

HIV treatment bulletin

S O U T H

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htb south

HIV Treatment Bulletin South

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To order copies send an email to: subscriptions@i-Base.org.uk

Editor: Polly Clayden

Contributing Editor: Simon Collins

Medical Consultants:

Dr Karen Beckerman, Albert Einstein College of Medicine. New York.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Paul Blanchard, British School of Osteopathy, London.

Dr Martin Fisher, Brighton & Sussex University Hospitals.

Prof. Diana Gibb, Medical Research Council, London.

Dr Gareth Hardy, Case Western Reserve Univ. Cleveland.

Dr Saye Khoo, University of Liverpool Hospital.

Dr Leigh Johnson, University of Cape Town.

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Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

Prof Francois Venter, RHRU, Johannesburg.

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We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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HIV i-Base

Fourth Floor, Thrale House

57 Great Suffolk Street, London SE1 0BB

T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489

<http://www.i-Base.info>

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HIV Treatment Bulletin was formally known as DrFAX

EDITORIAL

This issue leads with the most important and exciting research from the IAS conference in Rome and the 3rd International Workshop on HIV Pediatrics immediately preceding it. Our reports in this issue include an overview of the conference in the Introduction.

We conclude our reports from CROI this year and include exciting news on treatment access due to Gilead entering an agreement with the Medicines Patent Pool.

New recently approved drugs (in the USA) include the new NNRTI rilpivirine and a new triple drug fixed-dose combination of rilpivirine/tenofovir/FTC.

We also launched the i-Base/TAG 2011 pipeline report at IAS in Rome that updates the pipeline development of all important drugs, diagnostics and treatment strategies for HIV, hepatitis and TB. Please see below for details.

Southern African HIV Clinician's Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinician's Society has grown to a membership of over 15,000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

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

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

For more information about the Society or on how to become a member please visit:

<http://www.sahivsoc.org>

Tel: + 27 (011) 341 0162

Fax: +27 (011) 341 0161

HTB SUPPLEMENT

2011 pipeline report

For the second year i-Base have collaborated with TAG to produce the annual pipeline report.

This report covers the most recent and exciting developments in HIV, hepatitis and TB research.

The report was launched at the IAS conference in Rome but if you missed a print copy there, you will need to go online.

At 160 pages we are going green this year and publishing this in the UK as web articles and PDF file, although a limited print run of a second edition will be produced by TAG in the US.

Sections include:

- Introduction and executive summary
- Dedication
- The antiretroviral pipeline
- The paediatric antiretroviral pipeline
- HIV point of care diagnostics pipeline
- Patents and the pipeline: is access under threat?
- Preventive technologies, immune-based and gene therapies, and research toward a cure
- The hepatitis C treatment pipeline
- The tuberculosis diagnostic, treatment and vaccine pipelines

The report is dedicated to Dr Robert Carr and David Kato Kisule.

CONFERENCE REPORTS

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention

17–20 July 2011, Rome

Introduction

The biannual IAS Conference on HIV Pathogenesis, Treatment and Prevention is more scientifically focused than the World AIDS Conference held in alternate years and is considerably smaller. This makes both attending and reporting more manageable and concentrated.

This year the conference was held in Rome. While plenary lectures were held in the concert halls designed by Renzo Piano (the architect designing the Shard Tower in London), smaller meetings were often in rooms with a capacity of only 50 people and the poster and exhibition halls were less than ideal, being held in the venues garages.

Even prior to the conference, the frenzy to gain media coverage filled email boxes with press releases that made it clear that the meeting would be dominated by prevention studies.

The leading prevention reports, first and most importantly, involved the reduction in transmission from use of HIV treatment for HIV-positive people. The risk is not reduced to zero, but it is getting close, especially when condoms remain the mainstay of prevention work. It means that if a condom breaks, slips off, or is not used at all, an HIV positive person who has had an undetectable viral load for over six months would find it difficult to transmit HIV.

The shift in medical consensus is dramatic. While the Swiss Statement three years ago was met with anger publically from many prominent doctors, in private most also recognised that viral load was the driving factor behind transmission risk. It was good to hear Pietro Vernazza who authored the Swiss paper ask Myron Cohen after presenting the results of HPTN 052 on whether Cohen's new results had prompted a change of heart.

IAS in Rome included four oral presentations from the HPTN 052 study. Together they showed that HIV-positive people in high incidence resource limited settings (predominantly Africa, Asia and Latin America) who started treatment at a CD4 count of 350-550 reduced the risk of transmitting HIV to their HIV-negative primary partner by 96% compared to people waiting until their CD4 count was 250. This was a study that intensely integrated other prevention strategies - condom provision and counselling reduced transmission too, but treatment extended this significantly further.

The second way that treatment reduces transmission was supported by new studies reporting the benefits of PEP/PrEP strategies. These involved HIV negative people taking a daily pill of tenofovir/FTC, or tenofovir alone, which led to reductions in their risk of catching HIV.

As with previous meetings, the conference has an open-access searchable abstract database online.

<http://www.ias2011.org/>

However, many oral presentations are not included as webcasts or PowerPoint slides.

The 'Programme at a glance' can be searched for key words but requires a free software upgrade Silverlight which is quick and easy to do. Then from this page you can search abstracts or presentations.

<http://pag.ias2011.org/>

Sessions with PowerPoint slides or webcasts have relevant icons next to them. As with previous years, the PowerPoint links on the left under the session time are not active, so to download PowerPoint files scroll down to the bottom of the session page

We have also included reports from the 3rd International Workshop on HIV Pediatrics immediately preceding IAS 2011. This small annual meeting is becoming quite established and although abstracts are often submitted to both meetings, in this one they may often get an oral presentation instead of just a poster. For those specialising in paediatrics this meeting is a welcome opportunity to present and discuss work in a dedicated forum. Abstracts and presentations are online. We have included references from both meetings in our paediatric reports.

http://regist2.virology-education.com/abstractbook/2011_8.pdf

http://regist2.virology-education.com/2011/3HIVped/15_July.html

Reports in this issue of HTB include:

- Treatment is prevention: ARV treatment in HPTN-052 reduces transmission by at least 96%: single transmission in treatment arm occurred prior to viral suppression
- Daily oral tenofovir/FTC PrEP reduces heterosexual transmission by 63% in the TDF2 study
- Tenofovir/FTC vs tenofovir as daily oral PrEP: preliminary results from Partners PrEP
- Elvitegravir vs raltegravir: 48 week results in treatment-experienced patients
- Dolutegravir: 48 week results from phase II study in treatment-naïve patients
- Lersivirine: 48 week results compared to efavirenz in Phase II treatment-naïve study
- SPARTAC trial: treatment in primary infection for 48 weeks shows small delay in disease progression
- Hearing loss not associated with HIV in MACS and WIHS cohorts
- Pharmacokinetics of darunavir and fosamprenavir in pregnancy
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- No difference in AIDS-free survival in children starting ART with a CD4% between 15%–24% compared to deferring until less than 15% in the PREDICT trial
- Paediatric antiretroviral pipeline: update on etravirine and maraviroc

- More metabolic abnormalities in children receiving a PI compared to NNRTI in NEVEREST study
- Prematurity not associated with early mortality in infants on ART
- Free online resource for treatment decisions without access to genotype resistance tests

Unless stated otherwise, all references are the Programme and Abstracts of the 16th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17–20 July 2011, Rome.

Webcasts for major research at IAS

This years meeting had three main areas of interest.

Firstly, treatment as prevention – most notably in a study called HPTN-052 and PrEP studies. The *Treatment Is Prevention* session include links to abstracts, slides and webcasts from the HPTN-052 study.

<http://pag.ias2011.org/session.aspx?s=98>

Secondly, research relating to reservoirs, eradication and the cure was established throughout the programme. This included overviews of the different ways that this could be approached and preliminary results for early potential targets. Unfortunately very few of the lectures in these sessions are webcast. However, the overview by Anthony Fauci, is online and worth watching to understand the new strengthening steer from the US that dominates global research.

Tony Fauci: 30 years of HIV/AIDS: a scientific journey and a look to the future

<http://pag.ias2011.org/flash.aspx?pid=409>

Towards an HIV cure: insight into residual viral replication, establishment of reservoirs and understanding mechanisms of persistence

<http://pag.ias2011.org/session.aspx?s=70>

Towards an HIV cure: new strategies for an old challenge

<http://pag.ias2011.org/session.aspx?s=15>

Controversies in HIV cure research satellite meeting

<http://pag.ias2011.org/session.aspx?s=39>

Thirdly, there were important studies about New drugs and diagnostics and new strategies with oral presentations on new integrase inhibitors (elvitegravir and dolutegravir) and NNRTIs (lersivirine), using of HSV drugs (acyclovir/valacyclovir) and currently approved meds (maraviroc/atazanavir). Plus, also in the late breaker session, an exciting new rapid antibody test for cryptococcal meningitis developed in the UK that can be used at the point of care. These were presented mainly in the following two sessions.

New drugs and strategies

<http://pag.ias2011.org/session.aspx?s=55>

Late breaker Track B

<http://pag.ias2011.org/session.aspx?s=44>

6th IAS: PREVENTION

Treatment is prevention: ARV treatment in HPTN-052 reduces transmission by at least 96%: single transmission in treatment arm occurred prior to viral suppression

Simon Collins, HIV i-Base

Four of the six oral presentations in the ‘Treatment is prevention: the proof is here’ session reported on the results from HPTN 052. [1] This study had been unblinded four years earlier than planned due to a review by the data and safety monitoring board (DSMB), with all patients now being offered active treatment.

In summary, HIV-positive people on treatment had a 96% reduction in sexual transmission to their HIV-negative partners if they started ARVs with a CD4 count of 350-550 cells/mm³ compared to waiting until it dropped below 250 cells/mm³. As with all prevention studies, condoms, testing and intensive counselling was included throughout the study.

The main study results were presented by Myron Cohen from University of North Carolina. [2]

HPTN 052 screened over 10,000 couples in order to randomise 1763 HIV-positive people with CD4 counts 350-550 to either immediate or delayed HIV treatment (CD4 confirmed <250 or an AIDS-defining illness). Screening failure was mostly due to CD4 or other criteria in the positive partner, but 300 couples were already both HIV-positive. This was an international study predominantly recruiting in Africa (Botswana, Kenya, South Africa and Zimbabwe, n=954), Asia (India and Thailand, n=531) and Latin America (Brazil, n=276). Men and women were equally distributed as the positive partners. Median baseline CD4 count was 436 cells/mm³ (IQR 365-522) and viral load was approximately 25,000 copies/mL (IQR 6,000-80,000) respectively.

This was generally a low risk population with only 6-8% reporting recent unprotected sex and only 16% aged 18-25 years (~60% were 25-40 years and ~20% >40 years).

The primary transmission endpoint was the prevention of virologically linked transmissions with a primary clinical endpoint of WHO Stage 4 events (including pulmonary TB, severe bacterial infections and death).

Transmission events (n=39) occurred significantly less frequently in the immediate (n=4) compared to the deferred (n=35) treatment arms, p<0.0001. Of these, only 28/39 were linked transmissions (within the couple) with 1 case in the immediate arm vs 27 cases in the deferred arm, p=0.001 (see below for details). Eleven transmissions were either unlinked or undetermined. This translated to incidence rates of linked transmission of 0.1 (95%CI 0.00-0.04) vs 1.7 (95%CI 1.1-2.5) per 100 person years respectively over a median follow-up of 1.7 years.

The single transmission in the immediate treatment arm was detected at the first follow-up visit. However viral diversification analysis estimated that transmission occurred prior to the positive partner initiating treatment (baseline 87,000 viral load) or certainly prior to viral suppression to <400 copies/mL which was recorded at day 28.

Other transmission risk factors were similar between arms, including rates of STIs (low at <5% in both index and partner at baseline and during the study), sexual activity (approximately 70%) and condom use (>90% by all throughout).

Viral suppression (<400 copies/mL) was maintained by >90% of participants in the immediate arm. There was a slow increase in this percentage over time in the deferred arm as people started treatment (from <10% over the first year, 20% by month 24 and increasing to 50% at month 45, though with much fewer patients). The median viral load closest to the time of transmission in the deferred arm was considerable at 80,000 copies/mL but had a wide range from 600 to 630,000 copies/mL.

In multivariate analysis, treatment was the strongest protective effect [HR=0.04, 95%CI 0.01-0.28] compared to condom use [HR=0.33; 95%CI 0.12-0.91]. Factors associated with increased transmission included baseline viral load [per log increment: HR 2.84, 95%CI 1.51-5.41] and baseline CD4 count [per 100 count increment: HR 1.24 95%CI 1.00-1.54].

Table 1: Key demographics and results from HPTN 052

	Immediate (n=886)	Deferred (n=877)	
Baseline CD4 med (IQR)	442 (373-522)	428 (357-522)	
Baseline viral load med (IQR)	4.4 (3.8-4.9)	4.4 (3.9-4.9)	
Age (index partner)	33	32	
Married	94%	95%	
Any unprotected sex	6%	8%	
Linked transmissions (n)	1	27	HR 0.04 (95%CI 0.01-0.28)
WHO Stage IV events, pulmonary tuberculosis, severe bacterial infection or death (n=pts)	40 (2.4 per 100 PY)	65 (4.0 per 100PY)	HR 0.59, 95%CI: (0.40, 0.88), p=0.01
TB (n=events)	17	33	
Extrapulmonary tuberculosis (n)	3	17	p< 0.002
Deaths	10	13	HR 0.77, 95% CI: (0.34, 1.76), p>0.5
Adverse events	24%	5%	

The second presentation by Susan Eshelman from Johns Hopkins University School of Medicine focused on the analysis of linked transmission. [3] This included a helpful introduction to the three types of phylogenetic analyses used: phylogenetic analysis of HIV pol sequences using population sequencing, and statistical analysis of genetic distances from pol sequence

pairs for the clearest cases (n=26), and phylogenetic analysis of env sequences obtained by deep sequencing for more complex cases (n=12). Together these provided a high level of reliability for identifying whether the source of new infections was the HIV-positive partner or whether this was from another partner.

Transmissions in previous serodifferent couple studies have been from outside the main relationship in 25-50% cases.

The deep sequencing ('ultradeep pyrosequencing') supported linked two further cases and confirmed non-linkage for seven others (4 in the immediate and 3 in the deferred arm). Three cases remained unidentified (all in the deferred arm). Transmission linkage was not associated with index partner gender or CD4 count, geographical regions or time on study but this was strongly associated with study group and number of sexual partners in the three months prior to new seroconversions.

Results on the clinical outcomes for the HIV-positive participants in HPTN 052 were presented by Mina Hosseinipour from the UNC Project, Malawi. [4]

Results comparing the two groups were presented as ITT analyses and included the approximate 20% (184/877) people randomised to the deferred arm who started treatment during follow-up.

Over two years, median CD4 counts increased from 442 to 662 cells/mm³ in the immediate group compared to reducing from 428 to 390 cells/mm³ in the deferred arm. These differences are blunted as the deferred arm includes the response for the 20% people who started treatment. Viral suppression was achieved and maintained <400 copies/mL by >90% of the immediate arm. Less than 5% of patients on immediate treatment experienced virological failure during follow-up with most (60%) of these switching to a second-line combination.

The decision to start treatment in the deferred arm was driven by CD4 declines in 75% of cases. This occurred at a median count of 225 cells/mm³ (IQR 199–247), with 25% over people not starting until their CD4 count was less than 200. Treatment in both arms was predominantly AZT/3TC/efavirenz (70%) with ~10% using AZT/3TC/atazanavir, and ~10% using tenofovir/3TC/efavirenz. CD4 responses in the deferred arm were similar to absolute increase in the immediate treatment arm but remained significantly lower at all timepoints, reflecting the lower counts when starting treatment. Although there are fewer patients with longer duration of follow-up in the deferred arm, other studies have reported that baseline CD4 correlates with CD4 response after treatment.

The analysis by geographical region reported that about 80% of both the linked and unlinked transmission events occurred in African sites, likely a reflection of the higher background population prevalence rates in those countries, although the researchers highlighted higher rates of unprotected sex in the last week (by 9% vs 4% of African vs non-African) and higher sexual activity (>3 acts). However, baseline CD4 count, viral load and adjusted time to initiation, median adherence (99%) and treatment responses were similar between African and Asian sites.

Further details on clinical outcomes were presented by Beatriz Grinsztejn from the Oswaldo Cruz Foundation, Rio de Janeiro. [5]

Primary clinical events occurred at least once in 105 participants over 3304 person-years (PY) of follow-up; 40 in the immediate

arm (2.4/100PY) and 65 in the delayed arm (4.0/100PY), hazard ratio (HR) 0.59, 95% CI: (0.40, 0.88), p=0.01. Seventeen people experienced more than one event. Time to event was significantly shorter in the deferred arm (HR 0.6, 95%CI 0.4, 0.9, p=0.01)

CD4 counts were significantly higher in the immediate arm vs deferred arms for all clinical endpoints (TB 518 vs 316; bacterial infection (mainly pneumonia) 551 vs 337 and death 476 vs 372 cells/mm³ respectively).

The between-arm difference was driven by extrapulmonary tuberculosis with 3 cases in the immediate versus 17 cases in deferred arms (p< 0.002). These were peripheral lymph nodes (2 vs 4), abdominal (0 vs 8), pleural (1 vs 3), skeletal (0 vs 1) and meningeal (0 vs 1). Isoniazid prophylaxis was only being used by 4% of patients in each arm at baseline.

Of the 23 deaths observed, there was no difference between arms: 10 in the immediate arm and 13 in the delayed arm [HR 0.77, 95% CI: (0.34, 1.76), NS p>0.5]. Causes of death were similar, but with 3 vs 3 suicides; 0 vs 2 accidents; and 3 vs 6 unknown).

Adverse events potentially related to ART were reported in 24% of subjects in the immediate arm and 5% in the delayed arm, but severe or life-threatening events occurred equally in 14% of each group and grade 4 lab events were also similar (in <1-2% of participants).

Since the DSMB recommendation in April 2011, all participants in the deferred arm have been offered HAART based on the strength of the study findings. This study continues to monitor all participants and results will add to clinical data from use of earlier vs later treatment in people with CD4 counts >350 cells/mm³.

