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EDITORIAL

Welcome to the January–March 2017 edition of HTB South.

This edition provides a round-up of i-Base conference reports over the past six months and is distributed with The Southern African Journal of HIV Medicine.

Topics include:

- Antiretrovirals, particularly those under investigation for optimised ART for low- and middle-income countries like dolutegravir and lower dose efavirenz.
- Research for prevention, including a burgeoning PrEP pipeline.
- Potential new strategies for controlling HIV such as antibody therapy.
- Pregnancy, maternal health and infant outcomes.
- Paediatric HIV including new drugs and virological response.
- Tuberculosis, for which universal treatment for multidrug resistant TB is possible within current budgets with generic production and new strategies for children.

You can also find us online on the HIV i-Base and Clinicians Society websites.

Happy reading!

The Southern African HIV Clinicians Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinicians Society has grown to a membership of over 3,000 in the Sub Saharan region and internationally – a clear recognition of the services and support provided.

The Southern African HIV Clinicians Society is the largest special interest group within the South African Medical Association (SAMA). It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

For more information about the Society or on how to become a member please visit: **http://www.sahivsoc.org**

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CONFERENCE REPORTS

Congress on HIV Therapy, 23-26 October 2016, Glasgow

Introduction

This year the biennial Glasgow conference was held from 23-26 October 2016.

The meeting has a single-track programme making it easy to attend and follow everything. Important European research is often shown in Glasgow before it is presented at CROI. The Glasgow meeting also supports broad access by webcasting oral presentations.

The programme and abstract book are already online. Webcasts are usually added the day after they were presented.

Programme

http://www.hivglasgow.org/scientific-programme

Webcasts

http://www.hivglasgow.org/webcasts

Abstract book

Published as a supplement to the Journal of the IAS. International Congress of Drug Therapy in HIV Infection 23-26 October 2016, Glasgow, UK. JIAS (19) supplement 7 (2016). Online in several formats including PDF and html.

http://jiasociety.org/index.php/jias/issue/view/1485

The following reports from this conference are included in this issue of HTB South.

- Dolutegravir-based ART in combination with rifampicin-based TB treatment is safe in a small cohort of co-infected patients
- Once-daily raltegravir formulation matches twice-daily results in age, gender, race and baseline viral load/CD4 subgroup analyses
- Further reports of CNS-related side effects with dolutegravir

Dolutegravir-based ART in combination with rifampicin-based TB treatment is safe in a small cohort of co-infected patients

Polly Clayden, HIV i-Base

Twice daily dolutegravir in combination with rifampicin was well tolerated and produced good outcomes in a small retrospective study presented at HIV Drug Therapy Glasgow 2016. [1]

A rifampicin-based regimen is first-line TB treatment worldwide and co-administration of HIV and TB treatment is now standard of care. But there are significant drug interactions with ART as rifampicin is a potent inducer of cytochrome p450 and UGT.

Dolutegravir is a substrate of UGT1A1 and CYP3A4 so co-administration with rifampicin decreases dolutegravir plasma concentrations.

A previous phase 1 study showed 50 mg dolutegravir twice daily taken with rifampicin gave dolutegravir concentrations similar to those with 50 mg once daily. [2]

Muge Cevik and colleagues from Leeds Teaching Hospitals presented data from a retrospective case note review of TB/HIV co-infected patients who received rifampicin-based TB treatment with dolutegravir based ART. In this cohort, dolutegravir is used in co-infected patients who experience side effects with efavirenz or where efavirenz is contraindicated.

The investigators identified seven people (six women) who received a dolutegravir-based regimen in combination with rifampicin. Their median age was 41 years (range 27 to 48) and all were of black African origin. Five were ART naive. Three received dolutegravir with abacavir and 3TC and four FTC/TDF.

Median baseline CD4 count was 90 copies/mL (range: 3 to 365). Five people had very low CD4 count at baseline (<100 cells/mm3), four had viral load >100,000 copies/mL and only one was undetectable. At six months from starting ART, median CD4 count was 230 cells/mm3 (range: 104 to 625) and all but one had undetectable viral load.

One ART-experienced patient had viral load of 240,000 copies/mL at baseline. This was someone with transmitted antiretroviral resistance mutations to NRTIs (T69 deletion) and NNRTIs (Y181C and G190A). She had well documented poor adherence and had stopped her HIV treatment completely before re-starting ART with FTC/TDF plus dolutegravir (twice-daily) two weeks after starting TB treatment. At six months her viral load was 3,100 copies/mL. A month later she was undetectable but resistance testing showed a new M184 mutation and her regimen was changed.

All participants completed TB treatment and none experienced grade 3/4 side effects or TB-IRIS.

COMMENT

Alongside that in pregnant women, lack of data in people receiving concomitant TB treatment was one of the main reasons for WHO to recommend dolutegravir-based first-line ART as an alternative rather than preferred regimen. [3]

So far the evidence for using dolutegravir 50 mg twice daily in the presence of rifampicin comes from the PK study in HIV negative volunteers (fasted) mentioned above. Robust clinical data are urgently needed to demonstrate the efficacy, safety and tolerability of twice daily dolutegravir in combination with rifampicin.

The originator company ViiV Healthcare is sponsoring an open-label phase 3 study of dolutegravir (DTG) vs efavirenz with rifampicin co-treatment with an estimated primary completion date of December 2017.

In the meantime, there are probably a few small "real life" studies or reports of such co-treatment emerging – like this example from Glasgow. These smaller studies will need careful evaluation, to see how rigorous the methodology is.

But in the absence of better data – but expected increased use of dolutegravir, including in low-income settings [5] – it might be possible to add these to the interim data from the main clinical trial when the time comes to look at the evidence for the next iteration of the guidelines in 2017.

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Further reports of CNS-related side effects with dolutegravir

Simon Collins, HIV i-Base

Several studies at Glasgow 2016 provided additional information about real world experience with the integrase inhibitor dolutegravir.

Although registrational studies showed that dolutegravir has higher efficacy and fewer side effects compared to many other drugs, post marketing experience has included higher reports of CNS-related side effects in a minority of patients.

These CNS symptoms include dizziness, nervousness, depression, headache, reduced concentration, insomnia and other sleep problems and other unexplained pain.

Four studies reported on retrospective analyses from clinical cohorts – two in Germany, one in Spain and one in the UK. Two other UK studies reported on generally good results from switching from efavirenz to dolutegravir. And an analysis from the manufacturer ViiV Healthcare included evidence supporting this being an issue, but tried to minimise the results by suggesting this was only seen in an "outlier" study.

The largest cohort report was presented by Michael Sabranski from the Infectious Diseases Centre in Hamburg and colleagues. This was a retrospective analysis from all treatment-naive patients who started on an integrase inhibitor based combination at two large German out-patient clinics from 2007 to 2016 (but which excluded patients in clinical studies). [1]

The analysis included 1704 patients who used 1950 integrase-based combinations.

Rates of discontinuations linked to any side effect vs neuropsychiatric side effects were 7.6% vs 5.6% for dolutegravir (n=985), 7.6% vs 0.7% for elvitegravir (n=287) and 3.3% vs 1.9% for raltegravir (n=678), see Table 1.

The difference between dolutegravir and other two integrase inhibitors for neuropsychiatric side effects was significant (p<0.0001).

In multivariate analysis, neuropsychiatric side effects that led to dolutegravir discontinuation were observed significantly more frequently in women (hazard ratio [HR] 2.64; 95%CI: 1.23 to 5.65, p 0.012), patients older than 60 years (HR 2.86; 95%CI: 1.42 to 5.77, p 0.003) and HLA-B*57:01-negative patients who started abacavir at the same time (HR 2.42; 95%CI: 1.38 to 4.24, p 0.002).

These findings did not change when excluding patients who started in 2016 (following greater awareness of these side effects), although starting in 2016 (compared to 2014/2015) had a HR 11.36 95%CI 4.31 to 29.41, p<0.0001.

Symptoms generally resolved quickly after discontinuation (although they returned in six people who were later re-challenged with dolutegravir). Also importantly, no association was found in people with previous intolerance to efavirenz.

Table 1: Neuropsychiatric side effects leading to discontinuation

	dolutegravir	elvitegravir	raltegravir
N	985	287	678
Insomnia/sleep problems	36	2	4
Poor concentration	8	0	0
Dizziness	13	1	3
Headache/ paraesthesia	16	1	6
Depression	7	0	1

A second German study reported on 411 patients who were enrolled between March and May 2016 into the prospective non-interventional DOL-ART cohort to look at responses to dolutegravir outside a clinical study. This was a largely treatment experienced group with only one quarter being treatment-naive. During the first year 10.7% of patients experienced side effects with 4.4% discontinuing dolutegravir for this (including 1.2% for depression).

The Spanish study was a retrospective analysis of dolutegravir-related discontinuations from Hospital Ramon y Cajal in Madrid, presented by Maria Vivancos-Gallego and colleagues. [3]

From September 2014 to May 2016, 827/2470 patients (33.5%) using dolutegravir (naive and experienced, with 70% using single tablet combination with abacavir/3TC), 104/827 (12.6%) later discontinued dolutegravir for any reason. Side effects were the primary reason in 36/104 cases (34% of discontinuations and 4.3% of people using dolutegravir overall).

Most frequent toxicities leading to drug interruption included headache (n=9), high cholesterol (n=8), insomnia (n=7) and dizziness (n=6). One case was reported of serious mood disorders which recovered soon after discontinuation.

A similar retrospective analysis compiled from 178 patients using dolutegravir at the Royal Liverpool Hospital in Liverpool from June 2013 to June 2016 was presented as a poster. [4]

Approximately 29% were treatment-naive (52/178) and 71% were treatment experienced (126/178). Baseline demographics included: 72% men and 28% women; 78% Caucasian, 20% African/Caribbean and 2% Asian/other; and with median age 40 years (range 18 to 76).

Overall, side effects were recorded for 59/178 (33%) of this group with 20% of people (35/178) reporting CNS side effects. Other side effects included gastrointestinal (10%), neurological (7%), musculoskeletal (3%), lethargy (3%), skin related (2%) and urological (1%).

Two UK studies, presented results from people switching to dolutegravir because of neuropsychiatric side effects on efavirenz-based combinations.

An open label study randomised 40 patients with CNS side effects on efavirenz-based combinations to either immediately switch to dolutegravir or to switch following a four-week delay. The primary endpoint was rate of CNS toxicity measured by patient questionnaire at 4 weeks with numerous tolerability-related secondary endpoints. [5]

This group was largely male (38/40) with mean age 48 years (range 28 to 67).

CNS scores were significantly improved at 4 weeks post-switch and maintained at 12 weeks ($p<0.001$ at both time points). Statistically significant reductions were also reported for abnormal dreams ($p<0.001$), dizziness and depression ($p=0.008$) and improved for anxiety and depression scores, quality of life and quality of sleep.

In a related study, Michael Keegan from the Chelsea and Westminster Hospital in London reported on markers that might be related to the (currently unknown) pathogenesis of CNS complications associated to efavirenz. [6] Both indoleamine 2,3-dioxygenase-1 activity (IDO-1) and kynurenine/tryptophan ratios (KYN/TRP) improved following a switch from efavirenz to dolutegravir and these results also correlated with self-reported improvement of symptoms. Severe CNS side effects that included suicidal ideation was only reported in one case. Discontinuation rates were low however, with only 10/178 people stopping treatment (6%) with 8/10 (4%) being due to side effects.

Finally, ViiV Healthcare presented an analysis in a poster on psychiatric side effects in four randomised, blinded, placebo-controlled treatment-naive phase 3 studies. [7]

This included 2634 participants, half of whom received dolutegravir. Of the four studies presented (SPRING-2, SINGLE, FLAMINGO and ARIA), only one reported psychiatric side effects at higher than 5%. When Romina Quercia from ViiV presented a summary of this poster in an oral discussion, the results were controversially down-played as this study being an outlier due to lack of investigator assignment of the side effects being linked to the investigational drugs.

In practice, however, the outlier (SINGLE) was the only study where researchers would have been actively looking for CNS-related side effects. It was the only study with efavirenz in the comparator arm and it also included a questionnaire on CNS events. In SINGLE, anxiety was reported by 7% vs 7%, depression by 8% vs 10%, insomnia by 17% vs 11% and sleep problems by 10% vs 21%, all in the dolutegravir vs efavirenz groups respectively.

Most of these were low grade reports and the number of people discontinuing treatment were low, in SINGLE these occurred less often for the dolutegravir vs efavirenz group respectively (anxiety 0 vs 4, depression 1 vs 7, insomnia 1 vs 3 and sleep problems by 2 vs 7).

While ViiV tried to explained the results from SINGLE as at least partially due to a design bias that involved more careful receding of CNS-related side effects because efavirenz was the comparator, the double-blind study design actually makes this the study that would have been most likely to report unbiased results.

COMMENT

These real-world reports of CNS-related side effects with dolutegravir are similar to those from other research groups that we reported previously in HTB. [8, 9, 10]

The results do not detract from the importance of dolutegravir as an essential new HIV drug. Instead they highlight an area where greater care is needed when using the drug.

It is also reassuring that previous CNS problems with efavirenz are not predictive of similar risk with dolutegravir – indicating a likely different mechanism. However, the increased associations reported by Sabranski et al, with sex, age and abacavir use deserve further attention.

In discussions at the conference, few doctors were surprised by the results, with most reporting similar experiences when they have switched small but noticeable numbers of patients to alternative drugs because of CNS-related side effects.

The revised version of the EACS guidelines (October 2016) now includes a stronger reference to CNS side effects with dolutegravir. [11]

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Once-daily raltegravir formulation matches twice-daily results in age, gender, race and baseline viral load/ CD4 subgroup analyses

Simon Collins, HIV i-Base

The once-daily formulation of raltegravir showed similar efficacy and safety results compared to the original twice daily formulation across all demographic and baseline subgroups, further supporting non-inferiority compared to the current twice-daily version. [1]

The new formulation is dosed at 1200 mg once-daily (requiring 2 x 600 mg tablets) compared to the original formulation (dosed at 1 x 400 mg tablet twice-daily).

The new analysis was presented by Pedro Cahn from Fundacion Huesped, Buenos Aires, using pre-specified subgroups in the phase 3 ONCEMRK study.

The findings add to the primary efficacy and safety results that were presented at the IAS conference in Durban in July 2016 (that were also reported in HTB). In summary, 89% of participants suppressed viral load to <50 copies/mL at week 48 for both formulations with similar CD4 increases and safety results. [2, 3]

As with the primary analysis, the sub-group analysis found no differences between formulations by baseline viral load (above/ below 100,000 and 500,000 copies/mL), CD4 count (above/below 200 cells/mm3), age (above/below median 34 years), gender, race/ ethnicity or coinfection with HBV or HCV. No differences were seen by geographical location or for clade B vs C.

Side effects were also similar between the two formulations for all sub-groups.

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CONFERENCE REPORTS

2nd HIV Research for Prevention Conference (HIVR4P), 17–20 October 2016, Chicago

Introduction

This second biennial HIV Research for Prevention (HIVR4P) conference was held this year in Chicago from 17 to 21 October.

Although the conference programme is online, this does not link to the study abstracts, but the abstracts are available as a PDF file. These are also available using an App that is free to download.

The programme was very varied and included a strong focus this year on the pipeline for new formulations and compounds for pre-exposure prophylaxis (PrEP).

Importantly, all oral sessions are webcast 24 hours after the presentations.

Abstracts are published as an open-access supplement to AIDS Research and Human Retroviruses. (http://www.liebertpub.com/aid). Many conference posters are available to view and download online.

Programme:

http://www.professionalabstracts.com/hivr4p2016/iPlanner/#/grid

Webcasts:

http://webcasts.hivr4p.org

Abstract book:

http://hivr4p.org/images/HIVR4P_2016_Abstract_Book.pdf (PDF)

App:

Search Apple Store or PlayStore for "HIVR4P2016″

Posters:

http://www.abstractstosubmit.com/hivr4p2016/eposter

The following reports from this conference are included in this issue of HTB.

- A burgeoning PrEP pipeline: new drugs, formulations and delivery options
- Second case of drug resistant HIV infection in person adherent on PrEP
- TDF/FTC can be used as PrEP by breastfeeding mothers without risk to the baby
- Potential for EFdA as PrEP to prevent HIV transmission in women and their infants
- Antibody therapy leads to sustained post-treatment SIV control in macaques

A burgeoning PrEP pipeline: dozens of new drugs, formulations and delivery options

Simon Collins, HIV i-Base

A clear highlight for HIV R4P 2016 was the unexpected volume of research into new molecules and formulations for PrEP.

This large specialised event has worked effectively to focus on prevention research in a meeting that is large enough to include diversity but that is still small enough to meet and talk with researchers and to get a comprehensive overview of both preclinical and clinical studies.

The diversity of the studies is show by the number of new compounds being studied for PrEP. See also Table 1.

- Currently approved antiretrovirals (lamivudine, emtricitabine, tenfovir-DF, TAF, raltegravir, elvitegravir, darunavir, rilpivirine, etravirine and maraviroc).
- New compounds from existing classes: NNRTIs (dapivirine, MIV-170, IQP-0528); integrase inhibitors (cabotegravir, MK-2048); entry inhibitors (vivriviroc, 5P12-RANTES, DS003/BMS-599793, PIE-12 trimer D-peptide, Nifviroc); and NRTIs (EFdA).
- New compounds from new classes: neutralising antibodies (VRC01, griffithsin).

