were: 0.93 (90% CI 0.80 to 1.08), 0.84 (90% CI 0.72 to 0.99), 0.73 (90% CI 0.60 to 0.89).

Of 25 women, 23 were carriers of the CYP2B6 516G allele and only two were slow metabolisers.

EFV400 was well tolerated in pregnancy with no grade 3 or 4 laboratory abnormalities.

Cmax, AUC, and Ctrough in TT were 7%, 27% and 26% lower compared with PP but within ranges previously reported for EFV600 during TT and those measured in ARV-naive patients receiving EFV400 in ENCORE1. [2, 3]

All participants maintained a viral load <50 copies/mL, suggesting that EFV400 can be used in pregnant HIV positive women.

C O M M E N T

Like dolutegravir, EFV400 is an alternative option in 2016 WHO guidelines.

Evidence for efficacy in pregnancy at the lower dose (as described above) and with TB co-treatment (for which a PK study is ongoing) are needed for an unrestricted WHO recommendation.

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Stillbirth rate in HIV positive women in UK/Ireland is double that of the general population

Polly Clayden, HIV i-Base

Stillbirth rate in HIV positive women in UK/Ireland was around twice that reported in the general population in 2007–2015, despite declines in vertical transmission and increases in women conceiving on ART and delivering with undetectable viral load.

These findings from the UK and Ireland National Study on HIV and Pregnancy and Childhood (NSHPC) were presented at IAS 2017.

The study authors noted that stillbirth has multifactorial and incompletely understood causes. They previously reported higher rates than in the general population between 1990–2006: 1.1% vs 0.5%. This period saw big changes in maternal HIV treatment and vertical transmission interventions.

The more recent analysis was conducted to explore the current stillbirth rate and risk factors in HIV positive women delivering in UK/Ireland between 2007–2015 (reported to NSHPC by December 2016).

Stillbirth was defined as a baby delivered at 24 gestational weeks or more showing no signs of life.

During the study period, there were 10,316 pregnancies in 8069 mothers: 75.4% of mothers were born in sub-Saharan Africa; 49.4% conceived on ART; 55% received a PI-based regimen and 24.5% NNRTI-based; there were 43 (0.4%) vertical transmissions; and 89 (0.9%) stillbirths.

There was no decline in rate of stillbirth reported to the NSHPC over this period, p=0.24. The Office for National Statistics for England and Wales reported a stillbirth rate of 0.5% during the same period of time.

Compared with live births, stillbirths were more likely to be male (58.21 vs 41.79%), delivered pre-term (median 33 vs 39 gestational weeks), small for gestational age (54.84 vs 21.12%) and have congenital abnormalities (14.75 vs 2.85%). But data on gender, small for gestational age and congenital abnormalities were missing for approximately 25, 30 and 31% of

still births respectively.

In multivariate analysis, significant risk factors associated with stillbirth were: antenatal CD4 count ≤350cells/mm^3 and mother being primiparous, older and originating from sub-Saharan Africa or other non-western European countries. Delivery year, ART at conception and antenatal ART class attendance were not significantly associated with stillbirth. See Table 1.

Table 1: Adjusted risk factors associated with stillbirth

Risk factor		IRR (95% CI)
Maternal age (years)	<28	1.00
	28–32	3.38 (1.25 to 9.16)
	33–36	**3.57 (1.25 to 9.66)**
	>36	**4.12 (1.49 to 11.35)**
Parity	Primiparous	**1.85 (1.10 to 3.12)**
	Multiparous	1.00
Maternal origin	Europe/WEWC	1.00
	SSA	**3.26 (1.07 to 9.95)**
	Other	5.59 (1.49 to 21.48)
Maternal CD4 count	>350	1.00
	≤350	1.73 (1.05 to 2.86)

Key: IRR, incident rate ratio; SSA, sub-Saharan Africa; WEWC, westernised countries.

The authors pointed out the limitations to this study: NSHPC does not record data on other important risk factors for stillbirth eg maternal BMI, socio-economic status and smoking and there were limited data to classify stillbirth as antepartum or intrapartum. They also noted that details of stillbirths were under reported.

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IAS 2017: TREATMENT ACCESS

Swaziland nearly halves HIV incidence in five years

Polly Clayden, HIV i-Base

Swaziland saw a decrease in HIV incidence by almost half and a doubling of viral load suppression among adults, between 2011 and 2016, according to data from a population based survey presented at IAS 2017.

Swaziland has the highest national HIV prevalence in the world: 32% among a population of 1,451,428 in 2011 as measured by its first door-to-door testing survey.

In response, the Swazi government vastly expanded national HIV prevention and treatment services. Since 2011 the country has rapidly adopted new ART guidelines, now including treat all and nurse-led ART initiation as well as the promotion of HIV prevention services.

Between 2011 and 2016 the annual number of HIV tests increased from 180,433 to 410,947; the annual number of people starting ART increased from 14,184 to 22,554, the total number of people on ART from 72,402 to 171,266 and the number of men who had medical circumcision from 38,106 to 93,357.

In 2016–2017 the country conducted the Second Swaziland HIV Incidence Measurement Survey (SHIMS2) – a population-based HIV impact assessment (PHIA) among a nationally representative sample of the population age 15 years and above. The objective was to estimate HIV incidence and to estimate population viral load suppression (<1000 copies/mL).

This was a cross-sectional, two-stage cluster sample of 286 districts. A total of 6417 households were offered testing. People who consented to testing within the households had an HIV rapid test and a point-of-care CD4 test if they tested positive.

All HIV positive samples were tested for viral load and limiting antigen avidity (130 days) at a central laboratory. Results were compared with those from the 2011 survey.

The household response rate was 84% and 10,934 adults were tested. 2016–2017 results showed HIV prevalence to be stable since 2011: respectively 30.5 vs 32.1% overall, p=0.103; 24.1 vs 21.2% for men and 38.1 vs 38.8% for women.

But HIV incidence decreased by 44% overall, from 2.5 to 1.4%, p=0.012; 1.8 to 0.9% in men and 3.2 to 2.0 in women.