COMMENT

These results add to research that not only correlates viral load with risk of sexual transmission but specifically demonstrates a protective impact with treatment. The two cases of transmission in the early treatment arm (a second was discussed during the presentation) were both detected at the beginning of the study prior to the positive person reaching suppressed viraemia <400 copies/mL.

The fewer clinical endpoints from earlier treatment for the HIV-positive partners in this study are important but were driven by extrapulmonary TB. This clinical difference has significance for people in geographical regions where this study was run, but this aspect of the results was unexpected and has yet to be explained. A more generalisable benefit to people in Western countries is probably the reduced CD4 response in the deferred arm and this needs to be supported by longer follow-up. The ongoing START study will report on whether clinical benefits result from earlier treatment in Western countries.

It would be interesting to model the potential number of transmissions that have already been prevented over the last ten years from the seven million people globally on HAART. Given the financial constraints of access to treatment the additional impact on prevention should be included in future cost: benefit analysis.

The results from HPTN 052 clearly support offering an option for treatment to HIV-positive people who have HIV negative partners. This has been included in UK (BHIVA) guidelines for many years.

When access to treatment is limited with a waiting list using CD4 upper cut-offs to access treatment, those with the most severe medical should clearly be prioritised. However, the majority of the nine million people currently identified by UNAIDS and WHO analyses as requiring but not yet able to access treatment are likely to be undiagnosed. Broadening the CD4 criteria for access to treatment as prevention at higher CD4 counts is unlikely to directly deny access to treatment for more advanced patients.

It was unfortunate that a WHO guideline due to be launched at the IAS meeting, that included the recommendation for treatment people with CD4 counts higher than 350 and who have HIV-negative partners, based on the HPTN 052 study was withdrawn at the last minute. [6]

Although printed for a launch at the conference there is concern that while the scientific evidence is clear – and this should be the focus for clinical guidelines – practical issues on implementation have stalled their release perhaps under pressure from prominent WHO funders. It is difficult to understand how such a useful document that included broad community consultation and approval to the stage of print would have been retracted at such a late stage. WHO say this is due to a need to make “small modifications” and “to review their modeling data they used to inform investment structures”. The timeline for these changes are 2-3 months.

This plausibility for intervention from outside the extensive WHO guidelines writing and advisory panels is supported by an article in Science magazine that names the Gates Foundation specifically related to their interest in the latest PrEP results also being included. [7]

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Unless stated otherwise, all references are the Programme and Abstracts of the 16th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17–20 July 2011, Rome.

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Daily oral tenofovir/FTC PrEP reduces heterosexual transmission by 63% in the TDF2 study

Simon Collins, HIV i-Base

Results from the double-blind placebo-controlled TDF2 study presented in an oral presentation in Rome provided additional supportive data for the benefit of daily oral tenofovir/FTC (Truvada) to reduce sexual heterosexual transmission. [1]

While the iPrEX study first reported a strongly protective impact in high risk MSM, the lack of protection in the FemPrEP study earlier this year has still to be explained. [2, 3]

TDF2 randomised 1200 sexually active HIV-negative adults (age 18-49: approximately 90% were between 21-29 years) and followed them for a year. Over 90% of participants were single with only 3% having low educations (primary or less) with >70% having secondary and >20% having post-secondary education. HIV testing was monthly and as with all prevention studies, intensive counselling on safer sex and free condom distribution was provided throughout the study. An indication of the background risk in this population is that 16% of people failing screening (197/2533) were excluded due to already being HIV-positive and 20% due to not being sexually active.

A slightly higher percentage of people in the active vs placebo arm (34% vs 31%) did not complete the study due to loss to follow-up, withdrawal of consent, relocations or other reason. The study had a good gender balance with 45% women.

With 33 seroconversions, primary efficacy results reported a 63% reduced risk of transmission with Truvada based on 9 new infections in the active arm compared to 24 in placebo group (difference 62%: 95%CI 21.5 to 83.4, p=0.0133).

When restricting the analysis (post hoc?) to infections within 4 weeks of a study visit (ie where the monthly visit schedule was being followed and the participant was under a prescription period) the association became stronger. Out of 23 seroconversions, 4 occurred in the active arm and 19 in the placebo group with 78% protection efficacy (95% CI 41.2 to 93.6, p=0.0053).

Although it was emphasised that the study was underpowered to draw any conclusion by gender, in an ITT analysis (33 cases) the intervention appeared protective in men (p=0.026) but not women (p=0.107) and in the observed results (23 cases) the protection was seen on women (p=0.021) but not men (p=0.065). Whilst interesting to see if a gender effect can shed light on the results from FemPrEP, this will need to come from larger study numbers.

Resistance developed in one person enrolled in the active arm whose acute HIV infection was undiagnosed with K65R, M184V

and A62V conferring nucleoside cross resistance. The person has achieved viral suppression after starting treatment with AZT/3TC/lopinavir/ritonavir. One person in the placebo group had low-level K65R suggesting an infection with drug resistant HIV.

Side effects were commonly reported in both arms, usually mild, with nausea (19% vs 7%, $p=0.0001$) and vomiting (11% vs 7%, $p=0.005$) occurring more significantly in the active arm compared to the placebo arm, but resolving within the first month. There were no differences in laboratory abnormalities with one case of elevated creatinine in the active group that resolved when treatment was stopped.

References

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Tenofovir/FTC vs tenofovir as daily oral PrEP: preliminary results from Partners PrEP

Simon Collins, HIV i-Base

The final presentation in the Treatment is Prevention session was a summary of the first results from the Partners PrEP study that randomised the HIV-negative partner in 4758 HIV serodifferent heterosexual couples to daily tenofovir (TDF) vs tenofovir/FTC (TVD) vs placebo in a 1:1:1 ratio. [1]

The results presented were based on a DSMB analysis a week before the conference that recommended unblinding the placebo arm and switching those participants to active drugs. This was based on significantly reduced risks of transmission in both the active arms and was 18 months earlier than the planned study endpoint.

This study was run in nine sites in Kenya and Uganda with all participants receiving intensive healthcare and adherence counselling including free condoms. The negative partners were seen monthly for counselling with HIV and pregnancy testing and the positive partners were monitored for their HIV care every three months.

Baseline demographics were similar across the three arms and included age (of the negative partner) 33 years (IQR 28-40), with the positive partner diagnosed a median of 0.4 years (IQR 0.1-2.0 years), CD4 count 490 cells/mm³ (IQR 370-660) and viral load 3.9 log copies/mL (3.2-4.5 logs).

Nearly all couples were married (98%) with duration of relationship a median of 7 years (IQR 3-14). The positive partner was a woman in 40% of couples. Approximately 20% of positive partners started treatment during the study for their own health.

Study retention was high with fewer than 5% discontinuations over 7337 person years of follow up (median 12 months). Adherence was also estimated high at 97% based on pill count using returned bottles (98% of bottles were returned).

Up to May 2011, there were 90 new infections, 12 of which were HIV-positive at randomisation (3 TDF, 3 TVD, 6 placebo). Of the 78 transmissions that occurred as events for the primary endpoint, 18, 14 and 47 occurred in the TDF, TVD and placebo arms respectively. There was an incidence of 0.74, 0.53 and 1.92 per 100 patient years that produced protection rates of 62% (95%CI 34-78%, $p=0.0003$) in the tenofovir and 73% (95%CI 49-85%, $p<0.0001$) in the tenofovir/FTC arms compared to placebo.

The study reported of a similar response between the two active arms ($p=0.18$ for comparison, NS). However, protection was numerically greater with the dual therapy and the gender analysis reported wider confidence intervals for tenofovir monotherapy with lower levels that were lower.

For women, protection rates were 68% (29-85%) and 62% (19%-82%) in the TDF vs TVD arms; for men these were 55% (4-79%) vs 83% (49-94%). The plausibility for greater protection from dual therapy would be extended with either lower adherence or less-than-daily dosing, both of which might be key public health factors for considering use of PrEP outside of clinical trials.

Safety results were very similar between all three arms for serious events and lab abnormalities including creatinine increases (1%, mainly grade 1) and reduced phosphorus (9%, equal across arms). As with other PrEP studies, nausea and diarrhoea were significantly more common in the active arms, but generally only for the first month of treatment.

As with other PrEP research, results from the pharmacokinetic will be important to correlate drug levels with level of protection and partner viral load with risk of infection. Resistance results will also be analysed.

Reference

- Baeten J et al. Antiretroviral Pre-Exposure Prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP Study. Oral abstract MOAX0106. Webcast <http://pag.ias2011.org/flash.aspx?pid=886>

6th IAS: ANTIRETROVIRALS

Elvitegravir vs raltegravir: 48 week results in treatment-experienced patients

Simon Collins, HIV i-Base

Elvitegravir is a once-daily integrase inhibitor being developed by Gilead. This was a double-blind, placebo-controlled study that randomised 702 treatment-experienced patients to compare elvitegravir (150 mg once-daily; reduced to 85 mg with atazanavir/r or lopinavir/r) to raltegravir (400 mg twice-daily), each with a background regimen of sensitive boosted-PI plus a third sensitive drug selected by phenotype (from NRTI, maraviroc, etravirine or T-20) and including the use of 3TC/FTC with the M184V mutation. The primary endpoint was proportion of patients with viral load <50 copies/mL at week 48 (TLOVR analysis, ITT). This was a non-inferiority study with the lower limit of the 95%CI set at -10%.

Baseline characteristics included mean age 45 years; 18% were women; mean CD4 count 260 cells/mm³ (45% cell <200), median viral load ~ 20,000 copies/mL (with 26% >100,000 copies/mL) and approximately 5% and 15% of patients were coinfecting with HBV or HCV respectively. Approximately 63% patients had primary resistance to two or more classes (PI 33%, NRTI 72%, and NNRTI 61%), balanced between arms.

Choice of background PI was largely darunavir (58%), lopinavir/r (19%) or atazanavir (16%). The third drug was an NRTI in 80% of patients (tenofovir 59%, tenofovir/FTC 27%, abacavir 4%, 3TC 3%, other 7%) with 13% using etravirine and 6% using maraviroc.

At week 48 a similar virological response rate was reported in each arm: 59% vs 58% in the elvitegravir vs raltegravir arms respectively which was strongly significant for non-inferiority (difference 1.1%, 95%CI -6.0% to +8.2%; p= 0.001). Approximately 20% of patients in each arm were reported as discontinuing due to virological failure: due to viral rebound (11% vs 16%) or never suppressing (8% vs 5%) in the elvitegravir vs raltegravir arms respectively with 1% or patients in each arm failing due to a switch of background drugs. A summary of virological and safety results is included in Table 1.

However, discontinuations in a following slide were reported at 24% in each arm, mainly due to non-adherence, loss to follow-up or withdrawn consent and are detailed in Table 2, with virological failure reported in only 9 patients in each arm.

Table 1: Elvitegravir vs raltegravir in experienced patients, 48 week results

	ELV n=351	RAL n=351	ELV vs RAL
VL < 50 c/mL	59%	58%	95% CI, -6.0%–8.2%, p= 0.001 for non inferiority
Virological failure	20%	22%	
Discontinuations	24%	24%	
CD4 mean increase (on-treatment analysis)	+138	+147	
D/c due to AEs	9/354 (3%)	15/358 (4%)	
INI resistance	16/62 (26%)	15/76 (20%)	

Table 2: Reasons for discontinuation: elvitegravir vs raltegravir, n (%)

	ELV n=351	RAL n=351
Discontinuations	85 (24%)	83 (24%)
Non compliance	21	17
Lost to follow-up	22	21
Withdrew consent	15	9
Virological failure	9	9
Side effects	8	12
Death	0	7
Other (pregnancy or investigator decision)	3	2

When looking at drug resistance in the patients with virological failure, this included 61 and 75 people in the elvitegravir and raltegravir arms respectively. In this dataset, failure with integrase-associated mutations was reported at a comparable number though with increased frequency (16/60; 27% vs 15/72; 21%) in the elvitegravir vs the raltegravir patients. Development of new PI- or NRTI-associated resistance was generally low and similar between the two groups.

Less than 5% of participants discontinued due to side effects. The only difference between arms in terms of adverse events was a higher rate of diarrhoea with elvitegravir (12% vs 7%), not associated with discontinuation. This was similar for laboratory abnormalities, with a slightly higher percentage of patients reporting grade 3/4 ALT/AST elevations with raltegravir (~1-2% vs 5%).

This study concluded that this demonstrated that once daily elvitegravir was non-inferior to twice-daily raltegravir in treatment-experienced HIV-positive patients.

COMMENT

These are impressive results in treatment-experienced patients. The rate of 20% patients failing with integrase-associated mutations was considered low by the investigators given the low barrier to integrase mutations. This was partially explained by the low barrier to virological failure in the study design (<1 log by week 8).

Causes of the seven deaths were not apparently drug related. This included one intestinal perforation in the elvitegravir arm, and one lymphoma and two cardiovascular events in the raltegravir arm.

Reference

Molina J-F et al. Elvitegravir once-daily is non inferior to raltegravir twice-daily in treatment experienced patients: 48 week results from a phase 3 multicenter, randomized, double blind study. Oral late breaker abstract WELBB05.

<http://pag.ias2011.org/Abstracts.aspx?SID=44&AID=4757>

Webcast

<http://pag.ias2011.org/flash.aspx?pid=611>

Dolutegravir: 48 week results from phase II study in treatment-naïve patients

Simon Collins, HIV i-Base

Dolutegravir is an integrase inhibitor in development with ViiV Shionogi that in earlier development was referred to as GSK-572. Results from the first monotherapy studies were presented only two years ago and the rapid development programme now includes phase III studies in naïve patients (using a 50 mg once-daily dose) with results already reported from phase II studies in experienced patients (using a higher 50 mg twice-daily dose).

Results from week 24 of a Phase IIb dose-ranging study treatment naïve study were presented in Glasgow last year with 90-96% of patients in the dolutegravir arms reducing viral load to <50 copies/mL compared to 78% patients in the efavirenz arm. These were updated to week 48 at in an oral presentation in Rome. The initial steep viral decline seen with integrase inhibitors as a class was probably a factor in choosing a primary endpoint at week 16 but this extended data is more crucial to understand sustainability. [1]

The study randomised 205 treatment-naïve patients 1:1:1 to 10 mg, 25 mg or 50 mg of dolutegravir or efavirenz 600mg once-daily, plus either investigator choice of either tenofovir/FTC (used by two-thirds of patients) or abacavir/3TC.

Baseline viral load was originally low (approximately 30,000 copies/mL) with only 26% participants >100,000 copies/mL. This would increase effectiveness for the a viral suppression (requiring less than a 3 log drop to achieve undetectable levels. Participants were largely male (86%) and white (80%), with mean CD4 count of 324 cells/mm³ (63% were <350). Median age was 32 (range 20-79 years).

By week 48, suppression in the dolutegravir arms had dropped slightly to 88-91% compared to 82% in the efavirenz arms. No between group analyses were presented but the confidence intervals for all groups broadly overlapped. Virologic non-response/rebound rates were low and similar between arms (8%, 6%, 4% vs 6% in the efavirenz arm) with the lower response in the efavirenz arm driven by discontinuations related to side effects (0, 2%, 0 vs 8% respectively). In the small percentage of patients failing with viral rebound 0/3 (none in the 50 mg arm) showed evidence of integrase-related mutations, though patients were proactively switched early due to this potential concern.

Virological results were also presented using a <2 copies/mL viral load test – the first time perhaps for an ongoing Phase II study. At the 50 mg dose approximate suppression to <2 copies at weeks 16, 24 and 48 was 48% 65% and 52% respectively compared to 35%, 45% and 58% in the efavirenz arm. These are small study numbers and neither confidence intervals nor statistical comparisons were provided but these are unlikely to show significant differences. It may be notable that the <2 copies/mL results for the lower doses of dolutegravir were not presented. Given the increased research focus on greater suppression at levels below < 50 copies/mL and the conflicting results from some of the intensification studies with raltegravir (broadly finding no impact in blood but perhaps in some tissue sites) this class potential is likely to inform future studies.

CD4 increases were similar by week 48 with +231 cells/mm³ in the combined dolutegravir vs +174 in the efavirenz arm vs EFV (p=0.076), reducing a difference that was significantly higher at week 24.

No new serious adverse events were reported out to week 48. The two discontinuations from the dolutegravir arms were due to dyspepsia (25 mg arm) and Burkitt's lymphoma.

Grade 2-4 side effects were similar between arms, except for rash and CNS-related side effects occurring only in the efavirenz group. Nausea (11%), diarrhoea (8%) and headache (5%) were most frequently reported with dolutegravir compared to dizziness (18%), fatigue, insomnia and rash (8% each) with efavirenz. Grade 3/4 laboratory abnormalities occurred in 12% vs 14% of the combined dolutegravir vs efavirenz arm. Dolutegravir was associated with mean increases in creatinine (6.4-11.9 mmol/L) at week 1 that were stable to week 20 and decreased by week 48. In vitro data have shown that dolutegravir causes a benign inhibition of creatinine secretion. These were detailed in a separate poster presentation. [2]

Lipid changes were generally greater in the efavirenz arm but there were no differences either from baseline or between drugs in the TC/HDL ratio at week 48 (due to the impact of efavirenz in increasing HDL).

The pharmacokinetic summary slide showed an impact of dose on drug levels over 24 hours, but these had low inter-patient variability and at all doses remained above the IC₉₀ (0.064 ug/mL) with C_{min} levels [geometric mean (CV%)] of 0.30 (71), 0.54 (67) and 1.20 (62) and an inhibitory quotient of 4.7, 8.4 and 19-fold for the 10 mg, 25 mg and 50 mg doses respectively.

References

1. Van Lunzen J et al. Rapid, robust and sustained antiviral response with once-daily (QD) dolutegravir (DTG, S/GSK1349572), a next generation integrase inhibitor (INI) in combination therapy in antiretroviral-naïve adults: 48 week results from SPRING-1 (ING112276). Oral abstract TUAB0102.
<http://pag.ias2011.org/abstracts.aspx?aid=2803>
Webcast
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2. Min S et al. Safety profile of dolutegravir (DTG, S/GSK1349572), a next generation integrase inhibitor (INI) in combination therapy in antiretroviral (ART)-naïve and ART-experienced adults from phase 2b studies. IAS. 17-20 July 2011. Rome. Abstract TUPE238.
<http://pag.ias2011.org/abstracts.aspx?aid=2883>

Lersivirine: 48 week results compared to efavirenz in Phase II treatment-naïve study

Simon Collins, HIV i-Base

Lersivirine is a once-daily NNRTI from ViiV that was originally developed by Pfizer and previously called UK-453061 and that is promising due to a resistance pathway at V108I that appears distinct from the K103N or Y181C pathways associated with first-generation non-nukes.

