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EDITORIAL

This issue of HTB starts with reports from the long-running annual workshop on side effects.

PrEP studies included the first case of Fanconi-like symptoms in an HIV negative person and looking the risk:benefit of using tenofovir-DF in young people at risk of HIV infection.

Several studies reported new complications with integrase inhibitors, a French group looked at taking ART four days a week and a large US study found that higher levels of physical activity correlated not only with better health but also a higher CD4 count.

Reports from AIDS 2016 and associated meetings held in Durban in July range from a French study on another reduced dose maintenance strategy, concerns on pricing and access, especially in the context of pregnancy, and reviews of posters that were generally under-reported in other community coverage.

Four additional reports from Durban report on different aspects of the safety and efficacy of ART in children.

Then some good news. Firstly, the US FDA have approved the first generic formulation of dolutegravir. This will match the price of generic efavirenz and improve both quality of life and reducing costs in low income countries. Secondly, the Global Fund announced that funding targets for 2017-2019 have already been achieved. We also report a new WHO analysis that supports greater efficacy with dolutegravir compared to efavirenz.

Finally we update PrEP news for the UK, new US guidelines and cure research.

SUPPLEMENTS with this issue of HTB

This month, two i-Base treatment guides have been revised and updated. As with all i-Base publications these are available free, including in bulk for NHS clinics.

Please order online or using the form on the back cover.

Introduction to ART (September 2016)

This easy-to-understand guide to ART has been updated to include the newest drugs and formulations and to incorporate recent changes in treatment guidelines.

This is an ideal resource for anyone who is newly diagnosed or about to start ART.

HIV and quality of life: guide to side effects and long term health (September 2016)

As ART becomes more effective, each update to this guide reduces the information on side effects and expands the sections on quality of life, complications linked to ageing and lifestyle choices that can improve long-term health.

CONFERENCE REPORTS

18th International Workshop on Comorbidities

12 – 13 September, New York, USA

Introduction

The 18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV was held from 12-13 September 2016 in New York.

This long-running workshop, initially set up to look at lipodystrophy, continues to be an important focus for research into side effects of ART and other comorbidities. In addition to having an abstract-driven programme, plenary talks are notable for including lectures from outside the HIV field that address new issues and complications.

This year the meeting was held the New York Academy of Sciences at the World Trade Centre in New York, immediately following the 15th anniversary of the attacks on 9/11. A parallel between the immediate loss of life from both AIDS and the terrorist attacks was made during the opening welcome by the workshop co-chair Donald Kotler who was a doctor involved in early medical responses to both.

It was also important that a new scholarship award for best young investigator study was named to honor long-time HIV activist Bob Munk who before his death last year had been involved in this workshop since the first meetings, including as a community representative on the scientific steering committee for many years.

As well as the abstract-driven programme, plenary talks at the meeting are notable for including lectures that address new issues and complications often from expert from outside the HIV field. This year these talks included physiology of bone, metabolic regulation of ageing, adipose tissue as an HIV reservoir, smoking cessation and new treatments for LDL management.

Presentations from the workshop, including the programme and abstract book will be available from the conference website.

https://www.intmedpress.com/comorbidities

The following reports are included in this issue.

- Fanconi-like lab abnormalities reported with daily PrEP: shows importance of routine kidney monitoring
- Bone loss with PrEP in MSM aged 13-24
- Neurological side effects with integrase inhibitors cause discontinuations in clinical practice
- Atripla three days a week for two years: pilot switch study reports undetectable viral load with better bone, kidneys and sleep
- Raltegravir increases waist circumference compared to boosted PIs: greater with use of later ART
- Exercise associated with significantly reduced risk of serious health problems and higher CD4 counts in large multicentre US study

Fanconi-like lab abnormalities reported with daily PrEP: shows importance of routine kidney monitoring

Simon Collins, HIV i-Base

The first case of Fanconi syndrome associated with PrEP was reported in a poster at the 18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV. [1]

Diagnosis was based on changes in laboratory tests, without other symptoms, which reversed when PrEP was discontinued. This case was detected during routine monitoring in a prospective phase 4 PrEP study on ways to help adherence. [2]

The case was a 49 year-old man who was otherwise well and who was not taking other medications than daily tenofovir-DF/emtricitabine. His only related medical history included kidney stones seven years earlier.

At screening for the study, creatinine clearance (CrCl) by eGRF was 79.9 which dropped to 68.7 at week 4 and 58.9 at week 12. Additional monitoring showed significantly reduced serum phosphate and increased fractional phosphate excretion (FePi%). These abnormalities are consistent with kidney dysfunction that if allowed to progress would be associated with symptoms linked to Fancoini syndrome.

PrEP was immediately stopped and CrCl returned to near baseline levels over the next 12 weeks, see Table 1. No other abnormalities (glycosuria, haematuria, proteinuria) were detected at any timepoint by dipstick testing.

Importantly, PrEP was not restarted.

Table 1: Changes in renal markers linked to early Fanconi syndrome

Timepoint (weeks)	Screening	Wk 4	Wk 12	Wk 16	Wk 18	Wk 21	Wk 24
CrCl (eGFR) ml/min^2	79.1	68.7	58.9	69.1	66.6	71.0	74.0
Serum phosphate mg/dL (normal 2.7-4.5)	-	-	1.8	2.7	3.2	2.5	2.8
FePi% (normal 10-20)	-	-	26.6	12.2			

C O M M E N T

This person had a 25% drop in creatinine clearance and grade 2 hypophosphataemia with increased fractional excretion of phosphate. If there are no other features (proteinuria, glycosuria) there are not enough abnormalities to diagnose Fanconi syndrome (usually at least two of the three abnormalities are required).

This might therefore be a case of renal tubular dysfunction or possible FS/tubulopathy. It is possible that more extensive abnormalities would have developed with ongoing exposure – or that things would have stabilised, but discontinuation was appropriate.

This is an example where TAF (assuming similar efficacy is proven) would clearly be preferred for this patient.

However, the risk of rare side effects reported previously from TDF as HIV treatment, emphasises the importance of routine three-monthly kidney monitoring. If not detected early, symptoms could progress to include extreme fatigue which would hopefully then prompt kidney testing appropriate for PrEP.

Although Fanconi syndrome a serious side effect, this is now rarely reported when tenofovir-DF is used as part of an HIV combination. Early reports were often linked to use with didanosine which is now contraindicated, especially with a boosted protease inhibitor.

This is the first such case reported in PrEP studies.

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Bone loss with PrEP in MSM aged 13-24

Simon Collins, HIV i-Base

Results from an open-label study in young people using PrEP showed that its impact on bone health might be important if daily dosing is used for many years. [1]

In the short-term, the protection from HIV in this very high risk group, probably outweighs the small safety risk, but these results show the urgency of studying reduced dosing and for future PrEP options that have an even safer side effect profile. During the break between the end of the main study when PrEP was stopped and continued access to PrEP, six participants became HIV positive.

ATN 110 was a year-long open label PrEP demonstration study to expand safety data among 200 young men aged 18-22 at 12 US sites. All participants received daily PrEP and monitoring included DEXA screens for bone mineral density (BMD) at baseline and weeks 24 and 48. Participants who either lost or failed to gain bone or who had markers of reduced renal function entered an extension phase with further DEXA scans at 24 and 48 weeks after stopping PrEP.

Entry criteria for the extension phase included being younger than 20 with no increase in BMD or older than 20 with BMD with >1% decrease in BMD; or for all participants, a decrease of >0.5 in Z-score at hip, femoral neck or spine.

Median age of the group was 20 years. More than half were black, 17% were Hispanic and 21% were white. About 80% did not always use condoms (58% not used with most recent partner) and 22% had had a previous STI. About 1 in 5 had been forced to leave home for being gay and 1 in 3 had had sex for money.

Of 200 people in the initial study, 61 discontinued before week 48 (including 4 seroconversions). Of the 135 participants with week 48 DEXA, 102 met criteria for the extension safety phase - with 101 people meeting bone criteria and 1 person for renal changes. Of these 72/102 had follow-up DEXA scans when off PrEP and 15 people had scans after continuing on PrEP.