Overall viral load suppression more than doubled between 2011 and 2016–2017: from 34.8 to 71.3%, p=0.0001; 32.7 vs 63.0% in men and 35.9 vs 75% in women.

More women than men were diagnosed with HIV in 2016–2017: 88.6 vs 77.5%. Older people (25 years and over) were more likely to know their status: 87.1 vs 66.1%.

90-90-90 achievements were 85-87-92 overall.

C O M M E N T

Good news from Swaziland, which provoked much well-deserved applause from the audience.

This was the first direct measure of the national impact of five years of expanded HIV services, particularly ART coverage, on HIV incidence.

Swaziland is making continued efforts to reach and engage men and young women in order to achieve 90-90-90 targets across all populations.

Reference

Nkambule R et al. Substantial progress in confronting the HIV epidemic in Swaziland: first evidence of national impact. IAS 2017. 23–26 July 2017. Paris. Oral abstract MOAX0204LB.
http://programme.ias2017.org/Abstract/Abstract/5837 (abstract)

IAS 2017: PREVENTION

Gay men with undetectable viral load do not transmit HIV: Opposites Attract study supports U=U

Simon Collins, HIV i-Base

Further evidence reporting a lack of HIV transmission when viral load is undetectable on ART was presented at IAS 2017 from the prospective Opposites Attract study in gay men.

The study included 358 serodifferent gay male couples from Australia (n=157), Thailand (n=105) and Brazil (n=96) who were already not consistently using condoms. The final study results were presented in a late breaker oral abstract by Andrew Gulich from the University of New South Wales, Sydney. [1]

Similar to the design of the PARTNER study, undetectable viral load on ART was defined as <200 copies/mL and participants were asked to keep a diary in order to estimate approximate levels of exposure risk by sexual activity. Also, phylogenetic analysis (of pol and env genes) were used to determine whether any new infections were likely linked to the main partner.

By the end of 2016, the study had 591 couple years of follow up (CYFU) from 343 couples with at least one follow-up visit, of which 318 CYFU included periods when condoms were not used. Open relationships were common with almost 60% of couples reported sex outside the main partnership.

At baseline, only 80% of HIV positive partners were on ART, of whom just under 80% had undetectable viral load and STI prevalence was 14.3% and 11.7% in the positive and negative partners respectively.

From 16,889 times when condoms were not used, there were three new HIV diagnoses, but none of these were linked infections to the main partner, incidence 0/100 CYFU (95%CI: 0 to 0.62).

The study also reported risks by different activity, see Table 1.

Table 1: HIV incidence by exposure category in Opposites Attract study

	Linked trans-missions (n)	CYFU	CLAI acts (n)	Incidence per 100 CYFU (95% CI)
Overall	0	591.2	16,889	0 (0-0.62)
Any CLAI	0	318.0	16,889	0 (0-1.16)
Any CLAI, no daily PrEP	0	241.3	12,928	0 (0-1.53)
Insertive CLAI	0	210.0	8,389	0 (0-1.76)
Receptive CLAI	0	132.1	4,569	0 (0-2.79)
UVL (VL <200)	0	236.2	12,638	0 (0-1.56)
VL >200	0	5.17	290	0 (0-71.4)
STI diagnosed	0	23.2	1,007	0 (0-15.9)
First 6 months ART	0	10.0	341	0 (0-36.9)

Key : ART: antiretroviral treatment; CI: confidence interval; CLAI: condom-less anal intercourse; CYFU: Couple years of follow up; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection; UVL: undetectable viral load.

C O M M E N T

These important results are useful to read in association with earlier results, including the PARTNER study. [2]

Similar to PARTNER, undetectable was defined using a <200 copies/mL threshold and diaries were used to categorise different risk activity. Unlike PARTNER, enrolment criteria did not include being on ART or having undetectable viral load.

Taken together, both studies provide further evidence showing the lack of HIV transmission when viral load is undetectable, even when condoms are not used.

The barrier of proof should now shift towards producing evidence for whether HIV transmission is actually possible. This is especially in the absence of published cases in the ten years since the Swiss Statement first asserted that transmission could not take place. [3, 4]

This body of evidence makes it easy to understand why leading scientists, including from the IAS, the US NIH and BHIVA support the campaign to say that that Undetectable = Uninfectious (U=U). [5]

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IAS 2017: CURE RESEARCH

HIV remission news from IAS 2017

Richard Jefferys, TAG

The topic of HIV remission has already been the focus of several high-profile presentations at IAS 2017.

One of the first major news stories to emerge from the meeting involves a newly described example of prolonged HIV remission in a nine-year-old South African child presented by Avy Violari. [1]

The case was identified because the child was a participant in the Children with HIV Early Antiretroviral Therapy (CHER) trial, which took place from 2005-2011 in South Africa and evaluated immediate, time-limited (40- or 96-week) courses of antiretroviral therapy (ART) in perinatally infected infants compared to the strategy of deferring initiation until clinical or immunological signs of disease progression were evident (preliminary results from the study, demonstrating the benefits of immediate ART, were published in the New England Journal of Medicine in 2008). [2]

The child was diagnosed by HIV DNA PCR 32 days after birth, and displayed pre-treatment viral load levels of over 750,000 copies/mL and 151,000 copies/mL on days 39 and 60, respectively. ART was initiated after 61 days, with viral load declining to below 50 copies/mL at week 24 of on-treatment follow up. ART was subsequently stopped at week 40. The CHER protocol mandated restarting ART if certain immunological and/or clinical criteria were met, but the child has remained healthy and maintained a high CD4 count throughout follow up.