It was similarly impressive to see the range of new delivery systems and formulations that are in development. See also Table 2.

- Single and multi-compound vaginal rings.
- Other vaginal/rectal inserts or suppositories often designed to rapidly dissolve within a minute or two.
- Vaginal and rectal gels – sometimes developed for both or only one compartment.
- Small, thin fast-dissolving vaginal films of nanoformulations that instantly dissolve on contact with moisture. Including MK-2048, vivriviroc, TDF, VRC01 and others. These films deliver similar drug levels as gels but are much less messy.
- Long-acting soft implants – incorporating long-acting slow release formulations into something similar to a 1 mm in diameter, 2 cm long strip of cotton-like material that can be inserted under the skin, for example at the back of the neck.
- Long acting injections (cabotegravir).
- Fast absorbing small-volume rectal formulations that are designed to be rapidly absorbed into rectal tissue, similar to an enema.

Many of the new studies incorporated two, three or four compounds into new formulations, adding experimental compounds to already-approved drugs.

Together, this collective body of research suggest a huge potential for PrEP to become better and easier to use.

Other than cabotegravir LA injections and TAF which are in late phase studies by the drug manufacturers, this majority of this research at the meeting was almost entirely driven and presented by independent academic research groups, supported by either public or charitable funding. Although some pharmaceutical companies provided support in kind with drugs, many of the researchers said that this was often not the case, with some research groups having to manufacture their own versions of the active compounds of unlicensed compounds.

This pipeline also sets a challenge to regulators, funders and researchers to develop approval pathways that might compare multiple investigational compounds and formulations in the same study – both for faster proof of principal and to reduce research costs.

Many of the selected references included below could have been categorised under several sub-headings – (ie as new compounds and gels and multi-function combinations) but are only listed once, just to give an idea of the diversity of the PrEP pipeline.

Table 1: PrEP investigational compounds

Currently approved antiretrovirals	New compounds from existing classes	New compounds from new classes
NRTIs: lamivudine, emtricitabine, tenfovir-DF, TAF. NNRTIs: rilpivirine, etravirine. PIs: darunavir Integrase inhibitors: raltegravir, elvitegravir. Entry inhibitors: maraviroc	NRTIs: EFdA. NNRTIs: dapivirine, MIV-170, IQP-0528. integrase inhibitors: cabotegravir, MK-2048. Entry inhibitors: vivriviroc, 5P12-RANTES, DS003/ BMS-599793, PIE-12 trimer D-peptide, nifviroc	Neutralising antibodies: VRC01, griffithsin.

Table 2: PrEP pipeline for delivery systems and formulations

Formulation	Comment
Vaginal rings	Single and multiple compound. Combinations include coformulations of PrEP with contraception and STI treatment (HPV, HSV)
Vaginal and rectal inserts or suppositories	Designed to rapidly dissolve within a minute or two
Vaginal and rectal gels	Sometimes developed for both or only one compartment. Improved formulations – closer to lubricants.
Fast-dissolving films	Nanoformulations that instantly dissolve on contact with moisture. Including MK-2048, vivriviroc, TDF, VRC01 and others. Less messy than gels.
Long-acting soft implants	Long-acting slow release formulations that can be inserted under the skin similar to contraceptive implants.
Long acting injections	Cabotegravir
Rectal "douche" formulations	Hypo-osmotic for rapid absorption into tissue from small volumes.

COMMENT

This is an exciting period for prevention research. Even if only a few of these products in preclinical studies continue through clinical studies to approval, within 5-10 years TDF/FTC will look as archaic for PrEP as AZT monotherapy looks compared to modern ART.

Health advocates and PrEP users should be following (and driving) research into pipeline research just as treatment activists drove the development for ART.

One challenge – and it is a significant one – will be to develop better models and requirements for regulatory approval. PrEP studies are larger, more expensive and generally longer than ARV treatment studies with few surrogate markers of efficacy other than the impact on HIV transmission.

As PrEP becomes more effective the challenge to match results in control arms will become increasingly difficult, given that all participants in research studies need to receive the current standard of care as minimum.

This is likely to require public investment, perhaps using multiple new compound with early promise in the same studies.

SELECTED REFERENCES

All references are to the programme and abstracts of the 2nd HIV Research for Prevention Conference (HIVR4P), 17-21 October 2016. Abstracts are published as an open-access supplement to AIDS Research and Human Retroviruses. (http://www.liebertpub.com/aid). Many conference posters will be available to view and download online (http://www.abstractstosubmit.com/hivr4p2016/eposter/).

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VAGINAL AND RECTAL GELS

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FAST-DISSOLVING VAGINAL AND RECTAL TABLETS, IMPLANTS AND SUPPOSITORIES

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FAST-DISSOLVING FILMS (VAGINAL)

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Grab S et al. Extended release of a combination dapivirine/MK-2048 film for HIV prevention. Poster P07.43.

Ham A et al. IQP-0528: the pharmacokinetics of an anti-HIV NNRTI in non-human primates from various dosage forms. Poster PD03.05.

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Marshall LJ et al. Impact of vaginal ring geometry and drug loading on pharmacokinetics of dapivirine and darunavir in macaques. Poster abstract P07.13.

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DOUCHE APPLICATIONS

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Second case of drug resistant HIV infection in person adherent on PrEP

Simon Collins, HIV i-Base

Unfortunately, one of the studies that was widely reported from the R4P 2016 conference was a second case of HIV infection in a person who was very adherent to PrEP. [1]

This new report was presented as a late breaking oral abstract by Howard Grossman from the Cleveland Clinic, a doctor who is an advocate for PrEP and who has written about its benefits from a personal perspective.

The case involved an HIV negative man whose partner was on effective ART with undetectable viral load and who started daily PrEP in January 2016. Self-reported adherence was 100%, confirmed by high drug concentrations in plasma and hair samples.

This man tested HIV positive at his routine HIV screening in May using a 4th generation AgAb HIV test and only reported having condomless sex with two people other than his main partner (11 and 5.5 weeks earlier). His risk was as the active (insertive) partner. Phylogenetic analysis showed that the infection was not related to his main partner.

His viral load was undetectable (<20 copies/mL) and dolutegravir was added to tenofovir-DF/FTC as treatment. However, resistance testing of proviral HIV DNA detected RT mutations K65R, M184V, K103S, E138Q and Y188L associated with high level drug resistance to NRTIs including tenofovir, FTC and NNRTIs. Darunavir/cobicistat was added to ART and viral load continued to be undetectable.

One surprise from the questions after the session was almost an obsessive focus on adherence, even though this would have no impact on the extensive mutations actually seen in the genotypic test.

C O M M E N T

Although this case is disappointing, it is not unexpected, and unfortunately other cases are likely to be reported in the future. PrEP can only be active against HIV that is sensitive to the drugs used in PrEP. A similar case was reported earlier this year at CROI. [2]

Luckily, the prevalence of K65R/M184V mutations are low, detected in approximately 1% of new HIV diagnosis in the UK (and the US) although this will vary by geographic region. This person was just unlucky to become infected from limited exposure to other partners.

It might help explain the impact on overall PrEP efficacy to consider two distinct situations.

Firstly, that PrEP still remains close to 100% effective in the context of protection against HIV that is not resistant to PrEP drugs.

Secondly however, efficacy is likely to fall significantly, even in the context of perfect adherence, if exposure is to HIV with resistance to either TDF or FTC and that this drop to zero with exposure to HIV that is resistant to both TDF and FTC (ie with K65R and M184V).

The risk in this second scenario will be dependent on viral load of the source partner, and if this person was in acute infection they might not have been diagnosed or on ART.

Earlier in the session it was reported that up to 100,000 people have used PrEP in the US, so with only two cases of failure due to the risk of MDR infection overall efficacy is still incredibly high.

Dr Grossman remains committed to continuing to use PrEP himself.

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TDF/FTC can be used as PrEP by breastfeeding mothers without risk to the baby

Simon Collins, HIV i-Base

A study reporting that low TDF/FTC concentrations in breastmilk do not put a baby at risk will be important in enabling women to routinely use PrEP irrespective of whether or not they are breastfeeding.

Kenneth Mugwanya from University of Washington presented results from a pharmacokinetic study in 50 mother and infant pairs. The mothers were given daily PrEP for ten days with drug levels measured in both breast milk and infant plasma samples. [1]

Median age of the infants was 13 weeks.

Only very small quantities of tenofovir (median med 0.2 ng/mL) transferred to milk – approximately at 3% of blood levels in the mothers. Tenofovir was not quantifiable in 94% of infant plasma samples. Based on the milk concentration, the infants had TFV exposures at less than 0.01% of the proposed infant therapeutic dose (6 mg/kg).

Emtricitabine (FTC) concentrations in breast milk were also low, although somewhat higher (median 212.5 ng/mL). These concentrations were consistent with those seen with 3TC, abacavir and AZT. Overall, 47/49 samples had detectable FTC in infant plasma, but at small concentrations (13.2 ng/mL), equivalent to approximately 0.5% of the proposed therapeutic infant dose.

Even though this was a small study, it provides the first data to suggest that PrEP can be safely used by women who are breastfeeding.

Full results from the study were published as an open access paper in PLoS Medicine in September 2016. [2]

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Potential for EFdA as PrEP to prevent HIV transmission in women and their infants

Simon Collins, HIV i-Base

One of the most promising candidates for future PrEP is a small molecule, highly potent NRTI EFdA, for which limited data have been presented, mostly in animals.

It is notable then that a late breaker poster of several mouse studies was presented by Martina Kovarova, on behalf of an independent research group from University of North Carolina, rather than Merck who own the compound. [1]

As background, the poster notes that most HIV infections globally occur in women, that the majority of women are of child-bearing age, that without treatment 45% of women will transmit HIV to their baby mainly through breastfeeding and that only 31% of HIV positive children currently have access to ART.

This study used bone/liver/thymus (BLT) humanised mice as a preclinical model to study the efficacy of EFdA to prevent vaginal and oral transmission – with potential use to protect against sexual and breastfeeding transmission. The compound should generate excitement as it has the potential to be formulated in a slow-release small removable implant that would provide therapeutic doses for up to a year. EFdA has an IC50 of 14 nM, low cytotoxicity, sensitivity to drug resistant isolates and a low risk of drug resistance.

BLT and non-humanised mice were dosed with 10 mg/kg EFdA (approximately 5-fold higher than the equivalent human therapeutic dose) or left untreated. The ability to protect against in vitro challenge was tested in serum, cervicovaginal secretions and saliva. In all three samples, in vitro HIV inhibition was significantly higher from treated vs untreated animals ($p<0.01$ for serum and genital and $p<0.05$ for saliva).

The mice (6 untreated and 11 treated) were then exposed to three high dose vaginal challenges (approximately 100-fold higher than experienced for human sexual transmission) at 48 hour intervals while receiving daily EFdA for eight days. The degree of protection was highly significant with none of the treated mice becoming infected compared to all the control animals ($p<0.0002$).

Similar results were seen following oral exposure to high dose HIV with only 1/8 treated animals becoming infected compared to 5/5 untreated controls ($p=0.0031$).

These results will support clinical development of EFdA as a potential PrEP compound to prevent HIV transmission in women and their infants.

COMMENT

These results show good proof of concept. Even though the EFdA dose was higher than the comparative human therapeutic dose, the dose of HIV challenge was significantly higher again.

It is frustrating that so little data on this compound have been published by Merck, and that this exciting research into PrEP was conducted independently.

A similar poster on this research was also presented at IAS 2016 in Durban. [2]

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Antibody therapy leads to sustained post-treatment SIV control in macaques

Richard Jefferys, TAG

In an opening lecture for the R4P 2106 conference, Anthony Fauci from US NIAID, reported that sustained post-treatment control of SIV has been achieved in macaques using an antibody therapy developed for the treatment of inflammatory gastrointestinal (GI) disorders. [1]

The study had hit headlines the previous week when the results were published in the journal Science. [2]

The antibody targets a4b7, a receptor expressed on CD4 T cells (and other immune system cells) that is involved in promoting trafficking to the GI tract. Some, but not all [3], studies have suggested that a4b7 also plays a role in mediating HIV infection of target CD4 cells.

The rationale for the study came from previous experiments which found that infusions of the antibody prior to an SIVmac239 challenge [4] reduced post-infection viral loads in macaques and, in low-dose challenge studies, [5] lessened the risk of SIV acquisition. The mechanism remains unknown but the researchers hypothesise that it relates to inhibition of trafficking of CD4 T cells, natural killer cells and plasmacytoid dendritic cells to the gut, limiting the availability of target cells for SIV and also dampening the inflammatory immune response that promotes and disseminates virus replication.

In the latest work, 18 macaques were challenged with the same dose of SIVmac239 used in previous experiments (200 TCID 50) and all became infected. Five-weeks post-challenge, combination antiretroviral therapy (ART) was initiated in all animals and maintained for 90 days. Around three weeks prior to ART cessation, 11 macaques were administered the anti-a4b7 antibody by infusion while the remaining seven received a control antibody. The antibody administrations were then continued every three weeks (after ART withdrawal) until a total of eight infusions had been given, at which point all treatments were stopped. Three macaques developed antibodies against the anti-a4b7 antibody and were excluded from further study, so analyses were limited to eight animals in the anti-a4b7 group and seven controls.

After ART cessation, control macaques all experienced a rebound of SIV viral load within two weeks; levels averaged around a million copies/ml and persisted throughout follow up. Outcomes in recipients of the anti-a4b7 antibody were very different: two animals never rebounded, and the remaining six were able to exert control of SIV viral load within four weeks, for the most part to undetectable levels but with some intermittent blips. This suppression of SIV was maintained out to 81 weeks of follow up (the last anti-a4b7 antibody infusion occurred at week 32). Levels of proviral SIV DNA in GI tissues followed a similar pattern, persisting at detectable levels in the control animals but declining to undetectable levels in the anti-a4b7 antibody group from week 30 onwards.

Measurements of CD4 cell numbers in blood and gut showed an ongoing repopulation in the anti-a4b7 antibody group compared to declines in controls. Notably, this recovery included Th17 and Th22 CD4 T cell subsets, which are known to contribute to the maintenance of GI barrier integrity. In terms of possible mechanisms of viral load containment, increases in cytokine-producing natural killer cells and innate lymphoid cells were seen in the gut post-ART in the anti-a4b7 antibody recipients but not controls. Some evidence of preferential induction of antibodies against the V2 region of the SIV envelope was also reported. SIV-specific CD4 and CD8 T cell responses were assessed based on expression of CD107a, IFN-g, MIP-1-b or TNF-a but did not show significant differences between groups.

At the end of the presentation, Fauci updated the Science paper by noting that suppression in the animals had now continued out to two years.

C O M M E N T

The results of the study appear very encouraging, and the researchers are hoping to rapidly evaluate whether they have any relevance to humans. A small clinical trial of the anti-α4β7 antibody vedolizumab, which is FDA-approved for the treatment of ulcerative colitis and Crohn's disease, is now recruiting at the National Institutes of Health Clinical Center. [6]

The target population is HIV positive people who have been on suppressive ART for at least two years and the primary goal is assess safety (the antibody has been reported to have a favourable side effect profile for approved indications). [7] An ART interruption is planned to evaluate any effects on viral load rebound.

Media coverage of the paper has generally been accurate, but has had to wrestle with the uncertainty that exists among scientists regarding how ART-free control of viral load should be described. The press release issued by the researchers uses the term "sustained SIV remission" in the headline but adds: "also known as a 'functional cure'" in the body text. [8]

The problem, as TAG has highlighted in the past, is that it cannot be assumed that ART-free control of viral load automatically equates to a state of health that can be considered as remission or a functional cure ie a state of health equivalent to an HIV positive person on suppressive ART or a comparable HIV negative person. [9]

It is known from studies of elite controllers and individuals with HIV-2 infection that low or even undetectable viral loads do not necessarily completely eliminate the risk of disease progression. Thus, if an intervention leads to a state of ART-free control of viral load, it will be necessary to carefully evaluate immunological and health outcomes over a long period before concluding that HIV remission or a functional cure has been achieved.

One possible technical issue that has been noted about the study is that after the SIVmac239 challenge, peak viral loads averaged around three million copies/ml, which, as Louis Picker points out in an accompanying Science news article by Jon Cohen, [10] is unusually low for SIVmac239 – in one of the prior studies [4] by the same researchers, peak viral loads in controls averaged >32 million copies/mL.

The study authors do not address this apparent discrepancy. Although it would not explain the differences between the anti-

α4β7 antibody recipients and controls, the generalisability of the findings could be limited if the SIVmac239 challenge stock was unusually attenuated.

Source: TAG basic science blog. (17 October 2016). http://tagbasicscienceproject.typepad.com

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CONFERENCE REPORTS

21st International AIDS Conference (AIDS2016), 18–22 July 2016, Durban, South Africa

Introduction

The 21st International AIDS Conference (AIDS 2016) was held from 18-22 July 2016 in the coastal town of Durban in South Africa.

Attended by more than 18,000 delegates, this vital meeting covers all aspects of HIV research: from early basic science studies looking at mechanisms for a cure to real world practice for ensuring human rights are respected for the 35 million people living with HIV globally.

Historically, this meeting is significant for returning to Durban, sixteen years after the World AIDS Conference was first held in an African country.

Over this time, remarkable advances have been made in global healthcare but a continued theme for the conference was that this work is still only half completed. Although more than 17 million people now access HIV treatment (ART) globally, universal access is increasingly raised as the most appropriate target if the HIV epidemic is to ever be reduced.

