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EDITORIAL

Welcome to the January 2018 bumper issue of HTB South.

In this annual round-up we include reports on developments in HIV treatment and prevention that will affect low- and middle-income countries (LMICs) – particularly in Southern Africa – both now and in the not-too-distant future.

We have selected articles that mainly focus on ART optimisation, TB, pregnancy and paediatrics.

The big news for global HIV treatment in 2017 was a new pricing agreement, announced in September, that will speed up access to generic, dolutegravir-based fixed dose combinations (FDCs).

This will mean that HIV positive people in generic-accessible LMICs, can be treated at an annual cost per person of around US $75.

The FDCs combine tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD) and were developed by Mylan and Aurobindo under licensing agreements from ViiV Healthcare. Both generic manufacturers received tentative approval from the US FDA for TLD in August.

The new DTG-based regimens will help more countries to provide ART to more people and get nearer to 90-90-90 targets.

This year DTG (as well as PrEP) was added to the World Health Organisation (WHO) essential medicines list.

One of the reasons that DTG is an alternative and not a preferred option in WHO guidelines was the lack of data in pregnant women.

So, it was reassuring that reports presented at IAS 2017 on DTG use in pregnancy from Botswana, Europe and the Antiretroviral Pregnancy Registry, did not show an increased risk of adverse outcomes compared with other antiretrovirals.

But more data are needed, particularly with DTG exposure before conception, to reach definitive conclusions – and we expect that to be forthcoming in 2018 and a guideline change is likely.

Good news from Tanzania on breastfeeding was that no HIV exposed infants who were negative at birth, whose mothers started ART before delivery, had suppressed viral loads and exclusively breastfed, were HIV positive after breastfeeding, in a rural cohort.

And more good news was a report from the country with the highest national prevalence in the world, Swaziland, with 32% among a population of just under 1.5 million in 2011, saw a decrease in HIV incidence by almost half and a doubling of viral load suppression among adults.

Developments in paediatric ART included the FDA approval of raltegravir for treatment of neonates from birth to four weeks of age – weighing at least 2 kg. Raltegravir is now one of the few antiretrovirals approved for treating babies from birth.

And (like many groups in 2017), we published i-Base's refute of controversial BMJ analysis supporting older HIV drugs in pregnancy.

HIV treatment Bulletin (HTB) is available on our website:

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

As is Fit for Purpose, our twice-yearly review of developments in ART optimisation, and our more detailed review of the HIV treatment pipeline:

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

http://i-base.info/htb/31870

CONFERENCE REPORTS

16th European AIDS Conference (EACS 2017)

The 16th European AIDS Conference (EACS 2017) was held from 25-27 October 2017 in Milan, Italy.

This conference is held every two years (alternating with the Glasgow HIV Congress) and always provides a good focus for European HIV research.

This year the conference abstracts were available online in a searchable database as soon as the meeting started.

http://www.professionalabstracts.com/eacs2017/iplanner

Reports from this meeting include:

- Studies on dolutegravir and sleep, cardiovascular and CNS side effects, and risk of IRIS
- Twice-daily tenofovir alafenamide dose might overcome interaction with rifampicin
- No impact on bioavailability of D/C/F/TAF when tablet is split but TAF absorption is reduced if crushed
- No transmissions from breastfeeding in Tanzania cohort from mothers with undetectable viral load

Studies on dolutegravir and sleep, cardiovascular and CNS side effects, and risk of IRIS

Polly Clayden, HIV i-Base

Meta-analysis of randomised trials presented at EACS 2017 found a slightly higher risk of insomnia for dolutegravir (DTG) compared with other antiretrovirals (ARVs). But no difference for other CNS side effects. [1]

There was also no significant difference in the risk of cardiac serious adverse events (SAEs) between DTG and other ARVs. The risk of IRIS was low but the main trials excluded people with CDC stage C disease.

Observational data suggest higher risks of CNS adverse events for DTG, compared with other ARVs. There have been two case reports of myocarditis in people receiving DTG. And integrase inhibitors have been associated with IRIS in two cohort studies.

In response to these signals, Andrew Hill and Nikkita Mitchell from Liverpool University and Imperial College London, performed a meta-analysis to compare rates of each adverse event for DTG versus other ARVs – stratified by trial. They compared suicidality between DTG and efavirenz (EFV) and non-EFV controls in two separate analyses. This meta-analysis of randomised trials included 6,647 patient-years of follow-up.

For cardiac SAEs, the authors included trials: SINGLE, SAILING, FLAMINGO, SPRING-1, SPRING-2, ARIA, STRIIVING and NEAT SSAT 060. The analysis revealed 15/2,202 (0.7%) participants with cardiovascular SAEs receiving DTG compared with 8/2,215 (0.4%) receiving other ARVs (RR=1.69, NS). Only 1/25 (4%) cardiac SAE

in SPRING-1 was considered to be related to DTG; 1 other cardiac SAE in the same trial was considered unlikely to be related. There was additional case information available for 19/23 participants with cardiac SAEs. Of these 17/19 (89%) had underlying cardiac risk factors.

When the authors looked at suicidality in the SINGLE and SPRING-1 trials, there were 5/465 participants with reported SAEs receiving DTG (1.1%) compared with 6/469 (1.3%) receiving EFV (RR=0.87, NS). In the SAILING, FLAMINGO, SPRING-2, ARIA, STRIIVING, SWORD and NEAT SSAT 060 trials, suicidality SAEs were reported for 15/2,250 participants receiving DTG (0.7%) compared with 9/2,257 receiving other ARVs (0.4%) (RR=1.58, NS). The authors found no significant differences in other CNS endpoints between DTG and other ARVs.

The risk of grade 1-4 insomnia was higher for DTG compared with other ARVs: 165/2,716 (6.1%) vs 124/2,727 (4.5%) (RR=1.30, p=0.02).

IRIS was seen in 1/414 participants receiving DTG compared with 2/419 participants receiving EFV in SINGLE, 6/354 receiving DTG compared with 3/361 receiving raltegravir (RAL) in SAILING, and 1/411 DTG compared with 0/411 receiving RAL in SPRING-2. No cases of IRIS were reported in SPRING-1, FLAMINGO, STRIIVING or NEAT SSAT 060. Although there was no significant difference in the risk of IRIS between DTG and other ARVs, none of the randomised trials included people with low CD4 counts where the risk is likely to be elevated.

Importantly the authors reported that the overall risk of adverse events was lower for DTG than EFV in the SINGLE trial, darunavir/ritonavir (DRV/r) in FLAMINGO, and atazanavir/ritonavir (ATV/r) in ARIA.

They added that other completed randomised DTG trials should be included in new safety analyses: DAWNING (n=627), SWORD 1 and 2 (n=1024), Gilead trial 1489 (n=629) and Gilead trial 1490 (n=645). And they stressed the importance of continued pharmacovigilance with regular meta-analysis to monitor safety.

COMMENT

Monitoring of new ARVs is particularly important for DTG, which will be used to treat millions of people in low- and middle-income settings, in programmes that have already begun or will do so in the next couple of years.

Overall these data are reassuring – particularly learning from the authors that the non-significant relative risk for suicidality was way off p=0.05 (test for overall effect: z=0.53, p=0.6).

The risk of IRIS was low, but event rates were low and the main trials excluded those at greatest risk. Data from ongoing closer-to-real-life trials such as ADVANCE and NAMSAL in South Africa and Cameroon will provide more information on IRIS risk with DTG.

This group will continue to re-evaluate DTG safety as data from completed randomised trials becomes available.

Several other posters at EACS reported lower rates of DTG-related side effects with fewer differences to other integrase inhibitors.

The Dutch ATHENA cohort reported no differences in discontinuations between DTG and elvitegravir. [2]

The Italian ICONA cohort of 1057 patients (approximately 600 were naive) reported 2.5% discontinuations due to side effects at one year. [3]

A UK study reported a discontinuation rate of 2.2% out of 181 (50 naive) using DTG, with sleep changes manged by changing the timing of dosing. [4]

A German cohort of over 400 people starting DTG-based ART reported 5.8% discontinuations linked to side effects at 27 months. [5]

Also, an intensive six-month DTG sleep study in older participant (>60 years), was presented at the PK workshop earlier this year. This study reported that higher DTG Cmax and AUC were associated with reduced sleep time, there were no significant changes in sleep scores over the first 28 days after switching to DTG/abacavir/3TC. [6]

Anecdotal reports suggest that, unlike with EFV-associated CNS side effects, taking DTG in the morning might overcome difficulties with insomnia, without causing additional problems during the day.

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Twice-daily tenofovir alafenamide dose might overcome interaction with rifampicin

Polly Clayden, HIV i-Base

Twice-daily tenofovir alafenamide (TAF) plus rifampicin (RIF) provided similar exposures to once-daily TAF in pharmacokinetic (PK) study. This strategy might be a suitable option for people with HIV/TB coinfection.

TAF and tenofovir disoproxil fumarate (TDF) are prodrugs of tenofovir (TFV). TAF is more stable in plasma compared with TDF and gives about 90% lower plasma TFV exposures.

TAF is a substrate of drug transporters and RIF is a potent inducer and associated with drug-drug interactions and in turn lower drug exposures. The interaction between TAF and RIF has not previously been evaluated. Currently TDF is indicated for use with RIF but once-daily TAF is not.

Gilead Sciences, the originator company of TDF and TAF, conducted a PK study to look at twice-daily TAF co-administered with once-daily RIF. [1] The results were presented at EACS 2017.

The study aims were to evaluate the steady state PK of TAF, the active intracellular moiety tenofovir-diphosphate (TFV-DP), and the TAF major metabolite TFV, after co-administration of twice-daily TAF with once-daily RIF 600 mg, compared with once-daily TAF. It was a phase 1, open label, parallel design, multiple dose, single centre study in HIV/TB negative volunteers.

Participants were enrolled into two cohorts (26 in each cohort). TAF was given in the fixed dose combination (FDC) tablet bictegravir/emtricitabine/TAF (B/F/TAF 50/200/25 mg).

Cohort 1 received B/F/TAF once daily and cohort 2 B/F/TAF twice daily plus RIF 600 mg once daily, both two hours after food, for 28 days. Plasma and intracellular peripheral blood mononuclear cell (PBMC) PK was assessed on days 1 and 28.

Statistical comparisons used geometric least-square mean (GLSM) ratios and 90% confidence intervals (CI). Cohort 2 was the test regimen and cohort 1 was reference.

The evaluation revealed that with twice-daily administration of TAF plus RIF, exposures over 24 hours of TAF total plasma, overall systemic plasma TFV and intracellular PBMC-associated TFV-DP are expected to be reduced by <15%, about 20%, and about 24%, respectively, compared with once-daily TAF. See results table 1.

Table 1: TAF twice daily + RIF vs TAF once daily PK

Mean (%CV)	TAF once daily	TAF twice daily + RIF	GLSM ratio (90% CI)
Plasma TAF PK AUC 0–24 (ng*h/mL)	345 (52)	290 (48)	85.8 (69.7 to 106)
Plasma TFV PK AUC 0–24 (ng*h/mL)	348 (20)	277 (19)	79.9 (73.1 to 87.3)
Intracellular TFV-DP AUC 0–24 (fmol*h/106cells)			76.3 (58.7 to 99.2)

Notably, after twice-daily administration of TAF plus RIF, the mean (%CV) steady-state trough concentration of TFV-DP was 359 (58) fmol/106 cells, which is above the historical steady state TFV-DP concentrations achieved with TDF 300 mg.

C O M M E N T

TAF has the potential to replace TDF as part of an optimised generic first-line regimen for low- and middle-income countries (LMICs).

Due to TAF's low milligram dose (and lower amounts of active product ingredients) compared with TDF, this could reduce the annual cost per person from the recently agreed US $75 (for a fixed dose combination of TDF/lamivudine [3TC]/ dolutegravir [DTG]/ or TLD) further still. [2] Approval of two generic FDCs of TAF/3TC/DTG is expected by mid-2019.

TAF is not yet recommended in WHO or any national guidelines in LMICs as there are insufficient data on its use in pregnancy and in people with HIV/TB coinfection.

Previous investigations by Gilead showed co-administration with carbamazepine leads to a 55% decrease in TAF in plasma and results from modelling to predict the interaction with RIF suggested this reduction would be 73% in plasma. [3]

Results from the PK study described above are welcome and provide preliminary evidence for adjusting the TAF dose to twice daily with RIF. But the parallel design is a limitation, and there is no concurrent TDF comparison.

Further evidence will be available early 2018 from the RIFT study that is currently evaluating the effect of RIF on plasma PK of emtricitabine (FTC) and TAF and TFV-DP and FTC-triphosphate (FTC-TP). [4]

If, as the results above suggest, dosing TAF twice daily is the solution to co-administration with RIF this will potentially make HIV/TB co-treatment easier in for programmes in LMICs as twice-daily DTG also looks promising. Botswana is already using this strategy and results from INSPIRING [5] – looking at DTG and efavirenz-containing ART regimens in people with HIV/TB co-infection – will also be available early next year.

The TAF/3TC/DTG could be given twice daily – which is not possible with the TDF-containing FDC that requires giving the extra DTG as a single tablet.

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No impact on bioavailability of D/C/F/TAF when tablet is split but TAF absorption is reduced if crushed

Polly Clayden, HIV i-Base

There was no clinically relevant effect on the bioavailability of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) components when given as a split tablet compared with a tablet swallowed whole. [1] Crushing the tablet led to a modest decrease in TAF bioavailability.

Whether or not antiretroviral tablets, including fixed dose combinations (FDCs), can be split or crushed for people who are unable to swallow pills and sometimes for paediatric HIV is important to know.

The originator company, Janssen, previously evaluated the stability of D/C/F/TAF in vitro and found that the individual components remained stable: after splitting the tablet in half; and after crushing the tablet and exposing to liquids (water, orange juice, cranberry

juice and apple sauce). The components also did not absorb to PVC or silicone feeding tubes.

The company then assessed the relative bioavailabilty of D/C/F/TAF as a spilt or crushed tablet after oral administration compared with a whole tablet. These data were presented at EACS 2018.

This assessment was a phase 1, randomised, open-label, 3-period, 3-treatment, crossover study of a single dose of D/C/F/TAF (800/150/200/10 mg) given as a split or crushed tablet versus a whole tablet.

Thirty HIV negative adults aged 18–55 years were enrolled and the dose was given within 30 minutes of a standard breakfast. Tablets were: swallowed whole (reference); split with a tablet cutter (both halves swallowed); or crushed and mixed with apple sauce.

Full pharmacokinetic (PK) profiles were determined up to 72 hours (darunavir, cobicistat and emtricitabine), and 8 hours for TAF. Primary PK parameters were Cmax and AUC. Treatments were compared using a linear mixed effects model.

The assessment found no relative impact on the bioavailability of D/C/F/TAF components when given as split compared with whole tablet (least squares means ratio confidence intervals all within 80 to 125% boundaries).

There was no relevant impact on the bioavailability of darunavir, cobicistat and emtricitabine when given as a crushed tablet but approximately 20% decrease in the bioavailability of TAF.

The investigators noted that the clinical relevance of the decrease has not been assessed but it is expected to be minimal because of the wide therapeutic window for TAF.

COMMENT

It is good to have data to inform whether or not tablets can be split in half for people who have difficulties swallowing them whole.

The results for darunavir/cobicistat contrast with those for lopinavir/ritonavir for which crushing significantly reduced exposure of both components with a decrease in AUC by 45% lopinavir and 47% ritonavir in a study in older children. [2]

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No transmissions from breastfeeding in Tanzania cohort from mothers with undetectable viral load

Polly Clayden, HIV i-Base

No HIV exposed infants who were negative at birth, whose mothers started ART before delivery, had suppressed viral loads and exclusively breastfed, were HIV positive after breastfeeding, in a rural African cohort.

These findings from the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), Tanzania were presented at EACS 2017.

This study included infants born between January 2013 and May 2016 to mothers enrolled in KIULARCO who started ART before delivery, exclusively breastfed for five months or more, and whose infants had a negative viral load test at age 4–12 weeks.

The mothers' viral loads were measured once or twice up to 11 months after delivery. Infants testing was according to national guidelines.

Of 215 mothers with 219 pregnancies and 229 infants (10 twins), the median age at delivery was 33 years (IQR 29–36) and time since starting ART was 23 months (IQR 4–52).

Of the total mothers, 180 (84%) were in care, 2 (1%) died, 24 (11%) were lost to follow up and 9 (4%) transferred out.

A total of 335 viral load samples were tested from 219 post-partum in 215 women; 114 women had two samples.

During the breastfeeding period, 91% of mothers had viral <1000 copies/mL, with 75% <100 copies/mL.

As of 30 June 2017, of 229 infants 10% were lost to follow-up, 2% were transferred and 8% died 2% were still breastfeeding. Of 181 (79%) infants with final HIV status, 2 (1%) were infected through breastfeeding.

One HIV positive infant was born to a mother with high viral load (144,111 copies/mL) at one month post-delivery and the other to a mother who stopped ART during breastfeeding.

There was no vertical transmission through breastfeeding among mothers with suppressed viral load in this cohort, suggesting that this is very low risk. But loss to follow up and adherence problems can threaten the success of interventions to reduce vertical transmission through breastfeeding.