When stored samples were later accessed in order to measure viral load, the levels were found to be persistently below 20 copies/mL. The first postinterruption sample was taken eight weeks after stopping ART, so it's not known if viral load failed to rebound or if there was a transient increase that was rapidly controlled. Viral load has now remained undetectable for 8.75 years and counting, making this one of the longest reported cases of HIV remission. Another example is a French teenager first reported in 2015 and described in a paper in **The Lancet HIV** last year who has contained viral load to undetectable levels for over 12 years, after receiving a more prolonged course of ART in early life. [3, 4]

The researchers have conducted multiple analyses to try and gain insight into the factors that may have contributed to the outcome. Measurement of the HIV reservoir using a sensitive test for total HIV DNA revealed similar levels after one year and at 9.5 years of age: around 5 copies per million peripheral blood mononuclear cells (PBMC). However, no replication-competent virus could be detected using two different culture methods. Virus sequencing showed that the child was infected with HIV-1 from clade C, the most prevalent strain in South Africa.

The ELISA HIV antibody test was negative but weak reactivity to Gag p40 and p24 was detectable by Western blot. One exception to the generally weak HIV-specific antibody responses was a high IgA2 (a type of mucosal antibody) response to the gp41 protein. In studies of cellular immunity, a low-level CD4 T cell response to the HIV Gag protein was discernible with a whole blood intracellular cytokine assay, but no HIV-specific CD8 T cells could be detected.

Additional parameters that were investigated included the density of CCR5 molecules on CD4 T cells, which was found to be lower than HIV-negative controls – it is perhaps possible that lower CCR5 density contributed to the maintenance of an HIV-specific CD4 T cell response by reducing the susceptibility of these cells to HIV infection. Encouragingly, levels of immune activation were similar to HIV negative individuals and lower than those observed in elite controllers (in the latter group, elevated immune activation has been associated with disease progression despite persistently low viral loads). [5]

PD-1 expression was found to be high on both CD4 and CD8 cells compared to HIV- individuals and elite controllers; the significance of this finding remains to be elucidated. None of the beneficial HLA alleles that have been associated with elite control were present, although the child was heterozygous at all HLA loci and this has been linked to a better prognosis compared to homozygosity. [6]

The researchers note that other factors beyond the temporary course of ART likely contributed to the salutary outcome – the majority of participants in both the 40- and 96-week immediate ART arms of the CHER trial had met the criteria for restarting treatment by the time the study ended, and no other cases of HIV remission have yet been identified. [7]

The hope is that additional analyses will uncover novel correlates of immune control and aid the design of interventions aiming to induce HIV remission in larger numbers of HIV-positive individuals.

The news coverage of the case – which has been extensive – appears to have generally been accurate, although the BBC erred by describing the child as "virtually cured" in their headline – it is not known if viral load might rebound at some point in the future, as has occurred in some other examples of HIV remission. There are articles describing the child as either a girl or a boy, but Amy Green from the South African Health News Service interviewed Avy Violari and reports that gender is not being disclosed in order to protect the individual's privacy.

The New York Times article, authored by Donald McNeil Jr, has some poor mistakes: the opening paragraph erroneously states that the ART was given at "high doses" when the CHER trial employed normal pediatric dosing. Later in the piece, individuals who are homozygous for the CCR5delta32 mutation, which confers a high degree of resistance to HIV infection, are mistakenly referred to as elite controllers (elite controllers are HIV positive individuals who naturally contain HIV viral load to low levels in the absence of ART). Timothy Brown, the one individual considered cured of HIV infection, is said to have received a bone marrow transplant from an elite controller, which is not the case - his bone marrow donor was HIV negative and homozygous for the CCR5delta32 mutation. One of these errors has since been corrected, but two remain at the time of writing.

The first mention of the South African HIV remission case at the IAS conference came in a presentation by Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID) during the "Challenges and Opportunities in HIV Science" session [8] – this appears to explain the timing of the NIAID news release about the study. [9] Fauci's talk was titled: "Sustained ART-free HIV remission: opportunities and obstacles" (the slides are available for download) and he

offered some additional nuggets of news, as well as discussing issues to be considered when evaluating the remission cases that have been reported to date. [10]

In particular, he outlined two potential major contributors to HIV remission: in some cases, the size of the HIV reservoir may be so small that after an ART interruption the few latently infected CD4 T cells that are present remain dormant for an extended period, before one or more cells is activated and starts producing HIV (triggering viral load rebound). Fauci referred to this phenomenon as "stochastic reactivation," and evidence suggests it explains the period of remission documented in the Mississippi baby who was started on ART prior to developing detectable immune responses to HIV (it has also been posited to explain the adult examples of the Boston patients and an individual treated within days of infection at UCSF – see below). [11, 12]

In other instances – such as the South African child, the French teenager and the VISCONTI cohort participants – evidence suggests immunological control of HIV replication is contributing, although the exact mechanisms are unclear. [13]

Fauci noted that both of these phenomena could also be operational simultaneously, but presently the short answer as to precisely what explains a given case of HIV remission is: "we don't know."

On the topic of interventions aiming to induce HIV remission, Fauci offered a glimpse of unpublished data from two studies. The first was a clinical trial conducted at the National Institutes of Health (NIH) Clinical Center that evaluated the effect of therapeutic vaccination in HIV positive individuals started on ART within 12 weeks of a diagnosis of acute or early infection, who had maintained undetectable viral loads for over a year. [14]

A total of 30 participants enrolled, with 15 randomised to receive a prime-boost HIV vaccine regimen developed by Profectus Biosciences (comprising DNA and vesicular stomatitis virus vectors) and 15 randomised to receive placebo immunisations. The final vaccination was administered at week 48 of the study and, eight weeks later, all participants underwent a 16-week analytical ART interruption.

The results demonstrated that there were no significant differences in time to viral load rebound to over 40 copies/mL (or to over 400 copies/mL) between the vaccine and placebo groups. Fauci emphasised the importance of the placebo group by showing that at the end of the ATI period, 20% of controls had viral loads less than 20 copies/mL, 27% were below 400 copies/mL, and 40% were below 2,000 copies/ml. This finding may temper excitement about the single-arm study of therapeutic vaccination plus romidepsin that drew so much attention at CROI earlier this year. [15]

In that trial, the fact that 38% of participants maintained viral loads below 2,000 copies/mL at 4-6 months after an ATI was presented as evidence that the interventions had enhanced control of HIV replication, compared to historical studies of ART alone. Fauci suggested that preliminary clinical trials and animal studies using broadly neutralising antibodies (bNAbs) offer evidence that they may have more potential for enhancing post-treatment control of viral load than therapeutic vaccines.