This double-blind, placebo-controlled study randomised 193 patients (1:1:1) to either 500 mg or 750 mg of lersivirine or to standard dose efavirenz, each with once-daily tenofovir/FTC. The primary endpoint was the percentage of patients with viral load reduced to <50 copies/mL at 48 weeks with follow up out to 96 weeks (by ITT missing = failure analysis).

Although enrollment criteria for the study included a CD4 count >200 cells/mm³, at baseline this ranged from 122 to 955 (median 310) suggesting that a few more advanced patients were included on an experimental combination than the European regulatory guidelines recommend for Phase II studies. Baseline viral loads ranged from 1,500 to 1,600,000 (mean: 50,000 copies/mL). Approximately 35% of patients had baseline viral load >100,000 copies/mL and this was reflected in pre-specified analysis of the results.

Other baseline characteristics included: mean age 36 years (range 21-62); 27% were women; race: 60% white, 30% black, 10% other. While the majority of people had sub-type B, ~30% of people were sub-type C which was reflected in ~30% enrolled in sites in South Africa.

At week 48, the percentage of patients with viral load <50 copies/mL was 79%, 79% and 86% in the 500 mg, 750 mg and efavirenz groups respectively. Although the study was not powered to detect a difference in efficacy between arms, the lersivirine arms suggested a poorer response compared to efavirenz (500 mg: -9% difference; 80%CI -18.1, 0.8 and 750 mg: -8% difference; 80%CI -17.0, 1.2).

Results stratified by baseline viral load (which was lower in the >100K group) or geographical region (which was lower for

sites in South Africa) did not contradict this finding, see Table 1.

A mean CD4 count increased of approximately +190 cells/mm³ from baseline was similar between arms.

Virological failure occurred in 4, 5 and 3 patients in the 500 mg, 750 mg and efavirenz groups respectively, with people on lersivirine generally failing with M184V plus NNRTI mutations when resistance was isolated. The one person with identifiable mutations in the efavirenz arm failed with K103N alone.

Overall, the combined safety analysis reported a similar incidence of side effects in each group but fewer grade 3/4 events in the lersivirine groups (n= 2 and 3) compared to efavirenz (n=8) see Table 2. Laboratory abnormalities were infrequent and evenly distributed between arms. Lipids were broadly stable for lersivirine compared to increases in TC, LDL, HDL and TG for efavirenz, but this resulted in little difference between the LSV and EFV groups (+0.24 and -0.06 vs -0.3) in the change in the TC:HDL ratio used to evaluate cardiovascular risk.

However, the study concluded that both lersivirine doses showed similar efficacy to efavirenz over 48 weeks in treatment-naïve patients and had different side effect profiles compared with efavirenz.

Table 1: Viral efficacy of lersivirine vs efavirenz at week 48

	LSV 500 mg	LSV 750 mg	EFV 600mg
Primary endpoint % VL <50	79	79	86
Baseline viral load <100K	80	86	88
Baseline viral load >100K	75	62	82
Region A*	81	84	87
South Africa	72	68	83
Region A* baseline viral load <100 K	81	87	89
Region A* baseline viral load >100 K	81	77	85

* EU, Latin America, Australia, Canada

Table 2: Adverse events (AEs) with lersivirine vs efavirenz

N (%)	LSV 500 mg n=65	LSV 750 mg n=55	EFV 600 mg n=63
Any AE: n (%)	52 (80%)	56 (86%)	58 (92%)
Serious AE	4	5	6
Grade 3/4	4	9	14
Discontinuation AE	3	3	5
Nausea (all grades)	15	27	8
Headache (all grades)	15	11	9
Abnormal dreams	5	5	12
Dizziness	5	4	13
Rash	3	1	7

COMMENT

There is still a role for new NNRTI with activity against nevirapine and efavirenz associated resistance with an improved safety profile to efavirenz.

The higher reports of nausea and headache appeared to be low grade but limited data was available on duration and severity of these events.

Reference

Pozniak A et al. Efficacy and safety of lersivirine (UK-453,061) vs. efavirenz in antiretroviral treatment-naïve HIV-1-infected patients: week 48 primary analysis results from an ongoing, multicentre, randomised, double-blind, phase IIb trial (study A5271015). Oral Abstract TUAB0101.

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Webcast

<http://pag.ias2011.org/flash.aspx?pid=294>

SPARTAC trial: treatment in primary infection for 48 weeks shows small delay in disease progression

Polly Clayden, HIV i-Base

The main objective in the SPARTAC trial was to look at the impact on disease progression from two different short courses of antiretroviral treatment (ART) initiated during primary HIV infection compared to no immediate ART. Sarah Fidler from Imperial College London presented results from SPARTAC in an oral late breaker at IAS 2011.

In this study, adults with primary infection who were within 6 months of seroconversion were randomised to receive ART for 48 weeks, 12 weeks, or no therapy (standard of care, SOC). The primary endpoint was time from randomisation to either CD4 <350 cells/mm³ or initiation of continuous ART.

A sample size of 360 was calculated (using data from CASCADE) to provide 90% power to detect relative reduction in risk of time to primary endpoint of 50% - 25% in each of the ART arms – compared to SOC over four years of follow up.

A total of 366 participants were randomised from 35 sites in Australia, Brazil, Europe and Africa; 40% were from the UK and 35% South Africa. Of these, 60% were men (90% MSM) and 40% African women, with a median age overall of 31 years. As would be expected, the median baseline CD4 was high at 543 cells/mm³ and viral load was 4.7 logs (~50,000 copies/mL). Participants were followed for a median of 4.2 years and 19% were lost to follow up. The majority (92%) of participants received lopinavir/r plus AZT and 3TC.

The investigators found no difference in time to primary endpoint in participants receiving 12 weeks of ART compared to SOC (HR 0.93: 95%CI 0.67-1.29, p=0.67). However, 48 weeks of ART conferred a statistically significant delay (HR 0.63: 95%CI 0.45-0.90, p=0.01). The median time to primary endpoint was 157, 184 and 222 weeks for the SOC, 12 week and 48 week arms respectively. Although, Dr Fidler noted that the 65 week (95%CI 17-114) delay in the 48-week arm was not significantly greater than the time spent on treatment.

A post-hoc analysis revealed two findings. There was a significantly more rapid rate of disease progression among participants identified within 12 weeks of acquiring infection in the SOC arm. Secondly, the delay to primary endpoint observed previously with 48 weeks of treatment compared to SOC was greater in participants who initiated ART initiated within 12 weeks of infection (HR 0.48; 95%CI 0.3-0.78). Overall, the investigators reported a non-significant trend to greater delay to primary endpoint the closer ART was initiated to the estimated time of seroconversion ($p=0.09$, NS).

There was a reduction in viral load of approximately half a log after interrupting ART in the 48-week arm compared to SOC, which was sustained until 60 weeks after stopping treatment. The mean CD4 count over the entire study period was 138 cells/mm³ higher in the 48-week arm than standard of care.

There were no significant differences between arms in AIDS, death or serious adverse events. In contrast to SMART there was no rebound in IL-6 and a drop in d-Dimer, compared to baseline, four weeks after stopping ART.

COMMENT

By the time this study was completed the treatment landscape had changed considerably from when it was initially designed. So the big question now is “what would have happened with a continuous treatment arm?”.

As far as the implication for clinical practice is concerned, perhaps if someone is aware of their status and he or she wants to start treatment in primary infection there may be a slender argument to do so. But if they do start and are doing well, given the modest time off treatment until starting again, why stop?

Reference

Fidler S et al. The effect of short-course antiretroviral therapy in primary HIV infection: final results from an international randomised controlled trial; SPARTAC. 6th IAS Conference on HIV pathogenesis, treatment and prevention. 17-20 July 2011. Rome, Italy. Oral abstract WELBX06.

<http://pag.ias2011.org/abstracts.aspx?aid=4711>

6th IAS: SIDE EFFECT AND COMPLICATIONS

Hearing loss not associated with HIV in MACS and WIHS cohorts

Simon Collins, HIV i-Base

Hearing loss has been associated as a complication in HIV-positive people but it is unclear whether HIV is a direct factor or whether symptoms are more strongly correlated to risk factors reported in the general population. This will be increasingly important as the HIV population ages.

Researchers from Washington DC measured cochlear function in 334 men and 178 women from two of the earliest population cohorts established to look at differences between HIV-positive and HIV-negative patients (MACS and WIHS respectively), and related to this to social factors including noise exposure and HIV and treatment history.

The mean age was 54 years for the men (46% were HIV-positive), and 45 years for the women (77% were HIV-positive). People

were excluded if they had hearing-impaired clinical symptoms or recent use of ototoxic medication. Approximately 20% of people in each of the HIV-positive and HIV negative groups self-reported exposure to occupational noise.

Cochlear function was measured by distortion product otoacoustic emission (DPOAE) testing which is a non-invasive procedure using two separate tones to stimulate the cochlea. Each ear was measured twice, with a third test if results were inconsistent and the number of non-responses added as an outcome variable (0-4).

In multivariate analyses, a 10-year increase in age [OR 2.78; 95%CI 2.07, 3.73], being male [OR 5.60; 95%CI 2.98, 10.49], and being non-black [OR 2.75; 95%CI 1.57, 4.83] were significantly associated with a higher number of non-responses (all $p<0.001$), but not HIV status [OR 1.20; 95%CI 0.7, 2.02; $p=0.52$ NS]. However, neither occupational or non-occupational noise exposure was associated with reduced function ($p=0.33$ and $p=0.93$, respectively).

Age, race, and gender remained significant risk factors for increasing non-responses in the HIV-positive model. However, none of the HIV-related factors including use of monotherapy, combination therapy, HAART use, 100-cell increase in peak CD8, HIV viral load, and 100-cell increase in nadir CD4 count came near approaching statistical significance (with p-values ranging from 0.2 to 0.7).

The researchers concluded that HIV status, combination therapy, nadir CD4 count, peak CD8 count, and HIV viral load did not significantly predict decreased cochlear function in this patient group.

Reference

Torre P et al. Cochlear function among Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) participants. 16th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17–20 July 2011, Rome. Poster abstract TUPE138.

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Poster

<http://pag.ias2011.org/EPosterHandler.axd?aid=2957>

6th IAS: PREGNANCY

Pharmacokinetics of darunavir and fosamprenavir in pregnancy

Polly Clayden, HIV i-Base

Physiological changes in pregnancy can affect drug disposition. Plasma concentrations of several PIs – including lopinavir, atazanavir and saquinavir – currently prescribed to HIV-positive pregnant women, are decreased during this period. Pharmacokinetics (PK) for darunavir (DRV) and fosamprenavir (FPV) in pregnancy are not well characterised. Two posters presented at the paediatric workshop and IAS 2011 showed data from PK studies of these antiretrovirals in pregnant women. [1, 2]

Darunavir

Edmund Capparelli and colleagues from the IMPAACT P1026s study group presented PK and safety data of DRV dosed twice-daily (BID) and once-daily (QD) during the third trimester of pregnancy, at delivery and post partum. These data were shown at the paediatric workshop in Rome.

IMPAACT P1026s is an on-going, prospective, non-blinded study of antiretroviral PK in pregnancy. It comprises of two groups of women receiving ritonavir-boosted DRV either as 600/100mg BID, or 800/100 mg, QD, as part of an ART regimen during pregnancy and 6-12 weeks postpartum (PP).

All women had received at least two weeks of ART at the time of the evaluation. Intensive steady-state 12 or 24-hour PK profiles were performed during the 3rd trimester and PP. Cord blood and maternal samples were taken at delivery when possible. DRV concentrations were measured by HPLC (limit of detection 0.09 mcg/mL). The minimum exposure targets were DRV AUC₀₋₁₂ or 24 of 43.6 or 56.5 mcg*hr/mL, for BID or QD, respectively. This represents $\geq 70\%$ median for non-pregnant adults. PK data were available for 31 women (19 BID, 12 QD). Two PP PK evaluations (1 BID and 1 QD) were excluded for non-adherence with no detectable DRV concentrations. Geometric mean 3rd trimester/PP ratios were 0.74 (90% CI 0.54-0.92) and 0.76 (90% CI 0.64-0.91) for AUC and 1.42 (90% CI 1.09-1.84) and 1.31 (90% CI 1.10-1.55) for CL/Fs with BID and QD dosing respectively.

For the PK parameters presented below for 3rd trimester and PP the investigators indicated values with $p < 0.05$ compared to PP with an asterisk (*). They found, AUC₀₋₁₂ were median 50.7 (range 23.8-102)* mcg*hr/mL for 3rd trimester and 70.0 (range 40.3-175.5) mcg*hr/mL PP for women who received DRV/r 600/100mg BID. Of those with PK parameters available, 13/19 (68%) and 11/13 (85%) met the AUC-12 target. CL/F was 11.82 (range 7.58-26.4)* L/h and 8.57 (range 3.42-14.89) L/hr. C_{12h} was 3.13 (range 0.78-8.85) mcg/mL and 2.81 (range 1.61-5.50) mcg/mL.

AUC₀₋₂₄ were 67.7 (range 30.3-105.5) mcg*hr/mL and 87.9 (77.5- 150.2) mcg*hr/mL, for the women who received DRV/r 800/100mg QD. Of these 8/12 and 7/7 met the AUC₀₋₂₄ target. CL/F was 11.82 (7.58-26.4)* L/h and 9.10 (5.33-10.32) L/hr. C_{24h} was 1.37 (0.15-3.49) mcg/mL and 2.59 (<0.09-3.96) mcg/mL. A total of 20 paired samples of maternal delivery and cord blood were collected. Of these, 6 pairs had concentrations below the limit of detection. For the remainder (n=14) median cord blood DRV concentrations were 0.19 (<0.09-1.1) mcg/mL. Maternal delivery plasma DRV concentrations were 1.42 (<0.09-5.62) mcg/mL. The median ratio of cord blood/maternal delivery plasma concentrations was 0.24 (0.062-0.58) indicating limited transplacental transport of DRV.

The investigators concluded that lower troughs and AUC with QD compared to BID dosing combined with pregnancy lowering DRV exposure suggests BID dosing should be used in pregnancy and higher doses may be required.

Of note, not all women achieved viral suppression in both dosing groups (at delivery overall, 57% and 79% <50 and <400 copies/mL respectively), and there was at least one vertical transmission among 24 (77%) infants with data available at the time of this analysis.

Fosamprenavir

There are limited data describing safety and outcomes of FPV in pregnancy or plasma concentrations of FPV's active metabolite, amprenavir (APV), during pregnancy, PP and in cord blood.

Michelle Cespedes and colleagues from New York University School of Medicine showed findings from a phase I, open-label,

single-centre study to evaluate APV PK following dosing of ritonavir boosted FPV 700/100mg BID in pregnant women. The investigators evaluated steady-state PK in the second and/or third trimesters and 4-12 weeks PP. Maternal plasma and cord blood samples were taken at the time of delivery. APV concentrations were measured by LC-MS/MS, and PK were determined using WinNonlin. This study was presented at IAS 2011.

The study evaluated 10 women receiving DRV/r based regimens. Cord blood samples were available from six deliveries. The median ratio of cord blood/maternal APV concentrations was 0.27, again, indicating limited transplacental transfer of this PI. Individual APV AUC was 22-34% lower, C_{max} 9-41% lower and C₁₂ 27-28% lower in pregnancy than PP. See Table 1: Amprenavir concentrations during pregnancy.

Table 1: Amprenavir concentrations during pregnancy

Phase	2nd trimester n=6	3rd trimester n=9	Postpartum n=9
AUC ug*h/mL	26.80	32.77	41.73
Median (range)	(18.49-40.72)	(17.05-66.42)	(28.86-79.66)
C _{max} ug/mL	4.32	5.75	6.92
Median (range)	(3.07-5.87)	(3.26-10.98)	(3.56-9.97)
C _{12h} ug/mL	1.35	1.46	2.24
Median (range)	(0.88-1.67)	(0.66-2.33)	(1.17-5.32)

The investigators noted that although APV C₁₂ was 27-28% lower in pregnancy, HIV was well suppressed for all subjects at delivery. Maternal and cord blood concentrations were above mean protein binding-adjusted IC₅₀ (0.146 ug/mL) for wild-type virus.

Safety and outcomes data showed that FPV was well tolerated in this small study with no hepatic, renal, or adverse events attributed to ART.

At delivery, all women had viral loads < 400 copies/mL and nine women had <50 copies/mL. All infants were HIV PCR negative.

COMMENT

The recommendation from the first study that higher doses of DRV may be required is consistent with US recommendations with other PIs such as lopinavir and atazanavir.

BHIVA guidelines do not recommended a dose increase.

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Low birth weight and preterm delivery

Polly Clayden, HIV i-Base

Data describing the risk of low birth weight (LBW) and preterm delivery (PTD) associated with maternal HIV and antiretroviral exposure are conflicting and international consensus has not been reached. Two posters from the Antiretroviral Pregnancy Registry (APR) and the Perinatal HIV Research Unit (PHRU), Soweto, South Africa, presented at IAS 2011, showed findings from their analyses of LBW and PTD in their respective cohorts. [1, 2]

APR is a prospective exposure-driven birth registry to monitor for potential increased birth defects following ART exposure in pregnancy.

In this study, Karen Beckerman and colleagues analysed reports to the APR cohort from 1989-2010. They restricted outcomes to singleton live births without birth defects. After establishing overall LBW(<2500 g)/PTD(< 37 weeks) prevalence by type of ART (2 or more drug regimens with and without PI), the data were stratified for maternal age, race/ethnicity and CD4 count. Stratified analysis is based on the 2x2 chi-square test and Cochrane-Mantle-Haenzel.

The investigators found, among the 10082 live births with birth weight data available, 16% were <2500 g. Of those with reported estimated gestational age, 12.8% were <37 weeks. There were significantly higher LBW/PTD women receiving PI-containing regimens vs regimens without PI (LBW RR=1.22, p<0.001; PTD RR=1.27, p<0.001). But after controlling for maternal age, race/ethnicity and CD4 count they found no significant increase in incidence of LBW/PTD associated with PI exposure among groups with lower pre-existing risk. See Table 1: Low birth weight, preterm delivery and PI exposure in APR.