"Viral load monitoring during pregnancy and breastfeeding and strategies to trace back those lost to follow up should be a priority" the investigators recommended.

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9th IAS Conference on HIV Science (IAS 2017)

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

As with all IAS conferences, many of the key presentations are available online after the meeting. All abstracts are also posted online, with full versions of the posters and presentations often also available from the conference website.

http://www.ias2017.org

Webcasts are published to three different webpages:

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

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

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

Press conferences and other webcasts are online on a different IAS youtube channel. IAS 2017 press conference webcasts

Reports from this meeting include:

- Dolutegravir outperforms lopinavir/ritonavir second-line: interim results from the DAWNING study
- Reduced-dose darunavir is safe and effective in switch study
- Preliminary results on dolutegravir use in pregnancy are reassuring
- Low dose efavirenz (EFV400) can be used during pregnancy
- Screening HIV positive pregnant women for TB in South Africa increased detection by 10-fold
- Earlier ART reduces infant mortality in South Africa but risk of death and loss to follow up still high

ANTIRETROVIRALS

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

Polly Clayden, HIV i-Base

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

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

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

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

After two of three pre-planned analyses, the study Independent Data Monitoring Committee (IDMC) conducted an ad hoc review of week 24 data and large subsets from weeks 36 and 48. They recommended discontinuation of the LPV/r arm due to differences in rates of virologic nonresponse and increasing differences in rates of virologic failure favouring the DTG arm. Participants in the LPV/r could switch to the DTG one.

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

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

Participants were a median of 37 years of age, about a third were women, about 40% were of African origin, about half had CD4 count <200 cells/mm3 and 20% viral load >100,000 copies/mL.

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

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

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

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

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

COMMENT

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

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

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

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

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

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

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

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Reduced-dose darunavir is safe and effective in switch study

Polly Clayden HIV i-Base

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

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

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

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

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

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

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

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

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

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

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

COMMENT

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

A DRV/r 400/100 mg switch trial in South Africa is currently enrolling participants, stable on boosted lopinavir-based second-line. [3]

And plans for phase 2 and 3 studies in unsuppressed participants are underway.

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PREGNANCY

Preliminary results on dolutegravir use in pregnancy are reassuring

Polly Clayden, HIV i-Base

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

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

Botswana

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

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

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

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

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

This more recent analysis included women who started either efavirenz, tenofovir and emtricitabine (4593 delivered August 2014

to August 2016) or dolutegravir, tenofovir and emtricitabine (845 delivered November 2016 to April 2017) during singleton pregnancy.

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

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

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

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

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

European Pregnancy and Paediatric HIV Cohort Collaboration

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

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

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

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

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

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

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

Abnormalities were reported in 4 of 81 live born/still born infants (no defect in the still born infant): 4.9% (95% CI 1.4 to 12.2). See table 1. Notably, there was no pattern of defects and only infants I and 2 would be classified according to EUROCAT definitions.

Table 1: Congenital abnormalities dolutegravir exposure

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

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

Antiretroviral Pregnancy Registry

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

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

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

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

Antiretroviral exposure is classified by earliest trimester. When at least 200 exposures to a specific drug have been reported, APR

can calculate birth defect prevalence and compare it to internal and external comparator groups.

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

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

At enrolment, 56 (39.4%) women had a CD4 count >500 cells/mm3, 48 (33.8%) 200–499 cells/mm3, 31 (21.8%) < 200 cells/mm3 and results were missing for 7 (4.9%). Mothers were a median of 29 years old. The majority, 126, were from the US.

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

Four birth defects were reported among 133 live births (77 with first and 56 second/third trimester exposure).

Table 2: Congenital abnormalities in APR following dolutegravir exposure starting in first (total 74) or second/third (total 54) trimesters

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

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

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

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

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

COMMENT

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

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

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Low dose efavirenz (EFV400) can be used during pregnancy

Polly Clayden, HIV i-Base

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

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

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

the WHO disclaimer to allow wider EFV400 first-line use.

It was an open-label, multicentre study conducted in UK and Uganda in women receiving tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and EFV 600 mg with an undetectable viral load (<50 cells/mm3), who switched to TDF/FTC/EFV400.

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

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

The study enrolled 25 women of African origin: baseline median age and CD4 were 29 years (range 18 to 41) and 561 cells/mm3 (range 152 to 882), respectively. All women had baseline viral load <50 copies/mL at enrolment and remained undetectable throughout the study (there were only two viral load blips, both confirmed <50 copies/mL, when repeated).

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

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

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

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

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

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

COMMENT

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

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

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Screening HIV positive pregnant women for TB in South Africa increased detection by 10-fold

Polly Clayden, HIV i-Base

Universal TB screening of all HIV positive pregnant women increased case detection and was associated with reduced early infant mortality in a South African study presented at IAS 2017.

TB is a leading cause of maternal and infant morbidity and mortality in HIV positive pregnant women. Currently-recommended symptom-based screening of HIV positive pregnant women may not be sensitive enough.

Investigators from the Perinatal HIV Research Unit, University of the Witwatersrand and Johns Hopkins University, Baltimore conducted a cluster-randomised trial to compare universal sputum TB testing with standard symptom-based testing in this population.

The trial was conducted across 16 public-sector antenatal clinics in two health districts that were randomised to either strategy. HIV positive pregnant women without currently diagnosed TB were eligible.

In universal testing clinics, all women were asked to produce a sputum sample. In symptom clinics, only those with WHO criteria for TB testing (cough, fever, night sweats, or weight loss) were asked to.

Samples were tested using Xpert MTB/RIF. Halfway through the study liquid MGIT culture was added. Follow up of women and infants was two months postpartum.

During the study period (May 2015 to March 2017), 941 and 1100 HIV positive pregnant women were enrolled in the universal and symptom clinics, respectively. In both arms, median age was approximately 30 years, median gestational age 25 weeks, 8% had TB before, 99% were on ART, and CD4 count was 440 cells/mm3.

In universal and symptom clinics, respectively, 34/941 and 4/1100 women were diagnosed with TB during pregnancy. Universal clinics prevalence 3.6% (95% CI: 1.2 to 6.0) and symptom clinics 0.36% (95% CI: 0.0 to 1.1), p=0.01.

At two months post-partum, infant mortality in universal clinics was 1% compared with 2.2% in symptom clinics, p=0.134. Maternal death was 0.1% compared with 0.3%, respectively. Miscarriages and stillbirths were similar in both arms.

MGIT culture identified more TB than Xpert: 5.1% were MGIT positive compared with 1.4% Xpert positive, p<0.05.

The investigators concluded that universal TB screening of all HIV positive pregnant women increased case detection 10-fold and halved early infant and maternal deaths (but this was not statistically significant). Xpert detected one third the rate of TB compared with MGIT.

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PAEDIATRICS

Earlier ART reduces infant mortality in South Africa but risk of death and loss to follow up still high

Polly Clayden, HIV i-Base

Infants are starting ART earlier, with less disease progression and declines in mortality according to findings from the IeDEA-SA collaboration. But mortality and loss to follow up among infants starting ART remains unacceptably high.

Over the past few years there has been a significant expansion of universal ART for HIV positive children less than five years old. WHO recommendations have expanded the eligibility to 'treat all' in this age group – from only those less than one year in 2008, to all children less than five years old in 2013.

There has also been a shift towards early infant diagnosis (EID) and early infant ART (EIART) but little is known about the outcomes of children starting ART in the context of changing paediatric HIV testing and treatment guidelines.

Investigators from the IeDEA-SA showed results from an evaluation conducted to describe temporal trends in characteristics of infants starting ART in South Africa and six month outcomes. These data were presented at IAS 2017.

The analysis included infants starting ART less at less than three months old and described characteristics and outcomes over three guideline periods: 2006–2009, 2010–2012 and 2013 and after.

The median age at ART initiation of 1380 eligible infants was 56 days (IQR: 27 to 73). Median log viral load at ART initiation declined from 5.9 (IQR 5.4–6.4) in 2006–2009 to 5.4 (IQR: 3.9 to 6.3) in 2013+. Median absolute CD4 count increased progressively from 888 cells/mm3 (IQR: 380 to 1703) in 2006–2009 to 1526 (IQR: 659 to 2231) in 2013+, (both p<0.001).

After six months on ART, 78 (5.7%) children died overall. Mortality declined from 9.7% in 2006–2009 to 4.8% in 2013+ (p<0.001). Loss to follow up was 225 (17.6%) overall, declining from 22.4% in 2006–2009 to 14.4% in 2013+ (p=0.004).

Among the children lost to follow up, 72% had no visit after starting ART and 28% after at least one subsequent visit on ART.

In multivariate analysis, neither age, CD4 count, weight for age z-score nor ART initiation period were predictors for mortality.

The investigators concluded that children are starting ART earlier, with less advanced disease and decline in mortality. But about 40% still start ART with advanced disease and mortality estimates remain unacceptably high. Loss to follow up also remains high overall.

"Innovative approaches are required to ensure HIV infected infants have optimal treatment outcomes", the investigators wrote.

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9th International Workshop on HIV Paediatrics

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

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

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

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

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

http://www.infectiousdiseasesonline.com

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

Polly Clayden, HIV i-Base

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

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

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

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

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

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

In order to assess chemical stability before dosing in liquid, the investigators dispersed one 25mg chewable tablet by agitation

(stirring) for 10–15 minutes in 5 mL of each of the following vehicles: tap water, sterile water, apple juice, and breast milk, at room temperature.

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

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

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

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

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

Table 1: Chewable raltegravir weight band doses

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

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

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

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

C O M M E N T

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

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

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

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

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18th International Workshop on Clinical Pharmacology of Antiviral Therapy, 14–16 June 2017, Chicago

The annual pharmacology workshop focuses mainly on treatments for HIV and viral hepatitis.

But this year include a few presentations on other antivirals, hence its name change: International Workshop on Clinical Pharmacology of Antiviral Therapy (a workshop formally known as the International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy).

The abstract book and slides from most oral presentations are online at the conference website:

http://www.infectiousdiseasesonline.com/event/workshop/antiviralpk-2017

Articles in this issue are:

- Dolutegravir pharmacokinetics in pregnancy
- High rates of undocumented efavirenz side effects in Uganda

Dolutegravir pharmacokinetics in pregnancy

Polly Clayden, HIV i-Base

Dolutegravir exposure and trough concentrations in third trimester of pregnancy appear to be similar to postpartum, according to data from the PANNA Network presented at the 18th International Workshop on Clinical Pharmacology of Antiviral Therapy.

PANNA is a European clinical pharmacology network to investigate the pharmacokinetics (PK) of new antiretrovirals in HIV positive pregnant women receiving them as part of routine care.

The study objectives were to describe dolutegravir: PK in the third trimester and postpartum; safety and efficacy for mothers and infants; and placental transfer.

It enrolled nine women receiving dolutegravir 50mg once daily at four European hospitals (June 2015 to June 2017). Of these three women had only third trimester PK results and one woman was excluded from the PK analysis

At delivery women were a median age of 30 years old (range 21-42) and 38 weeks (range 34-40) gestation. Infant birth weight was a median of 3180 grams. Maternal ART regimens were dolutegravir plus: 4 (44%) tenofovir DF/emtricitabine; 4 (44%) abacavir/lamivudine; and 1(12%) darunavir/ritonavir + tenofovir DF.

The investigators performed PK sampling in the third trimester at approximately 33 weeks and postpartum 4-6 weeks after delivery (reference). Blood samples were taken: predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post dose. Cord blood was also taken at delivery to determine cord blood/maternal blood (CB/MB) ratio.

The resulting PK parameters for dolutegravir in third trimester and postpartum are described in Table 1.

Table 1: PK parameters dolutegravir third trimester and postpartum

Parameter	Third trimester (n=8)	Postpartum (n=5)	GM ratio (90% CI)
AUC 0-24h (h*mg/L)	42.9 (39)	44.8 (56)	0.95 (0.60 to 1.48)
Cmax (mg/L)	3.4 (33)	3.0 (41)	1.07 (0.78 to 1.47)
C24h (mg/L)	0.7 (109)	1.1 (71)	0.66 (0.32 to 1.36)
Tmax (h)	3.0 (1.0-4.5)	3.8 (0.5-8.0)	–
CL/F (L/h)	1.2 (39)	1.1 (56)	1.06 (0.67 to 1.66)
T1/2 (h)	9.9 (50)	14.9 (27)	0.75 (0.58 to 0.98)

Values are geometric mean (CV%); except for Tmax, median (range).

When the investigators looked at individual exposure and Ctrough in some women they observed a decrease in pregnancy but in others exposures were higher.

They also noted that levels at the end of the dosing interval remained above the IC90 for dolutegravir.

CB/MB ratio (n=5) was 1.4 (0.35-1.6) suggesting efficient placental transfer but limited by the small number of maternal infant pairs.

All women had a viral load <50 copies/mL approaching delivery. At the time of analysis seven infants were uninfected and one infant's status was unknown.

There was one intrauterine foetal death at 34 weeks gestation due to cholestasis pregnancy syndrome. No further birth defects were reported.

There were two serious adverse events, not related to study drug that required hospital admissions to rule out pre-eclampsia.

COMMENT

The PK parameters in third trimester are comparable with those from the IMPAACT P1026s reported at CROI last year. But the postpartum exposure is higher in the IMPAACT study. The reason for that difference is not clear.

REFERENCE

Bollen P et al. A comparison of the pharmacokinetics of dolutegravir in pregnancy and postpartum. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 14-16 June 2017, Chicago. Oral abstract 0_7.

High rates of undocumented efavirenz-related side effects in Uganda

Simon Collins, HIV i-Base

Although CNS side effects associated with efavirenz have led to newer drugs being recommended in in high income countries, WHO guidelines for low and middle income countries still recommend efavirenz for first-line therapy.

This difference in care between rich and poor countries is exaggerated by a genetic polymorphism (G516T in CYP P450 2B6) that significantly increases drug levels of efavirenz (by reducing clearance rates) being more common in African compared to Caucasian populations.

Kay Seden from University of Liverpool and colleagues from Makerere University, Uganda, presented results from a prospective, longitudinal observational study to report all side effects in a cohort of 246 Ugandan patients on antiretroviral therapy (ART).

Baseline demographics included mean age 35 years (IQR: 34 to 38), 62% women, median CD4 520 cells/mm3 (329 to 716).

Overall, 134/246 patients were taking an efavirenz-based combination. Of these, 58/134 (43%; 95%CI: 35 to 52%) reported CNS-assocaited side effects (nervous system and/or psychiatric disorders). Severity was self-graded >5/10 by 45 (61%): with 47 (64%), 25 (34%) and 2 (3%) reported as minor, moderate and severe, respectively.

The median duration of side effects was 28 months (IQR 19-42) and only 7% had been reported in medical notes.

In multivariate analysis, risk of side effects was not associated with patient factors such as age, sex, weight or clinical stage.

COMMENT

The researchers commented that many of these patients might benefit from using the lower 400 mg dose of efavirenz.

REFERENCE

Seden K et al. High prevalence and long duration of nervous system and psychiatric adverse drug reactions in Ugandan patients taking efavirenz 600mg daily. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 14-16 June 2017, Chicago. Poster abstract P_55.

11th INTEREST Workshop, 16-19 May 2017, Lilongwe, Malawi

The INTEREST Workshop, shows findings from African HIV treatment and prevention research and is largely attended by delegates from the continent.

This year, the workshop was held in Lilongwe, Malawi.

Although the programme is online, unfortunately neither the abstract book nor presentations are available.

http://interestworkshop.org/fullprogram

Reports in this issue include:

- Increased risk of ART failure after low-level viraemia in a large South African cohort
- Option B+ Malawi

Increased risk of ART failure after low-level viraemia in a large South African cohort

Polly Clayden, HIV i-Base

Viral load cut-off as defined by WHO guidelines fails to identify a significant number of HIV positive people at risk for virological failure, according to findings from South Africa presented at the 11th INTEREST workshop.

Current WHO ART recommendations define failure as viraemia above 1000 copies/mL during treatment. In high-income countries, with stricter viral load cut-off (50 copies/mL), detectable viral load below 1000 copies/mL during ART (low-level viraemia) has been linked to treatment failure.

The currently recommended preferred first-line ART regimen has a low genetic barrier to resistance: NNRTI + 2NRTI.

Lucas Hermans presented findings from an evaluation of low-level viraemia and its impact on ART failure in a large South African cohort managed according to WHO guidelines.

The study was conducted across 19 urban and 38 rural HIV treatment sites. Adult participants were included if they had received ART for 20 weeks or more and had viral load monitoring.

Low level viraemia was defined as 50-1000 copies/mL and stratified by level: 51-199, 200-399 and 400-999 copies/mL, and duration. Outcomes were ART failure above 1000 copies/mL and switch to second-line. The investigators used Cox proportional hazard models corrected for sex, age and baseline CD4, to estimate the association between low-level viraemia and subsequent viral failure in the subset of participants with 52 weeks or more of first-line ART without failure.

Overall 71,056 participants met inclusion criteria: 67,380 treated with first-line ART; 1,602 second-line ART and 2,074 with both. Virological failure on ART occurred in 21.6% of people on first-line ART; 35% of these resuppressed <1000 copies/mL on the same regimen.

Low level viraemia occurred in 12% per year; 23.1% of participants had low-level viraemia at any time during follow up and this was persistent in 21.3% of cases.