Fauci's own laboratory has reported that administering an antibody against the alpha4-beta7 integrin to SIV infected macaques led to surprisingly robust control of SIV replication after an ART interruption, [16] and in his presentation he showed the unpublished results of recent experiments aiming to shed light on the mechanisms involved. The approach that the researchers took was to deplete different types of immune cells in the animals controlling SIV viral load, then assess whether this led to an increase in viral replication. The experiments compared:

- Antibodies to the CD8 receptor alpha chain, which deplete CD8 T cells, natural killer T cells (NKTs) and natural killer (NK) cells.
- Antibodies to the CD8 receptor beta chain, which deplete CD8 T cells.
- Antibodies to CD20, which deplete B cells.

A transient rebound in viral load was only seen in recipients of antibodies to the CD8 receptor alpha chain, indicating that NKTs and NK cells are making an important contribution to the observed control of SIV replication. A clinical trial investigating the anti-HIV effects of the anti-alpha4-beta7 integrin antibody vedolizumab, which is FDA-approved for the treatment of ulcerative colitis and Crohn's disease, is ongoing at the NIH Clinical Center, [17] and another is due to start soon at the Ottawa Hospital Research Institute in Canada. [18]

Timothy Henrich from UCSF gave another presentation involving HIV remission today, in the same poster discussion session during which Avy Violari described the South African case. Henrich reported details relating to an individual who was mentioned several times during CROI earlier this year. Both Henrich's abstract and slide presentation are available on the IAS conference website. [19]

The individual in question was diagnosed within an estimated 10 days after acquiring HIV infection, because the exposure occurred in a short window between screening for a pre-exposure prophylaxis (PrEP) programme and the baseline visit at which TDF/FTC PrEP was first administered. When the baseline test results came back showing the presence of HIV, TDF/FTC was quickly switched to a four-drug ART regimen including TDF/FTC, darunavir/r and raltegravir. No HIV could be detected in blood or tissue samples during ART, although a low level of viraemia was briefly detected in one out of 10 humanised mice administered a large volume of cells sampled from the individual (this novel test is known as the murine viral outgrowth assay).

After 34 months of continuous ART, an analytical treatment interruption was undertaken, and no viral load rebound occurred for 220 days, during which time no HIV DNA or RNA was detectable in plasma or sampled CD4 T cells. After this prolonged period of HIV remission, viral load rebounded and was initially detected at a level of 36 copies/mL. Six days later viral load had increased to 59,800 copies/mL and ART was immediately restarted. Sequencing of the HIV genome demonstrated that the rebounding virus was identical to that sampled at the time of acute infection.

In a collaboration with Alison Hill, mathematical modelling studies estimated the size of the HIV reservoir to have been approximately 200 latently infected cells prior to the ART interruption. Based on Hill's prior work, a latent HIV reservoir of this size confers only a small (~1%) chance of achieving a lifelong cure, due to the risk of stochastic reactivation of one or more of the latently infected cells. [20]

Henrich and colleagues continue to evaluate enrollees in PrEP projects for evidence of recent HIV infection, and he showed a slide documenting that another individual has been started on ART very early as a result of the effort. Follow up of this second individual is ongoing.

In addition to several sessions and presentations related to HIV cure research at the main conference [21], IAS hosted a pre-conference HIV Cure & Cancer Forum at the Institut Curie. The abstracts and many of the presentations have already been made available online, and a brief report from the meeting will follow in a separate blog post. [22]

Source

Jefferys R. TAG Basic Science Blog (24 July 2017)

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2017/07/hiv-remission-news-from-ias-2017.html

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IAS 2017: OTHER NEWS

Publications launched at IAS 2017

Simon Collins, HIV i-Base

The IAS 2017 conference is used as a focus for many reports and special publications.

New publications will be added to the list below as they become available.

WHO HIV drug resistance report

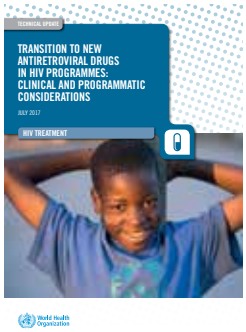
This new 70-page WHO report was produced with the Global Fund and the US CDS.

The report compiles current levels of HIV drug resistance in different key countries, with implications for choosing first-line ART.

In 6 of the 11 countries surveyed in Africa, Asia and Latin America, over 10% of people have drug resistance to at least one of the main HIV drug classes before starting treatment.

http://www.who.int/mediacentre/news/releases/2017/hiv-drug-resistance/en

Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations (WHO)



WHO has recommended adopting drug regimens with high potency, lower toxicity, high genetic barriers to resistance, usefulness across different populations and lower cost. The use of optimised drug regimens can improve the durability of the treatment and quality of care of people living with HIV.

Adopting optimised antiretroviral (ARV) drug regimens can significantly affect the speed at which the 90-90-90 targets are achieved, enhancing access to treatment and improving treatment outcomes with impact on treatment adherence, viral suppression and the quality of life of people living with HIV, reducing pressures on health systems and the risk of HIV transmission.

http://apps.who.int/iris/handle/10665/255887

http://apps.who.int/iris/bitstream/10665/255888/1/WHO-HIV-2017.20-eng.pdf (PDF)

HIV pipeline report (i-Base)

Annual review of the HIV research pipeline, this year available in full and summary versions.

This year this report is part of the i-Base Fit for Purpose Report on Treatment Optimisation (see below).

http://i-base.info/htb/31895

Fit for Purpose (i-Base)

The July 2017 Fit for Purpose: antiretroviral treatment optimisation for adults and children report provides a comprehensive overview of strategies for treating HIV globally. This includes timelines for new generic drugs and alternative dosing.