Several other important workshops were held before the main conference, including meetings focused on paediatrics, TB confection and HIV cure.

The AIDS 2016 programme is online as a searchable database.

http://programme.aids2016.org/Abstract/Index

Although the search is good at finding abstracts and when availble links to posters are included on this page, further links to webcasts, and slidesets are only accessible through the online conference programme.

http://programme.aids2016.org

This requires searching for and then viewing the conference session in the programme where the study is presented (whether as an oral abstract, plenary talk or other type of presentation). Once the session window is opened, a column to the right of the presentation title shows links to the abstract, plus slides and webcasts if available. Webcasts can either be viewed in the session window or as separate links on YouTube.

https://www.youtube.com/user/iasaidsconference/videos

A disappointingly large number of presentations are neither available as webcasts nor supported by slides. This is not acceptable for the few hundred presentations selected as highlight from many thousands accepted as posters.

The IAS conference should have sufficient confidence to make oral presentations conditional on consent to the presentation being available online. This is common practice for the annual CROI meetings which have a stronger scientific prestige.

Not highlighted in the programme when sessions will (or will not) be webcast is also unhelpful.

The following reports are included in this issue of HTB South.

- Dolutegravir is superior to boosted atazanavir in women in the ARIA study
- Dual therapy with dolutegravir + 3TC keep viral load undetectable: 48 week results from PADDLE study
- Once-daily raltegravir at last available: 48 week results from ONCEMRK study
- Dual long-acting cabotegravir plus rilpivirine injections: 48-week results from LATTE-2
- Efavirenz associated with suicide risk in analysis from START study
- PROMISE results support WHO recommendations for pregnant and breastfeeding women: more needs to be done to improve ART acceptability and adherence
- High risk of virological failure and loss to follow up postpartum in South Africa
- Birth weight and preterm delivery outcomes of vertically vs non-vertically infected HIV positive pregnant women
- High death rates among HIV positive women postpartum accessing ARVs
- Sub-Saharan African countries moving quickly to recommend "Treat All"
- Higher rates of eye complications in HIV positive people on ART
- ZERO: no linked HIV transmissions in PARTNER study after couples had sex 58,000 times without condoms

Dolutegravir is superior to boosted atazanavir in women in the ARIA study

Polly Clayden, HIV i-Base

Dolutegravir-based ART was superior to a boosted atazanavir-based regimen in treatment naive women at 48 weeks, according to data from the ARIA study presented at AIDS2016.

The ARIA study was performed to provide additional data on women receiving the dolutegravir (DTG)-based fixed dose combination (FDC) in which it is co-formulated with abacavir (ABC) and lamivudine (3TC). [1] The FDC is marketed by ViiV Healthcare as Triumeq and was first approved in August 2014 in the US. [2]

The study is multi-national, multi-site, open label, randomised, non-inferiority, phase 3b. It is ongoing and enrollment was from September 2013 to September 2014

Catherine Orrell from the University of Cape Town presented 48-week data, on behalf of the ARIA investigators, in an oral late breaker. [3]

Eligible women were: ART-naive, HLA-B*5701 negative, with viral load 500 copies/mL or more and hepatitis B negative. They were randomised 1:1 to 48 weeks of treatment with DTG/ABC/3TC or atazanavir/ritonavir plus tenofovir DF/emtricitabine (ATV/r + TDF/FTC) once daily, and stratified by viral load less than or above 100, 000 copies/mL and CD4 count less than or above 350 cells/mm3.

Women who became pregnant during the course of the study were withdrawn and offered entry into a DTG/ABC/3TC pregnancy study. [4]

The primary endpoint was the proportion of women with viral load <50 copies/mL at week 48 using the FDA Snapshot algorithm (-12% non-inferiority margin).

A total of 495 women were randomised and treated: 248 and 247 in the DTG/ABC/3TC and ATV/r + TDF/FTC arms respectively. The women were a median age of 37 years; approximately 43% were of African origin, 45% were white and 22% were Asian. About half of the participants had CD4 <350 cells/mm3 and about 28% had viral load >100,000 copies/mL. Participants were well matched for demographic and baseline characteristics. Of the women in the DTG/ABC/3TC arm, 83% (n=206) completed week 48, compared with 78% (192) in the ATV/r + TDF/FTC arm.

Five women in the DTG/ABC/3TC arm (2%) and eight in the ATV/r + TDF/FTC arm (3%) became pregnant and withdrew from the study.

In ITT analysis, DTG/ABC/3TC was superior to ATV/r + FTC/TDF at 48 weeks: 82% vs 71% of participants had viral load <50 copies/mL respectively, adjusted difference 10.5% (95% CI: 3.1% to 17.8%), p=0.005.

Differences in response were driven by Snapshot virologic non-response (6% vs 14%) and fewer discontinuations due to adverse events or death (4% vs 7%) in the DTG/ABC/3TC arm.

No participant receiving DTG/ABC/3TC developed INSTI or ABC/3TC resistance. DTG/ABC/3TC had a favourable safety profile to ATV/r + TDF/FTC and a similar overall profile for DTG to that reported in previous studies.

COMMENT

The participants in the registrational studies (typically for such studies) were approximately 80% men (and few non-white participants), so this clinical trial evaluating DTG in women is welcome. More important still is data on pregnant women – which is essential to DTG's recommendation in the WHO guidelines without restriction.

As noted above, five (2%) ARIA participants in the DTG/ABC/3TC FDC arm and eight (3%) in the ATV/r + TDF/FTC arm were discontinued from the randomised phase of the study due to pregnancy.

Of these pregnant women, four in each treatment group had undetectable viral load at the time of discontinuation. Two additional women became pregnant in the DTG/ABC/3TC FDC treatment group during the continuation phase of the study.

Of the seven women who became pregnant in the DTG/ABC/3TC arm (including during the continuation phase), three resulted in a normal infant with no apparent congenital anomaly, two women elected to terminate the pregnancy, one woman experienced an anembryonic pregnancy, and the outcome of one pregnancy was unknown. [5]

Other studies looking at DTG in pregnancy are described in Fit for Purpose 2016. [6]

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Dual therapy with dolutegravir + 3TC keep viral load undetectable: 48 week results from PADDLE study

Simon Collins, HIV i-Base

Updated results from the PADDLE study were a highlight of AIDS 2016 and were presented as an oral late-breaker on the last day. [1]

This was a small (n=20) single-arm open label study in treatment-naive participants that was notable for reporting at the EACS 2015 conference that rapid viral suppression to <50 copies by week 8 that was maintained to 24 weeks. Although median baseline viral load was low (24,000 copies/mL [IQR: 12,000 to 37,000]), four people were >100,000 copies/mL. [2]

The results at week 48 were similar, with suppression maintained to <50 copies/mL throughout in 18/20 participants.

Low level detectable viral load was reported at week 36 in one participant (at 246 copies/mL) who re-suppressed without a change in treatment (even though the study protocol recommended changing).

One participant committed suicide linked to "severe stress and emotional trauma" that was not judged related to the study medications.

COMMENT

These results are encouraging for the likelihood of this being a durable option, however small the dataset.

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Once-daily raltegravir at last available: 48-week results from ONCEMRK study

Simon Collins, HIV i-Base

After many years of research, Merck now have a once-daily formulation of raltegravir – though it requires two tablets and a higher milligram daily dose.

In addition to developing the new raltegravir formulation, non-inferiority needed to be shown in a randomised, double-blind placebo controlled phase 3 study, rather than relying on pharmacokinetic bioequivalence studies. The original raltegravir 400 mg twice-daily version was compared to the new 2 x 600 mg once-daily formulation, with background NRTIs tenofovir DF + FTC for all participants.

Results of this study were presented as a late-breaker oral abstract at AIDS 2016 by Pedro Cahn from Fundación Huesped, Buenos Aires.

Of the 802 participants randomised 2:1 to the once- vs twice-daily formulations, 797 received study drug and 732 (92%) completed follow-up to week 48.

Baseline characteristics overall included a study population that was 85% male, 59% white and mean age 36. Mean CD4 and viral load were 415 cells/mm3 and 4.6 log copies/mL respectively, with 28% having viral load >100,000 copies/mL.

At the primary endpoint at week 48, viral suppression to <40 copies/mL was reported by 88% of each arm with no significant differences related to efficacy or tolerability between arms. The once-daily formulation has slightly fewer serious side effects (5.8% vs 9.4%; difference -3.6% [95%CI -8.0 to +0.2]) and discontinuations due to side effects (0.8% vs 2.3%; difference -1.5 [95%CI -4.1 to + 0.1]), though neither difference was statistically significant.

Viral failure during the study (defined as non-suppression by week 24 or more than one consecutive blip >40 copies/mL) was reported in 7% of each group. Of these, approximately half resuppressed by week 48 without changing treatment: 20/26 vs 8/18 in the once-vs twice-daily arms groups respectively.

Of the 5/14 with drug resistance in the once-daily arm, 4/5 (0.9%) had resistance to raltegravir. Of the 3 people tested in the twice-daily arm, 2/3 had no resistance and 1/3 failed testing.

The study will continue until week 96 for secondary endpoint analyses.

C O M M E N T

Although raltegravir was the first integrase inhibitor to be approved – the results of more than a decade of commitment to this new class – the higher price compared to existing combinations meant that many people who could have benefitted were not able to access this drug.

As newer integrase inhibitors became available, the twice-daily formulation meant that even after lowering the price, raltegravir had a limited market.

In the meantime, some doctors reported switching the twice-daily 400 mg formulation to 800 mg once-daily after viral load was suppressed to <50 copies/mL. While these reports were largely positive this off-label use had limited uptake.

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Dual long-acting cabotegravir plus rilpivirine injections: 48-week results from LATTE-2

Simon Collins, HIV i-Base

Results from the first proof-of-principle for injection only antiretroviral treatment (ART) was presented as an oral late breaker by David Margolis from ViiV Healthcare.

This phase 2 study required an induction period using oral drugs and compared monthly and two-monthly intramuscular injections to a control group that remained on oral drugs throughout.

The was an open-label phase 2b study in 301 treatment-naive participants, randomised 2:2:1 to 4-weekly (4W) or 8-weekly (8W) injections or to oral ART (cabotegravir plus abacavir/3TC).

The 20-week induction phase used cabotegravir (30 mg once-daily) plus abacavir/3TC once-daily, adding in oral rilpivirine (25 mg once-daily) for the last four weeks. After induction, 91% (n=286) of participants continued into the randomised phase because their viral load was <50 copies/mL. The primary analysis at week 32 of the main study (ie starting after the induction period) was presented at CROI 2016 earlier this year – and these data were used to select the 4-weekly dose for phase 3 studies. [2]

At week 32, viral suppression to <50 copies/mL was achieved in 94%, 95% and 91% of the 4W, 8W and oral arms respectively, which met pre-specified criteria for showing each intramuscular injection (IM) arm was not worse than the oral treatment group. Virologic non-response rates were slightly lower in the 4W arm (<1% v 4% in the other arms) with lower non-virologic reasons for discontinuation in the 8W arm (vs 5% in each of the other two arms).

By week 48, the percentage with <50 copies/mL dropped slightly to 91%, 92% and 89% of the 4W, 8W and oral arms respectively. Virologic non-response was greater in the 8W vs 4W arms (7% vs <1%) but this lead to few discontinuations (<1% vs 0). Discontinuations due to side effects or death was lower in the 8W group (0 vs 5%).

Tolerability at 48 weeks – mainly linked to injection site reactions (ISRs) – was similar to the 32 week results. Slightly higher rates of ISRs in the 8W group levels out to approximately 30% of participants by week 48. Of these, 82% were mild and 17% were moderate: 90% resolved within 7 days. The most common symptoms were pain (67%, nodules (7%) and swelling (6%). Only 2/230 participants (<1%) discontinued due to ISRs.

Other side effects generally occurred at low levels and were similar between injection groups: fever 5% vs 3% vs 0; fatigue 4% vs 2% vs 1%; flu-like symptoms 2% vs 3% vs 0; in the 4W, 8W and oral arms respectively, with headache reported by 2% in all arms.

Virological failure only occurred in two people in the 8W arm and 1 person in the oral group. Mutations associated with drug resistance to integrase inhibitors (Q148R) were only reported in one person in the 8W group.

In a patient survey, participants reported higher rates of satisfaction with injections compared to oral drugs and higher preference for continuing with current combination.

C O M M E N T

Even with the potential obstacles and disadvantages of intramuscular injections with very long half-lives, the option to

not take daily pills has always been seen as exciting by many people – even now once-daily single pill formulations are available.

Injectable long-acting ART is steadily getting closer, with phase 3 studies now planned using 4-weekly injections.

Long-acting cabotegravir injections are also being studied at PrEP in a phase2b/3 study in HIV negative men and transgender women, compared to a control arm of daily oral tenofovir/FTC. [3]

A poster at AIDS 2016 from a phase 2 study of cabotegravir LA PrEP reported preference over daily oral PrEP. [4]

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Efavirenz associated with suicide risk in analysis from START study

Simon Collins, HIV i-Base

Suicide-related side effects are an important concern with efavirenz. Given how widely efavirenz continues to be used the main safety concern is whether current prescribing practice is sufficiently accurate to minimise these risks.

Earlier studies have reported that the risk is significantly higher than with other ARVs but also that doctors are careful to use alternative options for people who have a history of anxiety, depression or other psychiatric symptoms. [1, 2]

An oral presentation at AIDS 2016 provided information on both actual risk and prescriber awareness from a new analysis from the large international START study. [3]

START randomised more than 4600 treatment naive individuals with CD4 counts >500 cells/mm3 to either immediate ART or deferred ART (until the CD4 counts dropped to 350 cells/mm3). Importantly, before randomisation doctors were asked to pre-specify the choice of ART for all participants, irrespective of which group they would later join.

This design enabled the START researchers to identify appropriate control groups for participants who were either judged to be at risk or not at risk from suicide-related side effects in a way that could highlight the impact of efavirenz and also the underlying risk independent of ART.

START enrolled a largely young healthy group in early HIV infection. Baseline demographics have already been reported. [4, 5] Additionally, 270/4685 (5.8%) participants had a prior psychiatric diagnosis.

Efavirenz was pre-specified for 3516 participants (75%). This was less often in those with psychiatric diagnosis (40%) than without (77%). Although characteristics were similar between participants for whom efavirenz was pre-specified or not, prior psychiatric disease was less frequent (3.1% vs 13.9%) in the those pre-specified to use efavirenz, as was current use of psychiatric treatment (4.0% vs 15.1%). Also significant, was the higher used of efavirenz in low- and middle-income vs high-income countries (65% vs 35%).

In the study overall, there was no difference in suicidal behaviour between the early vs deferred arms (27 vs 24 events; HR 1.15 (0.66 to 1.99), p=0.63). Of the 52 events, 30 were suicide attempts and 16 events where people wanted to commit suicide. There were single cases of self harm and self harm ideation. The three people who died from suicide were all in the deferred arm and this occurred after starting treatment.

The majority of events occurred in those with a previous psychiatric history. The rate was 10-fold higher in people in whom efavirenz was prespecified and 3-fold higher in those pre-specified to use other ART, in people with a previous diagnosis (see Table 1). This, together with the higher rate of events in people pre-specified to use other ART (overall rates 1.28 vs 0.63 per 100 PY) show a generally high awareness not to prescribe efavirenz in people at highest risk.

Table 1: Suicide-related events by prespecified efavirenz use and psychiatric history

	Psychiatric history	No psychiatric history
EFV pre-specified	72.0 /100PY	220.2 /100PY
Other ART	81.7 /100PY	140.5 /100PY

A subgroup analysis that censored participants in the deferred group at the start of ART was then able to look more specifically at the role of efavirenz in people not thought to be at risk (ie who had been assigned to use efavirenz) and also at the roll of psychiatric-related events in people not exposed to efavirenz.

In this analysis there were 17 vs 3 events in the immediate vas deferred group assigned to receive efavirenz (HR 4.16; 95%CI 1.2 to 14.4), p=0.02) showing that in people without a psychiatric history, efavirenz was significantly related to a risk of suidcide-related events.

Similarly, in the people whose medical history might be associated with suicide-related events irrespective of ART, there were 9 vs 8 events (HR 1.04; p5%CI 0.4 to 2.7, p=0.93) for non-efavirenz versus their ART-naïve controls – indicating that other ART had no impact on people judged to be at high risk due to past history.

Both these analyses were protected by randomisation and therefore likely to provide high quality evidence. Also importantly, the interaction between these two groups was also statistically signficant (p=0.05 for difference in HRs), see Table 2.

In multivariate analysis, the factors that were significantly associated with risk of suicide-related events were: previous psychiatric diagnosis (HR 12.8; 95%CI 4.7 to 34.9, p<0.001), heavy alcohol use (HR 6.1; 95%CI 1.9 to 19.6, p = 0.003) and ever having used recreational drugs (HR 2.9; 95%CI 1.0 to 7.9, p=0.04).

Table 2: Suicidal and harming events by randomisation group

	n	Immediate ART		Deferred ART		HR	95%CI	p	P
		Events	Rate	Events	Rate				
Intention to treat (ITT) analysis									
EFV pre-specified	3516	18	0.34	11	0.21	1.42	0.6 to 1.9	0.37	0.23
EFV not pre-specified	1169	9	0.53	13	0.72	0.74	0.3 to 1.8	0.5	
Censoring deferred arm participants at ART initiation									
EFV pre-specified *	3516	17	0.35	3	0.08	4.16	1.2 to 14.4	0.02	0.05
EFV not pre-specified **	1137	9	0.59	8	0.69	1.04	0.4 to 2.7	0.93	

* 6/17 vs 0/3 were in people with psychiatric history.