The investigators concluded that among prospective reports to APR, increases in LBW/PTD were not associated with PI exposure in women with low background risk for these complications.

In a related study, Fatima Laher and colleagues from PHRU investigated risk factors for PTD in their cohort. They noted that prevalence for PTD is 17.5 in Southern Africa.

This study was a retrospective review of all HIV-positive pregnant women who received triple-combination ART between August 2004 and September 2010. Obstetric history, ART history, maternal CD4 count and viral load during pregnancy were recorded for all live births. Univariate analysis included variables associated with preterm delivery.

The investigators found, out of a total 223 pregnancies, 58 were electively terminated (26%), 19 were spontaneous miscarriages (8%), 16 did not yet have recorded outcomes (7%), and 4 were

stillbirths (2%). There were 126 (57%) live births, and 62/126 (49%) were PTDs with median gestational age 34.7 weeks (IQR 33.0-35.7). Mothers of preterm and term infants were similar in age, median 31.7 and 30.9 years respectively. Virological suppression <50 copies/mL during pregnancy was similar in both groups, 84% and 80% respectively.

The majority of women, 111/126 (88%) initiated ART was before conception. Maternal CD4 count during pregnancy below 200 cells/mm³ [OR 1.2; 95%CI 0.5-2.8, p=0.76], 350 cells/mm³ [OR 1.4; 95%CI 0.7-2.8, p=0.37], or 500 cells/mm³ [OR 1.1; 95%CI 0.4-2.8, p=0.87], were not risk factors for PTD.

Final-trimester maternal use of EFV-based regimens [OR 2.5; 95%CI 0.9-6.9, p=0.09], or PI-based regimens [OR 1.4; 95%CI 0.6-3.0, p=0.4], were not predictive of PTD compared to NVP-based regimens.

The investigators concluded that preterm delivery is common among pregnant ART-recipients in Soweto. Maternal CD4 count and final-trimester ART type seem not to predict preterm delivery. They noted that their small sample size in this study is a limitation.

COMMENT

The APR data are unsurprising as 85% of the pregnancies enrolled are from the US and the association with PTD and PIs is largely not observed in American cohorts. The Soweto data may reflect a high background PTD rate and, as the investigators note, a small sample size.

Recently published data from Botswana does show an increased risk of PTD in women receiving PIs in pregnancy. [3]

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Table 1: Low birth weight, preterm delivery and PI exposure in APR

	% of cohort (n/total)	Low birth weight		RR, PI vs no PI	Preterm delivery		RR, PI vs no PI
		% PI	% No PI		% PI	% No PI	
Low risk maternal characteristic	Live births with known BW or GA		
Age 20-34	77% (7340 BW, 7737 GA)	15.4	14.2	1.09 (0.22)	12.7	10.5	1.21(0.01)
Ethnicity White/ Latina	33% (3169 BW, 3360 GA)	13.2	12.7	1.04 (0.73)	11.6	11.5	1.00 (0.98)
CD4 count >500 cells/mm ³	32% (3065 BW, 3237 GA)	16.1	14.0	1.15 (0.15)	12.9	11.8	1.10 (0.37)

6th IAS: WOMEN'S HEALTH

Hormonal contraception and HIV transmission risk

Polly Clayden, HIV i-Base

Some epidemiological and laboratory studies have suggested that hormonal contraception can increase HIV transmission risk in women. There has been little research into the risk of transmission from women to men. To date findings have been inconsistent and WHO has called for high quality studies to look at potential interactions between hormonal contraception and HIV transmission.

Investigators from The Partners in Prevention HSV/HIV Transmission Study compared HIV incidence among women using hormonal contraception to those who were not. This analysis evaluated both HIV acquisition among women and transmission from women to men. Renee Heffron presented findings from this study in an oral presentation at IAS 2011. [1]

This was a prospective cohort study of 3790 serodiscordant couples from seven countries in East and southern Africa. The couples were enrolled from two studies conducted between 2004 and 2010, a randomised trial of acyclovir to reduce HIV transmission (n=3321) and a prospective cohort study of immune correlates of HIV protection (n=469).

Study participants were 18 years of age or older, and at enrollment the HIV-positive partners were not eligible for ART according to national guidelines. HIV-negative partners were tested quarterly and HIV-positive partners had CD4 measurements every six months and plasma and genital viral load at enrollment and six months later. The investigators used standardised questionnaires to measure sexual behaviour and contraceptive use.

They compared rates of HIV acquisition in women and HIV transmission from women to men using multivariate Cox proportional hazards regression and marginal structural modeling. The analyses were limited to infections acquired from the study partner (evaluated by viral genetic sequencing).

The negative partners were women in about a third (n=1314) of the couples evaluated, and two thirds (n=2476) were men.

Among the negative women, 21.2% overall used hormonal contraception at least once during follow up, of which 16% used injectable contraception at least once and 6.7% oral contraception. The HIV acquisition rates were 6.61 and 3.78 per 100 person-years in women currently using and not using hormonal contraception [AHR 1.98; 95%CI 1.06-3.68, p=0.03]. For injectable contraception the incidence rate was 6.85 per 100 person-years [AHR 2.05; 95%CI 1.06-3.68, p=0.04] and for oral contraception it was 5.94 per 100 person-years, [AHR 1.8 95%CI 0.55-5.82, p=0.33].

Overall, 33.3% of HIV-positive partners of negative men used hormonal contraception, 26.8% injectable and 8.9% oral. In these couples, HIV transmission rates from women to men were 2.61 and 1.51 per 100 person-years in those whose partners used and did not use hormonal contraception [AHR 1.91, 95%CI 1.12-3.45, p=0.02]. For injectable contraception the incidence rate was 2.64 per 100 patient years [AHR 1.95; 95%CI 1.06-3.58, p=0.03]. The incidence also increased in the group using oral contraception,

2.50 per 100 patient years, but as with HIV acquisition in negative women this did not reach statistical significance in this subgroup [AHR 2.09; 95%CI 0.75-5.84, p=0.16].

Results from marginal structural model analyses were consistent with those shown from the Cox proportional hazards regression.

When the investigators looked at this a possible explanation, there were significantly higher genital viral load concentrations overall in women using hormonal contraception [OR 1.51; 95%CI 1.13-2.01, p=0.01]. For injectable contraception these were significantly higher [OR 1.67; 95%CI 1.21-2.31, p=0.02]. But not for oral contraception [OR 1.06; 95%CI 0.62-1.84, p=0.49].

Dr Heffron noted that this was the first study to demonstrate that hormonal contraception increased an HIV-positive woman's risk of transmitting HIV to her partner.

She added that the benefits of effective hormonal contraception are unequivocal and must be balanced with the increase in risk of HIV infection. These possible risks should be discussed with women and couples alongside the importance of HIV prevention.

Strategies to improve access to and usage of lower dose and non-hormonal methods – IUDs, implants, patches or combination injectables are warranted – she concluded.

COMMENT

These findings understandably caused quite a stir and urgently need more investigation. This was followed by the report from Partners in Prevention that pregnancy doubles the risk of transmission from HIV-positive women to her male partner (to be reviewed in the next issue of HTB). [2]

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6th IAS: PAEDIATRIC CARE

No difference in AIDS-free survival in children starting ART with a CD4% between 15%–24% compared to deferring until less than 15% in the PREDICT trial

Polly Clayden, HIV i-Base

Information to guide initiation of treatment in children older than one year of age is scarce.

Results from the PREDICT trial - presented as late breakers at both IAS 2011 and the preceding pediatric workshop – found that deferring ART until CD4 count fell below 15% or the occurrence of CDC category C events did not affect AIDS-free survival in

COMMENT

children compared to starting ART at a CD4 count between 15% and 24%. [1]

PREDICT was conducted in 299 children from nine sites in Thailand and Cambodia between April 2006 and September 2008. Children were randomised to receive immediate ART or defer until their CD4 reached less than 15%. The children's baseline characteristics are shown in table 1.

The primary endpoints were AIDS free survival at week 144 and neurodevelopmental outcome by Beery visual motor interrogation test.

Table 1: Baseline characteristics of children in the PREDICT trial

Parameter	Immediate arm (n=149)	Deferred arm (n=150)
Age (years)	6.4 (3.7-8.0)	6.4 (4.2-8.7)
Female	77 (52%)	96 (64%)
Thai: Cambodian	90:59	89:61
CD4%	19 (16-22)	20 (17-23)
HIV RNA (log10)	4.9 (4.4-5.0)	4.7 (4.3-5.0)
Weight-for-age z-score	-1.3 (-2.0 to -0.8)	-1.3 (-2.0 to -0.8)
Height-for-age z-score	-1.6 (-2.5 to -0.8)	-1.7 (-2.6 to -0.9)

Age, CD4%, HIV RNA, weight-for-age z-score and height-for-age z-score are mean values.

Retention was high in this study (96%). At week 144, 69 (46%) children had started ART with a mean CD4 at initiation of 13.8% (SD±2.8%). Of these, 17 children were <5 years and had a mean CD4 count of 591 cells/mm³ (SD±508) and 52 children were >5 years and had a mean CD4 count of 309 cells/mm³ (SD±141).

AIDS-free survival was 97.9% (95% CI, 93.7 -99.3) in the immediate arm and 98.7% (95%CI 94.7-99.7) in the deferred arm. The incidence of CDC C events or death per 1000 person-years was 7.6 (95%CI 2.5-23.6) in the immediate arm and 4.9 (95%CI 1.2-19.7) in the deferred arm.

The incidence of CDC category B events per 1000 person-years was broadly similar in both arms, 88 (95%CI 61-123) in the immediate arm compared to 110 (95%CI 80-147) in the deferred arm. But there were more episodes of herpes zoster (2 vs 13) and thrombocytopenia (1 vs 10) in the immediate and deferred arms respectively. There were only two episodes of TB, one in each arm.

Weight for age z-score was similar, deferred vs immediate -0.12 (95%CI -0.25 to 0.01), p=0.074. But children grew at a slower rate in the deferred arm, height for age z-score, deferred vs immediate -0.23 (95%CI -0.38 to 0.08), p=0.003.

And at 144 weeks of follow up there was no significant difference by Beery visual motor test between the two arms; Beery score deferred vs immediate, 84.7 vs 86.8, p=0.5.

The investigators noted that at approximately three years of follow up, the rate of progression to AIDS is extremely low in both the immediate and deferred arms. The finding reflects a slow disease progression among HIV-infected children who survive the first year of life without treatment.

This study is important and a bit of a surprise to many as it appears to contradict both adult data and that for young infants. But the median age in the study reflects a population that have survived without treatment for the first few years and therefore selects a group of healthier children without rapid disease progression.

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Paediatric antiretroviral pipeline: update on etravirine and maraviroc

Polly Clayden, HIV i-Base

Data were presented at the paediatric workshop and IAS 2011 describing recent developments in the paediatric pipeline.

Etravirine

Thomas Kakuda from Tibotec showed pharmacokinetic (PK) data of the NNRTI etravirine (ETV) in treatment experienced children and adolescents aged 6 to <18 years. [1, 2]

These 24-week results are from PIANO (Pediatric trial with Intelence as an Active NNRTI Option). PIANO is an ongoing Phase II, open label trial looking at the safety, efficacy and PK of ETV 5.2mg/kg bid (maximum dose 200mg bid).

In this study, 101 children (6 to <12 years, n=41) and adolescents (12 to <18 years, n=60) received ETV plus background regimen of a boosted protease inhibitor plus nucleoside/nucleotide inhibitors with optional enfuvirtide and/or raltegravir for 48 weeks. The trial participants received 25mg and 100mg tablets of ETV.

Sparse samples for population PK were taken at weeks 4, 8, 12, 24 and 48. At week 24 two samples were collected, a trough and one at least an hour after ETV dose. ETV plasma concentrations were measured using a validated high performance liquid chromatography-mass spectrometry/mass spectrometry assay.

The investigators developed a paediatric population PK model based on previous adult modelling and supplemented with rich and sparsely sampled PK data from TMC125-C126 [HTB ref] and PIANO respectively. They used the model to determine ETV AUC_{12h} and C_{0h} for all participants enrolled in PIANO up to 24 weeks.

There were 476 plasma concentration time samples available from 101 participants completing 24 weeks. There was an overall mean (SD) AUC_{12h} and C_{0h} of 5236 (±4314) ng*h/mL and 347 (±342) ng/mL respectively. In children in the younger age group these values were 5764 (±4044) ng*h/mL and 381 (±321) ng/mL. In adolescents they were 4834 (±4483) ng*h/mL and 323 (±357) ng/mL respectively. Adult reference values from the DUET trial were 5506 (±4710) ng*h/mL and 393 (±391) ng/mL for AUC₁₂ and C_{0h} respectively.

The investigators observed slightly lower exposures in the adolescents compared to the adults despite the majority (93%) of adolescents receiving the adult ETV dose of 200mg bid.

A dose of 5.2 mg/kg ETV is expected to be recommended for this population.

A related poster authored by Gareth Tudor Williams and colleagues described safety and efficacy from the same study. [3] The incidence of serious adverse events (AEs, grade 3 or 4) was low. A total of eight participants discontinued the trial due to AEs, this occurred more frequently in the older (n=6) than younger (n=2) age group. The most common AEs were upper respiratory tract infection (n=27) and rash (n=23).

Approximately half (n=51) of participants achieved a viral load <50 copies/mL. Response rates were higher in children than adolescents, with 24/41 (59%) achieving an undetectable viral load compared to 28/60 (47%). Response was similar in participants in both age groups considered adherent (measured by pill count and questionnaire) compared to non-adherent, respectively 48% (<95% adherent) compared to 53% (>95% adherent).

Of 28 participants with available genotype results at the time of virological failure, 54% developed NNRTI resistance mutations, mainly Y181C, E138A and V90I.

Maraviroc

Carlo Giaquinto and colleagues presented preliminary PK data for the CCR5 antagonist maraviroc (MVC) in children and adolescents aged 2 to <18 years. [4, 5]

Data are from Study A4001031 - an ongoing open-label, non-comparative, multi-centre study in two stages (1: dose finding; 2: safety/efficacy) in treatment-experienced children, infected with CCR5-tropic HIV-1, receiving MVC 40-450 mg BID with optimised background therapy (OBT).

MVC PK were determined at Week 2. Participants (n=31) were stratified into four age cohorts. They were dosed twice daily. The initial dosing was calculated according to body surface area (BSA) with adjustments to take into account interactions between MVC and OBT (adult-recommended doses with/without CYP3A4 inhibitors/inducers).

Doses were adjusted and PK reevaluated if average concentrations (C_{avg}) at week 2 were <100 ng/mL. C_{avg} was estimated from AUC (AUC_{12h}) calculated from seven samples taken over 12 hours.

The investigators reported, out of 22 participants receiving MVC with a potent CYP3A4 inhibitor (protease inhibitor based regimens). Only one failed to meet the PK target with the initial dose (this was due to poor adherence). But all five participants who did not receive a protease inhibitor (two nevirapine based regimens; two raltegravir based regimens; one NRTI based regimen) needed at least twice the initial MVC dose.

At the time of enrolment into stage 2, one participant did not meet the target after two dose adjustments but responded well clinically so was therefore included in the PK analysis. See Table 1: Preliminary PK results for maraviroc in children and adolescents aged 2 to <18 years.

Table 1: Preliminary PK results for maraviroc in children and adolescents aged 2 to <18 years.

	Cohort 1 (n=2)	Cohort 2 (n=10)	Cohort 3 (n=5)	Cohort 4 (n=12)
Age (years)	2 to <6	6 to <12	6 to <12	12 to <18
Formulation	Liquid	Tablet	Liquid	Tablet
Sex (male/female)	2/0	4/6	3/2	4/8
Ethnicity (white/black/Asian)	0/0/2	0/8/2	1/4/0	4/6/2
C _{avg} , geometric mean (ng/mL)	178 (n=2)	247 (n=10)	221 (n=5)	242 (n=9)

The authors concluded that these preliminary data show that BSA-based dosing of MVC with CYP3A4 inhibitors provides MVC exposures associated with near- maximal efficacy (C_{avg}>100 ng/mL) in all age groups studied. But they noted that additional PK analyses are required to evaluate appropriate dosing when MVC is administered without CYP3A4 inhibitors in children.

A second poster from the same group showed safety and efficacy from the same study. [6]

At the time of analysis 35 children had been randomised (n=2, n=12, n=6 and n=15 in cohorts 1 to 4 respectively) and had received at least one dose of MVC. The median duration of treatment was 396, 493, 435 and 211 days in cohorts 1 to 4 respectively. The investigators observed 101 non-serious AEs in 21 patients; they considered 17 of these in 8 patients to be treatment related. Of those with elevated liver function test results, none were of grade 3 or higher. There were 8 serious adverse events of which none were judged to be treatment related and all resolved. There were no deaths.

Viral load <50 copies was achieved by 17/24 (71%) and 11/17 (65%) of participants at weeks 24 and 48 respectively. Five participants had virological failure; in four, this was due to poor adherence. The fifth had emergence of dual-mixed virus and developed 3TC resistance.

Enrollment in this study is continuing and long-term data will be collected and analysed.

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More metabolic abnormalities in children receiving a PI compared to NNRTI in NEVEREST study

Polly Clayden, HIV i-Base

NEVEREST was a study in which young children who were exposed to nevirapine as PMTCT and initiated on PI-based HAART were randomised to continue on this regimen or switch to a nevirapine based regimen (we report the final results from NEVEREST later in this issue of HTB).

NEVEREST investigators evaluated body composition and metabolic abnormalities in 156 children exiting the trial. The objectives were to compare lipid profiles, markers of inflammation and regional fat distribution in children receiving a PI-based regimen of LPV/r plus 3TC plus d4T to those switched to an NVP-based regimen.

The children's weight (kg) and height (cm) was measured and weight-for-age, height-for-age and BMI-for-age z-scores (WAZ, HAZ, BAZ) calculated. Fasting total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), C-reactive protein (CRP), viral load, absolute CD4 and CD4 percentage were obtained. Circumferences and skinfolds were also measured; waist to hip ratio (MWC:MHC) and skinfold sum (SFS) were calculated. Upper arm and thigh fat estimates (UFE, UTFE) were calculated by Rolland Cachera. Analyses were intent to treat.