It includes chapters on adult and paediatric pipeline reviews.

http://i-base.info/htb/31974

IAS/Lancet: Commission on the future of the HIV response and global health

This report on global responses to HIV is based on a programme launched at the previous IAS conference in Vancouver two years ago.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31874-3/fulltext

CONFERENCE REPORTS

9th International Workshop on HIV Paediatrics

21–22 July 2017, Paris

Introduction

The 9th International Workshop on HIV Paediatrics was held from 21–22 July 2017 in Paris.

The paediatrics workshop is the only HIV meeting devoted to research in prevention and treatment for infants, children and adolescents. Since 2009 it has preceded the IAS conference and dual submissions to both meetings are permitted.

As the meeting is so specific it often allows research that might be presented as a poster at IAS to be shown as an oral abstract, to a dedicated audience, and provides a good opportunity for focused discussion.

The abstracts as well as slides of the presentations and webcasts will be online when consent has been provided.

http://www.infectiousdiseasesonline.com

Reports in this issue of HTB are:

- Chewable raltegravir tablets can be crushed and dispersed in liquid for young children
- Inconsistencies between real-world data from UK and Ireland and EU recommendations for new antiretrovirals in pregnancy

Chewable raltegravir tablets can be crushed and dispersed in liquid for young children

Polly Clayden, HIV i-Base

Chewable raltegravir tablets can be crushed and stirred until dispersed in water, apple juice, or breast milk and given to younger children according to WHO weight bands. [1]

In vitro and modelling data suggest that this method of administration will result in therapeutic plasma concentrations. But, there are not yet efficacy/safety data to support such use of the chewable formulation.

There are limited suitable antiretroviral formulations for young HIV positive children. Raltegravir is the only integrase inhibitor approved for treating children down to 4 weeks of age.

Current raltegravir options for children using weight-based dosing at approximately 6 mg/kg twice daily include: chewable tablets (25 mg, 100 mg scored) for children ≥10 kg; oral granules for suspension for infants and younger children ≥4 weeks and ≥3 kg.

The granules for oral suspension are complicated to administer – they need careful measurement with a syringe for both reconstitution and dosing, and clean potable water.

The raltegravir originator company, Merck, conducted a study to investigate: 1. If crushing the chewable tablets could be used instead of the granules for oral suspension. 2. If the use of multiple tablets would meet established pharmacokinetic (PK) targets for safety and efficacy. The results were presented at the 9th International Workshop on HIV Paediatrics.

In order to assess chemical stability before dosing in liquid, the investigators dispersed one 25mg chewable tablet by agitation (stirring) for 10–15 minutes in 5 mL of each of the following vehicles: tap water, sterile water, apple juice, and breast milk, at room temperature.

Assay and degradable analyses were performed in two sets of samples for each liquid immediately after dispersion and after 30 minutes. Drug analyses were by reverse phase HPLC at room temperature under ambient conditions. Lower limit for detection of potential degradation products was 0.02%.

This revealed, after crushing in 5 mL of liquid, raltegravir chewable tablets achieved adequate stability for 30 minutes with each vehicle. There was no loss of active raltegravir or formation of degradates after this time period. Initial vs 30 minute results: sterile water 102.5–103.5%, tap water 99.5–99.0%, apple juice 95.5–97.0%, and breast milk 96.4–97.3%; all degradates were below 0.02%. Raltegravir 25 mg chewable tablets can be considered stable in all the tested vehicles.

The group performed dosing simulations in NONMEM using a population PK model that described data for raltegravir chewable tablets and established PK targets: C12 >75uM (>33 ng/mL), AUC0-12 14-45 uM*hr (6–20 mg*h/L), Cmax <19.63 uM (8724 ng/mL).

Weight was a significant covariate in this model, which used WHO weight bands.

Modelling and simulation suggested that PK targets are achieved by giving twice daily doses in increments of 25 mg (as available using raltegravir chewable tablets), for children in weight bands between 3–25kg. Doses are shown in Table 1.

Table 1: Chewable raltegravir weight band doses

WHO weight band	Raltegravir dose
3 to 5.9 kg	25 mg
6 to 9.9 kg	50 mg
10 to 13.9 kg	75 mg
14 to 19.9 kg	100 mg
20 to 24.9 kg	150 mg

The 14–19.9 kg and 20–24.9 kg weight bands could use 1 and 1.5 100 mg chewable tablets.

Results from the modelling and simulations represent simplified dosing: current prescribing information for raltegravir granules for oral suspension uses 4 weight bands for 3–10/11 kg. Modelling supports merging 20/30 mg and 40/60 mg doses to follow WHO weight bands.

The use of raltegravir chewable tablets has not yet been investigated clinically and is not approved in children less than 10 kg. But these in vitro data show that crushing chewable tablets is feasible and modelling and simulations predict that administering raltegravir in this way to young children is expected to lead to drug exposures associated with safety and efficacy.

C O M M E N T

It is important that the company for responded to requests to look at the feasibility of this method of administration.

Although raltegravir is approved in young children four weeks and above – an age group where antiretroviral options are scarce – use of the granules for suspension formulation is tricky and using the chewable tablets should be easier.

The IMPAACT P1101 study of raltegravir-containing regimen in HIV and TB co-infected children will use the dispersed chewable tablet, starting dose of 12 mg/kg (up to a maximum dose of 800 mg) orally twice daily, with two NRTIs plus rifampicin-containing regimen for treatment of TB in infants and children from four weeks of age. [2]

This aims to simplify the higher dose needed to overcome the interaction with rifampicin, which would be extra complicated to administer with the granules for oral suspension. The study will generate some clinical data in a few young children receiving dispersed chewable raltegravir.

References

1. Teppler H et al. Crushing of raltegravir (RAL) chewable tablets for administration in infants and young children. 9th International Workshop on HIV Pediatrics 2017. 21–22 July 2017. Paris. Poster abstract 37.

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http://www.impaactnetwork.org/DocFiles/P1101/V3/FINAL%20P1101%20Version%203.0_24APR2017.pdf

Inconsistencies between real-world data from UK and Ireland and EU recommendations for new antiretrovirals in pregnancy

Polly Clayden, HIV i-Base

Linking European Medicines Agency (EMA) labelling with real-world use of newly approved antiretrovirals in pregnancy in UK and Ireland showed inconsistencies between recommendations.