During the extension phase, BMD at both hip and whole body steadily returned to baseline levels over the next year without PrEP. BMD at the spine quickly returned to above baseline and by week 48 were significantly higher (p=0.04).

When looking the changes in absolute Z-score over time, hip and whole body, which had both dropped significantly when on PrEP had returned after to year off-PrEP to levels that were not significantly different to pre-PrEP baseline. Z-score for spine was still significantly lower though after 48 weeks of PrEP (p=0.001).

In a small number (n=15) of men who stayed on PrEP during the extension safety phase (one of who became HIV positive), whole body and hip BMD reduced further and spine increased slightly - though none of these changes were statistically significant.

In general, participants who had greatest bone loss when on PrEP had the greatest recovery when PrEP was stopped.

There were no fractures or serious renal events during the study.

C O M M E N T

This study was important for raising the unknown implication of using tenofovir-DF by people who are young enough for their bone to still be growing.

Although the results are useful in showing a return to baseline after stopping PrEP, the high rate of new HIV infections show that this is a group who is in real need of better HIV prevention options.

PrEP was only used for a year in this study, but someone this young might easily expect to continue using PrEP for 5-10 years if they continue to be at high risk, even if use is not continuous.

The post-PrEP recovery was also at a time when bone production was still active.

These and other data could perhaps be used to model the impact on BMD for 5 or 10 years if PrEP is only stopped after someone is too old for the optimal time for bone recovery.

Reference

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Neurological side effects with integrase inhibitors cause low rates of discontinuation in clinical practice

Simon Collins, HIV i-Base

An analysis from use of integrase inhibitors in clinical practice reported significantly higher rates of discontinuations related to side effects than seen in clinical studies and includes neurological complications with dolutegravir.

This was a retrospective analysis presented in an oral presentation at the 18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV by Esteban Martinez from University of Barcelona. [1]

The study included antiretroviral naive and experienced patients who received a first integrase-inhibitor based ART with at least one follow up visit, with the analysis looking for those who switched treatment within the first year.

Baseline characteristics of 1061 patients in the overall cohort included mean age 45, >80% men, and >50% were gay men. Median CD4 count at diagnosis was >350 (IQR approximately 200 to 550) cells/mm^3. Sensitivity analyses were run to allow for the great use of earlier integrase inhibitors.

The incidence of side-effect related discontinuations was 12.7% for raltegravir (71/557), 8/1% for elvitegravir (26/332) and 12/3% for dolutegravir (26/212). Based on incidence of 270, 167 and 263 events per 1000 patient years of follow up for raltegravir, elvitegravir and dolutegravir respectively, the unadjusted IRR compared to raltegravir was 0.62 (95%CI 0.39 to 0.97) for elvitegravir and 0.97 (95%CI 0.62 to 1.52) for dolutegravir, showing non-significant differences between drugs (p=0.821).

A further analysis for each drug compared discontinuations for naive compared to experienced patients. Although there were not statistically significant differences for raltegravir (unadjusted IRR 0.64 [95%CI 0.36 to 1.12, p=0.10) or elvitegravir (unIRR 1.66 [95%CI 0.53 to 2.53], p=0.70), with dolutegravir, treatment-experienced patients were more likely to discontinue compared to those who were naive (unIRR 3.11 [95%CI 1.03 to 9.39], p=0.03).

Although just over one-third of discontinuations overall (n=44/123) were due to side effects rather than other reasons, there were significant differences between drug: 28% with raltegravir (20/71), 62% with elvitegravir (16/26) and 31% with dolutegravir (8/26); p=0.008). So although elvitegravir was discontinued less frequently, when it was stopped this was more likely to be related to side effects than other reasons.

When categorised by type of side effect, multiple organs were involved but reports of CNS-related symptoms (disorientation, mood changes, sleep disturbance) were notable for similarity to side effects related to efavirenz, albeit at a much lower incidence. See Table 1.

This was reported with each drug but was significantly more important with dolutegravir (88%; 7/8) compared to raltegravir (35%; 7/20) and elvitegravir (19%; 3/16); p=0.005.

In adjusted analysis, only older age associated with overall discontinuations for any reason (adj HR 1.04 (95%CI 1.02 to 1.07; p=0.0007).

Table 1: Side effects associated with early discontinuation of integrase inhibitors

	Raltegravir (n=20; 3.6%)	Elvitegravir (n=16; 5.0%)	Dolutegravir (n=8; 3.8%)	p-value
CNS (n=17)	7 (35%)	3 (19%)	7 (88%)	0.005
Muscular (n=12)	3 (15%)	6 (38%)	3 (38%)	0.244
Digestive (n=11)	7 (35%)	4 (25%)	0	0.179
Skin/mucoses (n=6)	4 (20%)	2 (13%)	0	0.456
Systemic (n=5)	2 (10%)	0	3 (38%)	0.224
Respiratory	1 (5%)	0	0	1
Kidney	0	1	0	0.545
Number of organ systems				
1	17 (85%)	16 (100%)	5 (63%)	0.066
>1	3 (15%)	0	3 (37%)	

C O M M E N T

Although discontinuations were higher than in clinical trials, integrase inhibitors still generally have fewer side effects compared to drugs in other classes. This study is important for highlighting the range of problems that can occur.

All drugs look safest when first approved because by definition this occurs when data are limited to only several thousand people. Post marketing reports of side effects nearly always show more complicated problems with wider use.

Anecdotal reports of neurological problems with dolutegravir shortly after approval were sufficient for i-Base to add these side effects in online patient information. This was largely reported from people who switched away from dolutegravir within the first weeks of treatment.

A similar sized study at IAS 2015 reported discontinuation rates of 4.6% for raltegravir (24/522), 8.6% for elvitegravir (26/301) and 3.1% for dolutegravir (9/299). [2]

A letter published ahead of print in September 2016 in AIDS also reported higher rates of discontinuation of dolutegravir compared to clinical trials due to side effects. [3]

In this Dutch cohort of 556 patients, 102 of which were ARV-naive. Overall, 85/556 patients (15.3%) stopped dolutegravir, none due to virological failure, with 76/85 (13.7%) due to intolerability. Main symptoms were: insomnia and sleep disturbance (5.6%), gastrointestinal complaints (4.3%) and neuropsychiatric symptoms e.g. anxiety, psychosis and depression (4.3%). Dolutegravir was switched more frequently in combinations that included abacavir (adjusted RR 1.92 95%CI 1.09-3.38, p-log-rank 0.01).

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Atripla three days a week for two years: pilot switch study reports undetectable viral load with better bone, kidneys and sleep

Simon Collins, HIV i-Base

A small pilot study that switched people with undetectable viral load to reduced dosing of Atripla reported no viral load rebounds with follow-up results out to two years. [1]

The initial study randomised 61 participants with a long history of viral suppression (entry criteria included viral load <37 copies/mL for more than two years) to either switch to taking Atripla three times a well (on Mondays, Wednesdays and Fridays) or to continue with daily dosing.

The primary endpoint of viral suppression at week 24 was reported for all 30 participants in the reduced dose group (100%, 95%CI 98.3 to 100). Additionally, no viral loads blips (>37 copies/mL) were reported from more than 330 viral

load samples. Analysis using a viral load test with a 2 copy/mL cut-off showed no differences between baseline and week 24 samples in either arm.

Secondary endpoints favoured the reduced dose strategy with small but significantly better markers of renal function and bone health and for better quality sleep, indicating potential benefits from reducing exposure to both tenofovir-DF and efavirenz. Median urine albumin to creatinine ratio reduced by 1 vs 0 mg/g (p=0.047) and Beta-2 microglobulin reduced by – 158 ug/g vs + 312 (p=0.003) in the reduced vs daily groups respectively. Although sleep quality was reported as normal at baseline using the Pittsburgh Sleep Quality Index (median 4 on a scale of 1 to 10, when lower is better), by week 24 this improved more for the reduced dose arm, by –1.0 vs –0.5 (p=0.003).