** 5/9 vs 2/8 were in people with psychiatric history.

Simon Collins is a community representative on the START group working on this analysis.

C O M M E N T

The good news from START is that even with widespread use of efavirenz, especially in people who either started immediate treatment there were few serious reports of suicide-related behaviour and only three suicides.

Even with few events – a good thing – efavirenz was still associated with a significantly higher risk of suicide related complications, especially in those with a history of depression or other psychiatric conditions.

These results support the continue screening of patients for such history before starting efavirenz.

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PROMISE results support WHO recommendations for pregnant and breastfeeding women: more needs to be done to improve ART acceptability and adherence

Polly Clayden, HIV i-Base

Continued antiretroviral treatment was safe in women with higher CD4 counts after delivery and associated with improved maternal health – but virologic failure rates were high – according to data from the PROMISE study, presented at AIDS2016.

The study also revealed that acceptance of ART was low in this population and women needed time to consider starting treatment. And it found that ART during breastfeeding essentially eliminates vertical transmission by breast milk.

PROMISE (Promoting Maternal-Infant Survival Everywhere) is a multi-country, multicomponent study, that began in 2010 and included 5398 asymptomatic HIV positive pregnant women who were not eligible for antiretroviral treatment (ART) at the time of enrollment. The study included breast feeding (BF) and formula feeding (FF) women, depending on local guidelines. Participants were randomly assigned different antiretroviral strategies to look at vertical transmission during pregnancy and post-partum, infant safety, and maternal health.

Research questions include:

- **Antepartum (1077BF/FF**) Among HIV positive women who do not meet criteria for starting ART for their own health, what is the best intervention to prevent in utero and intrapartum HIV transmission to infants? Maternal ART vs a single drug prophylaxis regimen.
- **Postpartum (1077BF)** Among HIV positive women who do not meet criteria for starting ART for their own health, what is the best intervention to prevent transmission of HIV to infants during breastfeeding? Maternal ART vs single drug infant prophylaxis.
- **Maternal health** What is the best intervention to preserve maternal health after delivery? Stopping vs continuing ART.

The first part of the study (finally) provided randomised controlled trial (RCT) data to show that taking three drug ART in pregnancy was more effective in preventing vertical transmission than taking one drug during pregnancy, another in labour and two after delivery. [1, 2, 3]

These findings were reported on 4 November 2014 during a scheduled interim review of PROMISE by an independent data and safety monitoring board (DSMB). The US National Institutes of Health issued a press release explaining the results on 17 November 2014. [4]

Standard of care also changed during the course of the study: as PROMISE was ongoing, the START study showed ART in people with CD4 500 cells/mm3 or more reduces the risk of HIV disease progression. [5] PROMISE participants were informed of these results by the study group and women not receiving ART were strongly recommended to start immediately for their own health.

World Health Organization (WHO) guideline subsequently changed to recommend "Treat All" reflecting the START results. [6]

Several analyses from PROMISE were presented at AIDS 2016 – this commentary summarises results from studies looking at stopping or continuing ART postpartum, ART acceptability among women with higher CD4 counts and transmission during breastfeeding. The results broadly support the recommendations in the WHO guidelines – including lifelong ART for all pregnant and breastfeeding women – but also show that work needs to be done to improve adherence support and acceptability of ART among asymptomatic women.

Continuing ART postpartum benefits maternal health

In 2008/2009 when PROMISE was designed the health benefits of postpartum ART for women with high CD4 counts had not been evaluated in RCT. Judith Currier presented results from the component of PROMISE (1077HS) designed to assess the risks and benefits of continuing vs stopping ART among non-breastfeeding women after delivery. [7] She showed these findings in an oral late breaker presentation on behalf of the study team.

HIV positive, non-breastfeeding, postpartum women with no indication for ART based on local guidelines, and who had received ART during pregnancy for at least four weeks in the main study, were randomised to continue or stop ART within 42 days of delivery. Women were followed for 84 weeks after the last enrollment. Those who stopped were restarted when their CD4 count dropped below 350 cells/mm3 or otherwise clinically indicated.

ART was provided by the study. The majority of participants received a regimen of lopinavir/ritonavir (LPV/r) plus tenofovir DF and emtricitabine (TDF/FTC). Atazanavir/ritonavir and, in some settings, rilpivirine and raltegravir were also available. Overall 90% of women were on PI-based ART.

The primary composite endpoint included: death, time to AIDS event (WHO stage 4), and serious non-AIDS events (cardiovascular, renal or hepatic). The primary safety endpoint was time to first targeted grade 2, 3 or 4 event. Key secondary endpoints were: a composite of HIV/AIDS related or WHO 2/3 events; or time to WHO 2/3 events.

The planned study sample size of 2000 participants provided 90% power to detect a 50% reduction from an annual primary event rate of 2.07% (calculated from other clinical trials). But in November 2014 the DSMB approved stopping enrollment at 1630 participants due to longer than expected time to enrol (the longer follow up was expected to make up for smaller sample size). All analyses were intent to treat.

Participants were informed of the START results and all offered ART in June 2015.

There were1652 participants enrolled from 52 sites across eight countries: Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand and the US between January 2010 and November 2014. The majority were from Brazil (31%), Botswana (28%) and Thailand (18%).

Of the total, 827 and 825 women continued and stopped ART for a median of 2.31 vs 2.35 years; 79 (9.6%) vs 70 (8.5%) respectively discontinued the study. Adherence to randomly assigned treatment was generally good: 15% of women stopped ART in the continue arm and 12% restarted ART before the study threshold in the stop arm.

Median age was 28 years and 28% were black African, 16% Thai (16%) and 15% white. Median CD4 count at study entry was 696 cells/mm3, median ART exposure before delivery was 19 weeks and 91% had entry viral load <1000 copies/mL. During follow up 31% of the stop arm started ART at a median CD4 of 372 cells/mm3.

For the primary efficacy outcome events were very rare and not significantly different between arms. The events included: two cases of cervical cancer, and two deaths (one homicide and one unknown); and two cases of extrapulmonary TB, one toxoplasmosis and four deaths (one hepatic encephalopathy and one unknown), in the continue and stop arms respectively. The rate of safety endpoints was higher in the continue arm compared to the stop arm but this was not statistically significant.

WHO Stage 2 and 3 events were almost halved (44% reduction) with continued ART. The key events were: 16 herpes zoster and four bacterial infections; and six pulmonary TB, 43 herpes zoster, four thrombocytopenia, 10 oral candidiasis and 11 bacterial infections, in the continue and stop arms respectively. See Table 1.

Table 1: PROMISE 1077HS endpoints

Endpoint (time to first event)	**Continue ART**		**Stop ART**		**Hazard ratio (95% CI)**	**p-value**
	n	rate/100 py	n	rate/ 100 py		
Primary efficacy outcome	4	0.21	6	0.31	0.68 (0.19 to 2.40)	0.54
Primary safety endpoint	260	18.4 (15.7 to 21.4)	232	15.4 (13.1 to 18.2)		0.08
Secondary endpoints						
Composite endpoint	57	3.09	99	5.49	0.56 (0.41 to 0.78)	<0.001
WHO 2/3 events	39	2.02	80	4.36	0.47 (0.32 to 0.68)	<0.001

Toxicity rates were higher in the continue arm but the difference was not statistically significant.

Among participants randomised to continue ART, 189/827 (23%) had virologic failure at or after 24 weeks of treatment. Of the 155 (82%) with resistance testing, 103 (66%) failed with no evidence of resistance to their current regimen (suggesting non-adherence). Of the 52 with evidence of resistance: 22 had resistance to one of the drugs in the failing regimen; 14/25 (11%) failing a PI regimen and 8/27 (30%) failing an NNRTI regimen.

Low acceptance of ART among women with higher CD4 counts: they need more time to consider

Following the START results, in June 2015, all women not receiving ART at that time were recommended to start for their own health.

In a second oral late breaker, Lynda Stranix-Chibanda showed PROMISE participants' response to these recommendations and their reasons to accept or decline ART. [8]

The study used a mixed methods approach to collect responses from participants receiving the START information. Study staff contacted participants to return to the clinic and gave START results. This was done using a structured script, the language was chosen by the participant and the staff assessed comprehension. Information included that about the trial aims, study location and results.

Participants also attended a counselling session to discuss the implication of START for them as individuals. Those not receiving ART discussed the offer of starting with the study staff and decided whether or not to accept during that session.

Women selected their primary reason for accepting or rejecting the offer from a set of options. The results were recorded and categorised by the study staff.

All 1483 women not on ART were advised to start: 984 women (66%) accepted the offer but 499 (34%) declined. Acceptance rates varied by country, quite broadly, with a mean of 66% (Brazil) and range of 100% (Peru) to 37% (Tanzania). Reasons for accepting or declining ART after initial counselling session are shown in Table 2.

Table 2: Reasons for accepting or declining ART in PROMISE

Reason	1077BF/FF	1077HS
For accepting ART		
Concerned about health	46%	43%
Understands treatment is now recommended	35%	36%
Concerned about CD4 count	16%	13%
Other reason	2%	7%
For declining ART		
Wants more time to consider	44%	33%
Feels well/knows CD4 count is high	13%	28%
Concerned about HIV disclosure	9%	3%
Concerned about commitment to life-long ART	9%	7%
Concerned about potential side effects	8%	8%
Other reason	7%	14%
Knows not indicated in current guidelines	6%	0%
Too busy with childcare or other responsibilities	2%	5%
Concerned about adherence	1%	5%

Dr Stranix-Chibanda explained that a number of women were not willing to start ART after a single counselling session. This was despite exposure to considerable ART education and HIV monitoring within a well-resourced trial setting.

Women particularly needed time to consider starting ART and the researchers noted that the women continued to be offered ART through to study exit and the proportion remaining off ART decreases with each visit.

Breastfeeding

Finally, data were shown from the PROMISE 1077BF study, designed to compare transmission rates with maternal ART vs infant nevirapine (NVP) during extended breast feeding until 18 months post-delivery (the first randomised trial to do so). Taha Taha and colleagues showed these findings in a late breaker poster.

This postpartum component of PROMISE was conducted in 14 sites in: Indian, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe.

The study enrolled 2431 mothers and their HIV uninfected infants between June 2011 and October 2014. They were randomised at 6-14 days postpartum to maternal ART plus six weeks of daily infant NVP (n=1220) or daily infant NVP (n=1211). Women were asymptomatic with a median CD4 count 686 cells/mm3 and 97% WHO stage I). They were a median age of 26 years. Infants had a median gestational age of 39 weeks and birthweight of 2.9 kg.

Baseline characteristics were similar across study arms. The median duration of breastfeeding was 15 months was also similar across study arms (p=0.85).

Rates of HIV transmission during breastfeeding were very low and did not differ significantly between arms at 12 months postpartum these rates were 0.5% with maternal ART and 0.6% with infant nevirapine. Rates of infant survival were high (98.9%) and did not differ significantly between arms (p=0.72).

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High risk of virological failure and loss to follow up postpartum in South Africa

Polly Clayden, HIV i-Base

South African HIV positive women are at risk of loss to follow up and virologic failure postpartum, according to findings from a large study conducted in Johannesburg. Young women who conceive on ART are at higher risk of virological failure but more likely to remain in care compared with those who start ART in pregnancy.

There are limited data on postpartum loss to follow up and virological outcomes. At AIDS2016, Dorina Onoyal from the University of Witwatersrand presented results from a retrospective cohort study to examine the effect of timing of ART initiation before and during pregnancy on the risk of virological failure and loss to follow up in the first two years postpartum.

The study included 6971 women: 3068 (44.0%) controls (no record of pregnancy), 1968 (28.3%) incident pregnancies (conceived on ART) and 1935 (27.8%) prevalent pregnancies (ART started in pregnancy). Participants were aged 15 to 49 years, and started ART at 10 public clinics between 2004 and September 2014.

Women in the prevalent pregnancy group were more likely to be younger (52 vs 33%), have CD4 count <350 cells/mm3 (49 vs 29%) and to be anaemic (41 vs 20%), compared to those in the incident pregnancy group. A higher proportion of women with incident pregnancies had a single unsuppressed viral load result (30 vs 26%).

The investigators assessed the incidence and predictors of virological failure (two consecutive viral load>1000 copies/mL) and loss to follow up (>3 months late for a scheduled visit) during 24 months post-delivery or equivalent time (in controls) using Cox proportional hazards modelling. Virologic failure and loss to follow up were assessed separately.

Overall 563 (8.1%) women had postpartum virological failure at a rate of 5.0 per 100 person-years (95% CI 4.6-5.5) (crude rates): control group 5.0 per 100 person-years (95% CI 4.5-5.7); incident pregnancy group 5.7 per 100 person-years (95% CI 5.0-6.6); and prevalent pregnancy group 4.2 per 100 person-years (95% CI 3.5-5.0). Most failure occurred in women with low CD4 counts.

Virologic failure increased with years since delivery. Women in the prevalent pregnancy group with CD4 count <350 cells/mm3 and those in the incident pregnancy group with CD4 count >350 cells/mm3 at delivery had faster time to virological failure.

Predictors of postpartum virological failure among the incident pregnancy group were: anaemia at delivery, aHR 1.5 (95%CI 1.1-2.1); WHO stage 3 at delivery, aHR 1.6 (95% CI 1.1- 2.5); and virological failure in pregnancy, aHR 2.1 (95% CI 1.5-3.0). Older age (30-39), aHR: 0.6, (95% CI 0.3-1.0) and CD4 count >350 cells/mm3 at delivery, aHR: 0.2 (95% CI 0.1-0.3) were protective against virological failure.

Among the prevalent pregnancy group, the only predictor was a higher CD4 count (>350 cells/mm3) at delivery, which was protective against postpartum virological failure, aHR 0.3 (0.2-0.6).

Overall 1645/ 6971 (23.6%) of women were lost to follow-up at 24 months at a rate of 8.6 per 100 person-years (95% CI 8.2-9.0): control group 23%, 8.4 per 100 person-years; incident pregnancy group 19.4%, 6.5 per 100 person-years (95% CI 5.9-7.2); and the prevalent pregnancy group 27.9%, 11.2 per 100 person-years (95% CI 10.3-12.2).

Dr Onoyal noted that women in the prevalent pregnancy group tended to be lost to follow up earlier at a median time of about 9 months. The same group experienced viral failure at a median time of almost 12 months – so many will be lost before this can be determined. So although these women might appear to have a lower risk, they do not stay in the system long enough for postpartum viral failure to be recorded.

Predictors of loss to follow up in the incident pregnancy group were: lower education level (did not complete secondary school), aHR 1.6 (95% CI 1.0-2.5); receiving care at primary health facility compared to hospital based clinic aHR 1.7 (95% CI 1.3-2.1). But receiving care through an NGO was protective: aHR 0.7 (95% CI 0.5-1.0). Neither age nor any of the health indicators at baseline were predictive.

In the prevalent pregnancy group, similarly, educational level and clinic type were predictive of loss to follow up. Younger age (30 to 39 vs <25 years), aHR 0.8 (0.6-1.0) and being unemployed aHR 1.2 (1.0-1.4) were predictive. And women who received 7 months or more antenatal ART were more likely to be retained than those who received 3 months or less, aHR 0.4 (0.3-0.7).

Dr Onoyal concluded that young women who conceive on ART are a higher risk of postpartum viral failure but are more likely to remain in care, "so we can do something about it". Virologic failure seems so be associated with poor health at delivery, which might be the result of poor outcomes during pregnancy, she explained.

Women who conceive during pregnancy need adherence and support interventions targeted to the ART experienced. And women who start ART during pregnancy – who are more likely to be lost to follow up postpartum – need strengthened adherence and support programmes particularly among those diagnosed in the third trimester or at delivery.

COMMENT

This report highlights the huge importance of extra support for HIV positive women on ART in the postpartum period.

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Birth weight and preterm delivery outcomes of vertically vs non-vertically infected HIV positive pregnant women

Polly Clayden, HIV i-Base

Uninfected infants born to vertically infected HIV positive women might be at greater risk for lower birth weight than those born to non-vertically infected women, according to findings from the largest cohort of pregnant women to date.

This evaluation also suggested that although infants born to vertically infected women might be at greater risk, the absolute difference was small. Infants born to vertically infected women did not appear to be at increased risk for small for gestational age or preterm birth outcomes.

Data from a combined analysis of pregnant women and their

uninfected infants enrolled in the Paediatric HIV Cohort Study (PHACS) Surveillance Monitoring for ART Toxicities Study (SMARTT) and IMPAACT P1025 protocol – conducted to assess whether maternal perinatal infection and adverse could be associated with adverse infant outcomes – were shown at AIDS 2016.

The study looked at HIV positive women aged 13-30 years with singleton births enrolled in the two cohorts in US and Puerto Rico 1998-2013, for which birth weight, gestational age and maternal mode of HIV transmission data were available. Infant outcomes were compared between those born to vertically and non-vertically infected women.

Overall, 2270 women delivered 2692 infants: 270 born to vertically infected and 2422 to non-vertically infected women. Vertically infected women: were younger (mean age 21 vs 25 years); less often black (55% vs 67%); more likely to have CD4 count <200 cells/mm3 at enrolment (19% vs 11%); more likely to have viral load >400 copies/mL at delivery (28% vs 23%); more likely to receive a >3-class ART regimen during pregnancy (23% vs 2%); more likely to have pre-pregnancy BMI <18.5 kg/m3 (6% vs 3%); less likely to report tobacco (14% vs 20%) and substance use (1.7% vs. 3.3%) during pregnancy. All comparisons p<0.01.