Low-level viraemia between 51-199 copies/mL was common (59%). It was associated with increased hazard of failure of first-line ART, HR 3.0 (95% CI 2.8 to 3.3); ART failure without resuppression on same regimen, HR 3.2 (95% CI 3.0 to 3.5); and switching to second line, HR 2.9 (95% CI 2.4 to 3.4), compared to <50 copies/mL. The investigators saw a further increase in risk of failure with higher ranges and duration of low-level viraemia. And lower baseline CD4 was independently associated with low-level viraemia.

Dr Hermans noted that despite these risks, WHO guidelines do not recommend clinical intervention in cases of repeated low-level viraemia below the cut-off of 1000 copies/mL. "This poses concerns for long term virological suppression in WHO-guided treatment programmes", he suggested.

REFERENCES

Hermans LE et al. Increased risk of treatment failure after low-level viraemia in a large cohort of South African HIV positive patients treated according to under WHO guidelines. 11th INTEREST, 16-19 May 2017, Lilongwe, Malawi. Oral abstract 7.

A similar earlier analysis from this study was presented at CROI 2017:

Hermans LE et al. Increased risk of cART failure after low-level viremia under WHO guidelines. CROI 2017. 13-16 February 2017. Seattle, Washington. Oral abstract 113.

http://www.croiconference.org/sessions/increased-risk-cart-failure-after-low-level-viremia-under-who-guidelines (abstract)

http://www.croiwebcasts.org/console/player/33589 (webcast)

Option B+ Malawi

Polly Clayden, HIV i-Base

Malawi began Option B+ (universal lifelong ART for pregnant and breastfeeding women) in 2011, which led to a rapid scale up of women accessing ART irrespective of CD4 count.

Since then the Malawi programme has matured and Treat All has been adopted for all populations including pregnant women – both nationally and in WHO guidelines. As with non-pregnant adults, pregnant women receive a first-line ART regimen of efavirenz/tenofovir DF/lamivudine (EFV/TDF/3TC).

The 11th INTEREST Workshop – also conducted in Malawi – included a number of posters from studies designed to monitor and evaluate various aspects of the programme including: ART uptake, retention in care, long-term safety, treatment failure, and maternal and infant adverse events and outcomes.

These are: The National Evaluation of Malawi's PMTCT programme (NEMAPP), PROBE (PMTCT Retention of Option B+ Evaluation) study and The Option B+: ART Safety and Durability during First and Subsequent Pregnancies research study at Bwaila District Hospital in Lilongwe.

ART in pregnancy and partner's HIV disclosure protective against early infant transmission

NEMAPP reported good ART coverage and generally low vertical transmission. [1] Starting ART during pregnancy and partner's HIV status disclosure to the mother were protective against early infant transmission. [2]

NEMAPP is a two-year longitudinal cohort study across 54 health facilities, started in November 2014, using two-stage cluster sampling to evaluate infants at 4-12 weeks of age. Mothers attending an under-5 clinic were tested for HIV and HIV-exposed infants received DNA testing at baseline, 12 and 24 months.

Of 2125 HIV positive mothers, 2082 (96.1%) knew their status before or during pregnancy and 1865 (88.5% but varying widely between 54.9% and 100% across sites) were diagnosed and started ART in pregnancy. The vertical transmission rate was 4.2% (95% CI 2.9 to 6.1) overall: women receiving ART 2.5% (95% CI 1.6 to 3.9) and 17.9% (95% CI 13.0 to 21.2) for those not receiving ART. The rate of transmission varied from 1.4% (95% CI 0.5 to 3.9) in women who started ART before pregnancy to 20.2% (95% CI 5.8 to 50.7) in those starting ART postpartum.

Early infant transmission was lower if a woman started ART before compared with during their pregnancy: 2.3 vs 3.5%, p=0.014. It was also lower for those that disclosed their status to their partners: 2.0 vs 5.8%, p=0.008.

In multivariate analysis for the subgroup of women receiving ART during pregnancy, the likelihood of early infant transmission almost doubled if a woman started ART during compared with before pregnancy: aOR 1.9, p=0.032. Partner's HIV status disclosure to the mother was also significantly protective against early infant transmission, aOR 0.39, p=0.011.

Maternal health status or missed ART, exclusive breastfeeding and infant nevirapine prophylaxis were not associated with early transmission among mothers receiving ART.

Low maternal mortality and morbidity postpartum

Mothers had low mortality and morbidity at 4–26 weeks postpartum associated with increased ART uptake in asymptomatic women in an analysis of maternal health in NEMAPP. [3]

Of 1307 women evaluated, 67.3% (n=879) were 6-12 weeks postpartum and 1151 (n=88.1%) receiving ART.

At ART initiation 171 (13.1%) women had minor illness and 51 (3.9%) major illness according to self-reported health status. Of these 155/171 (90.6%) and 47 (90.4%) respectively reported improved health status.

In a nested cohort study including 580 women, their health status at enrollment was: 94% normal, 3.6% minor illness not affecting normal activities and 0.7% major illness needing daily assistance. Of the 580 women 56.2% had CD4 >500 cells/mm3 and 71.9% undetectable viral load.

More women receiving ART reported normal health than those who stopped ART (95.6 vs 87.5%) p<0.001, as did more women with CD4 >500 cells/mm3 (97.2 vs 92.8), p=0.02. In multivariate analysis adjusted for ART status and duration of known HIV status poor functional health was associated with CD4 <500 cells/mm3, aOR 2.6, p=0.03.

No difference in ART use or vertical transmission rates in adolescent mothers compared with older ones

Limited evidence suggests that vertical transmission prevention outcomes in young and adolescent women are worse than for adult women. [4]

A national evaluation comparing the use of services (uptake of antenatal testing and ART) and vertical transmission rates between young or adolescent mothers and adult mothers found adolescents less likely to be newly identified HIV positive. But among the known HIV positive women, there was no difference between age groups in ART use or vertical transmission rates.

The study included 33,744 mother-infant-pairs: 53.8% were defined as young (12-24 years) and 20.5% were adolescent (12-19 years) mothers. Overall 97.8% reported having an HIV test before or during last pregnancy.

Young mothers had more likely missed antenatal HIV testing than adult mothers: OR 1.8 (95% CI 1.2 to 2.7). Of all the mothers 11.3% were diagnosed with HIV before or during pregnancy; this was lower in young (4.6%) and adolescent (2.8%) mothers.

Adolescents were less likely newly identified HIV positive (previously negative) then young and adult mothers: OR 0.5 (95%CI 0.2 to 0.9). But newly identified HIV positive (previous unknown) young mothers might have missed earlier diagnoses more frequently than adult mothers: OR 3.5 (95% CI 0.9 to14.4).

Among the known HIV positive women, 94.7% reported receiving ART, with no difference between young or adolescent and adult mothers. Overall vertical transmission rate at 4-26 weeks was 4.7%, with no difference between young or adolescent and adult mothers.

Asymptomatic women and those with better treatment literacy more likely to access ART

Accessing ART in health centres, being asymptomatic and treatment literacy were associated with high ART uptake. [5] But after starting treatment, neither of these predictors were associated with default or transferring to another health facility, according to a national assessment of Option B+ outcomes.

This was a secondary data analysis of the PROBE study. PROBE was a retrospective cohort of women attending antenatal clinics. The main variables in the study were: women coming for a second routine visit (uptake) and default and transfer out (outcomes).

The analysis revealed, of 2739 women with 17,769 observations and complete information, 410 defaulted, 39 transferred out, 14 died and 4 stopped.

In Cox proportional hazards model the risk of defaulting was 30% lower in the Ministry of Health compared with Christian Health Association of Malawi facilities: HR 0.7 (95% CI 0.56 to 0.87). Pregnant women had a 64% higher risk of defaulting than breast feeding women: HR 1.64 (95% CI 1.29 to 2.07). Default rate was 21% lower among adults compared with adolescents: HR 0.79 (95% CI 0.62 to 0.99); 40% lower in women with ART education compared with those without: HR 0.6 (95% CI 0.47 to 0.77); and 61% higher in symptomatic women compared with asymptomatic: HR 1.61(95% CI 1.05 to 2.48).

In multistate model (using sub-hazards) women accessing services in health centres had 65% probability of ART uptake: SHR 0.35 (95% CI 0.30 to 0.41); 182% in women with ART education: SHR 2.82 (95% CI 2.43 to 3.26); and 19% lower among symptomatic women: SHR 0.81 (95% CI 0.70 to 0.94).

The investigators noted that after starting ART the risk of either defaulting or transferring to another facility was not significantly associated with any predictor.

Unmarried women and those in new relationships more likely to be lost to follow up

Of 299 newly diagnosed, ART naive pregnant women enrolled in the prospective observational study from May 2015 to November 2016 at Bwaila Hospital, 35 (12%) were lost to follow up, including 9/35 before delivery. [6] Being unmarried and in a newer relationship were associated with loss to follow up.

The study defined loss to follow up as missing after 90 days from last documented visit, excluding those that died. A trained community liaison was informed of all missed visits and traced the participants physically or by phone until they either found them or had made three attempts to do so.

At enrollment participants were a median age of 26 years (IQR 26-30) and the majority were married (89%) and/or had been in the relationship for one year or more (77%). The median follow up was 11 months (IQR 8-14). Three died during the study. Of the participants lost to follow up 6/35 (17%) were brought back into care after they were traced.

The overall incidence of loss to follow up per month was 1% (95% CI 0.8 to 1.5). Being married and staying longer in a relationship were associated with lower risk of loss to follow up, respectively: HR 0.4 (95% CI 0.18 to 0.88), p=0.023, and HR 0.43 (95% CI 0.22 and 0.84), p=0.01.

Although being unmarried and in a newer relationship were associated with loss to follow up the investigators added that this is not exhaustive. It is important to identify women undergoing socio-economic as well as treatment related risk factors to ensure that women are maintained in care and ART during pregnancy and beyond.

High rates of unintended pregnancy and low rates of contraception

Like many African countries that adopted Option B+ by 2015, Malawi has high fertility rates and infrequent use of contraception. An analysis of pregnancy intentions of women enrolled in the programme revealed extremely high rates of unintended pregnancies and low rates of contraceptive use. [7]

This prospective study included the 299 newly diagnosed, ART naive pregnant women in the cohort described above and 427 who had been receiving ART for six months or more.

The newly diagnosed women were: younger than those already receiving ART (26 vs 31 years); had been in a relationship for shorter time (5 vs 7.6 years); were less likely to have an HIV positive partner (11 vs 59%); and had fewer living children (1.8 vs 2.3), all p<0.05. Newly diagnosed women also had shorter travel time to the clinic. Similar proportions were married (88 vs 92%) and reported physical or verbal abuse (17 vs 15%).

The majority of participants reported having and unintended pregnancy: 55 vs 76%, newly diagnosed and receiving ART respectively. Only 6 vs 14% in the respective groups reported using contraception. Of those with an unintended pregnancy 7 vs 18% (12/164 vs 59/325) reported using contraception.

Multivariate analysis showed no significant difference between newly diagnosed women and those receiving ART in the rates of: mistimed pregnancy (OR 1.32); unwanted pregnancy (OR 2.27); contraceptive use (OR 1.44); and unintended pregnancy with contraceptive use (OR 1.76).

Overall 76% of women in the programme reported an unintended pregnancy and only 18% used any contraceptive method. “This highlights the missed opportunity to engage these women in family planning and suggests shortfalls in the integration of ART and family planning under Option B+ in Malawi”, the investigators wrote.

Lower viral load suppression at delivery with longer duration of ART

Unsurprisingly women in the cohort with longer duration of ART during pregnancy had lower risk of unsuppressed viral load at delivery. [8]

Women are frequently diagnosed with HIV and start ART late in

pregnancy but it is unclear whether they achieve viral suppression and how this varies with time on ART in Malawi. Investigators from the Bwaila district hospital study also looked prospectively at the association between time on ART and viral load (> 1000 and >40 copies/mL) at delivery in the newly diagnosed women.

For the 299 participants enrolled, the median gestation age at first antenatal visit was 22.1 weeks (IQR 18.1-26.3). The median duration of ART before delivery was 17 weeks (IQR 13-21). Of 253 (84.3%) with viral load measurements at delivery, 40 (15.9%) and 78 (31%) had >1000 and >40 copies/mL respectively.

Compared with women who had received ART for 12 weeks or less at the time of delivery, women who received ART for 13-20 weeks, RR 0.52 (95% CI 0.36 to 0.74), or 21-35 weeks, RR 0.26 (95% CI 0.14-0.48) were less likely to have viral load >40 copies/mL.

Hepatoxicity rate does not support routine laboratory monitoring

An analysis of hepatoxicity risk does not support routine laboratory monitoring pregnant women receiving EFV-based ART. [9]

Pregnant women start ART with TDF/3TC/EFV without routine liver enzyme monitoring. Previous studies have shown conflicting results risk for hepatotoxicity in pregnant women on EFV-based regimens.

This study was also conducted at Bwaila Hospital, in the cohort of 299 women.

The investigators evaluated laboratory values from the first 6 months on ART (enrollment, months 3 and 6) for DAIDS Grade 1 or higher alanine aminotransferase (ALT, >50 IU/L) (Fisher's exact tests)

Prevalence of elevated ALT at baseline was 0.3%, 0.4% at month 3, and 7.2% at month 6. The 6-month incidence of elevated ALT was 7.9%. Only 3 women (1.1%) had DAIDS Grade 3 or 4 ALT levels. All 3 women were postpartum and not taking other hepatotoxic medications. Of these women, one remained on TDF/3TC/EFV with resolved ALT levels, one switched to a non-EFV regimen, and one died of fulminant hepatitis despite ART discontinuation.

This analysis found no significant association with low CD4 count (p=0.62) or WHO stages >2 (p=0.28, although twice as many women developed elevated ALT compared with stage 1: 13.3 vs 6.7%) with the development of hepatoxicity. Data on viral hepatitis co-infection status were not available.

The investigators suggested that symptom monitoring is likely reasonable under a public health approach.

High prevalence of syphilis

Another analysis from Bwaila Hospital reported worrying prevalence of syphilis among HIV positive pregnant women. [10]

This cross-sectional study aimed to estimate the prevalence of syphilis and describe risk factors in this population.

Women were screened for syphilis using point-of-care rapid Alere determine TP tests. All women who tested positive were treated on the same day with a single dose of benzathine penicillin by intramuscular injection. Women testing positive were also encouraged to send their partners for treatment.

Of 350 pregnant women enrolled, the mean age was 28.3 years and mean gestational age was 22 weeks; 89% were married; and 88% lived with the partner.

The prevalence of syphilis in these women was 6% (95% CI 3.9% to 9.0%). Relationship duration was shorter in women testing positive for syphilis but this was not statistically significant. No factors (level of education, parity, marital status, WHO staging, and partner characteristics for current pregnancy) were significantly associated with the prevalence of syphilis.

"Aggressive measures are urgently needed to strengthen universal syphilis screening and testing efforts at antenatal clinics to prevent mother to child transmission of syphilis" the investigators wrote.

High rate of antenatal depression

Nearly half of the women in an antenatal depression study self-reported a history of anxiety or depression. [11]

Women included in this baseline analysis (n=729) were starting ART for the first time or had been on ART for 6 months or more.

The investigators assessed depressive symptoms using the Edinburgh Postnatal Depression Scale (EPDS). In Malawi, a score of >6 has been shown to indicate probable major depression, and was considered a positive result.

The majority of women were currently married (90%), unemployed (62%), and had not intended their pregnancy (68%). Nine percent (n=68) of women screened positive for depression, and 46% (n=328) self-reported a history of depression or anxiety.

Women were more likely to screen positive for depression: who self-reported a history of depression or anxiety aOR 2.83 (95% CI 1.63 to 4.92); had ever experienced verbal intimate partner violence aOR 2.01 (95% CI 1.12 to 3.60); had not intended their current pregnancy aOR 1.97 (95% CI 1.02 to 3.80), or were unmarried aOR 2.14 (95% CI 1.07- 4.27).

Depressive symptoms affect a notable proportion of HIV positive women in antenatal care on ART in Malawi (9.5%), and nearly half of the women self-reported a history of depression or anxiety. Clinicians in clinics without routine depression screening should be watchful for antenatal depression among women with a history of depression or anxiety, intimate partner violence, unintended pregnancy, or are unmarried.

Education and having an HIV positive partner protective against ART failure

An analysis of treatment failure among women already receiving ART at first antenatal visit found an overall prevalence of 7%. [12] Having more education and having an HIV positive partner were protective against ART failure.

This study, again at Bwaila Hospital, included 434 women. The median age of the women was 30.8 years (IQR 26.9-34.2); 93% were married and 82% attended antenatal clinic in the second trimester.

The overall prevalence of ART failure was 7.1% (95% CI 5.1 to 10.0). Women with secondary or tertiary education had reduced odds of ART failure compared with women with none or primary education: OR 0.67 (95% CI 0.27 to 1.70. For women who knew their partners' HIV status, those with HIV positive partners also had reduced odds of ART failure compared with those with negative partners: OR 0.45 (95% CI 0.10 to 2.03).

The investigators suggested countries with limited resources for viral load screening at first antenatal clinic visit should develop mechanisms to identify women at risk of having developed ART failure to prompt switch to an alternative and effective regimen during pregnancy.