A small but statistically significant increase in total cholesterol in the reduced dose group of + 4vs –5 mg/dL (p=0.019) was explained by the lipid impact of reducing levels of tenofovir-DF.

A three-year study extension that then allowed those on daily dosing to switch to reduced dosing at week 24 was accepted by all participants, with follow up results now presented for 61 people out to 24-30 months.

Viral suppression has been maintained throughout the 24 to 30 month extension phase with no study discontinuations. The single reported complication was one non-AIDS related neoplasia with this participant continuing on the reduced dose schedule.

Concern about the difficulty of remembering dosing with less than daily regimens was discussed in questions after the presentation. Although data was not presented formally on adherence, the study included additional adherence support to overcome these initial difficulties.

No participant accepted the option to switch back to daily dosing and the lack of drop-out or discontinuations for any reason supports further evaluation of this strategy in larger studies.

C O M M E N T

Although this is a small study, the durability reported in these results makes further research important given the likely continued pressure to widely use generic components of Atripla in first-line therapy, even when guidelines recommended better and newer options.

The benefits from reduced dose tenofovir-DF suggest this might even be preferable compared to the strategy of reducing the daily efavirenz dose to 400 mg.

Previous studies have suggested that daily dosing might not be needed given the long half-lives of efavirenz, tenofovir-DF and emtricitabine (ranging from 39->60 hours). For example, ten years ago the FOTO study (Five-On, Two Off) reported no viral blips >50 copies/mL when 30 for over a year. [2]

The BREATHER study in young people (age 8 to 24) reported non-inferiority from dropping weekend doses compared to daily dosing with 75% of participant reported significant improvement in quality of life. The BREATHER study was reported at CROI 2015 and published in Lancet HIV in June 2016. [3, 4]

At IAS 2016 in Durban this year, a French study reported three cases of viral rebound over a year in 100 participants with suppressed viral load switching to a reduced dose strategy of taking only four continuous doses each week, all of who resuppressed when returning to daily dosing. More importantly, all combinations of 2NRTIs + either a PI or NNRTI were included. Although 40 people were using efavirenz-based ART, 26 were using rilpivirine and 5 were using etravirine. There were 29 people using PI-based ART: 15 with darunavir/r, 13 using atazanavir/r and 1 using lopinavir/r. [5]

While these small studies are intriguing with tentative results that look promising, together with other reduced-dose maintenance strategies - including dolutegravir with and with 3TC - this might warrant a large well powered randomised study in order to really access both safety and efficacy.

Given the potential savings if this is successful, perhaps this could be a new focus for the INSIGHT research network that so effectively produced definitive data on controversial aspects of care in both the SMART and START studies.

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Raltegravir increases waist circumference more than boosted PIs: greater with use of later ART

Simon Collins, HIV i-Base

A large US ACTG study reported significantly different body changes with raltegravir compared to combinations using a boosted PI. [1]

While the results presented at the 18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV were not associated with different clinical outcomes, this could reduce quality of life for people who are trying to reduce weight and conversely have advantages for people with low BMI who are looking to gain weight.

As all participants used the same background NRTIs and randomisation should have balanced lifestyle and environmental factors equally, this suggests the results might be real. The results are surprising given boosted PIs need to be taken with food and that raltegravir has a lipid neutral side effect profile.

ACTG A5257 randomised more than 1800 treatment-naive adults 1:1:1 to raltegravir, atazanavir/r or darunavir/r with 96-week follow-up, running from 2009 to 2013. All participants also used tenofovir-DF/emtricitabine. Results from the main study were presented at CROI 2014, and results from a DEXA substudy (ACTG 5260) that showed no difference in body composition changes between groups, published earlier this year. [2, 3]

This analysis reported change in waist circumference (WC) from baseline to week 96 using standardised measurements across study sites. Previous studies have supported a strong associated between changes in WC to increases in visceral adipose tissue (VAT) confirmed by DEXA results.

The study looked from predictors of weight gain that included demographics (race/ethnicity, sex and age) and baseline characteristics (BMI, CD4 and viral load) in three models that presented ITT analyses and also adjusted for potential confounding factors (smoking, drug use, income and health insurance status).

Baseline demographics include approximately 75% men; mean age 37; ethnicity: black 42%, white 34%, Hispanic 22%; median WC and BMI were 90 cm and 26 kg/m^2 respectively.

Between week 0 and 96, WC increased by a mean of 3.4 cm (SD 8.1) in the study overall and showed steady increases in all three treatment arms: +4.0, +3.5 and +2.8 cm in the rategravir, atazanavir and darunavir arms respectively.

Results were different by sex and race with the much larger increases with raltegravir in black women. The mean increases in women were +5.9, +2.7 and +2.9 cm and in men were +3.7, +3.7 and 2.8 cm, in raltegravir, atazanavir and darunavir groups respectively. The results by race were +5.8, +4.0 and +2.3 for black participants compared to +3.7, +2.4 and +3.2 in non-black participants, again in raltegravir, atazanavir and darunavir groups respectively. These treatment effects continued after adjustment for lower CD4 and higher viral load at baseline which were both significantly associated with higher increases in WC ($p<0.0001$)

However, in the fully adjusted model which also corrected for multiple comparisons, only treatment group and baseline CD4 and viral load remained as predictors, with race and sex dropping out.

C O M M E N T

The results for raltegravir are surprising and difficult to understand given the DEXA substudy from the same study found no differences between treatment groups.

It would be interesting to know whether other analyses from the extensive ACTG research archive could see whether similar findings for raltegravir, integrase inhibitors or other individual drugs.

The overall association with lower baseline CD4 and higher viral load suggest that later use of ART is a higher risk for fat accumulation and that earlier use of ART might reduce incidence of fat accumulation.

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Exercise associated with significantly reduced risk of serious health problems and higher CD4 counts in large multicentre US study

Simon Collins, HIV i-Base

A large US study in over 11,000 people living with HIV reported significant benefits of exercise. [1]

These benefits included higher CD4 counts, better lipid and glucose levels and reduced incidence of heart disease and other comorbidities.

This was a prospective, longitudinal, multi-centre study, with more than 40,000 individual assessments of physical activity (PA). Approximately 11,000 people in the study had at least one assessment, with more than 8,000 people having two and more than 800 people having at least five reports.

This was a representative cohort, with approximate baseline characteristics including mean age 43 years old (range 19 to 82), approximately 80% male and 2% transgender. Roughly one-third were African American and 15% Hispanic. Mean CD4 count and viral load was >500 cells/mm^3 (+/– 280) and <200 copies/mL (+/– 1.2 log) respectively and mean weight and BMI was about 81 kg and 26.5 kg/m^2 (+/– 5).

Self-defined levels at baseline showed than more than two-thirds of the cohort had low or very low levels of PA: 26% very low (n=3058), 42% low (n=4957), 19% moderate (n=2177) and 13% high (n=1527).

Factors associated at baseline with levels of activity that were significantly lower included being women, transgender, heavier and African American; with lower CD4 counts and higher BMI, all $P<0.05$). Levels of HDL cholesterol were higher with lower triglycerides and fasting blood glucose.

In the multivariate longitudinal analysis, after adjusting for site, age, race, sex, insurance status, transmission risk, tobacco history, "d-drug" use and prescription medicines, higher PA was significantly associated with improved systolic blood pressure, HDL, triglyceride and glucose and higher CD4 count.

Low or very low PA independently predicted risk of cardiovascular disease and diabetes with risks lowering as the PA activity range increased.

Low PA consistently was linked to diagnosed cormorbidities: obesity (OR 1.9 [1.6-2.2]), cardiovascular disease (OR 2.0 [1.4-2.8]), stroke (OR 1.8 [1.2-2.7]), hypertension (OR 1.5 [1.3-1.8]), and diabetes (OR 2.5 [1.9-3.2]). Having two or more health complications was reported by 24% of those with high PA compared to 40% of those with low PA ($p<0.01$).