After adjustment (age, ethnicity, pre-pregnancy BMI, tobacco use, substance use, CD4 and maternal ART) mean birth weight z-score was lower in infants of vertically compared with non-vertically infected women: adjusted difference -0.13 (95% CI -0.24 to -0.01), p=0.03. Ethnicity, pre-pregnancy BMI, tobacco and substance use were also risk factors for low birth weight.

In this large American study, the investigators found no associations between maternal vertical transmission status and pre-term delivery or small for gestational age.

They concluded that future studies are warranted to understand mechanisms by which the intrauterine environment of vertically infected women might affect foetal growth.

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High death rates among HIV positive women postpartum accessing ARVs

Polly Clayden, HIV i-Base

Despite high uptake of ART in pregnancy and postpartum, HIV positive women were five times more likely than negative women to die within two years of delivery, regardless of their CD4 count – according to data from Botswana presented at AIDS 2016.

Rebecca Zash – on behalf of colleagues from the Harvard group in Botswana – showed findings from a study to determine 24-month mortality rate in positive and negative postpartum women and evaluate risk factors for HIV positive women in a setting with widespread use and ART and PMTCT.

The study recruited HIV positive and HIV negative mothers 18 years and older within 48 hours of delivery at five public hospital maternity. Women who were unable to provide a telephone contact for herself a family member or friend were excluded (Dr Zash noted that few participants were excluded for this criterion as mobile phones are widely used in Botswana).

Antiretrovirals were provided by the government (free for citizens) according to national guidelines. Recommendations and provision changed over the study period: before June 2012 WHO Option A (AZT/3TC/NVP for pregnant women with CD4 <250 cells/mm3 and AZT monotherapy for women with CD4 >250 cells/mm3; from June 2012 WHO Option B with TDF/FTC/EFV for pregnant women (adult ART cut-off moved to 350 cells/mm3).

Women were contacted by mobile phone at 1 and 3 months, then every 3 months until 24-months post-partum. Home visits were conducted if a participant could not be reached and the investigators attempted to confirm whether a woman was dead or alive with a family member if she was still unreachable.

From February 2012 to March 2013, 1499 HIV positive and 1501 HIV negative women were enrolled. Of these, 2979 (96%) had complete follow up data available: 106 (3.5%) were not followed after death of their child; 9 (0.3%) withdrew from the study; and 6 (0.2%) were lost to follow up.

HIV positive mothers were: older (median 29 vs 24 years); less likely to be reporting their first pregnancy (16% vs 45%)and had a lower socioeconomic status (by education, sanitary, electricity and drinking water at home indicators), compared with negative mothers. Approximately 90% of all women had a vaginal delivery.

Before conception, 34% received ART; during pregnancy 92% received antiretrovirals (71% ART and 29% AZT) and by 24 months follow up 79% received ART.

There were 26 total maternal deaths overall in 24-months post-partum (439 per 100,000 person-years), 22 among HIV positive women (758 per 100,000 person-years) and 4 among HIV-uninfected women (138 per 100,000 person-years). HIV positive women were five times more likely than HIV negative women to die: aHR 5.0 (95% CI 1.6-15.2).

There were 13 (59%) deaths among women who received ART in pregnancy and throughout follow up (ref); 2 (9%) in women who stopped ART or AZT postpartum but started ART in follow up, ahR 0.9 (95% CI 0.3-6.4); 4 (18%) in women who received ART or AZT in pregnancy but stopped postpartum, aHR 1.7 (95% CI 0.6-5.1); and 3 (14%) in women receiving no antiretrovirals during pregnancy, aHR 1.6 (95% CI 0.2-15.2).

In multivariate analysis maternal age, availability of indoor toilet, formal housing, Rh factor, preterm delivery and higher parity were not associated with mortality. Longer ART duration before delivery (>2 years) did not decrease mortality.

CD4 cell count in pregnancy was unrelated to mortality (median 421 cells/mm) p=0.20.

COMMENT

This depressing study demands further investigation into the causes of death among HIV positive women postpartum despite access to ART. This phenomenon is probably more widespread than has been documented to date. Identifying the extent and causes of mortality in order to put mechanisms in place to help to address this is a matter of urgency.

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Higher rates of eye complications in HIV positive people on ART

Simon Collins, HIV i-Base

A prospective South African study in 342 people looked at rates of optical complications and associations with HIV status and time on ART.

This group included: HIV-negative (n=105), HIV positive not on ART (n=16), HIV positive on ART for <12 months (short-term) (n=56) and HIV positive on ART for >36 months (long-term; n=165). All participants received full ophthalmic examination including fundoscopy.

Ocular disease was diagnosed in 218/342 people (64%). with HIV associated with a 3-fold higher rate or any ocular condition on (OR=3.1; 1.7-7.7; p< 0.001) and 2-fold risk of having more eye complaints (OR=1.9; 95% CI: 1.1-3.2, p=0.020), compared to HIV negative participants.

Conditions affecting the external eye, anterior chamber or posterior chamber, but not the neuro-ophthalmic segment, were significantly more common among HIV positive individuals (Table 1).

Within the HIV positive group, after adjusting for age, longer ART use was associated with higher rates of clinical cataract (57% vs. 38%; aOR 2.2, p=0.01) and HIV retinopathy (30% vs. 11%; age-aOR 3.4, p<0.05).

Table 1: Eye complications in HIV positive vs negative people

	HIV+ on ART	HIV-neg	OR (95%CI)	p-value
External Eye	40 (17%)	7 (7%)	2.8 (1.6 to 6.6)	0.015
Anterior Chamber	79 (33%)	18 (67%)	6.5 (0.8 to 5.0)	0.07
Posterior Chamber	58 (24%)	10 (10%)	3.1 (1.5 to 6.4)	0.001
Neuro-ophthalmic	8 (8%)	25 (11%)	ns	

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Sub-Saharan African countries moving quickly to recommend "Treat All"

Polly Clayden, HIV i-Base

There is broad support for universal treatment of people with HIV among fast track countries, and many are committed to adopting "Treat All" policies by the end of this year, say researchers from the World Health Organisation (WHO). But challenges to full implementation remain.

Meg Doherty and colleagues from WHO HIV/Hepatitis department showed findings from a survey of country level adoption of Treat All policies recommended in the 2016 Consolidated Antiretroviral Guidelines, as a poster presentation at AIDS2016.

"Progress towards the ending the AIDS epidemic by 2030 depends on adoption and implementation of global guidelines to optimally treat all people living with HIV and knowing how best to deliver interventions, they wrote.

WHO has implemented a country intelligence database since 2013 to better follow policy and practice trends at country level.

The researchers showed data for 144 low- and middle-income countries (LMIC) and 35 fast track counties, to July 2016. They found that 24% of all LMIC and 40% of fast track countries have adopted Treat All. A further 31% of LMIC and 40% of fast track countries plan to do so by the end of 2016. They noted that only 6% of all LMIC had adopted Treat All one year ago.

They expect that by the end of 2016 more than half LMIC and 80% of fast track countries will have adopted Treat All. But they also note that implementation is just getting started and most countries have not yet put Treat All policies into practice.

Option B+ is almost universally adopted but is not yet fully implemented. By the end of the year the researchers predict 58% of LMIC and fast track countries will have adopted Treat All for children.

The majority (90%) of LMIC adopted efavirenz plus TDF and 3TC (or FTC) as the preferred first-line regimen. Almost half of LMIC (47%) have fully implemented routine viral load; 26% have partially implemented it.

The researchers wrote: "With the 2016 Consolidated ARV Guidelines, WHO has rapidly updated global guidance to reflect new science regarding the benefit of early HIV treatment. There is broad support for universal treatment among fast track countries and many are committed to adopting Treat All policies by the end of 2016".

But implementation comes with challenges. And that the uptake of recommendations on task shifting, integration and decentralisation are lagging. They add that differentiated service models might be part of the solution as programmes expand.

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ZERO: no linked HIV transmissions in PARTNER study after couples had sex 58,000 times without condoms

Simon Collins, HIV i-Base

Published to coincide with AIDS 2016, and also presented at the conference, the PARTNER study results showing the impact of HIV treatment (ART) on reducing transmission will benefit millions of people globally.

These results question whether HIV transmission is anything other than a theoretical risk when someone is taking effective ART. This reverses the common assumption that, by definition, some level of risk always exists when one partner is HIV positive.

The PARTNER study provides good evidence that undetectable viral load might be a threshold below which sexual HIV transmission does not occur. The PARTNER study is important in that it included both gay and straight couples, that it measured risk in people who were not using condoms and that it estimated absolute risks.

Previous studies have almost exclusively been conducted in heterosexual people who still reported high rates of condom use. The PARTNER study provides more than three times the amount of follow-up time from people not using condoms than all the previous studies combined. This includes 500 couple-years of follow up from people having anal sex without condoms.

Study design and methods

Between September 2010 and May 2014 the PARTNER study prospectively enrolled 1166 serodifferent couples at 75 clinical sites in 14 European countries. Entry criteria included the positive partner having an undetectable viral load on ART and that the couples were not always using condoms when they had sex.

Follow-up included routine sexual health checks (including HIV testing for the negative partner) and each participant also completed a sexual history questionnaire for each period to look at different types of risk. Couples were only included in the final analysis when the most recent viral load for the positive partners was undetectable – defined as <200 copies/mL. The primary endpoint was the rate of within-partner transmissions, determined by phylogenetic analyses for all couples in which the negative partner became positive.

Results: zero linked transmissions

Of 1166 couples enrolled, 1004 couples had at least one follow-up visit and 888 couples provided 1238 couple years of follow-up (median 1.3 years, IQR 0.8 to 2.0) per couple. This included 548 heterosexual (HT) couples and 340 gay male couples. The main reasons for data not being included in the follow-up analysis were: not yet reaching first follow-up visit (n=162), lack of HIV test (n=20), use of PEP or PrEP (n=9), no condomless sex (n=15), viral load >200 copies/mL (n=55) and lack of viral load result (n=17). There were no significant differences between couples who contributed to follow-up data compared to those who did not.

Although 11 people became HIV positive, none of these infections were phylogenetically linked transmissions. This was after at least 58,000 distinct times when couples had penetrative sex without condoms.

Baseline demographics were reported – as with all results – by categories of HIV status, gender and sexuality, with some differences between groups. This makes summarising results complex, but the median age ranged from 40 to 44 (with IQR overall ranging from 31 to 50 years). Gay men and HT women were a few years younger than HT men. Approximately 80% of the HT men were white compared to 70% of women and 90% of gay men. A higher percentage of gay men had education to college/university or higher (approximately 50% compared to 19% to 35% for heterosexuals. Although some of these differences were significant, they reflect the diversity of people living with HIV (other than there were fewer very young adults involved).

HIV positive partners had been on ART for a median of 10.6 (IQR: 4.3 to 15.6), 7.5 (IQR: 3.3 to 14.2) and 4.8 (IQR: 1.9 to 11.4) years, for HT men, HT women and gay men respectively. At baseline, couples reported having had sex without condoms for a median of 2 years (IQR 0.5 to 6.3), with differences between groups. For example, HT couples had been having sex without condoms for roughly 3 years (IQR 0.7 to 11 years) compared to 1.5 years (IQR 0.5 to 4 years) for gay couples. Approximately 23% of couples were in new/recent relationships (<6 months). Self-reported adherence to ART was similarly high at >90% in the three positive groups. Similar proportions of each group also had CD4 counts >350 cells/mm3 (85% to 91%).

Based on data from the negative partners, overall, couples reported having sex without condoms just less than once a week: a median of 37 times a year (IQR 15 to 71). Gay couples reporting condomless sex at least 22,000 times (median 41 times a year; IQR 17 to 75) and HT couples more than 36,000 times (median 35; IQR 13 to 70). These were estimates from recall and partners did not always report the same numbers. Some couples reported sex outside the main relationship: 108 gay couples (33%) and 34 HT couples (4%).

None of the 11 incident HIV infections in negative partners (10 gay and one HT) were phylogenetically linked to the positive partner. Most people (8/11) reported having sex without condoms with people outside the main relationship. All samples (n=22) were successfully sequenced for pol and 91% (n=20) were sequenced for env. None of the partner sequences clustered together and the results were consistent after using several different analyses. Additional details for these analyses are described in the online supplementary material. [2]

Interpreting the 95% confidence interval

With zero transmissions, the upper limit of the 95% confidence interval (95%CI) for the overall study was 0.3 per 100 couple years of follow up (CYFU). Each category of specific risks, given that the calculations are a factor determined by study numbers and power, had different upper 95%CI boundaries: for example, 0.88 for HT sex overall vs 0.84 for gay sex overall.

This means that the upper 95%CI for receptive anal sex for gay men (2.70 with ejaculation and 1.68 without ejaculation) needs to be interpreted as a factor of sample size: there were fewer CYFU so the upper limit is by definition higher. While this calculation is developed to define the potential range within which the true risk might lie, the 95%CI should not be interpreted as indicating a risk that has been observed in the study. To illustrate this difficulty, the higher estimated risk for HT anal sex with upper 95%CI of 12.71 and 8.14 (with and without ejaculation, respectively) are driven by fewer CYFU with this as the primary risk rather than any biological reason for this to be much higher. Of note though, more than 20% of straight couples reported anal sex.

Also of note during the study, 91 HIV positive partners reported other STIs (n=16 HT men, 16 HT women and 59 gay men) – closely matching STIs in the negative partners, also without any increased risk reported for HIV transmission.

Two non-technical Q&A resources on these results are also online from i-Base and the PARTNER study. [3, 4]

An extension of the PARTNER study is continuing to collect further data on risk for gay men. PARTNER 2 continues to follow up gay couples in the PARTNER study and to recruit additional gay couples, in order to produce a similarly powered evidence base for gay men as for HT couples, with follow up until 2019. [5]

Simon Collins is a community representative on the steering committee of the PARTNER study.

COMMENT

These results are simple to understand – zero transmissions from over 58,000 individual times that people had sex without condoms. They are also notable for the complexity of the analysis that was needed to prove that none of the new diagnoses were linked transmissions from within the couple.

Together, this provides the strongest estimate of actual risk of HIV transmission when an HIV positive person has undetectable viral load – and that this risk is effectively zero. While no study cannot exclude the possibility that the true risk might lie within the upper limit of the 95%CI – even if the true value is actually zero due to some as yet unproven mechanism – the 95%CI can never be zero, just become increasingly close. Neither the presence of STIs nor likely viral load blips between tests had any impact in enabling transmission.

The results provide a dataset to question whether transmission with an undetectable viral load is actually possible. They should help normalise HIV and challenge stigma and discrimination.

The results challenge criminalisation laws that in many countries, including the US, continue to imprison hundreds of people based on assumptions of risk that these results disprove, even when condoms are used and viral load is undetectable.

Activist Sean Strub, from the SERO project (www.seroproject.com) said: "Hundreds of people living with HIV in the US have been charged with criminal offences for the perceived or potential risk of HIV exposure or transmission. Some are serving or have served long prison sentences for spitting, scratching or biting and others for not being able to prove they had disclosed their HIV positive status before having sexual contact (even in the absence of any risk of HIV transmission).

HIV criminalisation has created a viral underclass in the law, further burdening a disenfranchised community, putting a disproportionate share of the shared responsibility for preventing sexually-transmitted infections on one party, and discouraging people at risk from getting tested for HIV."

The results will also have a positive impact on quality of life of both HIV positive and HIV negative individuals who are in serodifferent relationships, irrespective of their choice to use condoms.

The ongoing PARTNER 2 study is continuing to follow-up gay couples and is still enrolling new couples to achieve a similar statistical power for anal sex compared to vaginal sex. For further details of sites please see the PARTNER2 website. [3]

This study generated such interest that within a few days of the i-Base reports being posted, Facebook links had been shared more than 300 times, with a reach of 40,000 people.

Several other HIV organisations translated the articles and versions in Spanish, Russian and Turkish were soon online, with edited versions being distributed in many other countries including South Africa and the US. [6, 7, 8, 9, 10]

This unprecedented level of interest for an i-Base report reflects the importance of these results to people living with HIV.

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CONFERENCE REPORTS

Global HIV Clinical Forum: Integrase Inhibitors, 16 July 2016, Durban

Introduction

This one-day workshop that focused on all things integrase was held just before the IAS 2016 conference in Durban.

The meeting has an excellent policy of putting slides for all oral presentations and webcasts of plenary talks as webcasts.

http://hiv-clinical-forum.com/global-hiv-forum_durban

Highlights include a talk by Charles Boucher on the characteristics of integrase inhibitor drug resistance and cross resistance, including cases of late development of resistance to dolutegravir.

A report in this issue of HTB South is:

- Raltegravir-based third-line ART in children and adolescents

Raltegravir-based third-line ART in children and adolescents

Polly Clayden, HIV i-Base

Five case studies from Uganda showed good responses in children and adolescents receiving raltegravir-based third-line ART.

The number of HIV positive children and adolescents failing second-line ART is increasing, leading to resistance to protease inhibitors. There are limited data describing response to raltegravir (RAL)-based third-line ART among children in low- and middle-income settings.

Victor Musiime described outcomes of five children and adolescents receiving RAL-based ART at Joint Clinical Research Centre (JCRC), Kampala, Uganda. These case studies were presented at the Global HIV Clinical Forum: Integrase Inhibitors meeting before IAS2016.