Results from this study by UCL Great Ormond Street Institute of Child Health were presented at the 9th International Workshop on HIV Paediatrics.

Data on safety and pregnancy outcomes are limited for new antiretrovirals as pregnant women are excluded from registrational trials. The EMA issues detailed guidance to better assess risk of exposure in pregnancy and lactation, during the post-marketing phase.

The vertical transmission rate in UK and Ireland is less than 0.4%. This is because a high proportion of women (60% in 2012–2014) conceive while already taking antiretroviral therapy (ART) and those initiating ART in pregnancy start as early as possible.

In order to evaluate the consistency between EMA safety information and recommendations and clinical experience to date, investigators compared labelling and real world use of three newly approved agents: rilpivirine (RPV), dolutegravir (DTG), and cobicistat (COBI).

Data sources were: the EMA public database (the European Public Assessment Reports and the Summary of Product Characteristics) for safety information; and the National Study of HIV in Pregnancy and Childhood (NSHPC) – a comprehensive population-based surveillance study on all HIV positive pregnant women in care in the UK and Ireland.

Data reported to the NSHPC was from 4831 pregnancies with estimated date of delivery (EDD) from 1 January 2013 to 31 March 2017.

EMA data showed distinct warnings and recommendations, despite no preclinical findings showing specific hazards. All three agents were labelled: “no or limited data” from humans.

Recommendations ranged from “talking to your doctor” to “unless clearly needed should not be given in pregnancy” as well as advising use of contraception for FTC/TDF/RPV (Eviplera) and FTC/TDF/EVG/COBI (Stribild) fixed dose combination (FDCs)

The EU black triangle label (“this medicinal product is subject to additional monitoring”) applies to both DTG as a single (Tivicay) or FDC of ABC/3TC/DTG (Triumeq) and COBI as single booster (Tybost) or part of FTC/TDF/EVG/COBI. Additional information included: DTG crosses the placenta, and COBI showed an increased risk of postimplantation loss in reproductive toxicity studies in rats

The NSHPC recorded a substantial increase in the use of the three agents between 2013 and 2016. Of 4526 pregnancies reported with EDD during this period, the number exposed to a RPV- or DTG-containing regimen increased more than 10-fold: from 0.5% in 2013 to 5.6% in 2016 and 0.3% to 3.3%, respectively.

Out of 4831 pregnancies included, 343 were exposed to one of the three agents: 112 to DTG (52 at conception), 198 to RPV (165 at conception) and 33 to COBI (23 at conception).

Of 240 pregnancies exposed to ART at conception: 156 (82.5%) livebirths, 22 (11.6%) spontaneous abortions, 2 (1.0%) ectopic pregnancies, 7 (3.7%) terminations, 2 (1.0%) stillbirths, 1 lost-to-follow-up and 51 pregnancies continuing to term.

Of 189 pregnancies with known outcomes, 6 (3%) had birth defects. See Table 1.

Table 1: Birth defects NSHPC

	Outcome	Defect	Regimen
1	Livebirth	Coarctation of aorta	FTC/TDF/RPV
2	Livebirth	Down’s syndrome	FTC/TDF/RPV
3	Livebirth	Encephalocele	FTC/TDF/RPV
4	Livebirth	Extra digits (polydactyly)	ABC/3TC/DTG

5	Termination	Trisomy 18	FTC/TDF/EVG/COBI
6	Termination	Cystic hygroma	FTC/TDF/EVG/COBI

These results show inconsistencies between EMA recommendations – which mostly advise avoiding use in pregnancy – with what happens in clinical practice. NSHPC shows use of new antiretrovirals soon after they are approved, including use at conception.

"There is a clear opportunity to develop this work further with the aim to draw stronger safety recommendations, to ensure better recommendations for patients and clinicians", the investigators wrote.

C O M M E N T

The gap between what happens in clinical practice and what the label says is usually quite wide for antiretroviral use in pregnancy. Although national and global guidelines are usually quicker to take data into account as it emerges from studies and routine use.

It would be helpful if originator companies were a bit more proactive in submitting new findings to regulatory agencies and these were reflected in the label in a timely fashion.

Ref: Rasi V et al. Real-world use of newly authorised antiretrovirals in pregnancy in the UK/Ireland and available safety data. 9th International Workshop on HIV Pediatrics. 21–22 July 2017. Paris. Poster abstract 78

TREATMENT ACCESS

First dolutegravir-based FDC gets FDA tentative approval

Polly Clayden, HIV i-Base

On 7 August 2017, the first generic dolutegravir-based fixed dose combination (FDC) by Mylan pharmaceuticals received tentative approval from the US FDA.

This is for a New Drug Application for dolutegravir, lamivudine and tenofovir disoproxil fumarate 50/300/300 mg tablets (TDF/3TC/DTG or TLD).

TLD combines antiretrovirals from two originator manufacturers: ViiV Healthcare's DTG and 3TC (via a license through the Medicines Patent Pool) and Gilead Science's TDF.

TLD will be available as a first-line regimen for people with HIV in countries with access to generic ARVs.

C O M M E N T

This is groundbreaking news: global use of integrase-based ART needed not just generic dolutegravir but a generic FDC.

As of June 2017, more than 20 low- and middle-income countries have included or are planning to include DTG in their national guidelines. [2] Botswana and Brazil have started providing DTG nationwide and Kenya, has started a pilot programme of phased introduction (similar programmes are planned in Uganda and Nigeria). To date these early adopter countries have used either originator products (Brazil and Botswana) or more recently (Kenya being the first country to introduce generic DTG) as a single generic formulation plus 2 NRTIs. [3]

The WHO pre-qualification programme is also assessing this version of TLD with results expected at the end of the year. More submissions of DTG, both single and FDC formulations are expected over the next year or two. [4] By the end of 2017 DTG single is expected to be registered in 56 countries and DTG-based FDCs in 38 countries.