At the time of analyses, children were a mean age of 5.1 (range 3.6 – 6.9) years and approximately half were boys; 85 (42 boys) were randomised to the PI arm and 71 (40 boys) to the NNRTI arm. There were no differences between the two groups in sex, age, total time on ART, time since randomisation, WAZ, HAZ or BAZ or proportion with viral load <50 copies/mL. But children in the NNRTI group had a higher CD4 count, 1480 cells/mm³ compared to 1356 cells/mm³, p=0.049.

The investigators found differences in metabolic measurements. Mean TC was greater in the PI group, 171 (SD±39) mg/dL vs 161 (SD±31) mg/dL, p=0.05 as was the proportion of children with hypercholesterolemia (TC >200 mg/dL), 18.8% vs 8.5%, p=0.03. They also observed lower mean HDL levels, 51 (SD±14) mg/dL vs 59 (SD±16) mg/dL, p=0.006 and higher mean LDL levels, 100 (SD 34) mg/dL vs 88 (SD±27) mg/dL, p=0.018, in the PI group. The mean TG level was also greater in the PI group, 94 (SD±39) mg/dL vs 72 (SD±29) mg/dL, p<0.001 as was the proportion with hypertriglyceridemia (TG >150 mg/dL), 12.9% vs 2.8%, p=0.038.

The children in the PI group had significantly greater amount of total body fat compared to those receiving an NNRTI, with a mean SFS of 43 (SD±11.1) mm vs 39 (SD±10.1) mm, p=0.029 and % body fat by BIA (Horlick Equation) of 0.17 (SD±0.7) vs 0.14 (SD±0.08), p=0.042.

The percentage of fat in the upper arm did not differ between groups but the percentage of fat in the upper thigh was greater in the PI group, p=0.021. Also the PI group had a smaller ratio of trunk fat relative to thigh fat, p=0.03.

The investigators wrote: "These unfavourable alterations in lipids and lipoproteins are of great concern with respect to potential increase in long term CVD risk and should be considered in treatment strategies, such as the reuse of NNRTIs for NNRTI-exposed infants".

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Prematurity not associated with early mortality in infants on ART

Polly Clayden, HIV i-Base

Prematurity is a known risk for infant mortality. Other risks include maternal immunosuppression, delayed initiation of ART and low baseline CD4 percentage.

Investigators from the Perinatal HIV Research Unit (PHRU) in Soweto, South Africa showed findings at the 2011 paediatric workshop from a cohort study designed to investigate prematurity among children born in 2009 and initiated on ART before one year of age. The study was a database and record review.

The background characteristics of the infants at time ART initiation are shown in Table 1.

The investigators reported no difference in mortality between preterm and term infants, respectively, 3% vs 4% (OR 1.9; 95%CI 0.5-6.7). Lost to follow up was 8% overall.

Univariate analysis revealed non-significant p-values for all variables ie preterm vs term, baseline CD4%, baseline viral load, breast vs formula feeding and maternal PMTCT. The investigators noted the small sample size and that the mortality rate was low in this study.

They concluded that although HIV-infected preterm infants have significantly lower CD4% than term infants, with early ART initiation they are not at increased risk of mortality.

Table 1: Background characteristics of term vs preterm infants at ART initiation

	Preterm (n=31)	Term (n=114)	p-value
Median age weeks (IQR)	8.5 (7.4 - 13.1)	9.9 (7.9-15.1)	0.19
Median CD4% (IQR)	26.6 (19.7-32.7)	31.5 (22.4-39.5)	0.025
Median CD4 cells/mm ³ (IQR)	1820 (1194-2409)	1768 (1217-2497)	0.87
Viral load log copies/mL (IQR)	5.9 (5.69-5.88)	5.9 (5.75-5.88)	0.89
Exclusive formula feeding (%)	24 (80%)	88 (79%)	0.93

Reference

Lazarus E et al. Prematurity is not a risk factor for early mortality in HIV-infected infants on antiretroviral therapy. 3rd International workshop on HIV paediatrics. 15-16 July 2011. Rome, Italy. Poster abstract P_18.

the Romanian and 0.69 and 68% for the South African test sets respectively. When the 57 case test set was used to compare the performance of the models with and without genotype information the results were 0.77 and 74% using the genotype, compared to 0.76 and 68% for the 'no-genotype' models.

The models are now available via the RDI's online treatment selection tool HIV-TRePS. Importantly, the resource includes the option to include, with permission, anonymised information on treatment decisions and outcomes to be collected to help further development of the system. [2]

The resource has been developed by researchers at RDI who were involved in much of the original pioneering work into HIV drug resistance technology and more recently have been developing prediction tools to interpret genotype results using computer-developed neural networks.

Future reports on how this resource is used in practice will be important given the extremely restricted access to resistance testing in most resource-limited countries and that this is unlikely to change in the near future.

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6th IAS: DRUG RESISTANCE

Free online resource for treatment decisions without access to genotype resistance tests

Simon Collins, HIV i-Base

Results from a new online resource developed to predict treatment outcomes for settings without access to genotypic resistance tests were presented in a poster at the conference. [1]

The system was developed by training computer models to predict virological response to therapy using data from approximately 15,000 treatment changes drawn from over 15 countries. The models use CD4, viral load, treatment history and the drugs in the new regimen in making their predictions and can generate predictions of response at selected time points out to 48 weeks for all available combinations or for a selected combination. The system includes the option to select drugs that are available in each country and to exclude drugs that are contraindicated.

The accuracy of the models was assessed with an independent test set of 800 cases. Two further test sets from Romania (n=39) and South Africa (n=56) were also reported together with subset of 57 cases from the 800 test set that had genotypes available.

The mean area under the curve and overall accuracy were 0.77 and 71% with the 800 test dataset (with similar results during cross validation). The comparable results were 0.68 and 67% for

CONFERENCE REPORTS

18th Conference on Retroviruses and Opportunistic Infections (CROI)

27 February–3 March 2011, Boston

Introduction

Our final reports from this important conference are:

- Monitoring treatment in resource limited settings: results from PHPT-3 and Stratal ANRS12110/ESTER trials
- DART: high rates of viral suppression after five years and a single CD4 test with a threshold of 250 cells/mm³ could reduce unnecessary switching
- Lopinavir/r monotherapy used as second-line therapy in resource-limited settings
- Pharmacokinetics of different rifabutin dosing strategies with lopinavir/ritonavir-based ART
- Initiation of ART during breastfeeding can induce multidrug resistance in infants
- Treating children previously exposed to single dose nevirapine: update on IMPAACT P1060 and NEVEREST
- Lopinavir/ritonavir oral solution toxicity in neonates
- Paediatric antiretroviral pipeline: darunavir and raltegravir

Unless mentioned otherwise, all references are to the Programme and Abstracts of the 18th Conference on Retroviruses and Opportunistic Infections, 28 February–2 March 2011, Boston.

<http://www.retroconference.org/AbstractSearch/>

Webcasts are available at the following link:

http://www.retroconference.org/2011/data/files/webcast_2011.htm

Monitoring treatment in resource limited settings: results from PHPT-3 and Stratal ANRS12110/ESTER trials

Polly Clayden, HIV i-Base

In resource-limited settings, optimal monitoring and switching criteria from first-line to second-line therapy is unclear. Results from two trials were shown as oral presentations that suggest that monitoring viral load is not essential for switch to second line. [1, 2]

Marc Lallemand showed data from PHPT-3, which was conducted in Thailand. This was a randomised double-blind (until first switch) non-inferiority trial. Participants were randomised to CD4 or viral load monitoring, which was conducted every three months.

Dr Lallemand explained that the trial was designed for a setting with only two lines of treatment and where second line is far more expensive than first line. The investigators wanted to test whether monitoring and switching people without viral load compromised their health or their future options.

PHPT-3 enrolled HIV-positive adults (CD4 count 50 to 250 cells/mm³, not hepatitis B or C co-infected), starting NNRTI-based HAART.

In the CD4 monitoring arm, patients switched to second-line protease inhibitor (PI)-based therapy when they had confirmed CD4 decline of 30% or more from peak, and in viral load monitoring they switched when they had confirmed viral load >400 copies/mL.

The primary endpoint was death, new AIDS-defining event or clinical failure - defined as CD4 <50 cells/mm³ - at 3 years. Secondary endpoints included proportions switching to second line, time to switch, resistance mutations at failure and future treatment options.

The trial enrolled 716 patients of which 60% were women. Their median CD4 count at baseline was 144 cells/mm³ (range 90 to 200 cells/mm³).

Regimens were 65% efavirenz-based regimen and 66% of participants received tenofovir/FTC. Other study drugs were nevirapine and AZT/3TC. At 3 years of follow up 93.3% of patients were evaluable. Ten percent stopped treatment for toxicity across both groups.

There were 58 clinical failures overall, 28 and 30 in the CD4 and viral load groups respectively. The respective rates of clinical failure per patient years were 2.3 vs 2.5 and of death 1.1 vs 1.4.

In multivariate analysis, anaemia, adjusted HR 2.7 (95% CI 1.5-4.8), p=0.001; CD4 <150 cells/mm³, AHR 2.3 (95% CI 1.2-4.2), p=0.009 and viral load >5 log, AHR 1.8 (95% CI 1.0-3.0), p=0.04, were predictive of clinical failure at 3 years.

The probability of switch to second-line (excluding toxicity/intolerance) was 5.2% (95% CI 3.2-8.4%) vs 7.5% (95% CI 5.0-11.1%) in the CD4 and viral load groups respectively, p=0.10.

The respective median times to switch were 11.7 months (95% CI 7.7-19.4) vs 24.7 (15.9-35.0), p=0.001. And the median duration of viraemia >400 copies/mL was 7.2 months (IQR 5.8 to 8.0) vs 15.8 months (8.5 to 20.4), p=0.002. But the median CD4 counts were 426 cells/mm³ vs 420 cells/mm³, respectively.

Dr Lallemand noted that 15/31 patients in the CD4 monitoring arm who switched to second-line had viral load <50 copies/mL at the time of switching.

Viral load was <50 copies/mL in 99% of patients at 3 years follow-up and patients with CD4 monitoring did not have fewer future treatment options, with the exception of one patient with multiple thymidine analogue mutations (D67N/M41L/L210W/T215Y).

Dr Lallemand concluded that, after 3 years, the rate of clinical failure was very low and did not differ between the two strategies. Most mutations had been selected at the time of virological failure. The additional time spent on failing treatment in the CD4 arm did not result in reduced future treatment options.

He noted that the conclusions from PHPT-3 are similar to those from DART and HBAC in adults and PENPACT-1 in children. He added that the need for viral load monitoring may be less important than close and regular safety, tolerability, adherence, and immunological monitoring. He remarked that the nurse/patient team with expert assistance from doctors, biologists and patient networks "maximizes efficacy and durability."

This was followed by a related presentation of data from the Stratal ANRS12110/ESTER trial.

Charles Kouanfack showed findings from a trial designed to compare clinical monitoring alone with laboratory and clinical monitoring. This trial was conducted in 9 rural district hospitals in Yaounde, Cameroon.

Dr Kouanfack explained, in Cameroon, the national programme followed WHO guidance for a public health approach based on decentralised, integrated HIV care delivery in facilities where laboratory monitoring is generally unavailable. He noted that the 2010 guidelines also state that using viral load monitoring to detect treatment failure and switch is recommended but has "low quality evidence".

Stratall ANRS12110/ESTER was a randomised non-inferiority trial enrolling HAART-naïve, HIV-positive adults with a WHO stage 3-4 disease or stage 2 and total lymphocyte count ≤ 1200 cells/mm³, who were followed for 2 years. Management was by the health workers in charge of routine activities.

The primary endpoint was mean increase in CD4. The increase in the clinical monitoring arm was judged to be non-inferior to that in the laboratory monitoring arm if the difference was less than or equal to 25%.

Secondary endpoints included: viral suppression, death, new stage 3 or 4 events, resistance, loss to follow up, adherence, treatment changes and toxicity.

Participants were monitored clinically 3 monthly in both arms and those in the laboratory monitoring arm also had CD4 and viral load measured every 6 months.

Switching to second line was indicated by grade 3 or 4 events in the clinical monitoring arm and persistent viral load >5000 copies/mL in the laboratory monitoring arm.

Of a total of 493 patients, 256 were assigned to clinical and 237 to laboratory monitoring. Of these, 93% were followed and included in the analysis. Patients were similar at baseline with CD4 counts of 179 cells/mm³ and 182 cells/mm³ in the clinical and laboratory monitored arms respectively. Both arms had high baseline viral loads of 5.6 log₁₀ copies/mL. Overall 70% were women. About 65% started treatment with d4T + 3TC + NVP.

The trial failed to demonstrate non-inferiority of clinical monitoring: the mean increase in the CD4 count was 175 cells/mm³ (95%CI 151-200) vs 206 cells/mm³ (95% CI 181-231) in the clinical and laboratory arms respectively. This gave a difference -31 (-63 to +2), the non-inferiority margin was -52 (-58 to -45). The analysis was last observation carried forward.

The analysis also revealed that 13 (6%) laboratory-monitored participants switched to second-line regimens because of treatment failure, compared to none of the clinically monitored participants, $p < 0.001$. But, viral suppression (49 vs 52%), resistance (both 10%), mortality (18 vs 14%), disease progression (36 vs 29%), adherence (both 64%), loss to follow-up (9 vs 8%), and toxicity (19 vs 25%) were similar between the two groups.

Dr Kouanfack concluded that failure to demonstrate non-inferiority of immunological recovery and the need to switch to second line in this trial supports the WHO recommendation of laboratory monitoring of HAART where possible.

He also concluded that the difference between the two strategies suggest that clinical monitoring alone can be used for at least the first two years of treatment in order to expand scale up and to take into account financial and infrastructural constraints in resource limited settings.

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Both webcasts: Research on Delivery of Care in Developing Countries. Monday 28 February 11 am.

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DART: high rates of viral suppression after five years and a single CD4 test with a threshold of 250 cells/mm³ could reduce unnecessary switching

Polly Clayden, HIV i-Base

DART was a randomised trial comparing clinically driven monitoring (CDM) to laboratory (CD4, haematology, biochemistry) plus clinical monitoring (LCM) of 3316 HAART-naïve adults conducted in Uganda and Zimbabwe. People in both monitoring arms showed high and similar 5-year survival rate – 90% vs 87% in the LCM and CDM arms respectively – differing by a small percentage that only occurred after two years of follow up. This compared to an historical 5-year survival rate prior to HAART of only 8% in the Uganda cohort. [1]

First line HAART in this trial was AZT/3TC plus either TDF (74%), ABC (9%) or NVP (16%). Participants needing to switch to second line received LPV/r plus NRTI/s and/or NNRTI. Neither the CDM nor LCM group had real time viral load monitoring.

Ugandan patients who did not participate in one of two, nested second line RCTs had a viral load test when they left the trial and joined the national programme.

Further findings from the DART trial were presented at CROI 2011.

Cissy Kityo and colleagues showed high rates of virological suppression at 5 years after HAART initiation among the Ugandan participants alive and in follow up. [2]

Both monitoring groups switched to second line therapy following WHO stage 4 or multiple stage 3 events; the LCM group also switched at CD4 < 100 cells/mm³.

A viral load measurement was available the end of the trial for the majority of eligible participants: 1207 (80%) and 187 (70%) respectively receiving first and second line at exit. The viral load sample was taken at a median of 5.2 years after initiation of HAART and 2.7 years after start of second line for those who had switched.

Of the participants who remained on first line, 81.9% (95%CI 78.5-84.9%) in LCM and 74.2% (95%CI 70.6-77.6%) in CDM had viral load < 200 copies/mL, $p = 0.001$. In the LCM group 5.6% (95% CI, 3.9-7.8%) had viral loads $\leq 10,000$ copies, which was lower than the 10.4% (95%CI 8.1-13.1%) of participants in CDM.

Of those who switched, viral loads were similar across the two monitoring groups, $p=0.6$. Viral load <200 copies/mL was achieved in 88.8% (95%CI 83.3-92.9%) of participants receiving second line.

When the investigators examined the CD4 count nearest to the exit viral load measurement (taken at a maximum of 6 months apart), they found a negative association, $r=-0.4$, as would be expected.

Of 283 (20%) participants with viral load ≥ 200 copies/mL, 29% in the LCM group and 42.2% in CDM had CD4 <200 cells/mm³.

The investigators noted that CD4 counts <100 cells/mm³ were rare in either arm; only 2 people in LCM and 7 in CDM.

A related study showed a single CD4 test with a threshold of ≥ 250 cells/mm³ could reduce inappropriate switching in clinically monitored patients. [3]

Charles Gilks and colleagues investigated the relationship between CD4 count at switch and the reason for doing so in all 675 (361 LCM and 314 CDM) DART participants switching to second line.

In the CDM arm, 206 (66%) switched due to WHO stage 4 events and 76 (24%)/32 (10%) participants single or multiple WHO stage 3 events, respectively. In LCM 265 (73%) participants switched because their CD4 count fell below 100 cells/mm³, 43 (12%) for other CD4 reasons, 37 (10%) due to WHO 4 events and 6 (23%)/10 (3%) single or multiple WHO stage 3 events.

In the LCM arm, clinical failure provoked switching in 7 (2%) of patients with CD4 ≥ 250 cells/mm³; 3 due to WHO stage 4 events, 1 single WHO stage 3 event and 3 for other CD4 reasons. This compared to 64 (20%) of participants who switched with CD4 \geq in the CDM arm, $p=0.001$. The investigators noted, however, that deaths within one year of switching were similar in CDM whether participants switched above or below 250 cells/mm³, 11/64 (17%) vs 33/250 (13%) respectively.

In the CDM group, switching due to a single WHO grade 3 event was significantly more frequent with a CD4 count of ≥ 250 cells/mm³ (27/76, 36%) compared to multiple WHO stage 3 events (4/32, 12%) or WHO stage 4 events (33/206, 16%), $p=0.001$.

Viral load measurements at switch were available for 108 and 113 participants in the LCM and CDM groups respectively. Of these, 15 (14%) vs 32 (28%) respectively were <400 copies/mL, $p=0.009$.

In the CDM group, 25/31 (81%) with clinical failure and CD4 ≥ 250 cells/mm³ had viral load <400 copies/mL vs 7/82 (9%) with CD4 <250 cells/mm³, $p<0.001$.