The investigators performed a chart and database review of children and adolescents less than 18 years of age attending JCRC with second-line failure; triple class antiretroviral drug resistance (NRTI, NNRTI and PI); and on RAL-based third-line ART.

Those that fulfilled the selection criteria underwent an assessment of: weight, CD4 count, viral load and World Health Organization (WHO) clinical stage at baseline and after switching to RAL-based ART. The investigators also reviewed the case histories and genotypic resistance test results before switching. Follow up was for a minimum of six and maximum of 54 months.

Of five cases evaluated, four were male and one was female. They switched to RAL at 9-15 years of age. Their third-line regimens were: darunavir/ritonavir (DRV/r) + RAL, n=3; etravirine (ETR) + DRV/r+ RAL, n=1; tenofovir DF (TDF) + lamivudine (3TC) + DRV/r + RAL (n=1).

All had received 2 NRTIs + 1 NNRTI first-line, and lopinavir/ritonavir (LPV/r)- based second-line ART. Each case had developed: 5 or more NRTI resistance associated mutations (RAMs); 2 or 3 NNRTI RAMs (n=4) and 1 NNRTI RAM (n=1); and 3 or 4 PI RAMs.

The investigators reported that all of the five children and adolescents evaluated achieved viral suppression, as well as increased weights and CD4 counts; none developed new WHO stage III/IV events after switching to RAL-based third-line ART.

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CONFERENCE REPORTS

8th International Workshop on HIV Paediatrics, 15-16 July 2016. Durban, South Africa

Introduction

The 8th International Workshop on HIV paediatrics was held from 15-16 July in Durban.

The slides of the presentations given during the meeting and the webcasts of these presentations, are published online when consent has been provided.

http://www.infectiousdiseasesonline.com/event/workshop/8th-int-workshop-hiv-pediatrics/

http://www.infectiousdiseasesonline.com/8th-pediatrics-presentation

Reports in this issue of HTB South are:

- No increased resistance with once daily dosing of abacavir and 3TC than twice daily dosing in the ARROW trial
- Raltegravir in HIV-exposed neonates
- Virological response without routine viral load monitoring in children: results from the ARROW trial
- Tenofovir-containing ART reduces bone mineral density in breast feeding women: results from IMPAACT P1084s

No increased resistance with once daily dosing of abacavir and 3TC than twice daily dosing in the ARROW trial

Polly Clayden, HIV i-Base

Once daily dosing of abacavir (ABC) and lamivudine (3TC) was non-inferior to twice daily dosing in development of viral resistance in the ARROW trial, according to data presented at the 8th International Workshop on HIV Paediatrics.

The ARROW trial – conducted in Uganda and Zimbabwe – showed that once daily dosing of ABC and 3TC was bioequivalent with twice daily dosing and gave similar treatment outcomes at 96 weeks.

In a resistance sub study, the ARROW investigators compared the development of viral resistance in children randomised to once vs twice daily dosing over the course of the trial.

A total of 669 participants receiving twice daily ABC and 3TC containing regimens, for at least 36 weeks, were randomly assigned to continue with twice daily dosing or switch to once daily. Viral load was tested retrospectively using stored plasma samples at 0, 48 and 96 weeks post randomisation. Samples with >1000 copies/mL were genotyped at the Joint Clinical Research Centre, Kampala, Uganda.

Participants were a median age 5.5 years (range 1.8-16.9). They had previously received twice daily ABC and 3TC based ART for a median of 1.8 years: 48% with nevirapine; 18% with efavirenz and 34% with AZT.

HIV genotypes were: 49% subtype A; 25% subtype C (including all Zimbawean participants) and 20% subtype A.

The investigators reported no difference between once daily vs twice daily ABC and 3TC in viral suppression at various time points (0, 48 and 96 weeks) and viral load thresholds (<80, <400 and <1000 copies/mL), all p-values non-significant.

There was no difference between once daily and twice daily in drug resistance mutations post baseline (p=0.15). The investigators found, overall 33%, 23% and 28% of participants had the L74V mutation at weeks 0, 48 and 96, respectively. At the same time points 42%, 28% and 34% had Y115F; and 6%, 6% and 5% had K65R. Only one participant receiving once daily triple NRTIs had Q151M at weeks 48 and 96. The investigators noted that thymidine analogue mutations were rare.

There was also no difference in intermediate/high level resistance to NRTIs between once daily and twice daily ABC and 3TC based regimens (p=0.15).

Among the subgroup of participants receiving an NNRTI plus ABC and 3TC regimen (WHO current recommendation) intermediate/high level resistance at 0, 48 and 96 weeks after randomisation was respectively: 15%, 16% and 8% for tenofovir DF and 0%, 4% and 2% for AZT, compared to 75%, 84% and 79% for ABC.

The investigators concluded that both tenofovir DF and AZT are second-line NRTI options for children failing ABC and 3TC based first-line ART.

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Raltegravir in HIV-exposed neonates

Polly Clayden, HIV i-Base

Daily raltegravir was well tolerated and met pharmacokinetic targets in full term HIV-exposed infants at high risk of infection, in a study presented at the 8th International Workshop on HIV Paediatrics.

Safety and dosing information for antiretroviral in neonates are limited. Raltegravir (RAL) is the first integrase inhibitor to be studied in neonates. It has potential to be used as both as prophylaxis and early intensive treatment in this population.

RAL is largely metabolised by the UGT1A1 enzyme. At birth UGT activity is low and it increases exponentially over the first weeks of life.

Previous research has shown high RAL plasma concentrations in vitro displace unconjugated bilirubin from albumin. This has the potential to increase neonatal risk of kernicterus.

The IMPAACT P1110 study is designed to evaluate safety,

pharmacokinetics (PK) and tolerability of RAL oral granules for suspension during the first six weeks of life.

This is a phase 1 study enrolling full-term HIV-exposed, high risk, neonates aged 48 hours or less, with a gestational age of at least 37 weeks and weighing at least two kilograms. Neonates with elevated bilirubin and those receiving phenytoin, phenobarbital or rifampicin are excluded.

Neonates are enrolled into two sequential cohorts: cohort 1 (n=16) receive two single RAL doses one week apart; cohort 2 infants (n=30) receive daily RAL for the first six weeks of life. The initial group of infants are born to mothers not receiving RAL. A subsequent group are born to mothers receiving RAL during pregnancy to delivery.

The investigators combined previously reported PK results from cohort 1 with that from older infants and children enrolled in IMPAACT P1066 in a population PK model and simulations using NONMEM. These were performed in order to develop daily RAL doses to be evaluated in 20 infants in cohort 2.

The investigators noted, developmental changes in absorption and clearance explored, with best fit if: absorption rate changed from 16% of maximum at birth to 90% at two weeks; and clearance changed from almost nil to a maximum at approximately six months of age.

PK targets were: Cmin >33 ng/mL; Cmax <8724 ng/mL; AUC12 (twice daily) 6-20 mg*h/L; and AUC24 (once daily) 12-40 mg*h/L.

The selected cohort 2 doses were: 1.5 mg/kg once daily, birth to day 7 of life; 3 mg/kg twice daily, 1 to 4 weeks of age; and 6 mg/kg twice daily, 4 to 6 weeks of age.

The investigators performed intensive sampling around the initial 1.5 mg dose: pre-dose and 1-2, 4-6, 6-10 and 20-24 hours post dose. Between 15-18 days of life after dose increased to 3mg/kg twice daily, further samples were collected at the same time points. After the second dose, each dose change, and at weeks 5-6 of life after dose increased to 6 mg/kg twice daily, samples were collected pre-dose and two hours post dose.

Data from 12 infants were available: 7 from Brazil, 3 from South Africa and 2 from US; 4 were female and 8 male; their gestational age was a median of 38 weeks and median birth weight 2.8 kg; 4 were delivered vaginally and 8 by caesarean section.

PK targets are: AUC24, 12-40 mg*h/L, AUC12, 6-20 mg*h/L and Cmin 33 ng/mL.

After the first dose of 1.5 mg/kg, geometric mean RAL AUC24 was 37.0 mg*h/L (range 18.6-78.3), 8/12 met target. For 3 mg/kg twice daily the geometric mean for RAL AUC24 was 11.8 mg*h/L (range 4.7-24.5), 9/12 met target. Cmin for 1.5 mg/kg was 833 ng/mL (range 191-2493), 12/12 met target; and for 3.0 mg/kg 120 ng/mL (range 11-666), 11/12 met target.

Sparse sampling confirmed that RAL plasma concentrations were within the expected range. The investigators observed no safety concerns with daily RAL administration through 6 weeks of life.

The investigators concluded that population analysis and simulations has a role in drug development for neonates. They noted that with the initial 1.5 mg/kg dose, Cmin was within target but AUC24 was above target range. But given the rapid increase in RAL metabolism over the first week of life, they considered this exposure to be acceptable.

IMPAACT P1110 cohort 2 in RAL-naive neonates is now closed: 26 infants enrolled as of 27 July 2016. The investigators are doing further modelling to allow enrolment of infants exposed to RAL in utero.

COMMENT

The study design for RAL, using population PK and simulations to facilitate drug development in neonates is excellent. The design is being adapted for other antiretrovirals to be studied in neonates.

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Virological response without routine viral load monitoring in children: results from the ARROW trial

Polly Clayden, HIV i-Base

Reassuring virological outcomes without routine viral load monitoring shown in the ARROW trial but viral rebound greater than 5000 copies/mL should prompt switch to second-line, according to data presented 8th International Workshop on HIV Paediatrics.

Although World Health Organization (WHO) guidelines recommend regular viral load monitoring for adults and children on ART, its availability in sub-Saharan Africa is still limited (estimated 25% in 2014).

In the ARROW trial, Ugandan and Zimbabwean children starting ART (according to 2006 criteria) were randomised to monitoring with vs without 3-monthly CD4 counts. Children were switched to second-line for WHO stage 4 or multiple stage 3.

Viral load was not measured in either group in real time or used for clinical management. But stored samples from all children were tested retrospectively when the trial closed and samples from 316 children were tested during the trial (4, 24, 36 and 48 weeks post-ART then 24 weekly). Viral loads were tested with lower limit of <80 copies/mL; samples with viral load >1000 copies/mL were genotyped.

As the trial was a factorial design, looking at induction/maintenance as well as monitoring strategies, some children received 4 drugs for the first 6 weeks. Long-term, two-thirds were treated with standard 2 NRTI plus NNRTI and the rest received 3 NRTIs.

The analyses included: a cross sectional study in 1127 participants that compared viral load suppression and resistance between randomised monitoring and treatment arms in the six months before trial closure or death (ITT); and a longitudinal study in 316 participants in which the investigators looked at predictors of viral load blips, persistent low level viral load, rebound and persistent low level viral load/rebound.

A total of 1206 ART-naive infants, children and adolescents started ART at a median age of 6 years (range 4 months to 17 years) with a median CD4 per cent of 12% (IQR 7-17%). Median follow up was 4 years (range 3.3-5.0) Only 5% and 4% of children with CD4 monitoring vs clinical monitoring respectively died. Only 63 (6%) switched to second-line ART. At the close of the trial, 1132 (94%) of participants were alive and in follow up. Viral loads were available for 1127 (99.6%).

At 4 years 80% of participants randomised to 2 NRTI plus NNRTI

had viral load <1000 copies/mL compared with 65% receiving 3 NRTIs. For <80 copies/mL these proportions were 74% and 52%. (Both comparisons p<0.001).

There were no differences in viral load outcomes by randomised monitoring strategy. CD4 vs clinical: 81% vs 79% (p=0.43); and 75% vs 73% (p=0.57), for <1000 and <80 copies/mL respectively.

There was no difference in intermediate/high level resistance to NRTIs and NNRTIs by monitoring strategy. Among participants with viral load >1000 copies/mL and genotype receiving 2 NRTI plus NNRTI (n=110, majority receiving 3TC and abacavir), only15% had intermediate/high-level resistance to tenofovir DF and 9% to AZT; 7% had K65R.

In the subset of participants with longitudinal viral load responses over 4 years, predictors of low level viral load/rebound were: 3 NRTI regimen vs 2 NRTI plus NNRTI (p<0.001); ART started at older age (p=0.03) and ART started at higher viral load (p=0.048).

After a median of 2.3 years of rebound a participants developed a median of 1 additional major NRTI mutation (p=0.009). The investigators noted that this had little impact on predicted drug susceptibility: only one participant developed intermediate/high level resistance to tenofovir DF and AZT.

Viral load response was similar in CD4 monitoring groups throughout follow-up (p>0.05).

The investigators noted that blips were common and low level viraemia may be followed by re-suppression. Persistent viraemia/rebound occurred only in a minority.

Participants with viral rebound < 5000 copies/mL developed slight increase in NRTI resistance over 2 years, suggesting there should not be a substantial delay in switching at this level.

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Tenofovir-containing ART reduces bone mineral density in breast feeding women: results from IMPAACT P1084s

Polly Clayden, HIV i-Base

Tenofovir DF containing ART decreases bone mineral density in HIV positive, breast feeding women, according to findings presented at the 8th International Workshop on HIV Paediatrics.

Both HIV and breast feeding (3-10% decline at 12 months) increase the risk of low bone mineral density (BMD). Antiretrovirals can also decrease BMD, and there has been particular concern about the impact of tenofovir DF.

A bone and kidney health sub study of the PROMISE trial – IMPAACT P1084s – included an evaluation of the effect of postnatal antiretroviral exposure on BMD among HIV positive breastfeeding women.

IMPAACT P1084s enrolled eligible mother-infant pairs from Zimbabwe, Uganda, South Africa and Malawi. The mothers and their uninfected infants had been randomised in the postpartum component of the PROMISE trial to receive either maternal tenofovir-based ART (TDF-ART) or infant nevirapine prophylaxis (NVP) for prevention of transmission while breastfeeding. At the time of enrolment mothers did not meet the criteria for starting ART.

Baseline characteristics were similar between the study arms: median age 26.5 years (23.3-30.0), BMI 24.7 kg (22.3-28.0), CD4 count 671.5 cells/mm3 (544.0-857.5) and viral load 400 copies/mL (86-2289). Median time to cessation of breastfeeding was 61 weeks.

The investigators measured maternal lumbar spine and hip BMD using DXA soon after delivery (5-21 days) and at approximately 74 weeks postpartum. They compared maternal ART to no maternal ART for per cent change in BMD between delivery and week 74 at the lumbar spine (primary outcome) and hip (analyses were ITT).

BMD decline between delivery and postpartum was significantly greater in women receiving ART during breast feeding compared with no ART.

Lumbar spine BMD per cent declined by: -2.06 (95% CI -2.9 to -1.23) in the TDF-ART arm (n=167) vs +1.09 (95% CI 0.11 to 2.07) in the NVP arm (n=170) giving a mean difference of -3.16% (95% CI -4.44 to -1.84), p<0.001.

Hip BMD per cent declined by: -5.37 (95% CI -5.99 to -4.76) in the TDF-ART arm (n=169) vs -3.05 (95% CI -3.72 to -2.38) in the NVP arm (n=166) giving a mean difference of -3.23% (95% CI -3.23 to -1.42), p<0.001.

The investigators were not able to show if BMD returned to baseline after cessation of breastfeeding. They concluded that these data "highlight the importance of BMD in settings where breastfeeding is standard as we enter the Treat All era".

REFERENCE

Stranix-Chibanda L et al. Impact of tenofovir-containing triple antiretroviral therapy (ART) on bone mineral density in HIV-infected breastfeeding women in sub-Saharan Africa. 8th International Workshop on HIV Paediatrics, 15-16 July 2016, Durban, South Africa. Oral abstract O_020.

CONFERENCE REPORTS

TB 2016 16-17 July 2016, Durban, South Africa

Introduction

The International AIDS Society (IAS) organised a two-day conference dedicated to this infectious disease immediately before AIDS 2016 in Durban, South Africa.

http://www.tb2016.org

This meeting incorporates the biannual SA TB Conference.

Reports in this issue are:

- Universal treatment of multi-drug resistant TB is possible within current budgets with generic production
- Shortened nine-month MDR-TB treatment works well in children and adolescents
- Levofloxacin: safety and tolerability in HIV positive and negative children treated for MDR-TB

Universal treatment of multi-drug resistant TB is possible within current budgets with generic production

Polly Clayden, HIV i-Base

Generic production could make novel multi-drug resistant tuberculosis (MDR-TB) regimens available for US $53-507 per treatment course according to data presented at TB2016. [1]

High drug prices contribute to slow progress with scaling up treatment of MDR-TB with novel regimens worldwide. Dzintars Gotham and colleagues from Imperial College London, Howard University, Washington and St Stephens Centre, London showed that competitive generic production could make universal coverage possible within current budgets.

This group have previously used similar methodology to look at cost of generic production of HIV and HCV treatment – they first presented data from the MDR-TB treatment production costs evaluation last year at EACS. [2]

For moxifloxacin, linezololid and clofazimine, the investigators estimated prices by obtaining the costs of active pharmaceutical ingredients (API) from Indian export data. For bedaquiline, delamanid and pretomanid (newer drugs so no comprehensive export data) they estimated the costs using those of synthetic processes and raw materials. To estimate generic prices, the investigators combined API per kilogram costs with dosage, manufacturing costs (including excipients, cost of tableting and packaging) and a 10-50% mark up.

