

HIV treatment bulletin

S O U T H

Volume 1 Number 1

HTB conference reports: January-August 2008

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htb south

HIV Treatment Bulletin

HTB is a quarterly journal published in electronic format by HIV i-Base.

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

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HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies. All editorial policies are strictly independent of funding sources.

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HIV i-Base is a registered charity no 1081905 and company reg no 3962064.

HTB was formally known as DrFax

EDITORIAL

Welcome to the first issue of *HTB south*. It is compiled from articles from HIV Treatment Bulletin - a review of the latest research and other HIV treatment news, particularly with implications for clinical practice. HTB is produced by HIV i-Base, a community organisation, based in London, UK.

This first issue for Southern Africa is a round up of conference reports from this year. We have included a balance of research conducted in the North and South, both with immediate implications for the region and for future treatment and strategies.

More detailed conference reports can be found on our website:

<http://www.i-base.info/htb/v9/htb9-1-2/index.html>

<http://www.i-base.info/htb/v9/htb9-3-4/index.html>

<http://www.i-base.info/htb/v9/htb9-5-6/index.html>

<http://www.i-base.info/htb/v9/htb9-7-8/index.html>

The next issue of HTB South will include reports from the 2008 HIV/AIDS Implementers' Meeting - Kampala, Uganda; the XVII International AIDS Conference, Mexico City and the Botswana HIV Conference, Gaborone.

HTB South is distributed electronically by HIV i-Base and the Southern African HIV Clinicians Society.

This issue was produced for the Botswana HIV Conference, 17-20 September 2008, Gaborone.

HTB South is supported by the UK Department for International Development (DfID).

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:

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CONFERENCE REPORTS

38th World Conference on Lung Health of the Union against TB and Lung Disease

December 2007, Cape Town

Treatment outcomes in patients who received rifampicin with nevirapine or efavirenz

Polly Clayden, HIV i-Base

In an oral presentation, Andrew Boule from the University of Cape Town showed findings from a prospective cohort study of adults receiving rifampicin based TB treatment with either nevirapine or efavirenz containing ART.

The study was conducted in Khayelitsha, a township outside Cape Town with a 30% HIV antenatal prevalence and TB case finding above 1500/100,000. The aim was to look at outcomes, in patients initiating NNRTI-based ART, who were already receiving rifampicin containing TB treatment.

The cohort were treatment naïve adults ≥ 14 years of age, ≤ 250 cells/mm³ enrolled between 2001 and June 2006. If they were receiving TB treatment there must have been 14 days overlap of TB and HIV treatment.

The analysis looked at four different treatment scenarios: people without TB starting either nevirapine or efavirenz and people receiving rifampicin-based TB treatment when starting nevirapine or efavirenz.

The investigators identified 4117 patients starting on ART during the study period. Of those, 2687 patients were without TB when they initiated HIV treatment; 1726 started on nevirapine and 961 efavirenz. The remaining 1283 started ART while receiving TB treatment, of these, 209 started with nevirapine and 1074 efavirenz.

The four treatment groups had similar baseline characteristics. There were however more women in the nevirapine vs efavirenz groups: 73.7% vs 62.1% ($p < 0.001$) with TB treatment, and 80% vs 51.7% ($p < 0.001$) without TB. Also in the TB treatment group, the patients receiving nevirapine had been receiving TB treatment for longer, a median of 87 days vs 73 days in the efavirenz group ($p < 0.001$). And the patients receiving nevirapine had higher median CD4 counts than those receiving efavirenz: 80 vs 61 cells/mm³ ($p = 0.002$) in the TB treatment group and 116 vs 93 cells/mm³ ($p < 0.001$) in the group without TB at baseline.

Viral load results were available for a subset of patients. The investigators defined a suboptimal response to HAART as failure to suppress viral load to less than 400 copies/mL. This occurred for approximately 15% at 6 months of the patients receiving nevirapine with TB treatment at 6 months vs between 6-9% for the patients receiving nevirapine ($n = 141$) without TB treatment or efavirenz. The same analysis at 18 months showed failure to suppress in approximately 20% vs 8-13% in the nevirapine with TB treatment ($n = 80$) and the other groups respectively.

The odds ratios for viral load > 400 copies/mL at 6, 12, 18 months and all time points combined, for patients receiving TB treatment were 2.1, 1.6, 1.4 and 1.7 respectively for those receiving nevirapine and 1.2, 0.9, 1.1 and 1.1 for those receiving efavirenz.

In multivariate analysis combining all four groups the odds ratios (with efavirenz and no TB treatment as reference) were: efavirenz/TB treatment at start 1.1 (95% CI 0.7-1.7); nevirapine/no TB 1.5 (95% CI 1.0-2.1); nevirapine, TB treatment at start 2.9 (95% CI 1.8-4.7), $p < 0.001$.