Saturday clinic feasible to improve retention in study

The addition of a Saturday clinic is a feasible way to reduce visit duration and accommodate retention in care. [13]

The Bwaila Hospital study enrollment did not meet its targets in the first year due to constraints including a shortage of clinic space and clinic overcrowding. The investigators hypothesised that adding a Saturday clinic would reduce overcrowding and visit duration during the week and would improve retention and enrollment.

This was an observational study of participant visit duration before and after Saturday clinic introduction and an anonymous Likert-type scale acceptability survey.

The investigators observed a total of 77 visits: 28 before and 49 after adding the Saturday clinic. They found the average time spent with a nurse during a follow-up visit went down from 78 minutes before to 57 minutes after the addition of the Saturday clinic, p=0.0337. But the average time spent with a clinician was not significantly affected, p=0.270.

The majority of women surveyed on both weekdays and Saturdays reported that time spent in clinic was acceptable. Six out of the 46 women surveyed said that Saturday was their preferred day. The effect of adding the Saturday clinic on retention is yet to be determined.

The addition of a Saturday clinic is a feasible way to reduce visit duration and accommodate retention. Subject surveys indicate this is an acceptable way to decrease crowding and improve subject satisfaction.

C O M M E N T

The 11th INTEREST Workshop included an abundance of data from the Malawi Option B+ programme. But some of these summaries are a bit sketchy as unfortunately not all the posters materialised at the meeting.

The observation that women with partners who have not disclosed their HIV status are more likely to transmit to their infants is important. This is the first time that HIV status disclosure between partners has been documented to affect vertical transmission at national level.

The study looking at contraception also noted that in Malawi 33% of pregnancies are mistimed and 11% unwanted. And 39% discontinue their modern contraceptive within 12 months due to method-related concerns/side effects (26%) or desire to become pregnant (26%). It would be interesting to know if any of the women with unintended pregnancies on ART and using contraception were using hormonal implant methods and this could be linked to EFV. This study highlights a missed opportunity to engage women in ART programmes with family planning.

The study linking longer duration of ART with viral suppression at delivery came as no surprise. That under a third of women had viral load <40 copies/mL is likely to be improved with the introduction of dolutegravir and swifter viral decline.

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2. Tippett Barr B et al. National evaluation of Option B+ in Malawi: high maternal ART coverage and low early infant transmission in all areas of the country. Poster abstract 182.
3. Tippett Barr B et al. Predictors of mother-to-child transmission in women on ART: results from a national evaluation of Malawi's PMTCT programme. Poster abstract 183.
4. Landes M et al. Maternal health and ART use at 4-26 weeks postpartum in Option B+ in Malawi. Poster abstract 88.
5. Van Lettow M et al. PMTCT programme utilisation and HIV transmission rates in young and adolescent mothers: a nationally representative sample of women screened at 4-26 weeks postpartum in Malawi. Poster abstract 181.
6. Mganga A et al. Uptake and ART outcomes of women initiating antiretroviral therapy under Option B+ in Malawi: Cox proportional hazards and multistate survival models. Poster abstract 143.
7. John M et al. Loss to follow up among newly diagnosed HIV positive pregnant women in the Option B+ programme in Malawi. Poster abstract 27.
8. Melhado C et al. Contraceptive failure and pregnancy intentions among ART-naive and ART adherent HIV-infected pregnant women enrolled in Option B+. Poster abstract 87.
9. Chagomerana et al. Viral suppression at delivery among pregnant women newly initiated on antiretroviral therapy (ART) during pregnancy: PMTCT Option B+ in Malawi. Poster abstract 151.
10. Harrington B et al. Incidence and timing of hepatoxicity among HIV positive pregnant women initiating efavirenz-based ART through Option B+ in Malawi. Poster abstract 136.
11. Phulusa J et al. Prevalence of syphilis infection among HIV-infected pregnant women attending antenatal clinic at Bwaila Hospital in Lilongwe, Malawi. Poster abstract 162.
12. Harrington B et al. Prevalence and factors associated with antenatal depression among women enrolled in Option B+ PMTCT in Malawi. Poster abstract 33.
13. Chagomerana et al. Prevalence of antiretroviral therapy (ART) treatment failure among HIV-infected pregnant women at first antenatal care: PMTCT Option B+ in Malawi. Poster abstract 148.
14. Stanczyk B et al. Evaluation of strategies for improving subject retention in The Option B+ ART safety and durability during first and subsequent pregnancies study. Poster abstract 66.

24th Conference on Retroviruses and Opportunistic Infections (CROI 2017), 13–16 February 2017, Seattle

CROI 2017 was held in Seattle where more than 4000 researchers and health workers, and a small number of activists, met to look at more than 1000 presentations.

Conference materials are all posted online, including comprehensive webcasts of all oral presentations.

Abstracts are available in a searchable database and most posters are available in PDF format from the abstract page.

http://www.croiconference.org

The following reports are included in this issue.

- Pre-ART drug resistance in rural South Africa but limited clinical impact with good adherence
- Increased risk of IRIS with integrase inhibitors reported in two studies
- Dolutegravir exposure increases when fixed dose combination tablets are crushed
- Dose reduction potential of nanoparticle ARV formulations confirmed in humans
- Breakthrough for treating XDR-TB and ameliorating TB-IRIS
- Significant interaction between once-weekly isoniazid/rifapentine and daily dolutegravir: study stopped due to toxicity
- Adverse pregnancy outcomes and risk factors in the PROMISE trial
- PrEP in pregnancy does not increase poor birth outcomes
- Pharmacokinetics, safety and efficacy of dolutegravir in very young children
- Raltegravir pharmacokinetic targets met in high-risk HIV-exposed infants
- Tenofovir alafenamide exposure is modestly higher in children than adults
- VRC01 in HIV-exposed newborns: first results support monthly injections for those at risk through breastfeeding
- World Health Organisation paediatric dosing tool
- Paediatric HIV: CROI 2017

ANTIRETROVIRALS

Pre-ART drug resistance in rural South Africa but limited clinical impact with good adherence

Polly Clayden, HIV i-Base

Results from the Africa Health Research Institute showed significant pretreatment antiretroviral resistance but this was not associated with reduced viral suppression with good adherence – according to findings from the ANRS 12249 TasP trial presented at CROI 2017.

Greater use of antiretroviral therapy (ART) in Treat All strategies might lead to higher levels of acquired and transmitted drug resistance (DR) and reduce ART efficacy.

The ANRS 12249 two arm cluster-randomised TasP trial was conducted in KwaZulu-Natal to evaluate the effect of early ART, started irrespective of CD4 count on HIV incidence. Participants were randomised to treat all HIV positive people or treat according to South African guidelines (CD4 350 or 500 cells/mm3) at the time of the trial, which took place between 9 March 2012 and 30 June 2016. The study did not show a difference between the two arms.

The second objective of the trial was to look at the prevalence of pre-treatment DR (PDR) and its impact on viral suppression (<400 copies mL) in ART naive participants starting first-line treatment in the trial. Two presentations at CROI 2017 described these findings. [1,2]

There were sequences available from 1337 participants at trial entry: 189 dried blood spot samples (participants diagnosed HIV positive but did not refer to TasP clinic); and plasma samples from 88 recently infected and 1060 chronically infected participants.

Pol gene Sanger sequencing was performed on dried blood spots with detection threshold 20%. Full or partial HIV genome sequencing was performed on plasma samples. Low level variants were called at a 2% level.

The overall prevalence for any PDR in majority virus for all participants was 8.7% (95% CI 7.3 to 10.3). Any PDR prevalence in chronic infection and recent infection at >2% threshold was 16.7% and 21.6% respectively.

PDR was predominantly to NNRTI drug class driven by K103N/S; there were low levels of K65R mutation; PI mutations were very rare.

When the investigators looked at antiretroviral susceptibility, 7% of participants would start ART with high level PDR to NNRTIs and only two fully active drugs out of three. But most participants would be susceptible to tenofovir and FTC.

Among participants with PDR, 74% had only one mutation. But 11% participants had three or more (up to seven) – the investigators noted that this was not observed among newly infected participants – suggesting that this group had previously received ART.

A total of 837 participants starting ART in the trial with follow up viral load results contributed to the evaluation of the impact of PDR on viral suppression: 93.3% received a fixed dose combination of efavirenz/tenofovir/FTC.

Participants were a median of 34 years of age at baseline with over one third aged 16-29; the majority (71.6%) were female and about half were eligible for ART according to South African guidelines. The prevalence of PDR mutations was similar to that observed in those starting ART overall (16.5%).

The median time to viral suppression (<50 copies/mL) was 3.61 months (IQR 3.19 to 3.71). The median time on ART was 1.36 years (IQR 0.91 to 2.13). Cumulative probability of suppression at 12 months was 94.5% (95% CI 92.7 to 96.0). Kaplan-Meier estimates showed no difference in viral suppression with or without DR at baseline.

In multivariate analysis adjusted for sex, age, baseline viral and adherence, high baseline viral load (>100,000 vs <10,000 copies/mL) was associated with a decreased rate of viral suppression: RR 0.48 (95% CI 0.39 to 0.59), p<0.0001. Good adherence (>95% vs

<95%) was associated with an increased rate of viral suppression: RR 1.29 (95% CI 1.04 to 1.60), p=0.017.

C O M M E N T

The prevalence of transmitted drug resistance is above the WHO threshold of 5% in this study conducted in rural South Africa. The investigators suggest that this might be overcome with optimal adherence. This study only has 16 months of follow up and longer-term outcomes are needed to confirm these findings.

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Increased risk of IRIS with integrase inhibitors reported in two studies

Polly Clayden, HIV i-Base

Two cohort studies – from the Netherlands and France – showed a higher risk of IRIS with integrase inhibitor-based ART than with other regimens. Findings from both studies were presented at CROI 2017.

HIV treatment with integrase inhibitor (INSTI) based ART is recommended as preferred first-line in most high-income countries and is expected to become standard of care in many low- and middle-income countries over the next few years.

The use of INSTI based ART is associated with an accelerated viral load decline and faster CD4 increase compared with PI or NNRTI based ART.

IRIS is a pathological inflammatory response to antigens of opportunistic infections (OIs). People with CD4 counts of less 200 cells/mm3 when they start ART are at an increased risk for IRIS. Typically phase 3 registrational studies of new antiretrovirals exclude people with low CD4 counts and active OIs.

ATHENA cohort

The Dutch findings were from a multicentre, retrospective observational study in the ATHENA cohort. [1] The investigators performed a chart review of all treatment-naive participants starting ART from 2009 onwards (when raltegravir was registered in the Netherlands) who were at risk for IRIS. This included people with: CD4 200 cells/mm3 or less at start of ART; on OI diagnosed before or after starting ART; and/or use of corticosteroids up to 12 months after starting ART; and/or died up to 12 months after starting ART.

The study used two definitions of IRIS.

1. According French et al, 2004 (An atypical presentation of an OI or tumour in a patient responding to ART with decline in viral load or increase in CD4 count); and
2. Diagnosed by the treating clinician (IRIS as most likely diagnosis in the patient file or IRIS in the differential diagnosis with initiation of treatment for IRIS – eg corticosteroids).

The primary endpoints were French IRIS and combined clinical or French IRIS in INSTI vs non-INSTI users (the investigators considered French IRIS to be more specific so participants with IRIS according to both definitions were categorised as French). Participants who switched from PI/NNRTI to or from INSTI were censored.

Of 18,355 participants in the ATHENA cohort, 369 met the study criteria and were included at time of analysis: 69 received INSTI based ART and 300 non-INSTI based. At HIV diagnosis, median CD4 count and viral load in the INSTI vs non-INSTI groups respectively was 36 vs 30 cells/mm3 and 446,694 vs 257,040 copies/mL. The majority of participants were men: respectively 74% and 83%. Median age overall was 43 years.

Incidence of French IRIS in the INSTI group was 19% and clinical IRIS 19%, compared to 9% and 7% in the non-INSTI group, with IRIS being three times more likely in the INSTI group according to either definition (OR: 3.25, 95%CI: 1.83 to 5.8).

Cox regression showed that INSTI use was independently associated with French as well as French/ clinical IRIS: HR 2.62 (95%CI: 1.35 to 5.1), p=0.0045, and HR 2.69 (95%CI: 1.63 to 4.44), p=0.0001, respectively.

IRIS was most frequently related to pneumocystis jirovecii pneumonia (PCP), candidiasis and mycobacterial infections.

Sex, age, ethnicity, mode of infection, calendar year, baseline CD4, CD4/CD8 ratio, highest viral load measurement, type of ART regimen, number and type of OI-events, time between start of OI treatment and start of ART and use of steroids for OIs, were not associated with an elevated HR for IRIS.

The investigators did not report any interaction between INSTI-use and any of the other characteristics that were significantly associated with IRIS.

Dat'AIDS cohort

The French study was from the Dat'AIDS cohort across French HIV centres that share the same electronic patient record system. [2]

The investigators selected participants starting ART with CD4 200 cells/mm3 or less (2010-2015) and admitted to hospital within six months and compared those receiving INSTI-based with non-INSTI regimens. Three HIV specialists blinded to the ART regimen performed the examination of the patients' medical charts.

IRIS was defined as symptoms consistent with an infectious or inflammatory condition associated with a viral load drop of >2 log10 copies/mL not explained by a new infection, the clinical course of a previous infection, or side-effects, according to adapted ACTG IRIS criteria.

The study included 2287 participants: 398 received INSTI based ART and 1889 non-INSTI. Median age was 45 years and 63% were men. The third drug was a boosted PI in 65%, NNRTI in 12%, and INSTI in 12%. At ART initiation, the median CD4 count and viral load were 34 vs 84 cells/mm3, and 5.3 vs 5.2 log10 copies/mL and in the INSTI vs non-INSTI groups respectively.

Median viral load was lower in the INSTI group after three months of ART: 1.7 vs 2.1 log10 copies/mL, p<0.001.

IRIS occurred in 3% of participants in the INSTI group compared with 1.5% in the non-INSTI: OR 1.99 (95%CI: 1.09 to 3.47), p=0.04.

IRIS was most frequently related to tuberculosis, Mycobacterium avium and progressive multifocal leukoencephalopathy (PML).

As with the previous study co-factors such as age, sex and mode of infection were not associated with increased risk of IRIS.

COMMENT

These two reports are from cohorts and not randomised so come with all the associated potential for confounding with cohort studies.

The Dat'AIDS investigators noted that the relative infrequency of IRIS events in their study (1.8% overall) might be explained by the strict definition of IRIS they used and that they focused exclusively on severe IRIS needing hospitalisation. They also suggested it might be possible that because of known interactions between PIs and rifampicin that people with a pre-existing mycobacterial disease could be more likely to receive an INSTI based regimen. They did not demonstrate this in the study but probably lacked power to find any significant difference in the choice of first-line ART in IRIS cases.

Possible confounding aside, people starting INSTI based ART with a CD4 count of 200 cells/mm3 or less appear to be at increased risk for IRIS. This is important for low- and middle-income countries for which a dolutegravir based regimen is now recommended as an alternative first-line by WHO, and is predicted to become the preferred regimen as evidence gaps are filled.

Two ongoing large randomised trials of first-line dolutegravir vs efavirenz in as-close-as-possible-to-real-life unselected African patients that are likely to include people with low CD4 cell counts – ADVANCE (South Africa) and NAMSAL (Cameroon) – plan to have results in 2019 – but incidence of IRIS should be raised now as an ongoing concern for DSMBs for each study. [3]

The ADVANZ-4 Trial (Spain) is comparing first-line ART with dolutegravir and darunavir/ritonavir, both with abacavir and 3TC, in people with very low CD4 counts: below 100 cells/mm3 before treatment. [4] It is a small study with only 108 participants but is looking at immune reconstitution with results expected at the end of this year.

In the meantime, there needs to be careful monitoring of people with low CD4 counts at increased risk for IRIS in early dolutegravir adopter countries such as Botswana and Brazil.

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Dolutegravir exposure increases when fixed dose combination tablets are crushed

Polly Clayden, HIV i-Base

Dolutegravir exposure was higher after crushing the originator fixed dose combination (FDC) tablet and taking with enteral nutrition, compared to taking the whole tablet.

These findings from a pharmacokinetic (PK) evaluation were presented at CROI 2017.

Marieke Roskam-Kwint and colleagues from the Radboud University, Nijmegen, Netherlands conducted a study to investigate whether the dolutegravir/abacavir/lamivudine FDC could be crushed and taken with enteral nutrition without altering PK.

The investigators explained that if people are unconscious or unable to swallow tablets for other reasons, antiretrovirals are sometimes crushed and dissolved before they are given. Crushing can influence PK, possibly leading to treatment failure and development of resistance with low exposure or toxicity if it is too high. They also note that a PK interaction between dolutegravir and enteral nutrition is possible, based on the known interaction between dolutegravir and cations in antacids and supplements.

This was an open-label, 3-period, randomised, cross-over, trial. Participants were randomly assigned to receive: a single dose of the FDC whole tablet fasted (reference); crushed and suspended FDC fasted (intervention 1); crushed and suspended FDC, followed by 250 mL enteral nutrition, taken orally (intervention 2). There was a 7-day washout period between different treatment periods.