They collected current drug prices from the Global Drug Facility (GDF) website, where these were available. For delamanid they used the recently announced price from the originator. As the price for pretomanid is yet to be announced, the investigators conservatively assumed pricing at their highest generic estimate.

The analysis revealed that novel regimens could be available for US $53-507 per treatment with generic production. In 2014, US $173 million were spent on second-line TB drugs through the GDF. Assuming this budget, the investigators calculated that estimated drug prices would allow the purchase of: 86-170% more STREAM B treatments (at least 202,000 more treatment courses); 401-679% more STREAM C (at least 386,000 more treatment courses); 406-689% STREAM D (at least 529 more treatment courses); 1362-3007% more MDR-END (at least 319 more treatment courses); 23-164% more PaMZ (at least 282,000 more treatment courses). See Table 1.

Table 1: Treatment courses that could be bought with a budget of US $173 million

Regimen	Current lowest cost	Estimated generic cost	Current number of treatment courses afforded	Estimated number of treatment courses afforded
STREAM arm B*, 9 months (moxifloxacin, clofazimine, ethambutol, pyrazinamide, isoniazid, prothionamide, kanamycin)	$734	$272-395	236, 000	438, 000 to 636, 000
STREAM arm C, 9 months (levofloxacin, clofazimine, ethambutol, pyrazinamide, isoniazid, prothionamide, bedaquiline)	$1,799	$231-359	96, 000	483, 000 to 749, 000
STREAM arm D, 6 months (levofloxacin, clofazimine, pyrazinamide, isoniazid, kanamycin, bedaquiline)	$1,325	$168-262	131, 000	660, 000 to 1,030, 000
MDR-END, 20 months (delamanid, linezolid, levofloxacin, pyrazinamide)	$7,408	$ 238-507	23, 000	342, 000 to 726, 000
PaMZ 6 months (pretomanid, moxifloxacin, pyrazinamide)	$140	$53-114	1, 236,000	1, 518, 000 to 3, 264, 000

* Newly recommended WHO shortened 9-month regimen

The investigators concluded that at existing prices current budgets are not sufficient to afford universal treatment of MDR-TB with novel regimes. But generic production could make novel regimens available for US $173 million – the amount spent on second-line drugs at current prices procured by the GDF in 2014.

COMMENT

Earlier findings from this excellent analysis were presented in October at EACS. But unlike that from HIV and HCV communities, so far the reaction from those working on TB has been lukewarm.

The annual incidence of MDR-TB is only 480,000, so there will not be the potential economies of scale seen with generic drugs to treat adult HIV and HCV.

Optimising treatment of paediatric HIV might be more analogous – where the number of priority drugs, formulations and regimens have had to be vastly pruned (and still needs more pruning) – to make sufficient volumes possible and procurement simpler.

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2. Gotham D et al. Target prices for novel treatments for drug-resistant tuberculosis. 15th European AIDS Conference (EACS). 21-24 October 2015. Barcelona, Spain. Oral abstract 351.

Shortened nine-month MDR-TB treatment works well in children and adolescents

Polly Clayden, HIV i-Base

The nine-month Bangladesh regimen for treatment of multidrug-resistant tuberculosis (MDR-TB) was successful in 83% of children and adolescents in an observational trial conducted in francophone Africa, presented at TB2016. [1]

Preliminary results presented previously at the 46th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union) in 2015 showed the regimen to be successful in 82% of adults participating in the study. It was coordinated by The Union and from January 2013 to March 2015 recruited participants in: Benin, Burkina Faso, Burundi, Cameroon, Ivory Coast, Niger, Central African Republic, Democratic Republic of Congo and Rwanda. [2,3]

The regimen was: four months of kanamycin, moxifloxacin, prothionamide, isoniazid, clofazamine, ethambutol, and pyrazinamide (4 Km Mfx Pto H Cfz E Z), and then five months of moxifloxacin, clofazamine, ethambutol and pyrazinamide (5 Mfx Cfz E Z). Treatment was directly observed throughout the study.

Bassirou Souleymane from Action Damien Niger showed the findings from the Bangladesh regimen for children and adolescents study in an oral presentation.

The investigators collected data on all participants aged less than 18 years who were diagnosed with rifampicin-resistant TB and treated with the regimen during the inclusion period of the study.

Forty-eight children and adolescents were started on treatment with the Bangladesh regimen: 23 (48%) girls, 5 (10%) aged 0-9 years, 9 (19%) HIV positive, and 30 (63%) previously treated for TB.

Treatment was successful in 83% of participants (56% cured, 27% treatment completed), and there was no significant difference by age (85% in 15-17 vs 80% in 0-15 year-olds). There were more deaths among participants with HIV than those without (22% vs 5%), but treatment success was similar according to HIV status among surviving participants (100% vs 92%).

Adverse events were reported in 62% of the participants, none of which was severe. Of 24 participants assessed after treatment ended, 21 were alive with confirmed treatment success, two had died and one had recurrence.

The investigators concluded that treatment with the nine-month Bangladesh regimen appeared to be excellent in children and adolescents irrespective of HIV status with very limited side effects. They encourage countries to adopt the shortened MDR-TB treatment regimen in this population.

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Levofloxacin: safety and tolerability in HIV positive and negative children treated for MDR-TB

Polly Clayden, HIV i-Base

Levofloxacin was safe and well tolerated in children with and without HIV in long-term use. The data provide additional support for its inclusion in paediatric TB treatment and prevention regimens. [1]

These findings were presented as a poster at TB2016 authored by South African investigators from: Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town; Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch University, Cape Town; and Western Cape Government Department of Health, Brewelskloof Hospital, Worcester.

Levofloxacin is a fluoroquinolone and a key component of MDR-TB treatment in children. The drug is also included in two phase 3 trials of preventive therapy in MDR-TB exposed adults and children. The most notable side effects of fluroquinolones include: arthropathy, neuropsychiatric symptoms and QT interval prolongation. There have been persistent concerns about the safety of fluoroquinolones in children because of arthropathy in juvenile animals. Prospective data on levofloxacin in children is scarce, particularly on its long-term use.

The data were from a prospective, observational, cohort study conducted in Western Cape, South Africa. Children with MDR-TB in this cohort are routinely treated with a 6-7 drug regimen. The regimens

include: a fluoroquinolone, a second-line injectable, ethionamide, terizidone, high-dose isoniazid, ethambutol, pyrazinamide, and occasionally other drugs such as PAS. At the beginning of the study levofloxacin was dosed at 10-15 mg/kg once daily and later at 15-20 mg/kg once daily.

There were 70 participants in the study with a median age of 2.1 years (range 0.4-7.3). Of these: 44% were 0-2; 50% were 2-5; and 6% were 6-15 years of age. Approximately half the group were girls; 17% were HIV-infected; and 23% and 35% respectively were underweight or short for their age. The children were followed for a total of 68.5 person years; median time 11.6 months (IQR 9.2-14.7).

The investigators reported that overall most adverse events were grade 1 or 2; the most frequent were vomiting (24 events in 19 children; 0.351 events/person-year) and ALT elevation (27 events in 22 children; 0.394 events/person-year). There were no arthritis events and only three grade 1 arthralgia events in three children (event rate 0.044 events/person-year).

Among grade 1 or 2 adverse events attributed to levofloxacin, vomiting (16 events in 14 children; 0.234 events/person year) and ALT elevation (18 events in 16 children; 0.263 events person year) remained the most reported.

There were three grade 3 and five grade 4 adverse events; seven were ALT elevation (none were attributed to levofloxacin) and one grade 3 headache, possibly related to levofloxacin. No adverse events led to permanent discontinuation of levofloxacin.

The investigators concluded that levofloxacin was safe and well tolerated and can be an option in TB treatment and preventative regimens. But they noted that making an assessment of adverse events associated with levofloxacin in multidrug regimens was hard – many adverse events were likely due to other second-line TB drugs. It is also likely that the event rates they reported overestimate those actually due to levofloxacin.

They suggested that mild arthralgia might be underestimated in young children but serious arthropathy is unlikely to have been missed. Neuropsychological events also might be underestimated. The investigators will report on QT prolongation elsewhere.

COMMENT

There are limited data on the use of second-line TB drugs in children. Second-line drugs are more toxic than those used in first-line treatment and adverse events are hard to monitor in children. Paediatric formulations are not usually available and doses using divided and/or crushed tablets are uncertain.

Pharmacokinetic data on which to base optimal dosing have been mostly absent until quite recently – thanks to the work of the Stellenbosch group who performed this levofloxacin evaluation. TB drugs are also frequently used with antiretrovirals in children with HIV and TB.

The data above are from a large ongoing study designed to characterise the pharmacokinetics and toxicity of second-line TB drugs for treatment and prevention of drug resistant TB in HIV positive and negative children, by age and HIV status.

We have previously reported findings from this excellent initiative as they have been presented. [2, 3, 4, 5]

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CONFERENCE REPORTS

17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, 8-10 June 2016, Washington DC, USA

Introduction

The 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, was held from 8 – 10 June 2016 in Washington DC.

The slides of the presentations given during the meeting and the webcasts of these presentations, are published online when consent has been provided:

http://www.infectiousdiseasesonline.com/_event/workshop/international-workshop-clinical-pharmacology-hiv-hepatitis-therapy-2016

The abstract book is also available in PDF format online:

http://regist2.virology-education.com/Abstractbook/2016_6.pdf

Natap.org has also published extensive reports from the workshop, many including full slide sets:

http://www.natap.org/2016/Pharm/Pharm.htm

Reports in this issue of HTB are:

- Modelling data might support use of low dose 400 mg efavirenz in pregnancy
- Pharmacokinetics of antiretrovirals comparable to that in non-pregnant women from three weeks after delivery

Modelling data might support use of low dose 400 mg efavirenz in pregnancy

Polly Clayden, HIV i-Base

Simulated exposure following 400 mg efavirenz once daily during third trimester of pregnancy, indicates that the lower dose might be adequate in this population, according to data presented at the 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy.

Efavirenz (EFV) 400 mg once daily is non-inferior to EFV 600 mg in adults and recommended by World Health Organisation as part of an alternative first-line regimen. [1] The pharmacokinetics (PK) of antiretrovirals can alter during pregnancy, leading to reduced drug exposure and the risk of virological failure and vertical transmission.

To date (and despite a lot of discussion) it remains unknown whether the 400 mg dose is adequate during pregnancy. And CYP2B6 polymorphisms influencing EFV clearance make this question a bit complicated.

Stein Schalkwijk from the PANNA Network, based at Radboud University Medical Centre, Nijmegen, alongside investigators from The Netherlands, South Africa, Thailand and the US IMPAACT 1026s group developed a physiologically-based population PK model to describe the PK of EFV in HIV positive pregnant and non-pregnant women. [2] They included published data, pooled from nine EFV pregnancy PK studies, and used the model to simulate EFV exposure following 400 mg EFV QD during third trimester of pregnancy.

Data from 249 women (1697 samples) were included in the model. Median non-pregnant weight was 59 kg (IQR 52-68). Median gestational age 35 (range 25-39) weeks. Among 41 (16%) women with genotype available: eight were categorised as slow metabolisers; 22 intermediate; and 11 fast metabolisers.

After controlling for pregnancy-induced changes in protein-binding and plasma liver flow, the investigators found that pregnancy had no effect on intrinsic clearance.

For 400 mg, the simulated median C12 in pregnancy were: 3.22 (IQR 2.23-4.57), 1.26 (IQR 0.92-1.75), and 0.82 (IQR 0.58-1.20) mg/L for slow, intermediate and fast metabolisers, respectively, compared to 4.37 (IQR 3.17-6.07), 1.74 (IQR 1.24 -2.32), and 1.17 (0.84-1.64) mg/L for non-pregnant women.

In slow, intermediate and fast metabolising pregnant women 1%, 30% and 61% had C12 below 1.0 mg/L, respectively, compared to 1%, 14%, and 38% in non-pregnant women.

The investigators reported that the frequencies of C12 below 0.7 mg/L were: 38% in pregnancy and 15% for non-pregnant fast metabolising women. But despite this increase in below target fast metabolising pregnant women, the predicted unbound concentrations were unchanged by pregnancy. Simulated EFV unbound concentrations showed 18% of C12 in fast metabolising pregnant women below the protein-binding-adjusted threshold of 0.7 mg/L, compared with 15% in non-pregnant women.

The investigators concluded that although pregnancy decreases total EFV C12, EFV unbound is predicted to be unchanged. Although this finding needs confirmation in human studies, it suggests that a dose reduction to 400 mg might be feasible.

COMMENT

A PK study of EFV 400 mg in pregnant women is underway at the St Stephen's Centre, Chelsea and Westminster Hospital, London. [3]

This study is recruiting women who are stable on EFV 600 mg once daily for more than 12 weeks and willing to take EFV 400 mg once daily at gestational age of 28 weeks (plus or minus three weeks).

The study should finally provide the evidence to guide global recommendations for this optimised EFV dose in pregnant women.

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Pharmacokinetics of antiretrovirals comparable to that in non-pregnant women from three weeks after delivery

Polly Clayden, HIV i-Base

When looking at pregnancy induced pharmacokinetic changes, timing of the postpartum control curve from three weeks after delivery was comparable to non-pregnant women, according to investigators form the PANNA study.

Pregnancy may induce changes in the pharmacokinetics (PK) of antiretrovirals, which could lead to sub-therapeutic levels. PANNA is a European clinical pharmacology network that investigates the PK of new antiretrovirals in HIV positive pregnant women.

The PANNA protocol includes taking PK curves in the third trimester of pregnancy (at approximately 33- weeks gestational age) and postpartum (at least two weeks after delivery). The postpartum curve is used as the intrapatient control curve for the non-pregnant woman.

The PANNA investigators found that sometimes, the postpartum curves are performed before the preferred period with a minimum of two weeks. They also noted that the choice of 2-6 weeks postpartum – although widely used in PK studies – has not been validated. So they assessed this timing and the effect of pregnancy on the PK of several antiretroviral agents in a study presented by Angela Colbers from PANNA at 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy.

Women with paired PK for the antiretrovirals for which lower exposure in pregnancy was observed were included in the analysis: emtricitabine, tenofovir DF, atazanavir/ritonavir, darunavir/ritonavir, raltegravir and maraviroc.

The investigators calculated relative ratios for AUC and Cmax for each participant and antiretroviral agent. They divided the ratio of the AUC in the third trimester/postpartum for each participant and antiretroviral agent by the geometric mean ratio of the third trimester/postpartum in the study population for that antiretroviral agent.

There were 157 paired PK parameters, from 62 participants, generated in the PANNA study, included in the analysis. Median age at delivery was 32 years (range 19-45); 60% were black, 39% white and 1% of other ethnicity. Weight at postpartum PK sampling was 71 kg (range 43-126), and weight at third trimester PK sampling was 76 kg (range 48-139).

The investigators reported they observed no statistically significant difference for AUC (p=0.337) or Cmax (p=0.227) relative to reference from week 3 postpartum onward (>week 8 pooled).

They concluded that no time effect was observed for postpartum curves taken at least 3-weeks post- delivery, and these curves were comparable to non-pregnant population means. They added that dose reductions (after dose increase in pregnancy) should be considered from two weeks post-delivery onwards.

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TREATMENT ACCESS

CHAI's ARV market report shows more people than ever on ART in 2015 – and on better ART: but still some way to go

Polly Clayden, HIV i-Base

Two million more people started ART in 2015, marking one of the largest annual increases. But we still have a long way to go as less than half of the 37 million people living with HIV worldwide are now receiving treatment, according to the 7th CHAI ARV Market Report.

The Clinton Health Access Initiative (CHAI) ensures rapid access to the best antiretroviral and diagnostic products at affordable prices for low- and middle-income countries (LMIC). And the organisation publishes an annual antiretroviral (ARV) market report for the public domain based on its work in over 30 countries. [1]

The latest issue reports that of the nearly 37 million people needing ART, 46% received it in 2015.This proportion included a growth of two million people receiving ART that year – one of the biggest annual increases ever.

In keeping with this increase, the overall LMIC market expanded to almost $US 2 billion in 2015. And cost of ART for adults per person year (PPPY) decreased by 6-10% in 2015 from 2014 for adults and second-line for children in generic accessible countries. It now costs about $US110 to treat an adult with a preferred ART regimen.

Over 70% of both adults and children received WHO preferred regimens (or optimal paediatric formulations as defined by the Interagency Task Team [IATT]). So, cost of treatment generally fell with higher volumes, while quality of treatment rose in generic accessible countries.

Three Indian generic manufacturers – Mylan, Cipla and Hetero – continued to supply approximately 70% of the generic accessible LMIC market.

More countries have adopted Treat All policies – including Botswana, Cambodia, Lesotho, Kenya and South Africa. And guidelines for oral PrEP are being considered for roll-out in many countries.

CHAI note that access to new generic drugs and formulations will provide benefits to people with HIV as well as cost savings.

The first generic dolutegravir (DTG) has now been tentatively approved by the FDA. Botswana became one of the first countries to include DTG in its national guidelines and several others will follow. Low dose efavirenz (EFV400) should be available in 2017 and tenofovir alafenamide (TAF) is also likely to come on to the ARV market over the next two or three years.

For children, the lopinavir/ritonavir (LPV/r) pellets have been launched in a number of countries and several are planning to use the abacavir/lamivudine (ABC/3TC) reduced strength, dispersible tablets.

CHAI are working with trial investigators, regulatory agencies and manufacturers to accelerate the development and availability of these new drugs and formulations.