The investigators noted a trend to switching for single WHO stage 3 events compared to multiple WHO stage 3 or stage 4, but this was not significant, $p=0.22$.

They concluded that among clinically monitored patients, a single CD4 test with a threshold of 250 cells/mm³ could identify up to 80% with viral load <400 copies/mL who are unlikely to benefit from second line therapy. In DART, nearly 40% of participants who failed clinically with a single WHO stage 3 event had CD4 >250 cells/mm³. They wrote: "Targeting this group would be particularly likely to avoid premature, costly switching to second line."

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Lopinavir/r monotherapy used as second-line therapy in resource-limited settings

Polly Clayden, HIV i-Base

WHO guidelines recommend the use of boosted protease inhibitors second line in resource limited settings. Findings from strategies looking at using lopinavir/ritonavir (LPV/r) have been uncertain to date, both in limited and richer resourced settings.

Two posters at CROI 2011 presented data from studies evaluating LPV/r monotherapy, with showed further conflicting results.

ACTG 5230 evaluated lopinavir/ritonavir (LPV/r) monotherapy in a pilot study. It was a single arm multinational trial with sites in Malawi, Tanzania, South Africa, Thailand and India.

Participants had previously received first line NNRTI-containing regimens for at least six months and had detectable viral load 1,000–200,000 copies/mL. All participants received LPV/r monotherapy BID. The primary endpoint was remaining on monotherapy without virological failure at 24 weeks. This was defined as: failure to suppress viral load to <400 copies/mL by week 24, or confirmed rebound to >400 copies/mL at or after week 16 following confirmed suppression.

People with virologic failure received intensification with emtricitabine (FTC) 200 mg/tenofovir (TDF) 300 mg.

There were 123 participants enrolled in this trial. About 60% were women and they were a median of 39 years of age, with a median CD4 of 164 cells/mm³ and viral load of 4.34 log₁₀ copies/mL (17% were $>100,000$ copies/mL).

Other baseline characteristics included: 93% with >1 year HAART, 98% with ≥ 1 NNRTI mutation and 95% with ≥ 1 NRTI mutation (87% M184V, 84% TAM, 11% K65R, 4% Q151M/L).

The majority, of participants completed 24 weeks of follow-up with the exception of one death at week 20 with a viral load of <400 copies/mL.

The investigators reported, at week 24, 107 (87%; 95% CI 80-92%) of participants remained on LPV/r monotherapy without virologic failure.

Of the remaining, 15 met the criteria for virologic failure and one added FTC/TDF before failure. Of 13 participants with data after intensification, 11 (85%) suppressed viral load to <400 copies/mL.

At virologic failure, 2/11 participants who were successfully sequenced had selected new resistance mutations (both had A71T and V82F). The overall mean CD4 count increase from baseline to week 24 was 107 cells/mm³. Overall 31 (25%) of participants experienced grade 3 or 4 toxicities. The most commonly reported grade 3 or 4 toxicities (9% of participants) were metabolic (mostly elevated lipids). Self reported adherence was high; at week 24, 83% of participants reported no missed doses.

The investigators concluded that LPV/r monotherapy showed promising preliminary activity as second-line HAART following failure of first-line NNRTI-containing regimens at 24 weeks. The lower bound of the 90% CI (81-92%) of the observed success rate (87%) was above 65%.

Torsak Bunupuradah and colleagues from the HIV STAR Study in Thailand looked at LPV/r monotherapy as second line but they also evaluated viral suppression to <50 copies/mL and included a comparison arm with triple therapy.

The STAR investigators enrolled 200 participants with viral load ≥ 1000 copies/mL on NNRTI-containing first line therapy. Participants were randomised to receive either LPV/r monotherapy or LPV/r + TDF + 3TC.

Treatment failure was defined as viral load >400 copies/mL at ≥ 24 weeks. Participants meeting these criteria in the monotherapy arm received intensification with TDF + 3TC.

Participants in this study were about 60% men with a median age of 37 years, CD4 of 188 cells/mm³, and viral load of 4.1 log₁₀ copies/mL.

Prior to switching, 92% of participants were receiving 3TC, 63% d4T, 23% AZT and 5% TDF. Nevirapine and efavirenz were received by 86% and 14% participants, respectively. Without significant differences between arms, 15% of participants had ≥ 3 TAMS, 82% had M184V/I, 6% had Q151M, and 7% had K65R.

By intent-to-treat analyses at 48 weeks, the proportion of patients with viral load <400 copies/mL the LPV/r monotherapy arm was 75% vs 86% in the TDF/3TC/LPV/r arm, $p=0.53$. But, only 61% of the LPV/r monotherapy arm vs 83% in TDF/3TC/LPV/r arm had a viral load <50 copies/mL, $p<0.01$.

Major PI mutations were detected in 1 of 2 LPV/r monotherapy and 0 of 3 TDF/3TC/LPV/r treated participants with genotype results following treatment failure. There was no significant difference in CD4 count increase between arms: 114 vs 137 cells/mm³ in the LPV/r monotherapy and TDF/3TC/LPV/r arms respectively. One death (unrelated to study drugs) was reported in each arm. Serious adverse events were reported in two patients in the LPV/r monotherapy arm and seven patients in the TDF/3TC/LPV/r arm.

The investigators concluded that LPV/r monotherapy should be used with caution as a second-line option, particularly in settings where close viral load monitoring is not available.

COMMENT

The ongoing EARNEST Trial (NCT00988039) will answer the question whether or not lopinavir/r monotherapy is a sufficiently potent regimen compared to lopinavir/r combined with two NRTIs or raltegravir.

Results from this trial are expected in 2013.

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Pharmacokinetics of different rifabutin dosing strategies with lopinavir/ritonavir-based ART

Polly Clayden, HIV i-Base

Interactions between rifampicin and protease inhibitors makes treating patients coinfecting with HIV and TB more complicated.

Rifabutin is an alternative rifamycin, which can be used in patients receiving a protease inhibitor. Recent findings suggest that the current recommended dose of lopinavir/r (LPV/r) is suboptimal. There are limited data regarding the newer formulation of LPV/r.

Investigators from University of Cape Town, International Union Against Tuberculosis and Lung Disease and WHO evaluated the pharmacokinetics (PK) of rifabutin in co-infected patients on a first line TB regimen before and after the initiation of LPV/r-based ART.

Suhashni Naiker and colleagues showed findings from this study in a poster at CROI 2011.

A group of 16 patients on stable rifabutin-containing TB regimens were initiated on LPV/r-containing HAART. At HAART initiation they were randomised to receive either: rifabutin 150 mg daily for 1 month followed by 150 mg 3 times weekly, or 3 times weekly doses followed by daily doses.

The investigators measured serial rifabutin and 25-O-desacetyl rifabutin concentrations during a dose interval after 4 weeks of rifabutin 300 mg daily, after 4 weeks of 150 mg rifabutin daily with LPV/r-based HAART, and after 4 weeks of rifabutin 150 mg 3 times a week with LPV/r-based ART.

At baseline the participants were a mean (SD) of 31.6 (5.5) years, 59.0 (9.4) kg, 160.1 (7.1) cm and 147 (43) CD4 cells/mm³. Ten were men. Two were not included in the analysis due to poor adherence.

The investigators reported median AUC₀₋₂₄ and C_{max}, for participants receiving 300 mg rifabutin daily, 150 mg rifabutin three times a week, and 150 mg rifabutin daily, respectively, of 3026 ng/mL.h and 297 ng/mL, 2307 ng/mL.h and 168 ng/mL, and 5010 ng/mL.h and 311 ng/mL.

They found that rifabutin was well tolerated at all dosing strategies. There was one case of uveitis that occurred before LPV/r was initiated, and one grade 2 transaminitis and one grade 2 neutropenia were also reported.

They concluded that rifabutin 150 mg daily used with LPV/r produces C_{max} concentrations within the recommended target range of 300 to 900 ng/mL.

Ref: Naiker S et al. Pharmacokinetic evaluation of different rifabutin dosing strategies in African TB patients on lopinavir/ritonavir-based ART. 18th CROI, 27 February–2 March 2011, Boston. Poster abstract 650. <http://www.retroconference.org/2011/Abstracts/41692.htm>

Initiation of ART during breastfeeding can induce multidrug resistance in infants

Polly Clayden, HIV i-Base

In resource-limited settings some HIV-positive women initiate ART during breastfeeding. This exposes infected infants to the risk emergence of resistance to the antiretrovirals in their mothers' regimen.

Investigators from the Post Exposure Prophylaxis of Infants (PEPI)-Malawi trial - in which infants were received up to 14 weeks of extended nevirapine (NVP) or extended NVP plus AZT - evaluated resistance in infants whose mothers began ART post-partum.

Interim data from this analysis was first presented as a poster at CROI. [1] Further findings were reported in a subsequent article in the April 24 2011 edition of AIDS. [2]

Infant plasma samples were collected at 14 weeks of age and tested using the ViroSeq HIV Genotyping System and LigAmp – a sensitive point mutation assay - to detect K103N (limit of detection 0.5%) and Y181C (limit of detection 1%). Later samples collected at 6 and 12 months of age were also analysed using LigAmp.

The investigators found that at 14 weeks 82/108 (75.9%) of infants evaluated had detectable NVP resistance using the Viroseq assay. The proportion of infants with K103N and/or Y181C detected by LigAmp was similar, 78/108 (72.2%), $p=0.45$. There were no significant differences between rates of resistance among infants receiving extended NVP or NVP plus AZT measured by either assay. Nor were: duration of prophylaxis received prior to infant diagnosis, maternal CD4 count, maternal single dose NVP use, or in utero infection, significantly associated with NVP resistance.

At 6 months, 38 out of 46 (82.6%) samples analysed still had K103N and/or Y181C. Again, results were similar across study arms, $p=1.0$. And at 12 months 19 out of 29 (66.5%) evaluable infants had these mutations in similar proportions across arms, $p=0.43$.

Although the data was not presented, the investigators noted that there was no significant difference in the percentage of the total viral population of either K103N or Y181C in infants in the two groups with these mutations at 6 and 12 months of age.

The investigators concluded that the frequent persistence of the K103N and Y181C mutations in infants after exposure to extended NVP prophylaxis, with or without AZT, may compromise the infants' subsequent response to NNRTI-based treatment.

References

1. Fogel J et al. Initiation of ART in women after delivery can induce multi-class drug resistance in breastfeeding HIV-infected infants: PEPI-Malawi Trial. 18th CROI, 27 February–2 March 2011, Boston. Poster abstract 761. <http://www.retroconference.org/2011/Abstracts/40399.htm>
2. Fogel J et al. Analysis of nevirapine (NVP) resistance in HIV-infected infants who receive extended NVP or NVP/zidovudine prophylaxis. AIDS 2011 25 911-917. 24 April 2011.

Treating children previously exposed to single dose nevirapine: update on IMPAACT P1060 and NEVEREST

Polly Clayden, HIV i-Base

Two oral presentations at CROI 2011 showed further findings from studies looking at treatment in children previously exposed or unexposed to maternal/infant single dose nevirapine (NVP) in prevention of mother to child transmission (PMTCT) programmes.

IMPAACT 1060

IMPAACT P1060 was a randomised trial to determine whether NVP- or lopinavir/ritonavir (LPV/r)-based treatment performed better in young children exposed and unexposed to single dose NVP. All children received AZT plus 3TC. The trial comprised of Cohort 1 (exposed children) and Cohort 2 (unexposed children). Data from Cohort 1 have previously been reported and this part of the study was stopped early after a scheduled Data Safety Monitoring Board (DSMB) review, as there was an unsurprising trend towards more failure in the children receiving NVP- compared to LPV/r-based treatment.

Peter Palumbo presented results from Cohort 2. This cohort enrolled children aged 2 to 36 months, who met WHO criteria for treatment and were unexposed to single dose NVP. Children were stratified by age $<$ or \geq 12 months. Children with TB were excluded from the trial.

The study had a composite primary endpoint of treatment failure, which comprised viral failure (<1 log₁₀ decline from baseline to after 12 to 24 weeks or >400 copies/mL at week 24), or permanent discontinuation of NVP or LPV/r, including death by 24 weeks. Rates were calculated from Kaplan-Meier curves for each treatment group and age group.

Secondary endpoints included time to virological failure by 24 weeks, time to treatment failure throughout follow up and time to virological failure or death throughout follow up.

P1060 Cohort 2 was fully enrolled with 288 children by March 2010 and had 48-week planned follow-up to March 2011. In October 2010, the DSMB recommended that the study was unblinded. All children had completed 24 weeks of follow up.

Dr Palumbo reported that the children's median age at enrollment was 1.7 years (73% >12 months) and their median baseline viral load and CD4 percentage were 535,632 copies/mL and 15% respectively. The majority (79%) of children were subtype C. The median follow-up was 72 weeks.

At week 24, 87 children had reached an endpoint; 60 in the NVP and 27 in the LPV/r arms. The overall difference in failure rate was 21.5% (95% CI, 11.2-31.8) in favour of LPV/r, $p<0.001$. This was similar in both age groups: 22.0% (<12 months) and 21.3% (≥ 12 months).

There was also a significant difference in time to off study drug, over the full length of the trial, $p<0.001$. There were 10 vs 3 deaths in the NVP vs LPV/r arms during the entire follow-up period (none judged related to study drugs), but this did not reach statistical significance, $p=0.63$.

There was a notable amendment during the course of the trial. In 2007 the recommended NVP dose in WHO guidelines increased from the FDA recommended dose of 7mg/kg to 160-200mg/m² (max 200mg). Only 32 children were enrolled under the lower

dose compared to 115 at the higher one but the investigators saw no effect associated with this change.

Dr Palumbo noted that the main reasons for off study were more virological failure, toxicity and death in the NVP arm.

As both the NEVEREST and P1060 Cohort 1 data had suggested poorer weight and CD4 improvement in children receiving LPV/r compared to NVP, the investigators also looked at this in Cohort 2. They did not find a statistically significant difference in CD4 improvement between the two arms but there was a difference in weight z-score favouring NVP at 24 and 48 weeks, respectively $p=0.007$ and $p=0.009$.

When the investigators looked at NVP resistance in samples from subsets of children at baseline and time of virological failure, they found 2.4% (5/206) with resistance at baseline compared to 56% (10/18) at time of virological failure.

These results were different to those in the sister study, OCTANE P1060, in which maternal data demonstrated non-inferiority of NVP- to LPV/r-based treatment, by the study definition, for NVP- unexposed women.

This highlighted the "unique and challenging situation of early paediatric HIV infection", Dr Palumbo said, including very high baseline viral load and the unforgiving nature of NVP resistance. LPV/r is already recommended for NVP-exposed children and discussions are ongoing as to whether this recommendation should expand to all young children, possibly up to three years of age.

These data once again point to the importance of developing new first and second line options for use in this age group.

NEVEREST

Louise Kuhn presented data from NEVEREST, a study designed to evaluate a treatment switch strategy from LPV/r to NVP in NVP-exposed children.

In this study, 323 children aged 6 weeks to 2 years and eligible for treatment were initiated on LPV/r plus 3TC plus d4T. After achieving a viral load <400 copies/mL and maintaining it for ≥ 3 months, children were randomised ($n=195$) to either remain on LPV/r ($n=99$) or switch to NVP ($n=96$). Time to any viral load >50 copies/mL or confirmed >1000 copies/mL was compared using Kaplan-Meier methods and log-rank tests.

Fifty-two week data post switch from this study has been reported previously. These data revealed a higher proportion of children suppressed to <50 copies/mL (the primary endpoint) in the NVP arm but also a higher proportion in that group with confirmed >1000 copies/mL.

Dr Kuhn showed longer term results from this study with follow up of 18-53 months.

There were three deaths in each group. At 36 months post randomisation, as with the earlier analysis, more children in the NVP group (40.5%) maintained viral load <50 copies/mL than those in the LPV/r group, $p=0.01$. Again, more in the NVP (23.9%) than in the LPV/r (11.1%) had confirmed >1000 copies/mL, $p=0.01$.

This difference persisted at 48 months, for <50 copies/mL and >1000 copies/mL, respectively $p=0.02$ and $p=0.08$.

At 6 months 59.1% of the failures in the NVP group had occurred vs 10% in the LPV/r group. By 12 months these proportions were

100% in the NVP group and 50% in the LPV/r group. Dr Kuhn noted that among children in the LPV/r group, 6% of failures occurred between 12 and 48 months.

Treatment failure >1000 copies/mL was associated with the presence of pre-treatment NVP mutations, $p=0.02$. There was no difference in response between children in the NVP and LPV/r groups in children who had no pre-treatment NVP resistance. Half the children with detectable NVP mutations failed when re-challenged with NVP.

Dr Kuhn concluded that viral load testing can identify all switch failures and that switching can be accomplished safely if viral load testing is available. Also that pre-treatment screening for resistance can be used to identify the children who could benefit from this strategy.

References

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2. Kuhn L et al. Long-term outcomes of switching children to NVP-based therapy after initial suppression with a PI based regimen. 18th CROI, 27 February–2 March 2011, Boston. Oral abstract 128. <http://www.retroconference.org/2011/Abstracts/41025.htm>

Lopinavir/ritonavir oral solution toxicity in neonates

Polly Clayden, HIV i-Base

Lopinavir/ritonavir (LPV/r, Kaletra) oral solution is approved by the FDA for infants 14 days of age and older. US guidelines do not recommend its use in preterm infants.

LPV/r oral solution has particular pharmacokinetic properties that make its use complicated in neonates. It contains high volumes of both ethanol (356.3 mg/mL, 42% volume solute/volume solution (v/v) and propylene glycol (152.7 mg/mL, 15.3% v/v).

Neonates have reduced alcohol dehydrogenase and CYP3A4 activity and immature renal function. Ethanol is 95% and propylene glycol is 55-75% metabolised in the liver by alcohol dehydrogenase. Ethanol inhibits the metabolism of propylene glycol by alcohol dehydrogenase leading to elevated concentrations. LPV is metabolised by CYP3A.

Reduced hepatic metabolism and renal clearance in neonates, particularly in preterm infants, can lead to accumulation of all three ingredients to toxic levels.

Acute ethanol toxicity is linked to central nervous system (CNS) and respiratory depression, and gastritis. Propylene glycol is also associated with CNS and respiratory depression, as well as renal failure and metabolic acidosis. LPV has been shown to cause PR and QT interval prolongation and AV block in adults with very high levels of the drug.