A 48-h PK profile was measured for all compounds. Geometric mean ratios (GMR) with 90% confidence interval (CI) for AUC0-inf and Cmax were calculated for intervention 1 and 2 vs reference. The definition of bioequivalence was standard: when the 90% CI was within 80–125% for AUC and Cmax.

The study included 22 HIV negative participants (21 white and 1 mixed-race, 10 female). Participants were a median of 25 years (range 18–54) years and BMI 23 kg/m2(range 20–27).

The investigators found for intervention 1 (crushed tablet fasting) vs reference (whole tablet), the GMR dolutegravir AUC0-inf was 129.5 (90%CI: 119 to 132) and Cmax was 129.5 (95%CI: 123 to 136). The GMRs and 90% CI for AUC0-inf and Cmax for abacavir and lamivudine were within the 80–125% bioequivalence range.

For intervention 2 (crushed tablet, ethereal nutrition) vs reference, the GMR dolutegravir AUC0-inf was 118.4 (90%CI: 112 to 125) and Cmax was 121.7 (95%CI: 115 to 128). Abacavir Cmax decreased by 17%.

As dolutegravir exposure increased by 26% and 30% for AUC0-inf and Cmax with crushed tablets and Cmax increased by 21% with crushed tablets plus ethereal nutrition compared to whole tablets fasted, bioequivalence could not be demonstrated.

The investigators recommended that the dolutegravir FDC can be crushed for people with difficulties swallowing or with an enteral feeding tube and can be combined with enteral nutrition. Although no dose-limiting toxicity of dolutegravir has been observed to date, they advise against crushing dolutegravir if someone needs twice daily dosing and to take it with food.

C O M M E N T

These data are also useful to inform possible paediatric administration of dolutegravir as pill crushing is sometimes used in this population.

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Dose reduction potential of nanoparticle ARV formulations confirmed in humans

Polly Clayden, HIV i-Base

First in-human trial results of nanoformulations of efavirenz and lopinavir confirmed the potential for a 50% dose reduction to the current standard oral dose of both antiretrovirals.

Andrew Owen presented these findings at CROI 2017 on behalf of colleagues from the University of Liverpool, St Stephens AIDS Trust, Chelsea and Westminster Hospital, London, Clinton Health Access Initiative, Boston, and the Medicines Patent Pool, Geneva.

Professor Owen explained that the group's solid drug nanoparticle (SDN) formulations of efavirenz (EFV) and lopinavir (LPV) have previously shown preclinical potential for dose reduction while maintaining pharmacokinetics (PK).

The aims of the human study were to: investigate the PK of the EFV and LPV SDN formulations in HIV negative participants; construct population PK models to describe the available data and compare PK to historical data from the originator products; and investigate multiple dosing and safety of the two SDN formulations.

The SDN formulations were powder filled capsules.

The investigators obtained consent from and screened five participants who then received 200mg nano-LPV (boosted with 100 mg originator ritonavir [RTV]) twice daily for seven days. A 12-hour PK profile was generated after the first dose, followed by steady-state PK after the last dose with 56-hour decay. A single plasma concentration was measured on day 3. Participants were assessed for safety at screening, day 1 (before morning and afternoon dose and 4 hours after afternoon dose), day 7, and at completion.

Four participants received 50mg nano-EFV once daily over 21 days ("to err on the side of caution"). A 72-hour PK profile was generated after the first dose, followed by steady-state PK profile after the final dose with 228-hour decay. Single plasma concentrations were measured on days 7, 14, and 17. Safety assessments (including physical examination with vital signs, ECG, urinalysis, laboratory testing) were made at screening, day 1, 2, 14, 21 and at completion.

Professor Owen reported that both SDNs were well tolerated at the studied doses, with no grade 3-4 adverse events.

The investigators used population PK models to analyse PK (one compartment model for LPV and two compartment for EFV), and the resulting models to simulate 1000 HIV negative participants dosed at 200/100 and 300/100 mg LPV/r twice daily, and 200 and 300 mg EFV once daily. These results were compared with simulated 400/100 mg twice-daily originator LPV/r and 600 mg or 400 mg once daily originator EFV.

The simulations predicted that 200mg nano-LPV twice daily (with 100mg originator RTV) would be bioequivalent to twice-daily originator LPV for AUC0-12, Cmax, and C12. See Table 1.

For nano-EFV, the simulations predicted that 300mg once daily would provide bioequivalence to 600mg once daily originator EFV for AUC0-24, Cmax and C12. For C24 bioequivalence not achieved because concentrations were predicted to be higher than those for originator EFV. Simulations were also made for 200mg nano-EFV vs 400mg originator EFV. See Table 1.

Dr Owen noted that there was an indication of an extended tail for both SDN formulations compared to originator formulations.

Table 1: Simulated comparisons of SDN and originator formulations of LPV and EFV

Drug/PK parameter	Geometric mean		Geometric mean ratio
Lopinavir	LPV SDN 200 mg	LPV originator 400 mg twice daily	GMR (90% CI)
C12 (mg/L)	4.16	4.02	1.04 (0.99-1.08)
AUC0-12 (mg.h/L)	72.35	79.07	0.92 (0.89-0.94)
Cmax (mg/L)	10.69	9.97	1.07 (1.05-1.10)
Efavirenz	EFV SDN 300 or 200 mg	EFV originator 600 or 400 mg once daily	GMR (90% CI)
AUC0-24 (mg.h/L)	51.56	58.61	0.88 (0.86-0.90)
C12 (mg/L)	2.03	2.51	0.81 (0.78-0.83)
C24 (mg/L)	1.90	1.44	1.32 (1.26-1.37)
Cmax (mg/L)	2.99	3.36	0.89 (0.87-0.91)

He explained that limitations to the study were small sample size, use of historical data rather than direct comparison with conventional formulations (stage 2 is ongoing), and dose prediction above studied doses assumes linear PK across adult doses.

Dr Owen concluded that these data confirm the potential for 50% dose reductions using a novel approach to formation of LPV and EFV SDNs. If confirmed in larger studies, this approach has the potential for estimated savings of up to US $243 million a year while also freeing up significant manufacturing capacity up to 930 tons a year.

He added that more formulation development is needed for future clinical translation: co-formulation, tableting, stability etc. And that this approach has wide applicability for drugs from various classes for numerous indications.

COMMENT

This group are currently working on a number of other antiretroviral development programmes for oral and long-acting SDN formulations: darunavir, atazanavir, ritonavir and dolutegravir.

If 400 mg EFV becomes the recommended dose SDN formulations can be targeted accordingly. The same applies to lower dose darunavir, if these dose reduction studies are successful.

There also might be benefits with SDN formulations for paediatric ART (particularly for infants and young children) as nanoparticles can be dispersed in water, which might mitigate the need for organic solvents.

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TUBERCULOSIS

Breakthrough for treating XDR-TB and ameliorating TB-IRIS

Richard Jefferys, TAG

Several important TB studies were presented as late breaker oral presentations at CROI 2017, on treatment for extensively drug-resistant TB (XDR-TB) and on TB-IRIS.

Highly promising results from the Nix-TB study were presented by Francesca Conradie of the University of the Witwatersrand in Johannesburg, on a breakthrough in treating XDR-TB, a condition normally requiring the use of debilitating, toxic injectable drugs. [1]

This small study uses a new combination of three oral drugs (bedaquiline, pretomanid, and linezolid). Of the 72 participants (39 men and 33 women) enrolled so far, 31/72 have reached the primary endpoint of being culture negative after 6 months follow-up. Of these, only two cases of relapse/reinfection were reported (still to be determined, but suspected reinfections), and only one case with XDR-TB. However, four participants died, all within the first eight weeks: 3/4 due to multi-organ TB (on autopsy) and 1 due to gastrointestinal bleed relating to erosive oesophagitis.

Tolerability was good with most side effects (peripheral neuropathy and myelosuppression relating to linezolid) being manageable, even with short dose interruptions.

This greatly shortened all-oral combination therefore provided extremely encouraging results both for safety and efficacy.

A short report by Jon Cohen in Science, included a comment that the combination would have likely efficacy for MDR-TB, whether Nix-TB data would be sufficient for pretomanid to become approved and the issues of cost and access. [2]

Immune reconstitution inflammatory syndrome (IRIS) is a potentially life-threatening consequence of the restoration of immune responses to opportunistic pathogens in people who initiate ART at low CD4 T cell counts.

Evidence suggests that immune responses can become exaggerated and overly inflammatory as a deficient, dysregulated immune system begins to recover due to ART-mediated HIV suppression. In some cases opportunistic infections can get worse before improving, a problem termed paradoxical IRIS. This is a particularly significant concern in tuberculosis (TB), with a reported mortality rate of around 3%. [3]

In an effort to reduce morbidity and mortality from paradoxical TB-IRIS, Graeme Meintjes and colleagues conducted a randomised trial evaluating a four-week course of the corticosteroid prednisone in individuals at risk. The encouraging results were debuted as a late-breaker at CROI, with Meintjes reporting a significant 30% reduction in the incidence of paradoxical TB-IRIS and a trend toward decreased hospitalisations in the prednisone arm. [4]

No evidence of an increase in cancer risk – which had been raised as a potential issue with prednisone – was observed. The evidence from the trial suggests that the approach should be adopted as the standard of care for individuals at risk for paradoxical TB-IRIS.

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Significant interaction between once-weekly isoniazid/rifapentine and daily dolutegravir: study stopped due to toxicity

Polly Clayden, HIV i-Base

Serious toxicities were seen in participants in a drug-drug interaction study of once-weekly isoniazid and rifapentine with once-daily dolutegravir, leading to its early termination – according to data presented at CROI 2017.

Once-weekly isoniazid (INH) and rifapentine (RPT) (wHP) is a three-month regimen for latent tuberculosis infection (LTBI). There are limited drug interaction data between wHP and antiretrovirals (ARVs). As with other rifamycins, RPT can induce CYP and UGT enzymes, and in turn reduce ARV drug exposure.

This study – conducted by the US NIH – was designed to look at the effect of wHP on the steady-state pharmacokinetics (PK) of dolutegravir (DTG). It was an open-label, intrasubject drug-drug interaction study in HIV-negative participants. The study had two phases: [1]. DTG once daily alone days 1- 4; [2]. DTG once daily with wHP for days 5-19. Plus, safety follow up days 20-34. DTG levels were measured at all PK visits, and RPT and INH levels on day 19.

Four participants were enrolled before the study was stopped: 3 men and 1 woman aged 21-46 years. One participant voluntarily withdrew from the study before day 19.

The study was stopped early due to the flu-like symptoms and transaminase elevations in two out of three participants who received three doses of wHP with DTG. The symptoms started about 8-10 hours after the last dose of DTG, RPT and INH on day 19 and resolved by 72 hours post-dose.

Following start of wHP, DTG Cmin was decreased by 42.7% on day 14 vs day 4; and by 74.4% on day 15. The Cmin was 5.3 x protein-adjusted IC90 for DTG (0.064 ug/mL) at this time point (range 0.9 to 11.0).

Exposure to RPT and its metabolite were similar to reference PK data, but INH exposure was 67- 92% higher than expected in the two participants that developed flu-like symptoms.

C O M M E N T

These data suggest that administration of DTG and wHP together should be avoided. The investigators noted that the mechanisms behind these reactions are unknown but cytokine assays revealed increases in a number of inflammatory markers. Additional investigations are underway.

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PREGNANCY

Adverse pregnancy outcomes and risk factors in the PROMISE trial

Polly Clayden, HIV i-Base

The multisite, multifactorial PROMISE trial found that antiretroviral therapy (ART) in pregnancy reduced vertical transmission, but also increased the frequency of several adverse birth outcomes compared with antenatal zidovudine (AZT) alone. [1]

PROMISE was conducted at 14 sites in seven countries: India, Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe.

The trial randomised HIV positive women with CD4 counts 350 cells/mm3 or more (not eligible for ART based on local guidelines), who were at least 14 weeks pregnant, but not in labour, to receive one of three antenatal regimens: AZT only (Arm A), AZT plus lamivudine (3TC) plus lopinavir/ritonavir (LPV/r) (Arm B), or tenofovir DF (TDF) plus emtricitabine (FTC) plus LPV/r (Arm C). Women receiving ART in PROMISE were randomised again to continue or stop their regimen after their first pregnancy.

Three posters at CROI 2017 reported findings from further investigations from the PROMISE trial into risk factors for adverse birth outcomes including in second pregnancies among women remaining on ART. [2, 3, 4]

Higher risk of adverse birth outcomes with lopinavir/ritonavir-based ART

The first poster showed results from an investigation into the association between antiretroviral regimen and adverse birth outcomes. LPV/r-containing ART was associated with a significantly increased risk of such outcomes after controlling for baseline factors and obstetrical complications. For severe birth outcomes, the risk was higher among women receiving TDF/FTC compared with AZT/3TC.

The investigators looked at: preterm delivery (<37 weeks); low birthweight <2500 g; composite outcome (preterm delivery, low birthweight, stillbirth, and spontaneous abortion); very preterm delivery (<34 weeks); very low birthweight (<1500 g); and severe composite outcome (very preterm delivery, very low birthweight, stillbirth, and spontaneous abortion).

They estimated gestational age at delivery by Ballard score. Multivariable models were adjusted for baseline factors: maternal age, BMI, viral load, CD4, alcohol use, country, gestational age at entry and number of previous preterm births and several obstetrical complications.

A total of 3423 women with a median age of 26 years, who enrolled and delivered in PROMISE were included in the analysis: 1507, Arm A; 1497, Arm B; and 419 Arm C.

For outcomes with preterm delivery and/or low birth rate, women receiving AZT+3TC+LPV/r (Arm B) and TDF+FTC+LPV/r (Arm C) each had higher risk for adverse birth outcomes compared with AZT alone (Arm A). When the analysis was restricted to severe outcomes, the risk associated with Arm C remained higher.

When the investigators compared the two ART regimens head-to-head, Arm C had a higher risk of severe adverse birth outcomes: very preterm delivery, AOR 2.56 (95%CI: 1.47 to 4.46) and very low birthweight, AOR 3.37 (95%CI: 1.33 to 8.53).

Several obstetrical and clinical risk factors for low birth weight and preterm delivery

An associated poster further described obstetrical and clinical risk factors for low birthweight and preterm delivery among women in PROMISE. In low-income countries, these conditions are linked to significant mortality and morbidity in newborns. Besides receipt of antenatal LPV/r-based ART, a number of obstetrical risk factors contributed to the adverse birth outcomes.

In the final multivariate models, adjusted for country and gestational age at entry, obstetrical risk factors for low birth weight and/or preterm delivery included several common complications of pregnancy: pregnancy induced hypertension; chronic hypertension; interuterine growth restriction; abruptio placenta; oligohydramnios; premature labour; premature rupture of membranes; and vaginal bleeding (low birthweight only).

Other clinical risk factors were: maternal BMI; multiple gestation; number of previous premature births; maternal age (preterm delivery only) and baseline viral load (preterm delivery only).

Although confidence intervals were very wide, the risk was extremely

elevated for several risk factors including: abruptio placenta AOR 20.33 (95%CI: 3.60 to 114.81) and premature rupture AOR 10.8 (95%CI: 4.9 to 23.8) for preterm delivery; and multiple gestation AOR 21.96 (95%CI: 11.05 to 43.64), interuterine growth restriction AOR 49.09 (95%CI: 5.66 to 425.66), oligohydramnios AOR 11.04 (95%CI: 3.49 to 34.90), and premature rupture of membranes AOR 12.79 (95%CI: 5.69 to 28.77), for low birthweight.

Spontaneous abortion and stillbirth more common among women conceiving on ART

A third poster from the PROMISE substudies showed results suggesting that women randomised to continue ART after their first pregnancy who subsequently conceived were more likely to have spontaneous abortion or stillbirth compared to women randomised to stop ART.

Rates of adverse pregnancy outcomes for women who conceive on ART might be increased, but data are conflicting.

Subsequent pregnancies occurred in 277/1652 (17%) women: 144/827 continued ART and 133/825 stopped ART).

A pregnancy outcome was available for 266 women with median age 26 years (IQR 22–30) and median CD4 638 cells/mm3 (IQR 492–833) at estimated conception. At the time of conception 65% of women were virologically suppressed.

Spontaneous abortions were more common in the continue ART arm. There was a significantly higher rate in this arm when spontaneous abortions and stillbirths were combined. See Table 1.

Twelve weeks before pregnancy diagnosis, 86% in the continue ART arm were on a boosted/non-boosted PI regimen vs 6% NNRTI. In the stop ART arm (15%) restarted ART before pregnancy diagnosis. Of these 74% were on a PI regimen vs 26% NNRTI. Among those in the stop ART arm restarting in pregnancy, 53 were on PI vs 27% NNRTI. Use of integrase inhibitors was very rare (<1%) as were regimens with NRTIs only.

Of 113 women in the continue ART arm on a regimen that included a boosted or non-boosted PI, 16% had a spontaneous abortion and 5% a stillbirth. Only 8 women in this arm were on an NNRTI without PI and half of these had a spontaneous abortion and none a stillbirth.