In this analysis age and gender were not significant but baseline CD4 (per 25 cell increase) 0.9 (95% CI 0.9-1.00), $p < 0.001$; baseline weight (per 10kg increase) 1.2 (95% CI 1.1-1.3), $p = 0.001$ and baseline viral load (per 1 log) 1.3 (95% CI 1.1-1.6), $p = 0.001$ were found to have an effect.

Additionally duration of ART (with 6 months as reference): 12 months 1.5 (95% CI 1.2-1.8) and 18 months 1.8 (95% CI 1.5-2.3), $p < 0.001$ were significantly associated with viral load > 400 copies/mL.

The study also looked at ART and TB treatment in patients who developed TB while receiving ART. The findings are limited by the small number of patients developing TB while on ART, but in this study there was no increased risk of viral load > 400 copies/mL with TB treatment: Adjusted HR 1.00 (0.5-2.00) for nevirapine, $p = 0.995$ and 1.2 (0.6-2.4) for efavirenz, $p = 0.703$.

Dr Boule summarised that receiving rifampicin-based TB treatment at the start of NVP-based ART was associated with an up to a two-fold increased risk of a viral load > 400 copies/mL in the first 18 months on ART. There was no increased risk with incident TB on nevirapine-based ART, but this analysis was limited by small numbers. He said that the most likely explanation for this is lead-in dosing of nevirapine in patients with pre-existing hepatic induction due to rifampicin. He suggested to always include a 400mg/day induction arm in the nevirapine/rifampicin groups in future research.

He noted there were more nevirapine substitutions due to toxicity in patients already on TB treatment but this difference was not significant after adjustment for potential confounders.

Overall the analysis is limited by small numbers in the nevirapine/rifampicin group which he explained is "unlikely to change as local policy no longer recommends nevirapine use whilst on rifampicin."

He described these findings as giving a "complex message" and recommended that if efavirenz is available a strong case can be made for using it for people receiving rifampicin based TB treatment in preference to nevirapine. "However, in spite of differences, 85% of patients on NVP/Rif at the start of ART achieved a viral load < 400 copies/ml at 6 months and 80% at 18 months – still highly effective in the absence of alternatives."

Ref: Boule A, Van Cutsem G, Cohen K et al. Antiretroviral treatment outcomes in patients who received rifampicin together with nevirapine or efavirenz. 38th World Conference on Lung Health of the Union against Tuberculosis and Lung disease. December 2007. Cape Town. Abstract TS 1893-12.

CONFERENCE REPORTS

15th Conference on Retroviruses and Opportunistic Infections

2-6 February 2008, Boston

This annual conference is one of the most important annual scientific meetings. Abstracts from the meeting and many of the most important oral abstract and overview sessions are online.

<http://www.retroconference.org>

CROI: ANTIRETROVIRALS

Increased risk of myocardial infarction associated with abacavir and ddI

Simon Collins, HIV i-Base

A poster presented by Caroline Sabin from the Royal Free Hospital looked at whether nucleoside analogues were associated with cardiovascular disease (CVD) seen in the large international D:A:D cohort study. [1] D:A:D includes over 33,000 patients from 11 prospective cohorts, in which 517 myocardial infarctions (MI) occurred over approximately seven years of follow up (157,912 patient years).

This group first reported that ARV treatment as a whole was associated with an increased risk of CVD. Over subsequent years, the study gained more power to look at drug-class effects and last year reported a 110% increased risk per year related to PI use, after adjusting for blood lipids and other metabolic parameters and demographics. No increased risk was seen with use of NNRTIs.

This study is now sufficiently powered to look at the impact of some individual ARVs, and in this adjusted multivariate analysis found a 90% increased risk from current or recent use (within six months) of abacavir (RR 1.90, 95%CI 1.47-2.45, $p < 0.01$) and a 49% increased risk with ddI (RR 1.49, 1.14-1.95, $p < 0.01$).

The absolute risk was highest in patients with highest underlying risk factors for CVD. When including the predicted 10-year Framingham risk in the regression model, the MI rate increased by 95% (1.95 [1.50, 2.55]; $p = 0.0001$) in those with a moderate 10-year CHD risk and by 142% (2.42 [1.74, 3.36]; $p = 0.0001$) in those with a high 10-year CHD risk, when compared to those with a low 10-year CHD risk.

This effect remained after adjustment for viral load, CD4, blood lipids and other metabolic factors'. No link was found with duration of use, or past use of either drug, leading the researchers to conclude that if this effect is causal, the unknown biological mechanism (s) appears reversible after stopping these drugs.

No increased risk was seen with the use of ATZ, d4T or 3TC. Exposure to tenofovir or FTC in the cohort was insufficient to include these drugs in the analysis.