Of a sub group of 50 participants with a single DXA scans, 94% had excess total body fat (defined as >30%), 33% excess visceral adipose tissue and 14% had lipoatrophy. Participants with low PA and high visceral fat had the highest triglyceride and lowest HDL-C levels.

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CONFERENCE REPORTS

21st International AIDS Conference (AIDS 2016)

18 – 22 July 2016, Durban, South Africa

Introduction

We continue our reports from the 21st International AIDS Conference (AIDS 2016) that was held from 18 – 22 July 2016 in the coastal town of Durban in South Africa.

The AIDS 2016 programme is online as a searchable database.

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

Oral abstracts (but so far not the full abstract book) are available as a PDF supplement to the Journal of the IAS.

http://www.jiasociety.org/index.php/jias/issue/view/1483

http://www.jiasociety.org/index.php/jias/article/download/21264/pdf_1 (PDF download)

Although the search is good at finding abstracts, further links to webcasts, slides and poster PDFs only appear to be accessible through the online conference programme.

http://programme.aids2016.org

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

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

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- Large disparities in costs of antiretrovirals between in low- and middle income countries
- High risk of virological failure and loss to follow up postpartum in South Africa
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Four day a week ART: sub-optimal drug levels but few virological failures

Simon Collins, HIV i-Base

A poster at AIDS 2016 reported on the use of reduced-dose maintenance therapy. This French study involved only taking ART for four rather than seven days a week. [1]

The open-label, single arm, ANRS-162 4D study enrolled 100 people on ART with undetectable viral load (<50 copies/mL) for at least a year on any combination of 2NRTIs and either an NNRTI or a booster-PI. After a one week "reflection" period and four-week screen, participants then switched to taking ART for four consecutive days each week with three days off. Participants were able to choose Monday to Thursday or Tuesday to Friday.

The primary endpoint was confirmed viral rebound >50 copies/mL throughout the 48 week study or discontinuation for more than 30 days for any reason. Secondary endpoints included other safety and laboratory markers, adherence and quality of life.

The study was powered to see 80% efficacy, allowing for a maximum of 10 treatment failures, including five virological failures. An independent Data and Safety Monitoring Board (DSMB) closely reviewed virological failures in real time.

This was a largely male (81%), Caucasian (80%) group. Median age was 47 (IQR 40 to 53) who had been diagnosed for 10 years (IQR 5 to 17), on treatment for 5 years (IQR 3 to 9 years) and virally suppressed for 4 years (IQR 2.3 to 6.4).

NNRTIs were used by 71% (40% efavirenz, 26% rilpivirine and 5% etravirine) and boosted PI's by 29% (15% darunavir, 13% atazanavir and 1% lopinavir).

By week 48, viral suppression was maintained by 96% participants (95%CI: 90% to 99%). Four participants had therapeutic failure, three with viral rebound (all reporting 100% adherence) and one discontinuation linked to the reduced dose strategy.

The three cases of viral rebound – to 271, 124 and 969 copies/mL – were in people taking lopinavir/r/3TC/abacavir, efavirenz/FTC/tenofovir-DF and atazanavir/r/3TC/abacavir, respectively. All three resuppressed after switching back to full daily dosing (seven days a week). The person discontinuing treatment had a viral load <20 copies/mL and was taking efavirenz/FTC/tenofovir-DF.

Over 48 weeks, liver enzymes improved significantly (reduced ALT, AST and GGT) but other biological markers showed no significant change (renal and lipids). Self-reported adherence to the strategy and a MEMS cap sub-study showed adherence was generally high throughout.

More of a concern were the sub-therapeutic drug levels during the off-periods reported for many participants and most combinations - see Table 1. Having drug levels fall and rise through the risk concentrations when drug resistance can occur must increase the potential risk for treatment failure and drug resistance. Only efavirenz maintained mean drug levels above the therapeutic target, but the standard deviation showed many people would have dropped well below this level.

Background NRTIs might have been more important in this strategy than the choice of NNRTI or PI. Most participants were using TDF/FTC (89%) with 11% (n=11) using abacavir/3TC (and 2/3 viral failures were using abacavir). The long half-life of FTC/tenofovir-DF might therefore providing sufficient safety cover as active dual therapy, as least for much of the 3-day off periods.

A large randomised maintenance study comparing 4/7 to 7/7 dosing is planned to start in early 2017.

Table 1: ART drug levels during on/off periods

ARV	n	ON mean (SD)	OFF mean (SD)	(OFF–ON) mean change (SD)	p-value
EFV	38	2218 (1046)	692 (391)	–69% (10%)	<0.0001
ETV	5	447 (360)	269 (266)	–47% (11%)	0.0625
RPV	26	106 (51)	39 (20)	–63% (13%)	<0.0001
ATV	12	1087 (644)	52 (146)	–69% (11%)	0.0005
DRV	15	2587 (1393)	17 (18)	–99% (0)	<0.0001
LPV	1	3922	0	–100%	

Key and target minimum efficacy levels (ng/mL): EFV - efavirenz (>1000); ETV - etravirine (>50); RPV - rilpivirine >40; ATV - atazanavir (>200); DRV - darunavir >2000; LPV - lopinavir >4000.

C O M M E N T

The three cases of viral rebound show that this strategy still need much greater study before it si used outside of a research setting.

The sub-therapeutic drugs levels are setting ideal circumstances for the development of drug resistance, and not seeing such cases during follow-up might just be due to low power for a small study. An alternative explanation is that FTC/tenofovir-DF provides sufficient continued activity to limit viral rebound.

However, the results could be interpreted as showing that modern ART is likely to retain viral suppression with significantly less than 100% adherence. The results might therefore reduce anxiety associated with missed occasional missed doses in someone who otherwise has a good history of viral suppression.

While other studies have hinted that the three drugs in Atripla have sufficiently long half-lives to cover reduced dosing strategies (see 3-day Atripla study reported above and FOTO etc), the results in this study are underpowered to comment on other combinations. [2, 3]

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Large disparities in costs of antiretrovirals between low- and middle-income countries

Polly Clayden, HIV i-Base

There are still vast differences in antiretroviral prices between countries with similar Gross National Income, according to data shown at AIDS 2016.

Dzintars Gotham and colleagues from Imperial College and St Stephens AIDS Trust, London, took a further look at disparities in global HIV drug pricing. [1] Early findings from this study were presented at IAS 2013 and found that middle-

income countries outside Africa paid, on average, four times more for antiretrovirals than African countries with similar Gross National Incomes (GNI). [2, 3]

There have been substantial drops in the prices for antiretrovirals in low-income countries but these low prices are not consistent in middle-income countries with large HIV epidemics. There is no established mechanism for fair pricing in these countries and several key antiretrovirals are still patent protected.

The investigators extracted prices and transactions for originator and generic antiretrovirals used in national treatment programmes from the WHO Global Price Reporting Mechanism database (over 100 countries), and a Russian government database. They calculated median prices for each country from 2013–2015 – presented as US$ per person per year. For each drug they calculated price differences as percentage increases relative to the lowest median price for that drug.

Two originator PIs had significantly higher median prices outside sub-Saharan Africa (SSA): lopinavir/ritonavir US $360 (non-SSA) vs $232 (SSA); and darunavir US $5760 (non-SSA) vs US$ 657 (SSA).

In Russia, which, the investigators noted, was re-classified as a high-income country in 2013 but has a large untreated HIV positive population, antiretroviral prices were much higher than in SSA: TDF/FTC cost US$ 2, 313 vs US$ 39 for the NTRI co-formulation in Botswana (+5930%).

The Russian price for darunavir was US $4, 695 (rising to a shocking $ 8,675 in Azerbaijan) vs US $ 379 in South Africa (+1239%); atazanavir/ritonavir was US$ 1, 204 vs US$ 123 in Togo (+647%) and lopinavir/ritonavir US$ 1, 434 vs Central African Republic US$ 214 (+581%).