Table 1: Pregnancy outcomes for initial subsequent pregnancy in PROMISE

	Continue ART (n=140)	Stop ART (n=126)	p-value
Live birth	100 (71%)	100 (79%)	
Spontaneous abortion	27 (19%)	13 (10%)	0.06
Stillbirth	6 (4%)	2 (2%)	0.29
Spontaneous abortion or stillbirth	33 (24%)	15 (12%)	0.02

Of 113 women in the continue ART arm on a regimen that included a boosted or non-boosted PI, 16% had a spontaneous abortion and 5% a stillbirth. Only 8 women in this arm were on an NNRTI without PI and half of these had a spontaneous abortion and none a stillbirth.

In the continue ART arm 15 women with a subsequent pregnancy were not receiving ART at the time of conception. In this group 27% had a spontaneous abortion.

In the stop ART arm, the majority of women were not receiving ART when they conceived (79%). Of these 12% had a spontaneous abortion and 1% stillbirth.

The investigators noted that pregnancy testing was frequent in PROMISE allowing for early detection of pregnancy and the opportunity to capture early losses that might be missed in clinical practice.

COMMENT

Large randomised trials such as PROMISE provide multiple opportunities to compare outcomes with various strategies and circumstances.

More research is needed to understand the potential mechanisms behind these findings. For the elevated risks with TDF/FTC/LPV/r, these might include an independent effect of TDF/FTC, drug-drug interactions with LPV/r or other biological factors.

Along with optimisation of ART regimens, public health interventions are urgently needed to address obstetrical risk factors. The potential for such factors must be thoroughly evaluated as part of comprehensive antenatal care for HIV positive women. The investigators rightly suggest that this includes educating women about early warning signs of adverse pregnancy so they can seek immediate medical care.

More data are needed to look at pregnancy outcomes on women who conceive on ART and this is particularly important as new regimens are introduced to ART programmes in the era of Treat all.

Observational data from Botswana, presented at CROI 2017, also show notable differences between regimens (among women conceiving on ART) but very high risk of adverse outcomes among HIV positive women receiving ART. [5]

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PrEP in pregnancy does not increase poor birth outcomes

Polly Clayden, HIV i-Base

No increase in poor birth outcomes with PrEP used throughout pregnancy in the Partners Demonstration project reported at CROI 2017.

There are limited safety data to guide the use of PrEP in pregnancy and women are currently counselled with the option to continue or discontinue it during this period.

Birth outcomes from infants exposed to FTC/TDF PrEP throughout pregnancy in the open label Partners Demonstration PrEP study, conducted in Kenya and Uganda, were compared with unexposed infants born to women randomised to placebo who became pregnant in the Partners PrEP Study (comparator).

Of 334 women receiving PrEP, 30 became pregnant and continued its use. Of 621 women receiving placebo, 79 became pregnant (85 pregnancies).

Women in the PrEP exposed and unexposed groups were a median of 25 and 28 years respectively and had a median of two children before study entry.

The investigators reported similar pregnancy outcomes in PrEP-exposed and un-exposed pregnancies. See Table 1.

Table 1: Pregnancy outcomes PrEP exposed vs unexposed infants

	PrEP-exposed	PrEP-unexposed	OR (95% CI) p-value
Preterm delivery	0	5 (7.7%)	0.4 (0 to 2.3) p=0.4
Pregnancy loss	5 (16.7%)	20 (23.5%)	0.8 (0.3 to 2.5) p=0.7
Congenital anomaly	0	5 (7.7%)	Fisher's exact p=0.3

They also reported that infant growth characteristics were similar at 12 months and any early detriment in PrEP exposed infants appeared to catch up by this time.

COMMENT

Data from this small cohort of PrEP exposed babies provide some reassurance that PrEP can be used safely throughout pregnancy.

REFERENCE

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PAEDIATRICS

Pharmacokinetics, safety and efficacy of dolutegravir in very young children

Polly Clayden, HIV i-Base

Dolutegravir granules-in-suspension achieved satisfactory exposures in children aged between 2 and 6 years, according to data presented at CROI 2017.

Dolutegravir was potent and well tolerated through four weeks in this analysis.

IMPAACT P1093 is an ongoing phase 1/2 open-label pharmacokinetic (PK) and dose finding study of dolutegravir in age-defined paediatric cohorts: 4 weeks to <18 years of age. Doses that provide dolutegravir exposure comparable to that from 50 mg once daily in adults with acceptable safety and tolerability are selected for each age group.

Dolutegravir is approved for children and adolescents aged 6 years and above, weighing at least 30 kg. Theodore Ruel and colleagues from P1093 presented 4 week results from an interim analysis of the 2 to <6 years cohort.

In this study children received dolutegravir granules-in-suspension at doses of ~0.8 mg/kg once daily. Children were ART-experienced but INSTI-naive at enrolment. They had been on a failing regimen for up to 12 weeks or off ART for at least 4 weeks. PK targets, based on adult data, were geometric means of: AUC24h range of 37 to 67 mg*hour/L (primary) and C24h range of 0.77 to 2.26 mg/L (secondary).

Intensive PK performed on 10 participants was used to determine the dose. The dolutegravir granules-in-suspension was evaluated at ~0.8 mg/kg once daily – based on data from the older P1093 cohorts.

PK was completed after oral administration of weight-based dose between days 5–10, after which the background regimen was optimised. Safety, tolerability, and viral load were assessed at 4 weeks, and the study is ongoing to 48 weeks.

At baseline the children (5 female and 5 male) were a median: age 4.3 years (IQR 3.6 to 4.6); weight 15.5 kg (13.8 to 15.9); CD4 count 1323 cells/mm3 (IQR 763 to 2441); CD4 percent 28.0% (IQR 22.0 to 31.4) and viral load 4.8 log10 copies /mL (IQR 4.7to 5.3).

Mean dolutegravir dose was 0.87 mg/kg (range 0.58 to 1.06). The geometric mean (CV%) AUC24h was 44.7 (36%) mg*hour/L and C24h was 0.51 (68%) mg/L. C24h was below the target but above the pharmacodynamic threshold reported in adults. There was considerable variability among the participants.

Viral load was <400 copies/mL in 8/10 participants and <50 copies/mL in 6/10 after 4 weeks of treatment. There were no grade 3 or 4 side effects or drug related discontinuations.

COMMENT

The granules-in-suspension formulation will not be commercially available but these data will form the basis for dolutegravir dosing as dispersible tablets to be studied in this and younger age cohorts, which are now enrolling.

REFERENCE

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Raltegravir pharmacokinetic targets met in high-risk HIV-exposed infants

Polly Clayden, HIV i-Base

Daily raltegravir was safe and well tolerated at six weeks of life and met pharmacokinetic targets in HIV-exposed infants, according to data from IMPAACT P1110 presented at CROI 2017.

Previous studies have shown raltegravir (RAL) elimination to be highly variable in the first weeks of life due to low UGT1A1 activity.

IMPAACT P1110 is a phase I multicentre study in full-term HIV-1 exposed neonates at high risk of HIV with or without maternal RAL exposure. It includes two cohorts: cohort 1 infants received two single RAL doses one week apart; cohort 2 infants received daily RAL dosing for first six weeks of life.

The study sites are in Brazil, South Africa and the US.

PK data from cohort 1 and from older infants and children in IMPAACT P1066 were combined in a population PK model. The model included maturation of absorption rate from 16% of max at birth to 90% at two weeks, and clearance from close to nil to max at approximately six months of age.

The model was used to perform simulations of possible daily dosing regimens for RAL-naive infants in cohort 2 (using oral granules for suspension). See Table 1.

Table 1: Raltegravir dosing in IMPAACT P1110

Days of life	Dose mg/kg	Frequency
1-7	1.5	Once daily
8-28	3.0	Twice daily
after 28	6.0	Twice daily

Plasma samples were collected at the following time points. First dose: pre-dose, 1-2, 6-10 and 20-24 hours post dose. Second dose: 3-6 hours post dose. Day 6-9 of life: pre-dose. Day 15-18 of life: pre-dose, 4-6 and 8-12 hours post-dose. Day 28-32 of life: pre-dose. Week 5-6 of life: pre-dose and 3-6 hours post-dose.

Exposure targets are: AUC24 12-40 mg*h/L; AUC12 6-20 mg*h/L; C12 or C24 > 33 ng/mL; and Cmax <8724 ng/mL.

Cohort 2 enrolled 26 infants: 46% female; 69% black, 12% white and 19% other; median gestation age 38.5 weeks and birth weight 2.93 kg. Evaluable PK and 6-week safety data were available for 25 infants.

The investigators reported no drug related adverse events. All RAL exposure targets were met; PK parameters are shown in Table 2.

Table 2: Raltegravir PK parameters IMPAACT 1110

	After initial dose: 1.5 mg/kg once daily (n=25)		**Day 15-18: 3.0 mg/kg twice daily (n=24)**	
	Geometric mean (CV)	Target	Geometric mean (CV)	Target
AUC (mg*h/L)	38.2 (38.4%)	11 above 13 met 0 below	14.3 (43.3%)	8 above 14 met 1 below
Trough (ng/mL)	948 (64.2%)	25 above 0 below	176 (93.8%)	22 above 1 below
Cmax (mg/mL)	2350 (35.0%)	0 above 25 below	2850 (41.9%)	0 above 24 below
Tmax (mg/mL)	5.4 (57.5%)		5.4 (57.5%)	
T1/2 (hours)	15.8 (174.8%)		15.8 (174.8%)	

The investigators noted that after the initial dose some infants had AUC24 slightly above target range – but they considered this to be acceptable given the rapid increase in RAL metabolism over the first week of life.

Infants born to mothers who received RAL and low birth weight infants are to be studied in IMPAACT P1110.

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Tenofovir alafenamide exposure modestly higher in children than adults

Polly Clayden, HIV i-Base

Tenofovir alafenamide (TAF) and its metabolite tenofovir (TFV) exposures are slightly higher in children aged 6-12 years compared with adults, according to data presented at CROI 2017.

The original tenofovir formulation, tenofovir disoproxil fumarate (TDF) is not a recommended first-line nucleos(t)ide reverse transcriptase inhibitor in children. This is due to its association with bone and renal toxicity – linked to plasma exposure. TAF provides 91% lower TFV exposure than TDF and is considered to have better renal and bone safety in adults and adolescents. There is interest in the potential benefits of TAF for paediatric HIV.

TAF is currently commercially available for adults and adolescents from the originator manufacturer (Gilead Sciences) within fixed dose combinations (FDC) and co-formulations, which are under investigation for children.

The company showed 24 week findings from a pharmacokinetic (PK), safety and efficacy study of the once daily FDC elvitegravir/

cobicistat/emtricitabine/TAF (E/C/F/TAF) 150/150/200/10 mg, which is approved for adults and adolescents aged 12 and above.

The study was a phase 2/3, single-arm, open-label, 48 week, switch trial. Eligible children were aged 6-12 years, weighing at least 25 kg and virologically suppressed (<50 copies/mL) on stable antiretroviral therapy (ART) for six months or more.

PK assessments were made on all the agents in the FDC, as well as TFV, at steady state. These were compared with adult values. Adverse events (AE), laboratory tests, including viral load, were also conducted. Bone mineral density (BMD) z-score was assessed every 24 weeks

The study enrolled 23 children: median age 10 years (range 8 to 11), median weight 31 kg (range 26 to 58), 14 (61%) female, 18 (78%) black, median CD4 count 969 cells/mm3 (range 603 to 1421).

At 24 weeks mean AUCtau were 333 h*ng/mL (45% coefficient of variation) and 440 (21% coefficient of variation) for TAF and TFV respectively. These were modestly higher than adult values, but within safe and efficacious ranges of adults. Exposures of the other agents in the FDC followed a similar pattern.

No child had a serious AE or one leading to study drug discontinuation. No child had proximal renal tubulopathy. Median per cent change in BMD at 24 weeks was +4.2% for spine and +1.2% for total body less head Median change in BMD height-adjusted z-score was +0.10 for spine and -0.12 for TBLH.

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VRC01 in HIV-exposed newborns: first results support monthly injections for those at risk through breastfeeding

Polly Clayden, HIV i-Base

Preliminary results suggest that VRC01 – an investigational HIV neutralising monoclonal antibody – administered subcutaneously to neonates is safe and well tolerated. Its half-life would support monthly injections for those at risk of HIV through breastfeeding. These data from IMPAACT P1112 were presented at CROI 2017.

IMPAACT P1112 is an ongoing, prospective, open label, dose escalating study of VRC01, given to infants at increased risk of HIV transmission as a single 20 or 40 mg/kg subcutaneous dose within 72 hours of birth. Study sites are in US, Puerto Rico, and South Africa.

Increased risk of infant HIV infection is defined as one or more of the following maternal risk factors: no antiretrovirals (ARV) in pregnancy; began or restarted ARV in third trimester; detectable viral load; prolonged ruptured membranes; two class ARV resistance.

Eligible infants were 36 weeks of gestation or more weighing at least 2 kg at birth. All infants received ARV prophylaxis according to local standard of care. After VRC01 immunisation they received safety assessments for 4 hours followed by safety and pharmacokinetic (PK) measurements at 24 hours, days 3, 7, 14, 28, weeks 8, 16 and 24. Target VRC01 level is 50 mcg/mL on day 28.

The study enrolled 27 infants: 52% male, 61% black, median age 2 days and birth weight 3105 grams. One infant in the 20 mg/kg group was incorrectly enrolled and one in the 40 mg/kg group was under dosed and excluded from the PK analysis.

VCR01 was well tolerated with no grade 3 and above systemic adverse events. Local injection site reactions were common, occurring in 6 and 11 infants in the 20 mg/kg and 40 mg/kg groups respectively. These resolved in four hours for 100% and 55% of infants in the respective dosing groups. The PK results are shown in Table 1.

Table 1: Infant PK of VRC01 after single 20 or 40 mg/kg subcutaneous dose

VRC01	Dose	Mean	SD	Median	Range
Cday28 (mcg/mL)	20 mg/kg	39.33	14.94	39.19	16.71 to 76.56
	40 mg/kg	75.22	21.38	74.79	47.61 to 122.59
Cmax (mcg/mL)	20 mg/kg	226.64	30.78	233.32	153.63 to 260.64
	40 mg/kg	378.37	79.20	390.27	247.44 to 536.60
Tmax (d)	20 mg/kg	2.7	2.2	2	1 to 7
	40 mg/kg	1.4	0.8	1	1 to 3
Half-life (d)	20 mg/kg	19.73	4.99	20.17	13.11 to 28.60

These preliminary results showed persistent levels of VRC01 through day 28 of life. The 40 mg/kg dose achieved the target level at day 28 compared with adults receiving 20 mg/kg intravenously.

The investigators suggest that the half-life of VRC01 supports monthly injections for infants at ongoing risk of vertical transmission of HIV through breastfeeding.

COMMENT

Despite the massive success in preventing vertical transmission of HIV with ARVs, children still become infected for a number of reasons. A long acting monoclonal antibody might further prevent transmission during breastfeeding.

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World Health Organisation paediatric dosing tool

Polly Clayden, HIV i-Base

A paediatric dosing tool developed by World Health Organisation (WHO) might assist in the design of clinical trials for dosing in children.

When finding a safe and effective dose for children, the approach in anti-infectives is to target drug exposures similar to those in successfully treated adults. Scaling pharmacokinetics (PK) is the first step.

Down to two or three years of age, body size accounts for most of the differences in doses between children and adults.

The paediatric dosing tool – developed by the WHO Paediatric ARV Working Group (PAWG) – uses allometric scaling to help evaluate antiretroviral dosing regimens. The WHO paediatric dosing tool was presented at CROI 2017.

Allometric scaling describes the nonlinear effect of body size on PK parameters. A milligram per kilogram (mg/kg) dose in children and adults causes under-dosing in children. Even without other available information, allometry is a better guess than constant mg/kg. But paediatric dosing regimens still use constant mg/kg dosing as first best guess.

The objective of the work by the PAWG is to bridge this gap. WHO proposes an easy-to-use tool to assist researchers not familiar with PK modelling to design and evaluate paediatric dosing regimens.

The tool operates in Microsoft Excel and has easy steps to follow with results displayed in real time. It uses allometric scaling to adjust for the effect of a child's body size on clearance and it targets the same area under the time-concentration curve (AUC) as that for adults. The lowest and highest values within a paediatric weight band are shown alongside the target.

The tool can also analyse multiple drugs in a fixed dose combination and used either standarised or customised weight bands. If the effect of maturation is known for a drug this can be specified.

The WHO group note that allometric scaling alone only works well down to two years of age. Below that immature organ function could mean that clearance might be lower than that predicted using only body size. This is specific to individual drugs. Other unaccounted for factors might also have an impact: lower protein binding in children; drug formulation differences; and poor absorption.

Another limitation is that terminal half-life is usually shorter in children so adult AUC targets might lead to higher Cmax and lower Cmin so it might be necessary to dose smaller children twice daily.

The group stress that the tool is to support the design of clinical trials for dosing in paediatrics and is "not a substitute for confirmatory studies". They add that the use of the tool in study design "would represent a significant step away from the constant mg/kg paradigm, possibly leading to improvements in the efficacy of paediatric dosing trials".

REFERENCE

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Paediatric HIV: CROI 2017

Polly Clayden, HIV i-Base

A number of presentations at CROI 2017 showed data on early HIV treatment and diagnostics in young children.

Treatment of acute infection in neonates

Just over 30% of infants achieved undetectable viral load and 10% became PCR negative after very early initiation of treatment in South African study. [1]

ART in primary infection may reduce the size of the viral reservoir and allow viral control off treatment. Infants can be identified soon after infection.