COMMENT

In the report, the authors from the usually measured organisation state that CHAI is "excited and optimistic about future opportunities in the ARV market". This is with good reason as recent years have shown both improved regimens and more people receiving ART. Newer drugs and formulations should enhance the market further.

CHAI's annual ARV reference price list for 2016 was also recently published and includes DTG for the first time at US$4.00 for a bottle of 30 tablets. [2] CHAI notes that The Global Fund's pricing served as an indicative reference before any generic manufacturer received approval and more refinement to this price is likely since Aurobindo's tentative US FDA approval.

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First generic version of dolutegravir approved by the FDA

Polly Clayden, HIV i-Base

Aurobindo Pharma receives US FDA tentative approval for dolutegravir – the first generic version to be approved.

This generic dolutegravir is expected to be launched in sub-Saharan Africa in late 2016 through a collaboration between Aurobindo, ViiV Healthcare, and the Clinton Health Access Initiative (CHAI). WHO included dolutegravir in its most recent first-line recommendations. Tentative approval allows this version to be used in PEPFAR programmes.

Aurobindo dolutegravir is bioequivalent and therapeutically equivalent to the reference originator product manufactured by ViiV.

ViiV and Aurobindo signed a licensing agreement in 2014 that allows Aurobindo to supply dolutegravir 50 mg in 92 licensed countries, following local regulatory approval. The generic version will be launched around three years from the approval of the originator product.

COMMENT

Aurobindo currently have approval for dolutegravir in Kenya and are expecting approvals in several other countries in the coming months. The single will be launched at an annual patient cost of around US$ 44. Dolutegravir-based generic fixed dose combination products are not far off.

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Brazil to start using dolutegravir first-line in its national programme

Polly Clayden, HIV i-Base

Brazil will begin to use dolutegravir in its national programme early next year. The Ministry of Health has negotiated a 70% price reduction with ViiV Healthcare.

On 28 September, the Brazilian Ministry of Health announced that it expects to be treating about 80,000 new first-line patients with dolutegravir plus 20,000 who switch from efavirenz due to side effects by the end of 2017.

Brazil has planned a phased process that will exclude pregnant women and people receiving co-treatment for TB. The agreed price is around US$ 500 per person per year for dolutegravir – and the country has bought 40 million tablets. "We are offering this treatment without budgetary impact," said the director of the ministry Adele Benzaken. (ie at no greater cost than efavirenz). Distribution will start in January 2017.

COMMENT

This is very good news. At this price, the overall Brazilian HIV budget will not be affected. And this news should be a useful bargaining tool for other middle-income countries that will hopefully be able to negotiate similar price levels for dolutegravir.

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Dolutegravir superior to standard dose efavirenz in WHO analysis

Polly Clayden, HIV i-Base

A systematic review and meta-analysis, conducted to inform the new World Health Organization (WHO) Consolidated Guidelines, found dolutegravir superior to standard dose efavirenz for both viral suppression and discontinuation rates. [1]

The analysis, published in online in the Lancet HIV, 6 September 2016, also showed low dose efavirenz to be superior to standard dose for discontinuation rates and CD4 count gains.

The investigators wrote: "A research question posed by WHO in anticipation of the guideline development was how INSTIs compared with efavirenz, and to this end our results suggest a clear hierarchy within the INSTI class with dolutegravir being the most efficacious, followed by raltegravir then elvitegravir." They suggest that although there are several reasons beyond safety and efficacy for WHO to continue to recommend standard dose efavirenz as the preferred first-line drug in the recent guidelines, these results signal the potential for future changes.

For the systematic review and network meta-analysis, the investigators searched MEDLINE, Embase, and the Cochrane register of Controlled trials for randomised clinical trials of antiretroviral regimens in treatment-naive adults and adolescents (aged 12 years and above) with HIV, published up to 5 July 2015.

In this analysis 3TC and FTC were considered to be interchangeable. ART regimens with one, two or four drugs (with the exception of boosted regimens) were not eligible. Regimens were defined according to their third drug with the other two NRTIs considered as the treatment backbone.

The primary outcomes were: viral suppression, mortality, AIDS defining illnesses, discontinuations, discontinuations due to adverse events, and serious adverse events. Secondary outcomes included mean change in CD4. The investigators used GRADE to rate the overall quality of the evidence.

The investigators found 5865 citations, they selected 513 of these for full text review and included 126 articles associated with 71 trials in the analysis. The final network of eligible comparisons – including both head-to head and indirect – between treatments included 34 032 patients randomised to 161 treatment groups.

In the assessment of viral suppression (using data from 70 trials, including 31 404 participants receiving 16 third drugs), the analysis revealed dolutegravir to be significantly better than efavirenz at 48 and 96 weeks: the odds ratio (OR) for viral suppression was 1·87 (95% CI 1·34–2·64) with dolutegravir and 1.90 (95% CI 1.40-2.59) at these time points respectively. Raltegravir was the only other third drug that was statistically superior to efavirenz: OR 1·40 (CI 95% 1·02-2.59) and 1.45 (1.07-1.95) at 48 and 96 weeks respectively.

The investigators noted that ritonavir-boosted lopinavir "fared worst" and was inferior to standard dose efavirenz and all INSTI.

The investigators also performed a random-effects network meta-analysis for discontinuations due to adverse events. This showed that dolutegravir had the most protective effect relative to efavirenz: OR 0·26 (95% Crl 0·14–0·47). Low dose efavirenz followed: OR 0·39 (95% Crl 0·16-0·92). They noted that although there was no statistical difference between dolutegravir and low dose efavirenz, their estimations suggested higher rates of discontinuations with the latter drug.

At 48 weeks the mean difference in CD4 count was about 20 cells/mm3 with all three INSTI compared with standard dose efavirenz. Low dose efavirenz was also superior to standard dose with a mean difference of approximately 25 cells/mm3.

Due to insufficient data, the investigators were unable to make any conclusions about mortality, AIDS defining illnesses (both low event rates) or serious adverse events.

In an accompanying commentary, [2] Anton Pozniak and Andrew Hill note that low-income and some middle income-countries will be able to access generic dolutegravir in the not-too-distant future at very low prices through voluntary licensing. But in other middle-income and all high-income countries, the patents on new antiretrovirals will remain for at least another 10 years, keeping the prices high.

The authors argue that in the WHO meta-analysis, the most common endpoints used to define viral suppression classified virological failures as discontinuation of their randomised treatment for any reason. But in most clinical trials with these endpoints only a minority of failures are truly virological. Most people have undetectable viral when they discontinue treatment, doing so because of adverse events or other reasons and can be switched onto alternative treatments to sustain long-term virological suppression, they write.

They explain that in the SINGLE trial, the virological failure rate was actually slightly higher for dolutegravir (10%) than efavirenz (7%). There

were more discontinuations for adverse events or other reasons in the efavirenz group (30%) than the dolutegravir group (18%) and a small non-significant risk resistance between the groups.

The authors go on to ask whether dolutegravir – which is significantly more expensive than generic efavirenz in most middle-income and high-income countries – is worth the additional cost. They note that one option, as proposed by the International Antiviral Society-USA treatment guidelines panel, would be to start people on low-cost generics and only switch to more expensive integrase inhibitors for adverse events. "Difficult decisions will need to be taken if we are to achieve the UNAIDS targets for antiretroviral treatment coverage", they conclude.

COMMENT

It's no big surprise that dolutegravir fared well in the WHO systematic review and network meta-analysis!

And the first generic version of dolutegravir is on its way: FDA tentative approval of the Aurobindo single was recently granted and it will be available to generic accessible countries for a per person annual cost of about US $44 under an agreement with ViiV and the Clinton Health Access Initiative (CHAI). [3] And dolutegravir-based fixed dose combinations are not far behind.

Hill and Pozniak and their group have looked extensively at prices of antiretrovirals in countries where voluntary licenses are not permitted such as in South America, South Asia and Eastern Europe. [4] They continue this discussion in the Journal of Virus Eradication, arguing for scale up of low-cost generics as patents expire in these regions in order to achieve 90-90-90 targets. [5]

Meanwhile a group of six non-profit organisations, led by the International Treatment Preparedness Coalition are working to make essential HIV medicines more affordable in middle-income countries. [6] They are supporting governments to issue selective compulsory licenses, which allow to generic companies produce the patented product without the consent of originator. They are also challenging undeserved patents.

Mechanisms to ensure fair pricing across middle-income countries need to be much improved to ensure equitable and sustainable access, particularly to improved treatments as they are recommended.

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PREGNANCY

Dolutegravir use in a London cohort – including nine pregnant women

Polly Clayden, HIV i-Base

Dolutegravir appeared to be safe and effective in pregnancy in a London cohort. Continued data collection is critical.

Antiretroviral registrational trials are not representative of real life HIV cohorts with fewer women and rare pregnancies. Rebecca Simons and colleagues from Guy's and St Thomas' NHS Foundation Trust, London, presented data from an assessment of dolutegravir (DTG) in a clinic cohort – since its approval for use in England in January 2015 – at the 22nd BHIVA conference. [1]

The investigators used electronic pharmacy dispensing records to identify patients receiving DTG (plus backbone) or the fixed dose combination (DTG/abacavir/3TC) between 14 January and 30 November 2015.

They identified 181 cohort participants: 127 (70%) men and 54 (30%) women; 9/54 were pregnant. Median age was 42 (range: 22 to 77); 54% white and 25% black-African. Overall 2% were coinfected with hepatitis B and 6% with hepatitis C.

Eight participants started on DTG and 43 the FDC, 38 were switched to DTG and 92 to the FDC.

The reasons for starting with a DTG-based regimen among treatment naive participants were: preference for an FDC (43%) and concern about CNS side-effects (20%). Reasons for switching included: simplification (31%), CNS or gastrointestinal side effects (26%) and virological failure (12%).

In the treatment-naive group, median baseline CD4 was 392 cells/mm3 (range 16-833) and viral load 61,983 copies/mL (range 271-2,018,536). At 12 weeks, 79% had undetectable viral load and 93% were undetectable by 24 weeks. Median time to suppression was 42 days.

In the switching group, median CD4 at switch was 508 cells/mm3 (range 21-1719) and viral load 61,983 copies/mL (range 271- 2,018,536; 72% had a viral load <20 copies/mL at switch; of those 100% remained undetectable. Thirty-eight participants (28%) had a detectable viral load at switch (median 372 copies/mL [range 51-869,544]); 91% suppressed by 12 weeks.

There were 9/181 (5%) discontinuations due to toxicity in the cohort of which symptoms improved in 7/9 after stopping DTG. The reasons for these were: dizziness (22%), insomnia (33%), malaise/myalgia (33%). One participant developed acute kidney injury (reduced eGFR by 52%), which improved after stopping DTG.

The pregnant cohort included nine women: median age 27 years (range 22-41); 6/9 black African, 3/9 black British and 1/9 white. They started/switched to DTG or FDC median gestation of 21/40 weeks (range: 8 to 32) with baseline viral load 4959 copies/mL (range: 19 to 40,025).

Reasons given for use were: rapid viral suppression needed (n=4), previous poor adherence (n=4), previous GI side effects with PI (n=1), avoiding future drug-drug interactions with contraceptive implant (n=1), food requirements (n=1), and tolerance and pill-burden (n=1).

DTG FDC was well tolerated with no discontinuations. All seven women who delivered achieved undetectable viral load <20 copies/mL at delivery, one woman had not yet delivered at the time of analysis and the outcome for the remaining woman was unknown. Four women delivered by elective caesarean section and three vaginally. There was one preterm delivery at 28 + 2 weeks in a woman with pre-existing hypertension. The investigators observed no birth defects and all infants to date are HIV DNA PCR negative.

The investigators wrote: "In this diverse but representative cohort, including a significant proportion of women, virological efficacy and discontinuation rates were similar to phase 3 studies. DTG appeared to be a safe and effective treatment in pregnancy although continued data collection will be required."

COMMENT

Like the small cohort receiving DTG/rifampicin shown at Glasgow and described above, [2] small real life studies will contribute to the body of evidence in populations not typically represented in registrational trials, but badly needed to inform global guidance.

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HIV positive and HIV negative pregnancies in the UK and Ireland have similar outcomes including for older women: impressive 15-year review

Polly Clayden, HIV i-Base

There has been an increase in pregnancies in HIV positive women in recent years in the UK. The proportion among older women has also grown. There has not been an increased risk of preterm delivery, low birth weight or vertical HIV transmission among older mothers. But, similar to the HIV negative population, older HIV positive mothers have a heightened risk of multiple birth, stillbirth or an infant with chromosomal abnormality compared to younger ones.

In the UK and Ireland, the National Study of HIV in Pregnancy and Childhood (NSHPC) collects comprehensive population-based surveillance data on all HIV positive pregnant women and their children.

Claire Townsend and colleagues conducted an analysis using NSHPC data to compare maternal characteristics and pregnancy outcomes in younger (<40 years) and older (>40 years) HIV positive women delivering in the UK and Ireland between 2000 and 2014.

They reported their findings in the 16 November 2016 edition of HIV Medicine.

The analysis included all singleton and multiple pregnancies reported by the end of June 2015 resulting in live birth or stillbirth to women diagnosed with HIV before delivery and delivering in 2000-2014. It found that among 15, 501 pregnancies, the proportion in older women rose from 2.1% (73/3419) in 2000-2004 to 8.9% (510/5748) in 2010-2014, p<0.001.

Older women were more likely to receive ART in pregnancy, and at conception. ART was also started slightly earlier in this age group: median 22.8% vs 23.5% weeks in younger women, p=0.02.

There was no evidence of an increased rate of emergency caesarean section or operative vaginal delivery among pregnancies in older vs younger women: 25.7% vs 23.9%, p=0.2, and 3.1% vs 4.6%, p=0.1, respectively. There was also no increased risk of preterm delivery or low birth weight among deliveries to older women. Infants of older women were slightly more likely to have very low (<1.5 kg) or high (>4 kg) birth weight but neither association reached statistical significance.

There was no difference in the rate of vertical transmission by maternal age: (older vs younger) 0.6% vs 0.8%, p=0.05. There were 13 maternal deaths but none were in older mothers.

The risk of multiple births increased in older vs younger women: 3.0% vs 1.9%, p=0.03. And the risk of an infant with a chromosomal abnormality was higher in older women: 1.6% vs 0.2%, p<0.001 (overall risk of congenital abnormality increased: 4.2% vs 2.8%, p=0.02; the rate of structural abnormalities was similar).

Older mothers had more stillbirths: 1.6 vs 1.0% in younger mothers. This was not statistically significant in univariate analysis: OR 1.70 (95% CI 0.99-3.01), p= 0.05. After adjustment for time period, parity (no previous births vs one or more previous birth) and type of ART, the association increased and reached statistical significance: AOR 2.39 (95% CI 1.32, 4.32), p=0.004. The authors noted that, in this model, the only other variable significantly associated with the outcome was time period.

The authors explain that these findings are consistent with studies in the HIV negative population showing associations between older mothers and outcomes such as multiple pregnancies, chromosomal abnormalities, and stillbirth.

When they compared their data on multiple maternity rates to general population rates in 2014 they found the results to be consistent with their own: 2.9% for women aged 40-44 years (compared with 3.0% in the NSHPC study) and ranging from 0.96% for 20-24 year old women to 2.3% for 35-39 year olds (compared with 1.9% for <40 year olds).

They also note that the doubled risk of stillbirth associated with older mothers is similar to that found in a meta-analysis of five studies in the general population in high-income countries. The stillbirth rates in HIV positive women were higher than in the general population: 0.47% overall, 0.76% for 40-44 year olds and 0.95% for >45 year olds, with the greatest difference seen for younger women.

Unlike other studies in HIV positive mothers, they did not observe an increased risk of preterm delivery, although the rate was higher overall than in the general population (13.2 vs 6.2%, respectively).

Limitations to this analysis are that few data are collected on background characteristics and clinical characteristics in pregnancy, and there was no information on factors such as smoking, or history of delivery complications or hypertension.

The authors concluded: "These findings have implications for pregnancy management of older HIV-positive women, given the increased risk of multiple births in this group, as well as pre-existing comorbidities and adverse outcomes such as stillbirth and chromosomal anomalies, as has been reported in the HIV negative population".

COMMENT

These data are very reassuring.

The study shows that since 2000, the overwhelming majority of more than 15,000 HIV positive women have had pregnancies without complications. This includes women above and below 40. And similar to the general population women are choosing to have children older than in the past.

Although older age (ie above 40) was linked to higher rates of some complications, very similar age effects occur in HIV negative woman (ie general population data). Most older women understand these slightly higher risks, but it is important that neither HIV itself, nor ART, seems to be as important as maternal age.

For those reading the Townsend et al article in a hurry, the abstract does not emphasise the similarities between outcomes in older HIV positive and negative women. But the discussion section is excellent – so it is worth taking the time to read to the end.

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http://i-base.info/ttfa

Entry-level curriculum relating to HIV and treatment.

Eight modules include: immune system and CD4 count; virology, HIV and viral load; an introduction to antiretrovirals (ARVs); side effects of ARVs; opportunistic infections and coinfections: HIV and pregnancy; drug users and HIV; and clinical trial design and the role of advocates

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 580 members from over 120 organisations.

http://www.ukcab.net

Phoneline and information services

Online Q&A service

An online question and answer service that now has over 3000 questions and comments online. Questions can be answered privately, or with permission, can be answered online.

http://www.i-base.info/qa

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http://i-base.info/order

HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it. However, any donation that your organisation can make towards our costs is greatly appreciated.

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From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

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