This version of TLD was notable for its swift tentative approval (it only took 6 months) and hopefully other products will follow suit. Then the time to obtain local registration (or a waiver) will be a hugely important factor for programmes transitioning to new DTG-based formulations. Increased availability of approved and/or prequalified generic FDCs will assure both price competition and supply security and will give national programmes confidence to make the transition.

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4. CHAI. ARV market report: the state of the antiretroviral market in low- and middle-income countries, 2015–2020. Issue 7, October 2017. https://clintonhealthaccess.org/arv-mket-report-2016

ANTIRETROVIRALS

FDA grant priority review for ibalizumab

Simon Collins, HIV i-Base

On 30 June 2017, Theratechnologies issued a press release about the US FDA decision to accept a priority review for ibalizumab, a monoclonal antibody currently in phase 3 studies as a treatment for multidrug resistant HIV.

The FDA also set a timeline of January 2018 to receive the application. Priority review reduces the time taken to review the application, once submitted, from approximately 10 months to 6 months.

The review was based on phase 3 results from the single arm, 24-week TMB-301 study that used ibalizumab in addition to optimised background ART in people with drug resistance to drugs from at least three classes.

Ibalizumab is an HIV entry inhibitor that is given by infusion every two weeks. It was also designated a breakthrough therapy by the FDA in 2015 and was granted Orphan Drug designation in 2014.

Ibalizumab is being developed by TaiMed Biologics, but with be marketed and distributed by Theratechnologies in the US

Reference

FDA grants priority review to HIV monoclonal antibody and long-acting investigational antiretroviral ibalizumab. (30 June 2017)

http://theratech.com/sites/default/files/news_release_en/nr-20170630-en.pdf (PDF)

HIV TRANSMISSION AND PREVENTION

Controversial PrEP study from NHS England due to start in September

Simon Collins, HIV i-Base

On 3 August 2017, a press release from NHS England provided an update on the upcoming PrEP IMPACT study. [1]

This study plans to enrol 10,000 people at up to 200 sexual health clinics across England, providing open-label oral PrEP to all participants. Some people might be able to enrol through their GP.

The study is supported by NHS officials, doctors and community groups that have been involved in the study.

However, as a strategy, the research is controversial for several reasons.

Firstly, there is already robust evidence that proves PrEP is both safe and effective. PrEP was approved in the US in 2012 and in Europe in July 2016 and many countries already make PrEP widely available, including in the US, France and Scotland.

So although the study will provide 10,000 people with access to PrEP, it can also be seen as a strategy to postpone routine access. NHS England has already delayed the decision on PrEP access by three years (the UK PROUD study released results in October 2014). In launching the new three-year study, NHS England further postpones the decision on providing PrEP - extending the delay to seven years.

Instead, on principal, doctors who have patients who are at high risk of HIV should also be able to prescribe PrEP, based on appropriate guidelines, especially to those who are not able to enrol in IMPACT.

Secondly, while 10,000 people might initially sound generous, other researchers including Andrew Hill who showed data at the BHIVA conference earlier this year, estimating the likely need to be closer to 150,000 people to reduce HIV nationally. Based on background incidence of 2%, treating 10,000 people might only prevent 200 infections - and there have been 6000 new diagnoses each year for the last decade. [2]

Also, for example, more than 5,000 people might already be using generic PrEP bought online – likely to be a leading factor in the recent reports of dramatic drops in HIV incidence reported from five high-incidence sexual health clinics. [3, 4]

That 10,000 might be too small a slice, is shown by rapid enrolment of 12,000 people within a year in several similar implementation PrEP studies in Australia (PrEPX, VicPrEP and EPIC) – a country with a smaller population and reduced HIV incidence. [5, 6, 7]

This is especially important in terms of broadening access to PrEP to include anyone whose circumstances support a benefit from PrEP but who were not included in the PROUD study. In the UK this includes greater numbers of women, transgender women and men, young people, higher proportions of black and ethnic populations etc. IMPACT currently plans to ring-fence up to 1000 study places for participants who are not gay men, but the details for how this will run nationally are unclear.

Rather than plan IMPACT as a long drawn out three-year study, IMPACT should be urged to rapidly enrol, and then expand if demand in the study is high. The cost from preventing HIV transmissions will already have saved NHS England the cost of the current study many times over.

Thirdly, in addition to expanding access, IMPACT should have early criteria for evaluating early success of the study. Research, by definition, is designed to answer scientific questions, and many studies are able to answer these questions much earlier than originally planned.

Three recent examples of early-study answers include the PROUD and IPERGAY PrEP studies and the international START study. In these cases the care and rigour of the study approach provided robust evidence much earlier than expected.

Fourthly, as background, IMPACT will use generic formulations of PrEP that are already approved in Europe and are priced at 90% lower than the current brand formulation. This will enable the NHS to use generic drugs while the current patent is still being challenged - enabling ten times as many people to be prescribed PrEP for the same price. [8]

Given that cost of patented PrEP is one of the reasons for NHS England delaying access, as soon as generic PrEP becomes approved in the UK – expected much sooner than the three-year life of this study – then access outside the IMPACT study should be urgently reviewed.

C O M M E N T

This study is primarily about the cost of PrEP and deferring NHS England providing access.

Although 10,000 people might now access PrEP in IMPACT, in the three years since the UK PROUD study first reported results in October 2014, more than 15,000 people have already tested HIV positive.

Overall, this policy to run another "study" has delayed access, and highlights the low priority given to sexual health of people at highest risk.

The benefit from the IMPACT study is that it saves the NHS short-term budget by getting earlier access to generic PrEP.