Cases of toxicity in neonates – particularly preterm - have been reported to the FDA Adverse Event Reporting System (AERS).

A poster authored by Debra Boxwell and colleagues from the FDA showed data from case studies from a search of the AERS database for all reports of toxicity in children 2 years of age or under following dosing with LPV/r oral solution.

The search revealed 10 unduplicated cases in neonates of whom 8 were preterm. Of the preterm infants, 3 were born at 28 weeks gestation, 1 at 30 weeks, 2 at 32 weeks and 2 at 34 weeks.

The documented adverse events included cardiac toxicity (bradycardia, complete AV block, bundle branch block, or cardiac failure; (n=7), acute renal failure (n=5), increased serum creatinine (n=1), elevated serum lactate level (n=2), hyperkalemia (n=4), respiratory failure (n=2), hypotonia (n=1), abnormal EEG (n=1), and CNS depression (n=1).

Outcomes included 1 death, 2 life threatening and 4 hospitalisations. Therapy was initiated on the day of birth in 7 neonates, day after birth in 1, day 34 in 1, and unknown in 1.

Onset the first adverse event occurred within 1 to 6 days (n = 8). Discontinuation of Kaletra (n=9) resulted in recovery within 1 day in 1, 2 days in 2, 3 days in 2, 6 days in 3, 20 days in 1 and was unknown in 1.

WHO set 25mg/kg as a maximum acceptable daily intake of propylene gel when it is used as a food additive. The European Medicines Agency (EMA) recommends that a 12.5mg/dL blood concentration of ethanol after a dose of any medication should not be exceeded. In IMPAACT P1030 – a PK sub-study in full-term infants 6 weeks of age – the mean steady state of LPV was 5.2±1.8ug/m² twice daily. When the FDA investigators looked at neonatal exposure to the three ingredients in the cases for which data were available, the results were far in excess of these recommendations. See Table 1: Neonatal exposure to lopinavir, ethanol and propylene glycol.

Table 1: Neonatal exposure to lopinavir, ethanol and propylene glycol

Reported LPV/r dose	Daily propylene glycol intake (mg/kg/day)	Calculated blood ethanol concentration per dose (mg/dL) ³	Highest measured LPV level (ug/mL)
230 mg/m ² BID	89.5	11.0	--
230mg/m ² BID	87.4	10.6	--
30mg TID	81.8	6.8	25.3
30mg TID	78.1	6.5	20.2
520mg QD	451.2 X 1	111	28.5
40mg BID	117.5	14.5	16.2
20mg/kg BID	76.4	11.3	29.2

The investigators concluded that the ten cases to the AERS suggest that neonates, especially those born preterm, who received LPV/r oral solution, were at increased risk of toxicities from drug accumulation. They added that the improvement of symptoms when the drug was stopped support this association.

There are limitations to the AERS however. Because reporting is voluntary, the quality of reporting is very variable. The database is subject to under reporting as well as reporting bias and both the numerator and the denominator are unknown for any event reviewed. Therefore the incidence or estimated risk cannot be calculated.

COMMENT

This analysis provoked a FDA label change and the lopinavir/r oral solution is not recommended for neonates particularly preterm.

Reference

Boxwell D et al. Neonatal toxicity of Kaletra oral solution—LPV, ethanol or propylene glycol? 18th CROI, 27 February–2 March 2011, Boston. Poster abstract 708.

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Paediatric antiretroviral pipeline: darunavir and raltegravir

Polly Clayden, HIV i-Base

Two posters at CROI 2011 presented pharmacokinetic (PK), efficacy and safety data of paediatric formulations of antiretroviral drugs. [1, 2]

Darunavir

ARIEL (TMC114-C228) is a 48-week, open-label, single-arm, phase II trial evaluating PK, safety and efficacy of darunavir/ritonavir (DRV/r) plus an optimised background regimen (OBR) in HIV-positive treatment-experienced children. Avy Violari and colleagues reported interim (24 week) data from ARIEL.

Children aged 3 to <6 years, weighing 10 to <20kg, with viral load >1000 copies/mL and <3 DRV resistance-associated mutations (RAM) at screening, received DRV. The formulation used in this study is a high concentrate oral suspension (100 mg/mL) - initially dosed at 20 mg/kg BID plus ritonavir (RTV) 2.6 to 3.2mg/kg BID with an OBR (≥2 active NRTI) - over 48 weeks.

After a PK analysis at week 2, the DRV dose was amended to 25mg/kg BID children weighing 10 to 15kg and 375mg BID fixed for those weighing 15 to <20 kg (following Data Safety Monitoring Board recommendations).

A total of 27 patients - 55.6% male and mean age 4.6 years at screening - with DRV/r + an OBR. At baseline, the children's median viral load was 4.51 log copies/mL, median CD4 count was 927 cells/mm³, and median CD4 percentage was 27.7% cells/mm³. The children had a median of 0 primary PI mutations at baseline and 4 PI RAM, 1 NRTI RAM, and 1 NNRTI RAM.

The majority of children, 23 (85.2%) experienced at least one adverse event (AE). One child discontinued treatment (due to grade 2 vomiting, believed to be associated with ritonavir). Most side effectss were grade 1-2. Grade 3-4 and serious side effects were reported in 18.5% and 11.1% of patients, respectively but none was considered treatment-related. Most commonly reported adverse events (occurring in over 10% of patients) were diarrhea, vomiting, pyrexia, nasopharyngitis, rhinitis, upper respiratory tract infection, hypokalemia, cough, acidosis, and alkalosis. One child had a grade 3 laboratory abnormality – neutropenia - but this was present since baseline and not considered to be related to treatment.

There was a steady increase in response from week 2 to 24. By week 24, 55.6% of the children met the primary efficacy endpoint of viral load <50 copies/mL (ITT-TLOVR). The mean increase in CD4 at week 24 was 109 cells/mm³.

Two children had DRV RAMs at baseline but both were <50 cells/mL at week 24. Eleven children (40.7%) were considered virological failures. None of the six children with paired baseline/endpoint genotype samples developed PI or NRTI RAMS.

Raltegravir

P1066 is an open-label study of raltegravir (RAL) in treatment experienced HIV-positive children and adolescents. Sharon Nachman and colleagues reported PK, and week 12 and 24 efficacy and safety data for treatment-experienced children aged 2 to 5 years receiving the RAL chewable tablet formulation.

In this dose finding study, intensive PK was initially performed on 4 children and once PK targets were met, 8 more were enrolled. Inclusion criteria included viral load >1000 copies/mL, prior ART experience but naïve to integrase inhibitors. A RAL chewable tablet 6 mg/kg twice daily was added to the existing regimen, intensive PK samples were taken between days 5 and 12. Once the dose was selected, an additional 9 children were enrolled to assess longer-term safety and efficacy.

PK parameters were evaluated and a dose was selected using an AUC_{12h} target (range 14 to 25uM*h) based on available PK data with a C_{12h} target to exceed the protein-adjusted IC₉₅ of RAL against wild type virus. The investigators compared PK parameters to existing data from 6 to 18 year old children and adolescents receiving the adult formulation and 6 to 11 year old children receiving RAL chewable tablet. Of the 12 children, 67% were female, they were a mean, age of 3 years old, viral load 4.14 log₁₀ copies/mL, CD4%, 33% cells/mm³, CD4 count, 1505 cells/mm³, and weight, 14.3 kg. They received a mean RAL dose of 6.24 mg/kg (0.67).

The geometric mean AUC₁₂ was 8.8hr*mg/L, 18uM*h; C_{12h} 32ng/mL, 71nM; C_{max} 4329ng/mL, 9.7uM; CL/F 10.5L/hr and %CV 77%. A 6mg/kg BID dose (maximum 300mg) was selected.

At week 24, by ITT analysis, 62% (95% CI, 53-92) of children (n=21) were <400 copies/mL and 52% (95% CI, 30-74) <50 copies/mL. CD4 gain from baseline was a median of 4.1% (95% CI 2.0-9.9) and 218 (95% CI 39-290) cells/mm³.

No child discontinued RAL due to AEs in this study. One child had grade 3 ALT (2 events), grade ≥3 AST and ungraded elevated GGT (5 events), considered possible treatment related. Three children had grade ≥3 neutropenia (7 events) but this was not judged to be treatment related. Other non-treatment related events were: grade 3 bronchopneumonia, grade 3 hydrogen ion concentration, ungraded lactic acidosis, decreased blood glucose, acute gastro enteritis and impetigo.

References

1. Violari A et al. ARIEL: 24-week safety and efficacy of DRV/r in treatment-experienced 3- to <6-year-old patients. 18th CROI, 27 February–2 March 2011, Boston. Poster abstract 713. <http://www.retroconference.org/2011/Abstracts/42411.htm>
2. Nachman S et al. Interim results from IMPAACT P1066: RAL oral chewable tablet formulation for 2- to 5-year-olds. 18th CROI, 27 February–2 March 2011, Boston. Poster abstract 715. <http://www.retroconference.org/2011/Abstracts/40427.htm>

ANTIRETROVIRALS

FDA approve new NNRTI rilpivirine (Edurant) in the US

On 20 May 2011, the FDA approved rilpivirine (Edurant) 25 mg tablets, as a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for use in combination with other antiretroviral to treat HIV.

The recommended dose of rilpivirine is one 25 mg tablet once daily taken orally with a meal.

The following points should be considered when initiating therapy with rilpivirine:

- More rilpivirine treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy
- The observed virologic failure rate in rilpivirine treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz
- More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz

Summary of clinical trial results

The approval of rilpivirine is based on Week 48 safety and efficacy analyses from two randomised, double blind, active controlled, phase 3 trials (TMC278-C209: ECHO and TMC278-C215: THRIVE) in treatment naïve subjects and Week 96 safety and efficacy analyses from a Phase 2b trial in treatment-naïve subjects.

The Week 48 efficacy outcome for the pooled data from TMC278-C209 and TMC278-C215 are as follows.

Overall, the proportion of subjects with HIV RNA <50 copies/mL was 83% for rilpivirine based regimen compared to 80% for efavirenz based regimen. The predicted difference (95% CI) of response rates is 2.0 (-2.1; 6.1). The overall virologic failure rate was 13% for the rilpivirine compared to 9% for the efavirenz. The proportion of patients who discontinued study due to an adverse event or death was 2% for rilpivirine and 7% for efavirenz.

Response rate was also calculated by baseline plasma viral load. For subjects with baseline plasma viral load ≤100,000 copies/mL, >100,000 to ≤500,000 copies/mL and >500,000 copies/mL, the proportion of subjects with HIV RNA < 50 copies/mL was 89%, 78% and 65% for rilpivirine compared to 83%, 78% and 73% for efavirenz respectively.

The virologic failure rate by baseline plasma viral load is as follows. For subjects with baseline plasma viral load ≤100,000 copies/mL, the proportion of subjects with virologic failure was 5% for both rilpivirine and efavirenz. For subjects with baseline plasma viral load >100,000 to ≤500,000 copies/mL and >500,000 copies/mL, the proportion of subjects with virologic failure was 20% and 29% for rilpivirine compared to 11% and 17% for efavirenz, respectively.

In the pooled resistance analysis from the Phase 3 Studies C209 and C215, the emergence of resistance among subjects was greater in the rilpivirine arm compared to the efavirenz arm. In

the combined studies, 41% (38/92) of the virologic failures in the rilpivirine arms had genotypic and phenotypic resistance to rilpivirine compared to 25% (15/60) of the virologic failures in the efavirenz arms who had genotypic and phenotypic resistance to efavirenz. Moreover, resistance to a background drug (emtricitabine, lamivudine, tenofovir, abacavir or zidovudine) emerged in 48% (44/92) of the virologic failures in the rilpivirine arms compared to 15% (9/60) in the efavirenz arms.

Emerging NNRTI substitutions in the rilpivirine virologic failures included V90I, K101E/P/T, E138K/G, V179I/L, Y181I/C, V189I, H221Y, F227C/L and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently on rilpivirine treatment commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and the tenofovir resistance-associated substitutions K65R or N emerged more frequently in rilpivirine virologic failures compared to efavirenz virologic failures.

Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure and development of rilpivirine resistance. In the pooled analyses of the Phase 3 clinical trials, 38 rilpivirine virologic failure subjects had evidence of rilpivirine resistance. Of these subjects, 89% (n = 34) were resistant to etravirine and efavirenz, and 63% (n = 24) were resistant to nevirapine. In the efavirenz arm, none of the 15 efavirenz-resistant virologic failures were resistant to etravirine at failure. Subjects experiencing virologic failure on rilpivirine developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on efavirenz.

Contraindications and drug interactions

Rilpivirine is contraindicated with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs:

- The anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- The antimycobacterials rifabutin, rifampin, rifapentine
- Proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- The glucocorticoid systemic dexamethasone (more than a single dose)
- St John's wort

Warnings and precautions

The Warnings and Precautions for rilpivirine include fat redistribution, immune reconstitution syndrome and the following:

Drug Interactions: Caution should be given to prescribing rilpivirine with drugs that may reduce the exposure of rilpivirine.

In healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram. Rilpivirine should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes.

Depressive Disorder: The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with rilpivirine. During the Phase 3 trials (N=1368), the incidence of depressive disorders (regardless of causality, severity) reported among rilpivirine (n = 686) or efavirenz (n = 682) was 8% and 6%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both rilpivirine and efavirenz. The incidence of discontinuation due to depressive disorders among rilpivirine or efavirenz was 1% in each arm. Suicide attempt was reported in 2 subjects in the rilpivirine arm while suicide ideation was reported in 1 subject in the rilpivirine arm and in 3 subjects in the efavirenz arm. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to rilpivirine, and if so, to determine whether the risks of continued therapy outweigh the benefits.

Side effects

The most common adverse drug reactions to rilpivirine (incidence > 2%) of at least moderate to severe intensity (\geq Grade 2) were depression, insomnia, headache and rash. The most common adverse drug reactions leading to discontinuation were psychiatric disorders: 10 (1%) subjects in the rilpivirine arm and 15 (2%) subjects in the efavirenz arm. Rash led to discontinuation in 1 (0.1%) subject in the rilpivirine arm and 10 (1.5%) subjects in the efavirenz arm

Rilpivirine is a product of Tibotec Therapeutics.

Source: FDA list serve (20 May 2011).

Please refer to the full prescribing information for details.

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

FDA approve new NNRTI-based fixed dose combination of rilpivirine/tenofovir/FTC (Complera) in the US

On 10 August 2011, US Food and Drug Administration (FDA) approved a fixed-dose combination of rilpivirine/tenofovir/FTC (Complera) with an indication in treatment-naïve adults. This is a single-tablet once-daily combination.

Approval was based on bioequivalence to the individual drugs taken separately, together with the phase 3 registrational studies for rilpivirine (ECHO and THRIVE) (see rilpivirine approval article above). [1]

References

1. US Food and Drug Administration approves Gilead sciences' Complera, a new complete once-daily, single-tablet regimen for HIV-1 infection in treatment-naïve adults. Gilead press release. (10 August 2011).
http://www.gilead.com/pr_1595280
Prescribing information
http://www.gilead.com/pdf/complera_pi.pdf

TREATMENT ACCESS

FDA approval of generic ARVs

Since the last issue of HTB, the US Food and Drug Administration (FDA) has granted tentative approval (or ** full approval) for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
AZT/3TC tablets, 300 mg/150 mg	Teva, USA **	25 May 2011
Tenofovir DF tablets, 300 mg	Strides, India	25 May 2011
Abacavir/3TC scored tablets, 60 mg/30 mg	Cipla, India	12 May 2011

** Full approval enables this generic to be sold in the US.

FDC: Fixed Dose Combination

“Tentative Approval” means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States. Tentative approval does, however make the product eligible for consideration for purchase under the PEPFAR program for use outside the United States.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf>

Effective patent dates are listed in the agency’s publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:

<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

An updated list of generic tentative approvals is available on the FDA website:

<http://www.fda.gov/oia/pepfar.htm>

Source: FDA list serve:

<http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

Gilead signs up for Medicines Patent Pool

Simon Collins, HIV i-Base

On 12 July, Gilead became the first commercial pharmaceutical company to sign up for the Medicines Patent Pool initiative to broaden generic manufacturing of antiretrovirals drugs for use in resource limited settings.

After many years in development, this programme was originally launched by UNITAID in November 2010 but now runs as an independent organisation. It aims to stimulate new drugs and formulations and increase access to HIV treatment by negotiating voluntary licenses on medicine patents.

The arrangement with Gilead includes tenofovir, FTC, the pharmacokinetic booster cobicistat and the integrase inhibitor elvitegravir. The agreement covers each drug individually and in appropriate combinations (as in the Gilead four-drug ‘Quad’ formulation). This is exciting as cobicistat, elvitegravir and the Quad are products still in clinical development. Importantly it provides some hope that integrase inhibitors will potentially be available in resource-limited countries.

The agreement provides Gilead with royalties calculated at 3-5% of generic sales, with royalties waived for any new paediatric formulations, and each license is granted for a limited number of countries: 111 for tenofovir and FTC, 102 of cobicistat and 99 for elvitegravir and Quad.

Médecins Sans Frontières in a press release following this news, while welcoming the news also highlighted limitations. [2]

MSF press release states that the agreement limits competition “by confining manufacturing to one country (India) and includes narrow supply options for APIs needed to make the drugs. Most critically, people living with HIV in certain middle-income countries are excluded. This contrasts sharply to the first Pool license granted by the US National Institutes of Health for all developing countries. If voluntary measures like the Patent Pool are unable to ensure people access to the medicines they need, countries that are left out will need to aggressively pursue non-voluntary paths such as compulsory licenses.”

The Patent Pool is negotiating with at least five other companies and have publically announced that talks with Boehringer-Ingelheim and Bristol-Myers Squibb have started. [3]

“Of all pharmaceutical companies with HIV medicines patents, only three are currently not in negotiation with the Pool. We call on Johnson & Johnson, Merck, and Abbott to follow the lead of their colleagues and enter into negotiations with us,” said Ellen ‘t Hoen, executive director of the Medicines Patent Pool.

The Pool received its first licence, related to darunavir, from the United States National Institutes of Health in September 2010.