The LEOPARD study tracks the response to ART in neonates started on ART in early infection at Rahima Moosa Mother and Child Hospital in Johannesburg.

Of 30 neonates who started ART within 48 hours of birth with six months or to one year follow up, over half (57%) were male and mean birth weight was 3015 grams. All infants received nevirapine (NVP), lamivudine (3TC) and zidovudine (AZT) with substitution of lopinavir/ritonavir (LPV/r) for nevirapine at median of 27 days (IQR 18 to 32) later.

Approximately 25% of mothers had received no treatment before delivery and 25% <12 weeks of ART; the remainder were already on ART or had received >12 weeks of treatment. Median infant viral load before ART was 30,000 copies/mL (range 60 to >2 million).

Viral load was measured at frequent intervals lower detection limit of 20 copies/mL and qualitative HIV diagnostic PCR tests were repeated.

Three of the 30 infants died at 43, 61 and 89 days respectively; all were male. Only one was low birth weight but all three had high baseline viral load.

There was wide variability in virological response among the remaining infants – from those who did not achieve undetectable viral load to three who became PCR negative. More than a third achieved and sustained undetectable viral load. The children remain in follow up.

Rapid decline of HIV DNA in infants starting very early ART

Infants receiving early ART experience very rapid early phase HIV and DNA decay according to a related study conducted at Stellenbosch University, South Africa. [2]

The study was designed to investigate total HIV DNA kinetics in infants who started ART as soon as possible after birth.

Eleven infants diagnosed through a public health sector birth diagnosis programme started ART 0 and 8 days after birth (median 3 days). Infants started ART with AZT/3TC/NVP, with NVP replaced by LPV/r after two weeks of age and AZT replaced by abacavir at three months of age.

Peripheral blood mononuclear cells (PBMCs) and plasma were processed at three monthly visits. Total DNA was measured with a sensitive quantitative PCR assay and RNA was also quantified.

Median baseline viral load was 4.0 (range 2.4 to 4.7) log10 copies/mL. Five infants were included in the kinetic study.

In three infants RNA declined to <100 copies/mL within 3.3 months. In the other two this occurred within 6.3 and 6.7 months. DNA decay

was in two phases, very fast in the first two weeks, then relatively slow but progressive.

DNA decay in three infants with <100 copies/mL before 3.3 months, phase 1: conditional R2 0.97 (95%CI: 0.90 to 1.00); median decay -2.3 log10 copies/month (range -2.1 to -2.7); 200 fold/month (range 122 to 545). Half-life 4 days (range 3.4 to 4.4).

Phase 2 in five infants: conditional R2 0.97 (95% CI: 0.90 to 1.00); median decay -0.15 log10 copies/month (range -0.13 to -0.2); 65 fold/year (range 33 to 222). Half-life 60.7 days (range 46.9 to 72.4).

The first phase was much faster than that reported in adults. The investigators noted that it was a conservative estimate as baseline DNA could be even higher as they divided by total cells in dried blood spots and only about 50% were lymphocytes. Second phase decay is much faster than in infants starting ART at two months.

Very rapid early phase HIV RNA and DNA decay poses a diagnostic challenge in infants receiving ARV prophylaxis or presumptive ART before definitive diagnosis.

Lack of evidence of ongoing HIV replication after eight years on ART

Children started on continuous ART in the CHER trial showed no sign of viral evolution after 7 to 8 years of treatment. [3]

In this study the investigators performed single-genome sequencing of the p6-PR-RT region of the HIV genome on plasma RNA before ART or PBMC DNA shortly after starting ART and on PBMC DNA approximately eight years after starting treatment. They compared HIV populations phylogenetically to look for emerging new variants. They also tested for panmixia to see if populations shifted over time. And they measured diversity of populations to see if there is accumulation over time.

Ten children were included: eight who started ART at less than 12 months and were fully suppressed on ART for 7 to 8 years and two replication controls who had viraemia for 1 to 3 years before or during ART.

The two controls showed clear evidence of HIV evolution. Data on one control with 1.3 years with detectable viral load out of 6.9 years on ART showed increased viral diversity (baseline 0.1%, long term 0.6%), a significant virus population shift by panmixia (p<10-4), and longer branches in ML trees.

The eight children with fully suppressed virus did diverge from founder virus. Data on one case who started ART at 1.8 years and remained on treatment for 8.1 years showed populations that were virtually identical, no panmixia shift (p=0.3) and no significant increase in viral diversity (baseline 0.04%, long term 0.1%). Results were similar among the eight children with suppressed virus.

"These data from early ART-treated children strongly refute the concepts that ongoing HIV replication is common on current ART regimens and that it replenishes the HIV reservoir", the investigators wrote.

Nevirapine dosing regimen achieved target concentrations in HIV-exposed low birth weight infants

Data from IMPAACT P1106 showed nevirapine (NVP) dosed at 2 mg/kg once daily (birth to 14 days old) followed by 4 mg/kg daily achieved trough concentrations above the 0.1 ug/mL prophylaxis target in low birth weight infants <2500 g. [4]

IMPAACT P1106 is a Phase 4 study on PK and safety in low birth weight infants receiving antiretroviral and tuberculosis medicines as part of their clinical care in two South African sites.

Arm 1 looked at NVP HIV prophylaxis. Infants were stratified by birth weight: <1400 g (n=12), 1400 to <1800 g (n=12), and 1800 to <2500 g (n=16). PK samples and safety data were collected at study entry (day 7 to 14) and at 4, 6, 10, 16 and 24 weeks of age.

The study enrolled 40 low birth weight infants with mean birth weight of 1675 g (range 950 to 2460 g) and mean gestational age of 33 weeks (range 28 to 40).

There were 94 NVP trough concentrations available from 27 infants with mean weight of 2147 g (range 965 to 6050 g) and mean postmenstrual age of 37 weeks (range 29 to 56 weeks) at time of sampling.

The mean NVP trough concentration was: 1.87 ug/mL (range < 0.02 to 10.69); 6/94 (6%) < 0.1 µg/mL. Below target samples were all from later visits (median postmenstrual age 44 weeks; median weight of 3903 grams) when at home receiving NVP from caregiver.

At first visit, lower gestational age was associated with higher NVP concentration normalised for dose: r= -0.47, p=0.02. Across all visits, NVP trough concentrations were inversely related to infant postnatal age: r= -0.45, p<0.001).

Three infants died: two from sudden unexpected death and one from confirmed sepsis. Nine infants had Grade 3/4 expected AEs (common in premature infants), most frequent presumed or confirmed sepsis (n=6). Ten infants had Grade 3/4 unexpected AEs, most common being pneumonia (n=4). All AEs were unrelated to nevirapine.

Lopinavir/ritonavir super-boosting overcomes rifampicin interactions in children

Super-boosting LPV/r for a 1:1 ratio was safe and effective and overcomes rifampicin interaction for TB/HIV co-treated children in a South African study. [5]

This was an open-label, prospective, non-inferiority study evaluating super-boosted LPV/r (1:1) during rifampicin co-treatment compared with LPV/r (4:1) after stopping TB treatment in children weighing 3 to 15 kg.

Eighty of 96 enrolled children completed the study; 30% were <12 months at enrolment and seven completed the study before 12 months of age. TB treatment was started before ART in 73% children.

The percentage of modelled Cmin levels below target (<1 mg/L) was 7.6% (95% CI 0.4% to 16.2%) for super-boosting during rifampicin co-treatment, vs 8.8% (95%CI: 0.6% to 19.8%) without rifampicin. The median difference was -1.1% (95%CI: -6.9% to 3.2%), confirming the non-inferiority (10% threshold) of LPV exposure during super-boosting with rifampicin to standard LPV/r without rifampicin.

Lopinavir/ritonavir started at seven days of life impairs infant growth

The ANRS 12174 trial comparing LPV/r vs 3TC in HIV exposed uninfected children showed LPV/r started at seven days was associated with lower weight gain. [6]

In the trial, conducted in Burkina Faso, South Africa, Uganda and Zambia, 1273 HIV uninfected, breastfed children born to HIV positive mothers were randomised at seven days to either 3TC or LPV/r until the end of breastfeeding (maximum 50 weeks) as pre-exposure prophylaxis.

Infants were weighed and measured monthly and their z-scores calculated and compared. The analysis included 1266 children, with 14537 visits.

There was no difference in the height for age z-score between arms. But the weight for age score was lower in the LPV/r arm than in the 3TC arm: difference of means -0.22 (95% CI -0.34 to -0.09) p<0.01, at 26 weeks, and of -0.25 (95% CI -0.46 to -0.03), p=0.02, at 50 weeks.

The impact of LPV/r was greater for girls and, and in Burkina Faso and Uganda than in Zambia and South Africa.

The investigators will continue to follow up the children and look at whether or not this effect persists at five years old.

Targeted HIV screening at birth can identify most in utero transmissions

In utero transmission only occurred among infants identified as high risk in Botswana – using information available from the mother or her obstetric record at the time of delivery. [7] Targeting high risk infants will identify the large majority of in utero HIV transmissions

Botswana tests for in utero and intrapartum vertical transmission by infant HIV PCR at six weeks. The Early Infant Treatment Study was conducted to identify HIV infected infants at birth and offer immediate ART. Abstract eBook

Mothers were assessed for risk factors, which included: <8 weeks ART in pregnancy, last CD4 known <250 cells/mm3, last viral load >400 copies/mL, poor ART adherence in pregnancy, lack of maternal AZT in labour, and lack of infant post-exposure prophylaxis. Infants received heel stick and dried blood spots were collected for testing by PCR.

In the first year of the study, 4086 HIV exposed infants were delivered, 3541 (87%) had not been discharged, 2580 (63%) were eligible, and 2303 (56%) agreed to be screened for HIV.

Of those screened, 369 (16%) were identified as high risk for HIV. Twelve (0.5%) of the 2303 infants were identified as HIV positive at birth.

All 12 positive infants were identified as high risk at the time of screening, and all were identifiable as high risk by either: <8 weeks of maternal ART in pregnancy (9/157) or lack of maternal HIV suppression at last viral load test (3/6).

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TREATMENT ACCESS

Generic dolutegravir-based FDCs at US $75 a year for low- and middle-income countries

Polly Clayden, HIV i-Base

A new pricing agreement has been announced that will speed up access to generic, dolutegravir-based fixed dose combinations (FDCs).

This will enable treatment of HIV in low- and middle-income countries (LMICs) at an annual cost per person of around US $75. [1]

This announcement was made on 21 September 2017 at UNGA by the governments of South Africa and Kenya with UNAIDS, the Clinton Health Access Initiative (CHAI), the Bill & Melinda Gates Foundation, Unitaid, DFID, PEPFAR, USAID, and the Global Fund, in collaboration with Mylan Laboratories Limited and Aurobindo Pharma.

The new products combine tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TDF/3TC/DTG, TLD) and were developed by Mylan and Aurobindo under licensing agreements from ViiV Healthcare, the originator of DTG. Both generic manufacturers received tentative approval from the US FDA for TLD in August of this year. [2]

The agreements, which set ceiling prices for TLD, apply to public sector purchasers and will offer substantial reductions compared with the price of efavirenz-based FDCs (around US $100 per person per year) [3]. This could lead to savings of up to US $900 million over the next six years in South Africa. Across the 92 countries covered under ViiV's dolutegravir licensing agreement, six-year savings have been estimated at US $1 billion.

COMMENT

2017 is proving to be a banner year for ART optimisation.

Further price reductions are anticipated in the not too distant future, with the arrival of new FDCs that will replace TDF with the much lower dose tenofovir alafenamide (TAF).

Meanwhile several studies are underway to fill the evidence gaps associated with these regimens so they can be universally recommended in LMICs – including for pregnant women and people coinfected with TB.

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First dolutegravir-based FDC gets FDA tentative approval

Polly Clayden, HIV i-Base

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

This is for a New Drug Application for dolutegravir, lamivudine and tenofovir disoproxil fumarate 50/300/300 mg tablets (TDF/3TC/DTG or TLD). [1]

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

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

COMMENT

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

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

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

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

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WHO adds dolutegravir and PrEP to updated Essential Medicine List

Polly Clayden, HIV i-Base

Dolutegravir for treatment of HIV and PrEP with tenofovir alone, or in combination with FTC or 3TC are among the additions to the updated version of the World Health Organisation (WHO) Model list of essential medicines – according to a press release 6 June 2017.

The WHO Essential Medicines List (EML) is used by many countries to help increase access to medicines and guide decisions on which ones should be made available to their populations. Launched in 1977, the EML is updated every two years.

The updated EML has added 30 drugs for adults and 25 for children, giving a total of 433 considered essential to public health.

This version includes "the biggest revision of the antibiotics section in the EML's 40-year history", in which WHO experts have grouped antibiotics into three categories: access, watch and reserve.

As well as dolutegravir and PrEP for HIV, other new additions include drugs for hepatitis C and TB. Co-formulated sofosbuvir + velpatasvir is included, which is the first combination therapy to treat all six types of hepatitis C. And newly added TB medicines are: delamanid for children and adolescents with MDR-TB; clofazimine for children and adults with MDR-TB; and paediatric fixed-dose combination formulations of isoniazid, rifampicin, ethambutol and pyrazinamide.

COMMENT

Andrew Hill and his group have now estimated the real costs of the entire EML using the same methodology they first applied to HIV drugs and then extended to hepatitis, TB and cancer.

These costings will be released in the near future and there are many lessons to be learned from HIV access and pricing campaigns that could be applied to other essential medicines for low- and middle-income countries.

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PREGNANCY

Experts disagree with controversial BMJ support for older HIV drugs in pregnancy

Polly Clayden, HIV i-Base

Two expert groups have announced that they do not support BMJ Rapid Recommendations favouring a zidovudine and lamivudine-based ART regimen over one that includes tenofovir and emtricitabine in HIV positive pregnant women.

On 21 September 2017, BMJ Open published a controversial analysis and accompanying clinical practice guideline on ART in HIV positive women concluding with low certainty evidence that: "tenofovir/emtricitabine is likely to increase stillbirth/early neonatal death and early premature delivery compared with zidovudine/lamivudine". [1, 2]

The guideline was informed by a systematic review, but the conclusion relies on the results of the PROMISE study. [3] The authors of the review, Siemieniuk et al, note: "The evidence for a likely increase of early premature delivery and neonatal mortality with tenofovir and emtricitabine comes mostly from a single study".

Although several large observational studies do not support this recommendation, nor do previous systematic reviews [4–7], Siemieniuk et al did not consider this evidence to be of sufficiently high quality to inform their recommendations.

The PROMISE investigators swiftly submitted a response to the BMJ disagreeing with the Siemieniuk interpretation of their data, stating: "We are the primary authors of the PROMISE study cited as the evidence for the recommendation in this paper; we disagree with the final conclusion based on our data." [8]

The BHIVA pregnancy guideline writing group also published a response on the BHIVA website in which they write: 'We do not support the BMJ recommendations "ART in pregnant women living with HIV: a clinical practice guideline". [9]

PROMISE study

PROMISE compared zidovudine/single-dose nevirapine (AZT-alone) to lopinavir/ritonavir (LPV/r)-based ART either with AZT/lamivudine (AZT-ART) or tenofovir disoproxil fumarate/emtricitabine (TDF-ART) for the prevention of vertical transmission in women with CD4 cell count >350 cells/mm3.

The study was enrolled during two periods. The comparisons with TDF-ART were made in women who were randomised between the three study arms, in the second period of the study.

During the first year and a half of enrolment (when 65% of participants enrolled) only hepatitis B (HBV)-coinfected women were randomised to TDF-ART vs AZT-ART vs AZT-alone.

Only after a protocol modification, in the second year and a half of enrolment (when 35% of participants enrolled), were all participants randomised to all three arms, irrespective of HBV. As a result, PROMISE only compared TDF-ART with AZT-ART or AZT-alone in the second period of the study.

This comparison found a lower rate of very preterm delivery (<34 weeks) in the AZT-ART arm vs the TDF-ART arm (2.6% vs 6.00%, p=0.04), leading to a difference in early infant mortality (<14 days),

in the respective arms (0.6% vs 4.4%, p=0.001). Over 40% of very preterm deliveries and 47% of early infant deaths occurred in the second period of enrolment.

Notably there was no significant difference between the TDF-ART and AZT-alone arms in very preterm delivery (6.0% vs 3.2%, p=0.10) or early infant mortality (4.4% vs 3.2%, p=0.43). There was also an imbalance in neonatal deaths in the AZT-ART arm: 88% (15/17) of which occurred during the first period of the trial and the remaining 12% during the three-arm comparison. So, it might be that the AZT-arm had artificially low rates of both events and not that the TDF-ART arm had increased the risk.

PROMISE did not combine analysis of stillbirth and early infant mortality and there were no differences in rates of stillbirth and spontaneous abortion in the AZT-alone, AZT-ART and TDF-ART arms.

It is also important that the ART regimens used in PROMISE were LPV/r-based and the investigators noted that there are inconsistent findings on the association of PI-based ART and preterm delivery.

As well as this, LPV/r was given with a dose increase during the third trimester to 600/150 mg twice daily (standard dose is 400/100 mg twice daily) in PROMISE to overcome decreased plasma levels in late pregnancy. A potential explanation for the differences seen might be a pharmacokinetic interaction between LPV/r and TDF resulting in increased plasma and intracellular levels of tenofovir.