The analysis also revealed Senegal and Moldova had significantly increased prices compared with other countries from the same and outside their respective regions.

In Moldova prices ranged from +2250% to +210% of the minimum lowest prices: darunavir/ritonavir was US$ 8, 535 compared with the South African price of US$ 379; and TDF/FTC was US$ 82 compared with US$ 39 in Botswana.

In Senegal the percentage increase compared with the minimum lowest prices ranged from +387% to +180%: TDF/FTC US$ 151 compared with US$ 39 in Botswana; and abacavir US$ 203 compared with US$ 113 in Botswana.

C O M M E N T

Non-African countries continue to fare badly for low-cost antiretrovirals and once again this research group reveals stark contrasts in pricing even across countries in Africa.

Aggressive intellectual property rules could make new priority drugs like dolutegravir (although the recently announced price for the ViiV dolutegravir of US$ 400 per-person year sets a good precedence for middle-income countries) and tenofovir alafenamide completely out of reach for many people with HIV living in countries that do not bene t from low generic prices.

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

Polly Clayden, HIV i-Base

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

There are limited data on postpartum loss to follow up and virological outcomes. At AIDS 2016, Dorina Onoyal from the University of Witwatersrand presented results from a retrospective cohort study to examine the effect of timing of ART initiation before and during pregnancy on the risk of virological failure and loss to follow up in the first two years postpartum.

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

Women in the prevalent pregnancy group were more likely to be younger (52 vs 33%), have CD4 count <350 cells/mm^3 (49 vs 29%) and to be anaemic (41 vs 20%), compared to those in the incident pregnancy group. A higher proportion of women with incident pregnancies had a single unsuppressed viral load result (30 vs 26%).

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

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

Virologic failure increased with years since delivery. Women in the prevalent pregnancy group with CD4 count <350 cells/mm^3 and those in the incident pregnancy group with CD4 count >350 cells/mm^3 at delivery had faster time to virological failure.

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

Among the prevalent pregnancy group, the only predictor was a higher CD4 count (>350 cells/mm^3) at delivery, which was protective against postpartum virological failure, aHR 0.3 (0.2–0.6).

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

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

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

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

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

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

C O M M E N T

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

Reference

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

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

Reference

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High death rates among HIV positive women postpartum accessing ARVs

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

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

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

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

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

C O M M E N T

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

Reference

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Higher rates of eye complications in HIV positive people on ART

Simon Collins, HIV i-Base

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

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

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

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

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

Table 1: Eye complications in HIV positive vs negative people

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

Ref: Peters R et al. Ocular conditions are more common among HIV-infected individuals using ART for an extended period of time. AIDS 2016, Durban. Poster abstract WEPE108

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Short reports on selected Durban posters

Simon Collins, HIV i-Base

IAS conferences include thousands of posters and the majority are only displayed for a day and often only part of a day. The following summaries are from a few studies could easily have warranted oral presentations.

- Elite controllers in an African cohort
- Detecting HIV in primary infection: example of Bangkok cohort
- Rapid viral rebound in five vertically infected children with negative antibody and DNA PCR after two years on ART
- Associations between HIV and high rates of HPV infection in young MSM
- EFdA potential for annual PrEP implant
- Four day a week ART: sub-optimal drug levels but few virological failures

Elite controllers in an African cohort

Out of 245 women aged 21-33 in KwaZuluNatal, 12/245 (5%) were viraemic controllers and 2/245 (<1%) were elite controllers (EC) with viral load kept undetectable without treatment.

Both the EC had initial viraemia (12,000 and 2,000) with the first case presenting during seroconversion with symptoms but have maintained CD4 counts >500 cells/mm^3 (average 900) and undetectable viral load for more than six years without ART.

Both had HLA haplotypes well-described as being associated with slow progression, including HLA-B81* and HLA-B57* respectively. Other details, including immunological changes are reported in the poster.

The importance of this finding is that cure-related research can be run in countries with different HIV sub-types and that this inclusion is important for all cure strategies.

Ref: Moosa Y et al. HIV virological controllers in an African cohort. IDS 2016, Durban. Poster abstract TUPEA013.

http://programme.aids2016.org/Abstract/Abstract/9050 (Abstract)

http://programme.aids2016.org/PAGMaterial/eposters/0_9050.pdf (PDF poster)

Detecting HIV in primary infection: example of Bangkok cohort

From 2009 to 2015, the main community testing centre in Bangkok used viral load testing to find people who were still in primary HIV infection (PHI).

From over 9,000 people testing (and more than 21,000 tests), one third were HIV positive using rapid HIV antibody tests. Subsequent testing with either a viral load test or 4th generation AgAb test in 5,806 people with negative results was able to identify 68 people (1%) with acute HIV infection.

Median age of people in acute infection was 27 years (IQR 23 to 32) and most reported recent high risk activity. Of note, 72% of people with AHI did not report any AHI symptoms.

In the 75% with viral load results, median viral load was 5.4 log copies/mL (IQR: 3.4 to 6.8).

Ref: Leelawiwat W et al. Acute HIV-1 infection in men who have sex with men attending the clinic for voluntary counseling and testing services in Bangkok, Thailand. AIDS 2016, Durban. Poster abstract TUPEA021.

http://programme.aids2016.org/Abstract/Abstract/666 (Abstract)

http://programme.aids2016.org/PAGMaterial/eposters/0_666.pdf (PDF poster)

Rapid viral rebound in five vertically infected children with negative antibody and DNA PCR after two years on ART

Five cases were reported in a poster describing children who had been infected at birth and started ART (four within a year and one at 21 months). Viral load was undetectable in all children by 21 to 35 months of treatment.

After about two years of ART, HIV antibody and DNA PCR tests turned negative in all cases. This lead to health workers mistakenly telling the parents that their children did not have HIV.

Following the interruption for a median duration of 6 weeks, viral load rebounded to high levels in all children (range 135,000 to 8,400,000 copies/mL). CD4% dropped by up to 15% within 3 months. Treatment was re-started and all children became undetectable within 6 to 9 months and have maintained suppression for 18 to 24 months.

Ref: Mekonen T et al. Structured antiretroviral treatment interruptions in vertically HIV-1 infected children with complete pro-viral DNA PCR reversions in Namibia, following durable viral suppression, led to rapid rebound viraemias and significant immunologic destruction. AIDS 2016, Durban. Poster abstract TUPEA086.

http://programme.aids2016.org/Abstract/Abstract/3098 (Abstract)

Associations between HIV and high rates of HPV infection in young MSM

A prospective sexual health study of young gay and bisexual men in New York included 104 men provided oral samples and 99 anal samples for HPV testing as part of routine sexual health screening.

Mean age was 24 years old; 48.2% Hispanic/Latino, 32.4% Black, 9.3% White, 10.2% Asian/Pacific Islander or other race.

Prevalence was 13% for HIV, 38% for anal HPV and 6% for oral HPV (all strains).

Approximately 60% of both anal and oral HPV were high risk strains.

Additionally, 11.8% of this sample tested positive for quadrivalent vaccine strains (6,11,16,18) while 21.6% tested positive for the nonavalent vaccine strains (6,11,16,18,31,33,45,52,58).

The presence of anal HPV (any type) was associated with an HIV seropositive status (OR=5.63, 95% CI=1.44, 21.97; p=0.013) as was the presence of oral HPV (OR=12.13, 95% CI=2.37, 62.12; p=0.003).

Ref: Kapadia F et al. Associations between HPV and HIV among young, gay, bisexual and other men who have sex with men: preliminary findings from the P18 cohort study. AIDS 2016, Durban. Poster abstract TUPE211.

http://programme.aids2016.org/Abstract/Abstract/8947

EFdA potential for annual PrEP implant

Early data from using the investigational NRTI EFdA reported PrEP efficacy against oral and vaginal exposure in humanised BLT mice (bone marrow, liver, thymus).

Although this is early pre-clinical data, the results are important because EdFA is being developed as a slow-release (and removable) implant formulation that has the potential to provide therapeutic drug levels from a once-yearly implant.