References

1. Patent Pool press release. The Medicines Patent Pool announces first licensing agreement with a pharmaceutical company. (12 July 2011).
<http://www.medicinespatentpool.org/LICENSING/Current-Licences/Medicines-Patent-Pool-and-Gilead-Licence-Agreement>
2. MSF press release. MSF reaction to Gilead’s announcement about AIDS drugs/patent pool. (12 July 2011).
<http://www.pharma-mag.com/News/tabid/63/EntryId/331/MSF-Reaction-to-Gileads-Announcement-about-AIDS-Drugs-Patent-Pool.aspx>
3. Patent Pool press release. The Medicines Patent Pool announces negotiations with two additional pharmaceutical companies, landmark licensing deal. (18 July 2011).
<http://www.medicinespatentpool.org/NEWS-ROOM/Journalists/BI-BMS-Enter-Negotiations>

Further information

Medicines Patent Pool
<http://www.medicinespatentpool.org/>
UNITAID
<http://www.unitaid.eu/>

DRUG INTERACTIONS

Dolutegravir (S/GSK1349572) with multivitamins or acid reducing agents

hiv-druginteractions.org

Dolutegravir (S/GSK1349572) is an unboosted, once-daily, next-generation HIV integrase inhibitor. The effects of multivitamins (One-A-Day Maximum, single tablet), antacid (Maalox 20 mL single dose with or 2 hours after dolutegravir) and omeprazole (40 mg once daily for 5 days) on single doses of dolutegravir (50 mg) were studied in HIV-negative subjects.

Coadministration of the multivitamin modestly decreased dolutegravir AUC and C_{max} by 33% and 35%, respectively. Concurrent antacid co-administration reduced dolutegravir AUC and C_{max} by 74% and 72%, respectively. Staggered antacid dosing significantly diminished this interaction, with a reduction in dolutegravir AUC of 26% and C_{max} of 18%. Omeprazole did not significantly affect dolutegravir exposure (no change in AUC, 9% decrease in C_{max}).

Dolutegravir can be taken with proton pump inhibitors and multivitamins without dose adjustment but should be administered 2 hours before or 6 hours after antacids. The mechanism of the antacid interaction with dolutegravir is likely to result from chelation with metal cations in the antacid rather than an effect of pH and would be consistent with the omeprazole data.

Source: hiv-druginteractions.org (23 June 2011).

Ref: Patel P et al. Pharmacokinetics of the HIV integrase inhibitor S/GSK1349572 co-administered with acid-reducing agents and multivitamins in healthy volunteers. *J Antimicrob Chemother*, 2011, 66(7): 1567-1572.

<http://www.ncbi.nlm.nih.gov/pubmed/21493648>

Case Reports – Cushing’s syndrome with atazanavir/ritonavir

hiv-druginteractions.org

Two cases have been reported recently of patients developing Cushing’s syndrome when treated with atazanavir/ritonavir and corticosteroids.

The first case describes a 75 year old man with a history of HIV for 27 years, hepatitis C, hypothyroidism, recurrent deep venous thrombosis, hypertension, and chronic kidney disease was admitted for treatment of worsening chronic diarrhea and bright red blood per rectum. [1]

His antiretroviral regimen was atazanavir/ritonavir (300/100 mg daily), lamivudine (150 mg daily) and nevirapine (300 mg twice daily). Other medications included atenolol, atropine/diphenoxylate, calcitriol, cholecalciferol, fondaparinux, levothyroxine, lisinopril, loperamide, ranitidine, testosterone patch, trazodone, and vardenafil. Colonoscopy showed lymphocytic colitis at multiple biopsy sites and oral budesonide (3 mg 3 times a day) was started.

The patient’s diarrhea improved, but he was admitted 12 days later with 10.4 kg weight gain, severe leg and facial swelling,

and uncontrolled hypertension. Physical examination was notable for blood pressure 177/102 mm Hg, cushingoid facies, and 2+ pedal and pretibial edema to the knees. As the colitis had improved dramatically with budesonide therapy, the plan was to continue it for a full 6-week treatment course, if possible. Amlodipine, hydralazine, and furosemide were added to control the hypertension and edema, but budesonide was discontinued after 3 weeks because of persistent severe edema that was refractory to furosemide.

The patient developed edema, weight gain, uncontrolled hypertension, cushingoid facies, hypokalemia, and metabolic alkalosis shortly after initiation of budesonide, with resolution of all symptoms soon after it was stopped. Congestive heart failure, liver disease, and nephrotic syndrome were ruled out as causes of the edema, which supported the diagnosis of iatrogenic Cushing’s syndrome. Although budesonide concentrations were not measured, the very low serum cortisol level (0.8 µg/dL) in a clinical setting of hypercortisolism provides strong indirect evidence that levels of an exogenous corticosteroid (ie, budesonide) were high.

Budesonide is inactivated through extensive first-pass metabolism by hepatic CYP3A4. The P-glycoprotein (PGP) export pump also limits budesonide serum concentrations by promoting the gastrointestinal excretion of CYP3A4 substrates. By inhibiting CYP3A4 and PGP, protease inhibitors such as ritonavir and atazanavir limit both the first-pass metabolism and gastrointestinal excretion of CYP3A4 substrates and result in increased serum concentrations of steroids.

The second case was of Cushing’s syndrome and adrenal axis suppression in a patient treated with ritonavir and corticosteroid eye drops. [2]

A 51-year-old woman with HIV presented with weight gain and a 1-month history of right hip pain. Her ART included tenofovir (300 mg once daily), emtricitabine (200 mg once daily), and atazanavir/ritonavir (300/100 mg once daily). Because of previous bilateral cytomegalovirus retinitis, complicated by immune recovery uveitis with severe, chronic, cystoid macular oedema, she was also using dexamethasone 0.1% eye drops six times daily, and betamethasone 0.1% eye ointment at night, in both eyes.

On examination, she was noted to have central adiposity and enlargement of the dorsocervical fat, but no peripheral lipotrophy. An MRI scan of the hip showed avascular necrosis. A tetracosactide (Synacthen) stimulation test showed marked suppression of the pituitary-adrenal axis, with a baseline cortisol of less than 25 nmol/L rising to only 37 nmol/L 30 min after administration of tetracosactide 250mg (normal response at 30 min, >570 nmol/L). Adrenocorticotrophic hormone (ACTH) was undetectable.

The presence of adrenal axis suppression with low ACTH, in the context of Cushingoid features and avascular necrosis of the hip, suggested ongoing exposure to high systemic levels of exogenous corticosteroids. Ritonavir and atazanavir were substituted with efavirenz (600 mg once daily), while continuing the steroid eye drops. Oral hydrocortisone 15 mg daily was added to avoid precipitating crisis due to adrenal insufficiency. Over the following year, the patient’s weight declined, with marked improvement in her adrenal function. Analysis of stored serum samples revealed elevated levels of dexamethasone at presentation (1.4-1.7 nmol/L) which fell dramatically after discontinuation of protease inhibitor therapy (undetectable to 0.181 nmol/L).

Although prior courses of oral and intravenous corticosteroids may have contributed to adrenal axis suppression, the close temporal correlation between discontinuation of ritonavir, reversal of weight gain and recovery of adrenal function, combined with detectable levels of dexamethasone in the blood, strongly suggests that co-administration of ritonavir was responsible for the accumulation of excessive systemic levels of topical ocular corticosteroids, resulting in adrenal axis suppression and Cushing's syndrome.

Source: hiv-druginteractions.org (24 June 2011).

References

1. Frankel JK. Cushing's syndrome due to antiretroviral-budesonide interaction. *Ann Pharmacother*, 2011, 45(6): 823-824. <http://www.ncbi.nlm.nih.gov/pubmed/21558486>
2. Molloy A et al. Cushing's syndrome and adrenal axis suppression in a patient treated with ritonavir and corticosteroid eye drops. *AIDS*, 2011, 25(10): 1337-1338. <http://www.ncbi.nlm.nih.gov/pubmed/21659797>

Lopinavir and rifampicin interaction in HIV-positive patients

hiv-druginteractions.org

Coadministration of rifampicin dramatically reduces plasma lopinavir (LPV) concentrations. In healthy volunteers, doubling the dose of lopinavir-ritonavir (LPV/r) capsules overcame this interaction, but a subsequent study of double doses of the tablets was stopped early owing to hepatotoxicity. However, healthy-volunteer study findings may not apply to HIV-positive adults.

This study evaluated the steady-state pharmacokinetics of LPV in HIV-infected adults stable on LPV/r tablets (400/100 mg twice daily) who were given rifampicin (600 mg daily), and the dose of the LPV/r gradually increased over a period of two weeks (first to 600/150 twice daily and then to 800/200 mg twice daily). Twenty-one subjects started the study, but two were withdrawn due to grade 3/4 transaminitis.

The median [IQR] pre-dose LPV concentrations were 8.1 (6.2 to 9.8) mg/L at baseline, 1.7 (0.3 to 3.0) mg/L after 7 days of rifampicin, 5.9 (2.1 to 9.9) mg/L with 1.5 times the dose of LPV/r, and 10.8 (7.0 to 13.1) mg/L with double-dose LPV/r. There were no significant differences in the LPV AUC, C_{max}, pre-dose concentrations, 12-hour concentration, or half-life between the baseline and double-dose LPV/r time points.

Doubling the dose of the tablet formulation of LPV/r overcame induction by rifampicin, with less hepatotoxicity occurring in this cohort of HIV-infected participants than reported in healthy-volunteer studies. The cohort consisted of HIV-infected patients who were virologically suppress with high CD4 counts – the risk of hepatotoxicity may be different in HIV-infected individuals with TB and/or with different CD4 counts.

Source: hiv-druginteractions.org (28 June 2011).

Ref: Decloedt EH et al. Pharmacokinetics of lopinavir in HIV-infected adults receiving rifampin with adjusted doses of lopinavir-ritonavir tablets. *Antimicrob Agents Chemother*, 2011, 55(7): 3195-3200.

<http://www.ncbi.nlm.nih.gov/pubmed/21537021>

PREVENTION

HPTN 052 study stopped early: significant reduction in HIV transmission from early use of HIV treatment in serodifferent partners

Although more detailed results have since been presented (see earlier report from IAS Rome conference earlier in this issue), the following summary information was reported as a press release from the US NIAID.

Initiation of Antiretroviral Treatment Protects Uninfected Sexual Partners from HIV Infection (HPTN Study 052): 96% reduction in HIV transmission, according to study conducted by HIV Prevention Trials Network

Men and women infected with HIV reduced the risk of transmitting the virus to their sexual partners through initiation of oral antiretroviral therapy (ART), according to findings from a large multinational clinical study conducted by the HIV Prevention Trials Network (HPTN), a global partnership dedicated to reducing the transmission of HIV through cutting-edge biomedical, behavioral, and structural interventions.

The study, known as HPTN 052, was designed to evaluate whether immediate versus delayed use of ART by HIV-infected individuals would reduce transmission of HIV to their HIV-uninfected partners and potentially benefit the HIV-infected individual as well. Findings from the study were reviewed by an independent Data and Safety Monitoring Board (DSMB). The DSMB recommended that the results be released as soon as possible and that the findings be shared with study participants and investigators. The DSMB concluded that initiation of ART by HIV-infected individuals substantially protected their HIV-uninfected sexual partners from acquiring HIV infection, with a 96 percent reduction in risk of HIV transmission. HPTN 052 is the first randomised clinical trial to show that treating an HIV-infected individual with ART can reduce the risk of sexual transmission of HIV to an uninfected partner.

HPTN 052 began in April 2005 and enrolled 1,763 HIV-serodiscordant couples (couples that have one member who is HIV-infected and the other who is HIV-uninfected), the vast majority of which (97 percent) were heterosexual. The study was conducted at 13 sites across Africa, Asia and the Americas. The HIV-infected person was required to have a CD4 cell count between 350-550 per cubic millimeter (cells/mm³) at enrollment, and therefore did not require HIV treatment for his or her own health. Couples were randomized to one of two groups. In one group, the HIV-infected person immediately began taking ART (immediate ART group). In the other group, the HIV-infected person began ART when his or her CD4 cell count fell below 250 cells/mm³ or if he/she developed an AIDS-related illness (the delayed ART group).

Throughout the study, both groups received HIV-related care that included counseling on safe sex practices, free condoms, treatment for sexually transmitted infections, regular HIV testing, and frequent evaluation and treatment for any complications related to HIV infection. Each group received the same amount of care and counseling. Any HIV-uninfected person who became HIV-infected during the course of the study was referred to local

services for appropriate medical care and treatment.

In its review, the DSMB found a total of 39 cases of HIV infection among the previously uninfected partners. Of those, 28 were linked through genetic analysis to the HIV-infected partner as the source of infection. Seven infections were not linked to the HIV-infected partner, and four infections are still undergoing analysis. Of the 28 linked infections, 27 infections occurred among the 877 couples in which the HIV-infected partner did not begin antiretroviral therapy immediately. Only one case of HIV infection occurred among those couples where the HIV-infected partner began immediate antiretroviral therapy. This finding was statistically significant and means that earlier initiation of antiretrovirals led to a 96 percent reduction in HIV transmission to the HIV-uninfected partner. The infections were confirmed by genetic analysis of viruses from both partners.

Additionally, 17 cases of extrapulmonary tuberculosis occurred in the HIV-infected partners in the deferred treatment arm compared with three cases in the immediate treatment arm, a statistically significant difference. There were also 23 deaths during the study. Ten occurred in the immediate treatment group and 13 in the deferred treatment group, a difference that did not reach statistical significance.

The press release noted that the ongoing international clinical study called Strategic Timing of Antiretroviral Therapy (START) also funded by NIAID is examining the optimal time for asymptomatic HIV-infected individuals to begin antiretrovirals.

<http://www.niaid.nih.gov/news/newsreleases/2011/Pages/START.aspx>

Source: NIAID Press release. (12 May 2011)

For additional information about the HPTN 052 study, see the Questions and Answers information on the NIAID website.

<http://www.niaid.nih.gov/news/QA/Pages/HPTN052qa.aspx>

ON THE WEB

Online conferences:

Treatment as prevention: online presentation

Online presentation by Wafaa El-Sadr from the International Treatment as Prevention Workshop, 4–6 May 2011, Vancouver, Canada.

http://www.youtube.com/watch?v=RK6aswNV08E&feature=channel_video_title

Other material including over 35 other presentations from this workshop are available at:

<http://www.cfenet.ubc.ca/node/5536/>

CCR5 tropism guidelines

The final version of the CCR5 tropism guidelines available as a word file (according to the publisher guidelines) on the web-site of the European Society of Antiviral Resistance (ESAR). ESAR is the successor of the EuropeHIVResistance Network.

To download the word-file you have to scroll to the bottom of this page:

http://www.esar-society.eu/index.cfm/t/Tropism_Guidelines/vid/5436FB5B-B04D-6E04-05EDE1DDA908FBF7

UN High Level Meeting on HIV and AIDS

8-10 June 2011, New York

Webcasts from this meeting include the interventions by women activists:

Tatyana Afanasiady from the Ukrainian Network of People Living with HIV at the opening session. Speaking as an openly HIV positive woman and drug user.

<http://www.unmultimedia.org/tv/webcast/2011/06/23682.html> (English and Russian)

Siphiwe Hlope, Alessandra Nilo, Adrienne Germain, a powerful young woman speaker from Zimbabwe, Lisette Trinidad from Peru, and several other strong statements from women in the Women Panel meeting.

<http://www.unmultimedia.org/tv/webcast/2011/06/panel-4-women-girls-and-hiv-english.html>

Anandi regional coordinator for Asia and the Pacific for the International Community of women living with HIV.

<http://www.unmultimedia.org/tv/webcast/2011/06/side-event-aids-health-and-sustainable-development-who-owns-the-aids-response-high-level-meeting-on-aids-original-language.html>

Silvia Petretti, speaking at the closing plenary on why people with HIV and key populations need to be at the centre of the fight against the HIV epidemic.

<http://www.unmultimedia.org/tv/webcast/2011/06/global-network-of-people-living-with-hiv-2011-high-level-meeting-on-aids-95th-plenary-meeting.html>

FUTURE MEETINGS

2011 conference listing

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.

51st ICAAC

17–20 September 2011, Chicago

<http://www.icaac.org/>

13th European AIDS Conference (EACS)

12–15 October 2011, Serbia

<http://www.europeanaidscinicalsociety.org>

2nd International Workshop on HIV & Ageing

October 2011, Baltimore, USA

<http://www.virology-education.com>

4th Annual BHIVA Conference for the Management of HIV / Hepatitis Co-infection

16 November 2011, London

<http://www.bhiva.org>

BHIVA Autumn Conference including CHIVA Parallel Sessions

17–18 November 2011, London

<http://www.bhiva.org>

19th Conference on Retroviruses and OIs (CROI)

5–8 March 2012, Seattle

<http://retroconference.org>

18th Annual BHIVA Conference

17–20 April 2012, Birmingham

<http://www.bhiva.org>

HIV i-BASE

HIV i-Base is an HIV-positive led treatment information service. We produce information both for clinicians and other health workers and for people with HIV.

Our publications are used and have been adapted in many countries and settings.

Our fully searchable website is designed to be fast to access, easy to use, and simple to navigate.

All i-Base publications are available online.

<http://www.i-base.info>

i-Base produce five non-technical treatment guides, which are available online as web pages and PDF files.

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

- Introduction to combination therapy
- A guide to changing treatment
- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV

The site also includes a web-based Q&A section for people to ask questions about treatment:

<http://www.i-base.info/questions>

Recent questions include:

- If I am exclusively breastfeeding, is it still safe to give my baby water or ORS?
- Will my CD4 increase using ARVs in pregnancy?
- Why does my doctor want to switch me from Combivir...?
- What is my risk of viral load rebounding?
- If I donated blood does this mean I am HIV-negative?
- What is the cost of Truvada?
- Are meds working ok in pregnancy?
- How long will we be taking pills?
- How can my partner test HIV positive and I test HIV negative?
- Am I addicted to sex since my diagnosis?
- Can I get HIV from a cold sore?
- How do I know if my meds are causing bone problems?
- What are the risks of cocaine on CD4 counts for someone on HIV meds?

We have also posted online a set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.

<http://www.i-base.info/clinicforms>



HIV i-Base
www.i-Base.info



Southern African HIV Clinician's Society
www.sahivsoc.org

HIV i-Base, 4th Floor, 57 Great Suffolk Street, London, SE1 0BB.
T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489