By contrast, NHS Scotland are now providing PrEP even though this uses the higher price brand version. [9]

References

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HEPATITIS COINFECTION

UK outbreak of hepatitis A in gay men: shortages of HAV and HBV vaccines escalated to 'national incident'

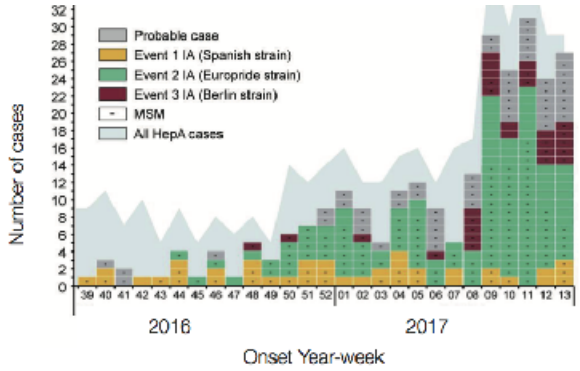
Simon Collins, HIV i-Base

In May 2017, Public Health England (PHE) published details of an ongoing investigation of an outbreak of hepatitis A (HAV) that had been occurring predominantly in MSM in London and other European cities for almost a year. [1]

Between July 2016 and 2 April 2017, 266 cases associated with the outbreak had been identified in England. At least 74% of these were among MSM, and 63% of cases were in London. Some cases in the wider population were linked to the outbreak.

The outbreak comprises three concurrently-circulating genotype 1a strains, previously not seen in England. Hepatitis A outbreaks caused by the same strains are concurrently occurring in 12 European countries and elsewhere in the UK outside of England. [2, 3]

Table 1. Hepatitis A cases in England (PHE)



This led to a joint recommendation from PHE, BHIVA and BASHH to offer vaccination to all at-risk gay men with one or more recent partners at GUM clinics in affected areas. [4]

Guidance was for all MSM attending GUM and HIV clinics should be opportunistically offered a single dose of adult monovalent hepatitis A vaccine, where available, unless they have documented evidence of two doses of hepatitis A vaccine or of previous hepatitis A illness.

Patients should not be asked to wait until results of HAV Ab levels. In the event of a shortage of the monovalent vaccine, some alternative options have been proposed using paediatric vaccines or combined hepatitis A and B vaccines. For example:

- CD4 count <500 cells/mm^3: two doses of paediatric hepatitis A vaccine.
- CD4 count ≥500 cells/mm^3: single dose of paediatric hepatitis A vaccine Remaining hepatitis A and B doses can be given using either monovalent or combination vaccine.
- For post exposure immunisation for HIV positive individuals schedules detailed in the Green Book and BHIVA should be followed. [5, 6]

On 8 August 2017, a new joint statement was published from PHE, BHIVA and BASHH. [7]

This now expands the concern about the vaccine shortage for hepatitis B (HBV) and notes that shortages of both HAV and HBV vaccines have been escalated to a national incident. It also includes new guidance for vaccine allocation for people living with HIV.

It also notes in respect to the HBV vaccine: "as manufacturers have reduced maximum ordering quantities for NHS Trusts, GUM and HIV clinics will have further limits applied to their orders, while other customers (such as travel clinics and GPs) will not be receiving any adult vaccine until further notice".

PHE has issued recommendations that include temporary dose sparing advice to preserve adult and paediatric monovalent hepatitis B vaccine stock for those at highest immediate need and with the greatest ability to benefit, and to sustain supplies over the period of shortage. [8]

A patient information leaflet has been developed for people who have been told that they wait for vaccine, although this leaflet makes no mention of HIV. [9]

C O M M E N T

Some London clinics with large HIV units are already reporting supply problems with both HAV and HBV monovalent vaccines.

Vaccine shortages are being reported in other European countries.

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FDA approves sofosbuvir/velpatasvir/voxilaprevir (Vosevi) second-line DAA HCV treatment in the US in the US

Simon Collins, HIV i-Base

On 18 July 2017, the US FDA approved a fixed dose combination of sofosbuvir/velpatasvir/voxilaprevir (400/100/100) for treatment of DAA-experienced adults with chronic hepatitis C (HCV).

The indication is for adults with genotype 1, 2, 3, 4, 5 or 6 with unsuccessful treatment using an NS5A inhibitor-containing regimen, or with genotype 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor.

Approval is based on results from the phase 3 POLARIS-1 and POLARIS-4 studies, which used 12 weeks of Vosevi in direct-acting antiviral-experienced chronic HCV-infected patients without cirrhosis or with compensated cirrhosis.

Sofosbuvir/velpatasvir/voxilaprevir is manufactured by Gilead Sciences and marketed with the brandname Vosevi.

Reference

Gilead press statement. US Food and Drug Administration approves Gilead's Vosevi (sofosbuvir/velpatasvir/voxilaprevir) for re-treatment of adults with chronic hepatitis C virus. (18 July 2017).

http://www.gilead.com/news/press-releases

FUTURE MEETINGS

Conference listing 2017/18

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

Registration details, including for community and community press are included on the relevant websites.

21st Annual Antiviral Therapy & Drug Resistance Meeting

21 September 2017, London

www.mediscript.ltd.uk

8th International Workshop on HIV & Ageing

2–3 October 2017, New York, USA

www.virology-education.com

cliniQ's 4th international Trans Health Matters conference

17 October 2017, venue tbc, London

https://www.eventbrite.co.uk/e/cliniq-trans-health-matters-2017-tickets-34763486524

19th International Workshop on Comorbidities and Adverse Drug Reactions in HIV

23–25 October 2017, Milan, Italy

www.intmedpress.com

16th European AIDS Conference

25–27 October 2017, Milan, Italy

www.eacsociety.org

International Workshop on HIV Drug Resistance and Treatment Strategies (IWHDR)

6–8 November 2017, Johannesburg

www.HIVresistance2017.co.za

Hepatology Highlights for the Healthcare Specialist in collaboration with BVHG

15 November 2017, London, UK

http://www.bhiva.org

BHIVA Autumn Conference

16-17 November 2017, London, UK

http://www.bhiva.orgHepatitis A

Conference on Retroviruses and Opportunistic Infections (CROI 2018)

March 4–7 2018, Boston

http://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 (September 2016)
- HIV & quality of life: side effects & better 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 (February 2015)
- Guide to HIV, pregnancy & women's health (December 2015)

New pocket guides

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

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

We hope these are especially useful as low literacy resources.

The leaflets use simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

Order publications and subscribe by post, fax or online

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Editor: Simon Collins

Contributing Editor: Polly Clayden

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