Ref: Wahl A et al. HIV pre-exposure prophylaxis for women and infants prevents vaginal and oral HIV transmission in a pre-clinical model of HIV infection. AIDS 2016, Durban. Poster abstract TUPEA025.

http://programme.aids2016.org/Abstract/Abstract/9652 (Abstract)

Four day a week ART: sub-optimal drug levels but few virological failures

Available as a PDF online and reported above in HTB, this poster reported on low rebound after 48 weeks in people on stable ART who switched to taking treatment for only four consecutive days each week.

This included people on any PI or NNRTI containing combination. Although most people had suboptimal drugs levels of the PI or NNRTI component, there were few viral rebounds, highlighting the likely role of tenofovir-DF/FTC as the main background NRTIs.

Ref: de Truchis P et al. Efficacy of a maintenance four-days-a-week regimen, the ANRS162-4D trial. AIDS 2016. Poster THPEB063.

http://programme.aids2016.org/Abstract/Abstract/5947 (Abstract)

http://programme.aids2016.org/PAGMaterial/eposters/0_5947.pdf (PDF poster)

CONFERENCE REPORTS

Global HIV Clinical Forum: Integrase Inhibitors

16 July 2016, Durban

Introduction

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

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

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

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

https://vimeo.com/179309540

An additional report in this issue of HTB is:

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

Raltegravir-based third-line ART in children and adolescents

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

Reference

Musiime V et al. Response to raltegravir based third-line antiretroviral therapy among Ugandan children: A case series from an urban HIV clinic. Global HIV Clinical Forum: Integrase Inhibitors. 16 July 2016, Durban, South Africa. Oral abstract O_04.

http://regist2.virology-education.com/2016/hivforumdurban/10_Musiime.pdf

CONFERENCE REPORTS

8th International Workshop on HIV Paediatrics

15–16 July 2016. Durban, South Africa.

Introduction

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

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

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

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

Reports in this issue of HTB are:

- Raltegravir in HIV-exposed neonates
- Virological response without routine viral load monitoring in children: results from the ARROW trial
- Tenofovir-containing ART reduces bone mineral density in breast feeding women: results from IMPAACT P1084s

Raltegravir in HIV-exposed neonates

Polly Clayden, HIV i-Base

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

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

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

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

The IMPAACT P1110 study is designed to evaluate safety, pharmacokinetics (PK) and tolerability of RAL oral granules for suspension during the first six weeks of life.

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

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

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

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

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

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

The investigators performed intensive sampling around the initial 1.5 mg dose: pre-dose and 1–2, 4–6, 6–10 and 20–24

hours post dose. Between 15–18 days of life after dose increased to 3mg/kg twice daily, further samples were collected at the same time points. After the second dose, each dose change, and at weeks 5–6 of life after dose increased to 6 mg/kg twice daily, samples were collected pre-dose and two hours post dose.

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

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

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

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

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

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

C O M M E N T

The study design for RAL, using population PK and simulations to facilitate drug development in neonates is excellent.

The design is being adapted for other antiretrovirals to be studied in neonates.

Reference

Clarke D et al. Raltegravir (RAL) pharmacokinetics (PK) and safety in HIV-1 exposed neonates at high risk of infection (IMPAACT P1110). 8th International Workshop on HIV Paediatrics 15–16 July 2016, Durban, South Africa. Oral abstract O_06.

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

Polly Clayden, HIV i-Base

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

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

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

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

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

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

A total of 1206 ART-naive infants, children and adolescents started ART at a median age of 6 years (range 4 months to 17 years) with a median CD4 per cent of 12% (IQR 7–17%). Median follow up was 4 years (range 3.3–5.0) Only 5% and 4% of children with CD4 monitoring vs clinical monitoring respectively died. Only 63 (6%) switched to second-line

ART. At the close of the trial, 1132 (94%) of participants were alive and in follow up. Viral loads were available for 1127 (99.6%).

At 4 years 80% of participants randomised to 2 NRTI plus NNRTI had viral load <1000 copies/mL compared with 65% receiving 3 NRTIs. For <80 copies/mL these proportions were 74% and 52%. (Both comparisons p<0.001).

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

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

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

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

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

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

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

Reference

Prendergast A et al. Virological response and resistance among HIV-infected children on first-line therapy without routine virological monitoring. 8th International Workshop on HIV Paediatrics, 15–16 July 2016, Durban, South Africa. Oral abstract O_03.

http://regist2.virology-education.com/2016/8Pediatrics/08_Prendergast.pdf

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

Polly Clayden, HIV i-Base

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

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

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

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

Baseline characteristics were similar between the study arms: median age 26.5 years (23.3–30.0), BMI 24.7 kg (22.3–28.0), CD4 count 671.5 cells/mm^3 (544.0–857.5) and viral load 400 copies/mL (86–2289). Median time to cessation of breastfeeding was 61 weeks.

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

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

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

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

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

Reference

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

TREATMENT ACCESS

First generic version of dolutegravir approved by the FDA

Polly Clayden, HIV i-Base

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

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

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

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

C O M M E N T

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

Reference

Press Release: Aurobindo Pharma receives US FDA tentative approval for dolutegravir. 22 September 2016.

http://www.clintonhealthaccess.org/usfda-tentative-approval-dolutegravir/

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

Polly Clayden, HIV i-Base

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

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

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

C O M M E N T

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

Reference

Luiz G. Medicamento dolutegravir é nova opção do SUS para pacientes com HIV. 28 September 2016.

http://g1.globo.com/bemestar/noticia/2016/09/medicamento-dolutagravir-e-nova-opcao-do-sus-para-pacientes-com-hiv.html

Global Fund to reach US $13 billion target for 2017-2019: UK pledges up to $1.3 billion

Simon Collins, HIV i-Base

The Global Fund issued a press release at the end of the 5th replenishment conference held in Montreal on 16-17 September, reporting that US $12.9 billion was already pledged toward the target of $13 billion for 2017–2019. [1]

In a review of this announcement, Aidspan detailed some of the larger funders, noting also that the strong US dollar was working against the final pledges, when converted from some other national currencies. [2]

The US remains the largest donor pledging up to $4.3 billion, committing to match one dollar for every two dollars in pledges made by other donors through to September 2017. Canada, pledged CAD $804 million, a 24% increase over its 2013 pledge. Italy increased its pledge by 40% to €140 million and the European Commission increased its pledge by 28% to €475 million. Japan continued to pledge US $800 million which was a significant increase given the relative drop in the value of the yen. Germany increased its pledge by 33% to €800 million and France's pledge of €1.08 billion to match previous commitment.

The UK announced a pledge of £1.1 billion, with an additional matching fund of up to £200 million (targeted only for malaria). For 2014–2016, the UK contributed £800 million. This is conditional of the Global Fund meeting terms of a "performance agreement" although it is unclear why the UK should try to impose special term. [3]

Although China has the third largest economy in the world, it had only given US$15 million in 2013, and this year only offered to invest later. Denmark (pledge: 300 Danish krone) and Saudi Arabia (pledge: US $15 million) were down about 40% from their 2013 commitments. Spain has not contributed since 2010, but announced they would still be making a pledge at a later date.

Several African countries made important commitments including US $5 million from Kenya and US $5 million from South Africa. Nigeria pledged US $10 million for 2017, to be renewed each year, for a potential total of US$30 million for 2017–2019. Benin, a new donor, pledged US $2 million Namibia pledged US $1.5 million and Zimbabwe, Togo, Cote d'Ivoire, and Senegal each pledged US $1 million. [4]

The Bill and Melinda Gates Foundation made the largest private foundation pledge: matching its US $ 0.5 billion pledge for 2014-2016, and added another US $100 million later.

Comic Relief and Catholic Relief Services made pledges of US $12.8 million and US $5 million, respectively.