The investigators emphasised that because the study only included PI-based ART, data could not be generalised to TDF-based ART in regimens with other classes of ARVs such as the efavirenz (EFV)-based ART regimen currently recommended in pregnancy by the WHO.

PROMISE investigators response

In their response, published in BMJ Open on 19 September, the PROMISE investigators stress that they did not analyse stillbirth with early neonatal death in their study. [8] They note that: "Contrary to the authors' statement, the pathophysiology of stillbirth and early neonatal death are not necessarily the same and hence the PROMISE team did not feel it was appropriate to combine these endpoints". They add that the rates of spontaneous abortion and stillbirth were not significantly different between the three arms.

In the BMJ review, Siemieniuk et al combined data on stillbirth/early infant death from two hepatitis B mono-infection studies with very few events; neither included HIV positive pregnant women, which the PROMISE investigators also query.

And they explain that both AZT-ART and TDF-ART were associated with increased preterm delivery (<37 weeks) compared to AZT-alone and there was no significant difference in rate of preterm delivery between the AZT-ART and TDF-ART arms during the second period of the study.

It was only when they evaluated very preterm delivery (<34 weeks) that they observed a difference, with a higher rate in the TDF-ART compared to AZT-ART arm, p=0.04. But the rate of very preterm delivery in the TDF-ART was not significantly different than AZT-alone arm, p=0.10.

They suggest that both ART regimens might be associated with preterm delivery, with AZT-ART increasing this between 34–36 weeks and TDF-ART possibly increasing very preterm delivery <34 weeks. But the PROMISE investigators were not willing to draw a definitive conclusion from these data.

They also note that the AZT-ART arm appeared to have a very low rate of infant mortality during the second period of the study when it was compared to TDF-ART.

And they raise concerns about potential pharmacokinetic interactions between LPV/r and TDF.

Overall the PROMISE investigators felt it was inappropriate to use their study to make definitive conclusions on use of TDF-ART in pregnancy. They emphasise again that, as the study only included PI-based ART, it cannot be generalised to TDF-ART with third agents such as the widely used and recommended EFV-based regimen.

They note the recent study by Zash et al from Botswana, which compared birth outcomes, including preterm delivery and neonatal death, among HIV-positive women. [7] In this study, all other ART regimens (including AZT/3TC/LPV/r) were associated with higher risk of adverse outcome; increased risk of preterm birth, very preterm birth and neonatal death than EFV/TDF/FTC.

In conclusion, they write: "While the PROMISE team strongly supports further evaluation of the safety of ART regimens in pregnancy for the woman and her infant in order to find the optimal ART regimen, the PROMISE team does not agree that the PROMISE trial results support a recommendation against using a TDF-based ART regimen in pregnancy".

BHIVA response

The BHIVA recommendation, published on 21 September 2017, is to continue or to start TDF or ABC with FTC or 3TC as an NRTI backbone in pregnancy. [9]

The statement also addresses the use of TDF/FTC as PrEP saying: "We do not think this data should influence use tenofovir/emtricitabine for pre-exposure prophylaxis in women of child-bearing potential".

The BHIVA group notes that that UK guidelines do not recommend the use of LPV/r for the treatment of HIV in adults, including pregnant women, and certainly not at the higher dose used in the third trimester in PROMISE. They also explain that PROMISE looked at outcomes in women starting ART. Most women in UK will conceive on ART, most commonly with TDF/FTC backbone and PROMISE does not address that group.

As both arms received LPV/r the BMJ panel suggest that TDF/FTC is the cause of the difference. The BHIVA group also highlight data showing increased levels of both drugs when co-administered at standard doses.

They cite the Zash et al study that included 11,932 HIV positive women, where preterm birth, very preterm birth, small and very small size for gestational age, stillbirth, and neonatal death were evaluated. In this large cohort, the risk for any adverse or severe adverse birth outcome was lowest among infants exposed to TDF/FTC/EFV, and the highest risk of adverse outcomes with observed in women receiving LPV/r-based regimes.

As well as the recommendation to continue or start TDF or ABC with FTC or 3TC as the NRTI backbone (Grading: 2C), BHIVA recommend that the third agent should be one of the following: EFV, raltegravir, rilpivirine, ritonavir-boosted darunavir or ritonavir-boosted atazanavir, as recommended in BHIVA adult treatment guidelines.

On PrEP they add: "the group does not think this data should influence decisions to use tenofovir/emtricitabine for pre-exposure prophylaxis in women of child-bearing potential".

COMMENT

Both the PROMISE investigators and the BHIVA group responses clearly disagree with the BMJ panel. Both responses explain their reasons and are worth reading in full.

A few other things are notable in the Siemieniuk et al review.

Firstly, Siemieniuk et al emphasise the trustworthiness of their findings a couple of times: "Our approach contrasts with a prior effort that pooled randomised controlled trials (RCTs) with far less trustworthy observational studies" and "The BMJ Rapid Recommendation initiative attempts to provide timely, unconflicted and trustworthy recommendations for clinical situations where new evidence might change practice". It is not clear if they are implying that previous systematic reviews, the conclusions of the WHO and other guideline panels are then conflicted and untrustworthy.

Secondly, both the PROMISE and BHIVA responses acknowledge that observational data generally produce a lower grade of evidence compared with data from RCTs. But the PROMISE investigators rightly point out that it is improbable that there will be other RCTs and there have been a number of observational studies suggesting that TDF-ART is safe in combination with NNRTIs. But Siemieniuk et al conclude that TDF might not be safe based on one RCT with that is difficult to interpret as noted by the PROMISE investigators.

In their discussion of the Nachega et al systematic review (the "prior effort" above), Siemieniuk et al say that it "assumed equal credibility in randomised and observational studies" and "pooled RCTs and observational studies which, given the much higher certainty associated RCTs, we consider inadvisable and, indeed, inappropriate". [6] But Nachega et al explain in their methods that they assessed the quality of evidence using the GRADE approach which considers the difference between observational data and RCTs.

Thirdly, Siemieniuk et al also state that other studies have found "that TDF-based cART regimens are safe for women and their infants." But neither of the studies they mention – Nachega et al and Mofenson et al – draw an unqualified conclusion that TDF is safe. [5, 6] Both discuss PROMISE and the potential problems with interpretation. They respectively conclude: "TDF-based ART in pregnancy appears generally safe for women and their infants.

However, data remain limited and further studies are needed, particularly to assess neonatal mortality and infant growth/bone effects." And: "Although additional surveillance is important, given the available safety data, the benefits of PrEP use for prevention by pregnant/lactating women at high risk of HIV acquisition (and its accompanying increased risk of mother to child HIV transmission) appear to far outweigh the potential risks of foetal, infant and maternal TDF exposure."

Finally, the selection of studies in non-pregnant adults by Siemieniuk et al seems strange given the changes in maternal physiology that occur in pregnancy and the potential to alter absorption, distribution, and elimination (and in turn toxicity) of antiretrovirals.

Most problematic is the inclusion data from studies that included mostly men (using an endpoint of 26 weeks after enrolment to approximate the timeline of a woman starting ART in the second trimester).

It makes for curious reading of analyses of "maternal" clinical and laboratory adverse events when three out of four RCTs were conducted in non-pregnant adults.

Far from being trustworthy, the BMJ paper used inappropriate methodology to produce recommendations that would likely produce harm.

A similarly flawed Cochrane review was recently rapidly criticised for concluding that highly effective hepatitis C drugs had no proven benefit on reducing serious long-term outcomes. [10]

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Pregnancy common in ART trials in sub-Saharan Africa despite exclusion criteria

Polly Clayden, HIV i-Base

A new analysis from two ANRS studies reports that HIV positive women in clinical trials in sub-Saharan Africa are likely to get pregnant as often as those receiving care outside of research settings and questions why pregnancy is still commonly an exclusion criterion.

Instead, the investigators say it is essential to take a pragmatic approach and revisit the relevance of the criteria for exclusion of pregnant women in such trials.

An increasing number of ART clinical trials are now conducted in sub-Saharan Africa, a region with the highest fertility rate in the world and a very high social value associated with child bearing.

Pregnancy and breast feeding are exclusion criteria in the majority of antiretroviral therapy (ART) clinical trials. Women of child bearing age agree to defer pregnancy for the duration of the study and are counselled before enrolment on using dual protection (condoms and a non-barrier contraceptive method), which are usually provided free.

A previous study conducted in Botswana reported a pregnancy rate of 7.9 per 100 person years (PY), despite women's verbal agreement to defer childbearing until after the study was closed.

Investigators from ANRS12169-2LADY and ANRS12286-MOBIDIP trials – comparing three boosted PI regimens, and the efficacy of a mono or dual-therapy of PI with or without 3TC respectively, conducted in Cameroon, Senegal and Burkina Faso – described their experience of pregnancies among women participants. These findings were published online in HIV Clinical Trials, 1 November 2017.

The goal of the study was to describe the reproductive behaviour and pregnancy outcomes among women on second-line ART enrolled in the trials and compare them with those of HIV positive women in non-research settings.

The investigators reported 66 women had 84 pregnancies between January 2010 and July 2015 (1046.3 PY of follow up). The majority (51) of women had one pregnancy during follow up, 12 had two and three had three.

Compared with the other women participants in 2LADY, women who became pregnant were: younger (31 vs 36 years, p<0.001), less likely to be single (24.2% vs 40.1%, p=0.005), were more likely to have disclosed their HIV status to their partner (95.5 vs 31.7, p<0.001), and had been receiving ART for a shorter time before enrollment (3.5 vs 4.2 years, p<0.001). There were no differences in CD4 or viral load at enrollment.

Sixty pregnancies (71.4%) were in women receiving lopinavir and 27 (32.1%) in those receiving darunavir.

The investigators noted that 13 of 66 women who became pregnant had received medroxyprogesterone before pregnancy. But these women received a median of only one dose. Seven women received medroxyprogesterone or a levonorgestrel-releasing implant after pregnancy.

The overall pregnancy rate (per 100 PY) was 8.03 (95%CI: 6.5 to 9.9). Twenty women (7.1%), including two pregnant women lost to follow up at time of analysis. The pregnancy rate was highest in Senegal, 10.0 (95%CI: 6.4 to 15.7) vs Cameroon, 7.5 (95%CI: 5.6 to 9.9) and Burkina Faso, 7.9 (95%CI: 4.9 to 12.7).

The median time from enrollment to first pregnancy was 1.7 months. The investigators found that the incidence of pregnancy was stable during the first two years, then declined, and peaked again after four years of follow up – partially because of recurrent pregnancies.

The 84 pregnancies resulted in: 60 (73.2%) live births, 13 (15.8%) miscarriages, three (3.6%) stillbirths, two (2.4%) extra-uterine pregnancies and four (4.8%) voluntary abortions. Two women were lost to follow up. The overall fertility rate was 5.73 live births per 100 PY (95%CI: 4.45 to 7.39).

The median gestation was 38 weeks (IQR 37 to 40) and median birth weight 2.9 kg (IQR 2.6 to 3.2). Nine (15%) infants had low birth weight, four of them were also premature. The investigators only recorded one birth defect (ankyloglossia). Four infants needed resuscitation at birth; one died from respiratory disease. One woman died of bleeding at delivery.

In multivariate analysis, miscarriages/stillbirths were not associated either with age, CD4 nadir, duration of ART, CD4 count, or viral load at the start of pregnancy. The investigators noted a trend in an increased proportion of miscarriages/stillbirths with darunavir vs lopinavir exposure: OR 3.1 (95%CI: 0.9 to 10.1).

The investigators looked at the scarce published data on the reproductive behavior of HIV positive women in West and Central Africa, and found the few studies available to be very heterogeneous in terms of population sample, types of data collected, study period, and ART availability, making comparisons hard. But the reproductive behaviour of HIV positive women enrolled in clinical trials in sub-Saharan Africa appeared to be similar to that of women in non-research settings.

They concluded that this finding needs to be taken into account when planning trials in such regions with high fertility rates. The option to get pregnant in a trial should be discussed in ethics committees in the context of the level of risk associated with investigational antiretrovirals during pregnancy. Family planning counselling and contraception options need to improve.

The investigators also noted that the reported rate of miscarriage/stillbirth in this study is not different from those reported in HIV negative women, which is reassuring for HIV positive women considering pregnancy and receiving ART.

COMMENT

This study was conducted in African countries with some of the highest fertility rates in the world: in Burkina Faso and Senegal women have an average of almost 6 and almost 5 children respectively. So, the finding that women of child-bearing age get pregnant in clinical trials with long follow up is unsurprising.

The more salient point to take from this article is that pregnancy is frequently an exclusion criterion for ART trials and women who conceive during this period are often switched from an investigational drug or regimen, sometimes not until later in pregnancy, when it is detected.

In some cases, it might be more appropriate to continue on the study drug (in the context of level of risk/benefit) with careful monitoring, and this needs to be taken into account when designing trials that include women of child-bearing age.

If women do continue on study drug in pregnancy, it is important that the data on maternal and infant outcomes is captured. New antiretrovirals always have scant information to guide recommendations in pregnancy after approval for high-income countries and this can delay their inclusion in global guidelines.

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PAEDIATRICS

FDA approves raltegravir for newborns

Polly Clayden, HIV i-Base

At the end of November 2017, the US FDA approved raltegravir for treatment, in combination with other antiretrovirals, of neonates from birth to four weeks of age, weighing at least 2 kg. [1, 2]

This approval was supported by data from IMPAACT P1110 – an open label, clinical trial looking at the safety and pharmacokinetics of raltegravir oral suspension in 42 full term, HIV-exposed newborns, at high risk of vertical transmission.

Raltegravir is not recommended in pre-term newborns or infants weighing less than 2 kg, as no data are yet available in these populations. If the mother has taken raltegravir within two to 24 hours before delivery, the newborn's first dose should be given between 24 to 48 hours after birth.

C O M M E N T

Raltegravir is now one of the few antiretrovirals approved for treating babies from birth.

Having the option to use an integrase inhibitor from birth is a significant development for paediatric HIV.

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Long-acting ART for children is a deferred priority despite achievable dosing

Polly Clayden, HIV i-Base

Optimal doses of long-acting injectable antiretrovirals cabotegravir and rilpivirine were predicted for different weight bands in children and adolescents.

Long-acting injectable antiretrovirals could be future alternatives to oral formulations and might help to address adherence. There is great interest in the potential use of these formulations in the treatment of paediatric HIV.

Clinical trials of new drugs in children and adolescents are delayed by both ethical and logistical barriers complicating the identification of appropriate doses. Physiologically-based pharmacokinetic (PK) modelling can inform dose finding before clinical trials are conducted.

Researchers from the University of Liverpool and Johns Hopkins conducted a study to simulate potential dosing strategies of long-acting injectable depot formulations of cabotegravir and rilpivirine in children and adolescents (aged 3 to18 years) using such modelling.

The researchers developed whole-body physiologically-based PK models to act as the anatomical, physiological and molecular processes as well as age-related changes in children and adolescents using allometric equations.

The models were validated for the two long-acting injectable intramuscular agents in adults. The characteristics of children and adolescents were validated using available literature.

PK data generated through the physiologically-based PK simulations were similar to that observed in adult clinical data.

The researchers predicted optimal doses of long-acting injectable cabotegravir and rilpivirine using the release rate for existing clinical formulations, for different weight groups of children and adolescents.

They found the intramuscular loading dose and maintenance dose of cabotegravir across various weight bands in children weighing from 15-70 kg ranged from 200-600 mg and from 100-250 mg, respectively. For rilpivirine these ranged from 250–550 mg and from 150-500 mg, respectively.

"The reported findings represent a rational platform for the identification of suitable dosing strategies and can inform prospective clinical investigation of long-acting injectable formulations in children and adolescents" the researchers wrote.

C O M M E N T

The paediatric investigation plan for these long-acting drugs includes their use in both treatment and prevention.

However, there is a waiver for young children less than two years (for treatment) and less than 12 years for prevention. But there is also a deferral for children that are two years and above.

This means that these agents will only potentially be available for use in the paediatric population many years after they are likely to be approved for adults.

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PUBLICATIONS & SERVICES FROM I-BASE

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Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

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

RSS news feed is available for HIV Treatment Bulletin for web and PDA.

An average of 200,000 pages from individual ISP accounts contact the website each month, with over 6000 hits a day.

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i-Base treatment guides

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

- Introduction to ART
- HIV testing and risks of sexual transmission
- HIV and quality of life: side effects & complications
- Guide to changing treatment and drug resistance
- Guide to HIV, pregnancy & women's health
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support
- UK guide to PrEP

Publications and reports

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published every two months in print, PDF and online editions.

HTB South

A quarterly bulletin based on HTB but with additional articles relevant to Southern Africa. HTB South is distributed in print format by the Southern African HIV Clinicians Society (www.sahivsoc.org) to over 20,000 doctors and healthcare workers. It is also available as a PDF file and is posted online to the i-Base website.

HTB Turkey

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB.

HTB West Balkans

HIV Bilten is an edition of HTB in Bosnian, Monteragrin, Croatian and Serbian, for the West Balkans, produced by Q Club.

Why we must provide HIV treatment information

Text from activists from 25 countries and 50 colour photographs by Wolfgang Tillmans.

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http://www.ukcab.net

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