References

1. Global Fund press statement. Global Fund Donors Pledge Nearly $13 Billion to Help End Epidemics. (13 September 2016). http://www.theglobalfund.org/en/news/2016-09-17_Global_Fund_Donors_Pledge_Nearly_$13_Billion_to_Help_End_Epidemics
2. Global Fund Observer (GFO). The Global Fund reports pledges of US$12.9 billion at the end of the replenishment conference. (20 September 2016). http://www.aidspan.org/node/3906
3. UK Government policy paper. Performance Agreement: UK and the Global Fund to fight Aids, Tuberculosis and Malaria. (17 September 2016) https://www.gov.uk/government/publications/performance-agreement-uk-and-the-global-fund-to-fight-aids-tuberculosis-and-malaria
4. Global Fund press release. African Countries Step Up Contributions to the Global Fund. (19 September 2016). http://www.theglobalfund.org/en/news/2016-09-16_African_Countries_Step_Up_Contributions_to_the_Global_Fund

ANTIRETROVIRALS

First generic TDF/FTC approved in EU

Simon Collins, HIV i-Base

On 15 September 2016, the European Medicines Agenecy (EMA) noted a positive summary of opinion for the first generic combination of tenofovir/emtricitabine. [1]

The notice came from the Committee for Medicinal Products for Human Use (CHMP) who have adopted a positive opinion, recommending the granting of a marketing authorisation for tenofovir disoproxil Zentiva/emtricitabine, produced by the Czech-based generic company Zentiva, which has been owned by Sanofi-Aventis since 2008. [2]

Zentiva will be available as 200 mg/245 mg film-coated tablets.

Emtricitabine/tenofovir disoproxil Zentiva is a generic version of Truvada which has been authorised in the EU since 21 February 2005. Studies have demonstrated bioequivalence to the reference product Truvada.

The full indication is: "Emtricitabine/tenofovir disoproxil Zentiva is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults".

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

Summaries of opinion are usually formally approved by the EU within two months.

C O M M E N T

The implications for use of this combined generic in the UK are unclear, but when available this would enable use as treatment and PrEP.

Zentiva did not reply to an email asking about proposed marketing in the UK and related pricing.

References

1. EMA Committee for Medicinal Products for Human Use (CHMP). Emtricitabine/tenofovir disoproxil Zentiva, Summary of opinion (initial authorisation). EMA/CHMP/596525/2016. (15 September 2016).
   http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004137/WC500212887.pdf
2. Sanofi, Zentiva in $2.6B buyout. (22 September 2008).
   http://www.fiercepharma.com/pharma/sanofi-zentiva-2-6b-buyout
   http://www.sanofi.co.za/l/za/en/layout.jsp?scat=DD324295-1B29-40E8-B280-7A2EB627CB94

Single-pill PI-based combination submitted to EMA

Simon Collins, HIV i-Base

On 12 September 2016, a press statement from Janssen reported that the company have submitted an application to the European Medicine Agency (EMA) for a single pill PI-based combination.

This formulation includes darunavir (800 mg), cobicistat (150mg), emtricitabine (200 mg) and tenofovir alafenamide (10 mg). Tenofovir alafenamide (TAF) is the new version of tenofovir- DF.

The indication is for treatment of adults and adolescents (aged 12 years and older with body weight of at least 40 kg).

C O M M E N T

The potential benefits of this new formulation will depend on it being priced comparable to a combination with the NRTI component being similar to generic alternatives.

Reference

Janssen Submits Marketing Authorisation Application for Darunavir-Based Single Tablet Regimen for Treatment of HIV-1 to European Medicines Agency. (12 September 2016).

http://www.janssen.com/janssen-submits-marketing-authorisation-application-darunavir-based-single-tablet-regimen-treatment

Dolutegravir superior to standard dose efavirenz in WHO analysis

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

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

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

At 48 weeks the mean difference in CD4 count was about 20 cells/mm^3 with all three INSTI compared with standard dose efavirenz. Low dose efavirenz was also superior to standard dose with a mean difference of approximately 25 cells/mm^3.

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

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

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

They explain that in the SINGLE trial, the virological failure rate was actually slightly higher for dolutegravir (10%) than efavirenz (7%). There were more discontinuations for adverse events or other reasons in the efavirenz group (30%) than the dolutegravir group (18%) and a small non-significant risk resistance between the groups.

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

C O M M E N T

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

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

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

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

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

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6. Make medicines affordable.
   http://makemedicinesaffordable.org/en/home

TREATMENT GUIDELINES

US DHHS guidelines updated (July 2016)

Simon Collins, HIV i-Base

The leading US DHHS treatment guidelines were updated in July 2016.

Main changes include:

- Updated to include new drugs and formulations, all with TAF instead of TDF.
- In general, TAF is recommended whenever TDF is recommended.
- Small changes include references to universal use of resistance tests before starting ART. This is based on 10-17% of new diagnoses in the US including resistance to at least one drug. ART should not be delayed while waiting for the results of these tests.

  Testing for integrase inhibitor resistance is not needed in most circumstances.
- The guidelines note that a new commercial test (GenoSure) is available to test cell-associate HIV DNA (ie for people with undetectable viral load) but that there is insufficient data to recommend use. (See: http://www.monogrambio.com/hiv-tests/suppression-management/genosure-archive).

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Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. July 2016.

https://www.aidsinfo.nih.gov/guidelines

CURE RESEARCH

HIV persistence: defective virus copies accumulate rapidly after infection

Richard Jefferys, TAG

A major challenge in measuring the reservoir of HIV that persists despite antiretroviral therapy (ART) is that many of the virus genomes that can be found integrated into the DNA of CD4 T cells are incomplete or mutated in ways that preclude further rounds of replication.

For researchers aiming to develop a cure, it is important to try and distinguish between defective virus copies and intact viruses capable of rekindling the infection when ART is interrupted.

A new study from the laboratory of Robert Siliciano, published in the latest issue of *Nature Medicine*, attempts to assess the proportions of defective and replication competent HIV in people on ART, comparing individuals who began treatment very early after infection to those who started later. [1]

Siliciano and colleagues used genetic sequencing techniques to measure the number of intact HIV DNA sequences in ten individuals who started ART more than 180 days after infection, and compared the results to a cohort of nine people who started within 100 days of infection (most had begun within 60 days).

The researchers were surprised to find that defective copies of HIV accumulated rapidly: in the early-treated individuals, only 7% of the HIV DNA copies that could be detected were intact. In the cohort that initiated ART during chronic infection, the proportion of intact viruses was expected to be lower and that proved to be the case: only 2% of virus genomes were complete, and 98% of the HIV DNA in this group was defective.

The average size of the replication competent HIV reservoir was estimated to be 12 infectious proviruses per million resting CD4 T cells in the early-treated group compared to 37 infectious proviruses per million resting CD4 T cells in the individuals who began ART later, although the researchers note there was "substantial person-to-person variation." These data appear to suggest that the impact of early ART on the size of the HIV reservoir may not be as dramatic as had been thought, but there are some caveats:

- While most of the early-treated cohort began ART within three months of infection, other studies attempting to ascertain the effect of early treatment on the size of the HIV reservoir have included individuals who initiated ART within a matter of days. The techniques used in this paper have yet to be applied to measuring the reservoir in such ultra-early-treated people.
- A difference of 12 vs. 37 infectious proviruses per million resting CD4 T cells may seem relatively slight, but a threefold larger HIV reservoir may be more significant when you consider the whole body (which has been estimated to contain 1.9 – 3.5 trillion lymphocytes). [2]
- The differences in the total amount of HIV DNA detectable in the early vs. later treated cohorts are far greater than was observed for intact proviruses. In the examples provided in the paper, the amount of HIV DNA detectable in the early-treated group ranges from 72-315 copies per million resting CD4 T cells, compared to 1,333-9,785 copies per million resting CD4 T cells in the individuals treated later. While the DNA mostly represents defective virus copies, they are not necessarily benign.

  A recent study from the laboratory of Anthony Fauci at NIAID found that at least some defective proviruses can still produce HIV proteins and therefore potentially contribute to persistent inflammation and immune activation in HIV-positive people. [3]

  A separate study, also published recently, found HIV DNA in multiple tissues evaluated at autopsy and reported that there appeared to be an association with tissue pathology. [4]

  Measures of total HIV DNA have also shown correlations with various clinical parameters in HIV-positive people, as outlined in a new review by Christine Rouzioux and colleagues. [5]

The study results underscore that, despite a great deal of effort, the optimum method for measuring the replication-competent HIV reservoir remains unknown. The current gold standard is the quantitative virus outgrowth assay (QVOA), but this requires the sampling and activation of very large numbers of cells and is expensive and time consuming.

Furthermore, the Siliciano laboratory found that levels of intact HIV DNA sequences (which they suggest represent "probably the closest estimate of the true size of the latent reservoir") did not correlate with results obtained by QVOA.

The development of accurate and reliable tests for measuring the HIV reservoir continues to be a major priority for the HIV cure research field.

Source

TAG Basic Science Blog. (14 September 2016).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2016/09/hiv-persistence-defective-virus-copies-accumulate-rapidly-after-infection.html

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HIV PREVENTION

PrEP update: EU approval, extended access for PROUD participants, TAF studies underway

Simon Collins, HIV i-Base

It has been a busy time for PrEP.

TDF/FTC approved as PrEP in Europe

On 22 August 2016 the European Medicines Agency (EMA) finally granted approval for tenofovir DF/emtricitabine to be used as PrEP. [1]

As noted in the previous issue of HTB, this has come four years too late – following initial active blocking by the EMA. [2]

The new marketing authorization allows use of TDF/FTC as PrEP in all 28 countries of the European Union, subject to national regulatory authority approval of required pharmacovigilance materials in each country.

In addition to the European Union, Truvada is also authorised for PrEP in Australia, Canada, Kenya, Peru, South Africa and the United States.

Update on NHS England commissioning

The formal 45-day community consultation for NHS England to decide on PrEP ended in mid-September, with responses likely to run into several hundred submissions.

NICE is likely to formally publish results from the review in October and the results from the appeal by NHS England to the judicial review (that found the NHS has the authority to commission PrEP) is expected later in the month.

Gilead reverses decision to allow extended access to PrEP for participants in PROUD study

On 2 September 2016, Gilead announced that participants in the UK PROUD study would be able to access PrEP for an additional three months. [3]

Earlier this year, when it became clear that NHS England were extending the timeline for considering access to PrEP, Gilead had refused appeals to provide additional PrEP to cover this shortfall.

This welcome change by Gilead is likely a result of continued pressure from the PROUD researchers and other community responses.

TAF PrEP studies underway in US: UK sites due to join shortly providing other access to PrEP

A large international double-blind phase 3 placebo controlled study will randomise 5000 HIV negative people to either TDF/FTC or TAF/FTC. Some US sites are already enrolling and 12 UK sites are planned. [4]

The primary endpoint for this study with a new formulation of TDF will be the number of new infections at 48 weeks, plus numerous secondary endpoints.

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ON THE WEB

Conference materials and online publications

HIV Reservoir Characterisation Symposium

Abstract from this workshop held on 19 September 2016 in Ghent.

http://viruseradication.com/journal-details/Abstracts_of_the_HIV_Reservoir_Characterization_Symposium

Topics in HIV Medicine: CROI 2016 summaries

The May/June 2016 of IAS-USA's Topics in HIV Medicine is online free with comprehensive summaries report from CROI 2016.

https://www.iasusa.org/tam/may-june2016

Basic Science Review - Stevenson M.

Hot Spots in HIV Infection and Advances in HIV Prevention - Buchbinder SP and Liu AY.

Neurologic Complications of HIV Infection - Spudich SS and Ances B.

Complications of HIV Infection and Antiretroviral Therapy - Havlir DV and Currier JS.

Viral Hepatitis and Liver Fibrosis - Luetkemeyer AF and Wyles DL.

Advances in Antiretroviral Therapy - Taylor BS et al.

Journal of the IAS: special issue on PrEP

Produced to coincide with the opening of the Treatment for Prevention (R4P) conference being held in Chicago in October 2016.

http://www.jiasociety.org/index.php/jias/pages/view/special#supplements

Transgender populations and HIV: unique risks, challenges and opportunities

Wansom T, Guadamuz TE and Vasan S.

http://viruseradication.com/journal-details/Transgender_populations_and_HIV:_unique_risks,_challenges_and_opportunities/

Due to unique social, behavioural, structural and biological issues, transgender (TG) populations, especially TG women, are at high risk for HIV acquisition.

This increased risk is multifactorial, due to differing psychosocial risk factors, poorer access to TG-specific healthcare, a higher likelihood of using exogenous hormones or fillers without direct medical supervision, interactions between

hormonal therapy and antiretroviral therapy, and direct effects of hormonal therapy on HIV acquisition and immune control.

Further research is needed to elucidate these mechanisms of risk and to help design interventions to reduce HIV risk among transgender populations.

HIV in primary care – an essential guide for GPs, practice nurses and other members of the primary healthcare team.

MEDFASH

HIV in Primary Care: an essential guide for GPs, practice nurses and other members of the primary healthcare team. Third edition by Dr Philippa Matthews, Dr Sara Madge, Dr Surinder Singh and Dr Nick Theobald. With forewords by Professor Maureen Baker, Chair of Council, Royal College of General Practitioners, and Silvia Petretti, Deputy Chief Executive, Positively UK.

Revised and updated for 2016, this 128-page booklet provides essential information about HIV for GPs and the primary healthcare team, specifically: the clinical diagnosis of HIV in primary care (with photos), how to offer an HIV test and give results, primary healthcare for people with HIV including reproductive health and immunisation, how to complement HIV specialist care, and practice policies and systems. It concludes with a quick reference guide to antiretrovirals, drug interactions and side effects, managing HIV-related problems, information for patients and a list of useful HIV and sexual health organisations and websites.

HIV in Primary Care is instructive, practical and easy to use with a comprehensive index and full colour illustrations.

Printed copies of the new edition can be obtained from MEDFASH at £12 per copy (bulk discounts available) by contacting: enquiries@medfash.bma.org.uk, or the pdf version can be downloaded for £5.

http://www.medfash.org.uk/publications

FUTURE MEETINGS

Conference listing 2016

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

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

7th BHIVA Conference for the Management of HIV/Hepatitis Co-infection

12 October 2016, London

http://www.bhiva.org

BHIVA Autumn Conference 2016

13–14 October 2016, London

http://www.bhiva.org

HIV Research for Prevention Conference (HIVR4P) 2016

17-20 October 2016, Chicago

http://www.hivr4p.org

European HIV Clinical Forum: Integrase Inhibitors

22 October 2016, Glasgow

http://hiv-forum.com

Congress on HIV Therapy (Glasgow 2016)

23-26 October 2016

http://hivglasgow.org

24th Conference on Retroviruses and Opportunistic Infections (CROI 2017)

13-16 February 2017, Seattle

23rd Annual Conference of the British HIV Association (BHIVA)

4–7 April 2017, Liverpool

http://www.bhiva.org

9th IAS Conference on HIV Science

23-26 July 2017, Paris, France

http://www.ias2017.org

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

6-8 November 2017, Johannesburg

http://www.HIVresistance2017.co.za

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

All i-Base publications are available online, including editions of the treatment guides.

http://www.i-Base.info

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

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

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

i-Base treatment guides

i-Base produces six booklets that comprehensively cover important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

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

- NEW: Introduction to ART (September 2016)
- NEW: HIV & quality of life: side effects & long term health (Sept 2016)
- NEW: Guide to PrEP in the UK (June 2016)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)

Three new pocket guides: ART, pregnancy and side effects

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

The first three pocket leaflets are on (i) Side effects and Quality of Life (ii) HIV and pregnancy and (iii) Into to ART.

We hope these are especially useful as a low literacy resource. The leaflets use simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

Order publications and subscribe by post, fax or online

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

http://i-base.info/order

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