Simon Collins is the community representative on the D:A:D Steering Committee.

Ref: Sabin C, Worm S, Weber R et al. Do thymidine analogues, abacavir, didanosine and lamivudine contribute to the risk of myocardial infarction? The D:A:D study. 15th CROI, 3-6 February 2008, Boston.

Abstract 957c.

The poster is available in PDF format from:

<http://cphiv.dk>

C O M M E N T

This was one of the most discussed studies from the meeting and it is unclear why it didn't receive an oral session.

Even though the mechanism is unknown, reporting a ARV risk that is only slightly short of the lower estimated risk for a current smoker, in a trial as well powered as D:A:D, is likely to have an impact on prescription practice for patients with high underlying Framingham risk.

For patients currently stable on treatment, with low cardiovascular risk, or who have limited treatment choices, the benefit of abacavir may still outweigh any low increase in absolute risk. Recent analyses from the SMART study suggest that viral suppression < 50 copies/mL reduces risk while higher levels of viraemia increase risk.

These decisions clearly should be assessed on an individual case basis.

Related articles:

Position statement by the D:A:D steering committee

<http://www.i-base.info/htb/v9/htb9-1-2/Position.html>

Abacavir, ddI and risk of heart attack: additional published data and statements from the EMEA and FDA

<http://www.i-base.info/htb/v9/htb9-5-6/Abacavir.html>

Atazanavir/r vs lopinavir/r in treatment-naïve patients: 48 week results

Simon Collins, HIV i-Base

Although widely used off-label, atazanavir/r is not currently approved in Europe for use in first-line combinations, nor recommended in European guidelines, due to limited data in naïve patients. Results from a large randomised international head-to-head study against lopinavir/r, sponsored by BMS, are therefore important to report.

Jean-Michel Molina from St Louis Hospital, Paris, presented the 48-week analysis from this 96-week CASTLE study. This was a non-inferiority study (10% margin) and the primary endpoint was the proportion of patients with HIV RNA < 50 copies/mL at week 48.

The trial randomised 883 treatment-naïve patients to either atazanavir 300 mg / ritonavir 100 mg once-daily or lopinavir/ritonavir 400 mg/100 mg twice-daily, both in combination with fixed-dose tenofovir/FTC once-daily.

Baseline demographics and characteristics included median CD4 count 205 cells/mm³ (range 2-810) with 12% less than 50 cells/mm³; and viral load around 5 log copies/mL (range

2.6-5.9), with 50% patients starting above 100,000 copies/mL. Only around 5% had CDC class C diagnosis, and 12% were coinfecting with hepatitis B or C.

Only around 10% of patients discontinued prior to week 48, with a balance between each arm, detailed in Table 1.

Table 1: Patient disposition at week 48

	ATZ/r	LPV/r
Randomised (n)	440	443
Treated (n)	438	440
Discontinued	39 (9%)	58 (13%)
AE's	10 (2%)	14 (3%)
Death	4 (<1%)	4 (<1%)
Efficacy	5 (1%)	8 (2%)
LTFU	6 (1%)	6 (1%)
Adherence	6 (1%)	9 (2%)
Withdrew consent	4 (<1%)	13 (3%)
Other	4 (<1%)	4 (<1%)

The percentage of patients with viral load <50 copies/mL at week 48 in the atazanavir/r and lopinavir/r arms was 78% vs 76% (estimated difference 1.9, 95% CI -3.6 to 7.4), by intent-to-treat analysis.

Stratified by baseline viral load, the results were 82% vs 81% (<100,000 copies/mL) and 74% vs 72% (>100,000 copies/mL), in the ATZ/r and LPV/r groups respectively, with no statistical difference between arms.

A post-hoc analysis of results by baseline CD4 counts showed no impact for ATZ/r, but a statistically significant poorer response for the LPV/r arm, ranging from 80% <50 copies/mL in patients with >200 CD4 cells/mm³ to 63% for those starting with <50 cells/mm³, p = 0.0085.

CD4 response was similar in each arm (+203 vs + 219 cells/mm³).

Side effects generally reflected the known profile of each drug, with ATZ/r having higher incidence of jaundice, and LPV/r reporting greater GI-related ae's, that are detailed in Table 2.

Table 2: Adverse events in CASTLE study

	ATZ/r n=441 (%)	LPV/r n=437 (%)
Serious AE's	54 (12%)	42 (10%)
All grade 2-4	115 (26%)	129 (30%)
Jaundice *	16 (4%)	0
Nausea *	17 (4%)	33 (8%)
Diarrhoea *	10 (2%)	50 (11%)
Rash *	14 (3%)	9 (2%)
Renal (all grades)	14 (3%)	9 (2%)
Total bilirubin >2.5xULN	146 (34%)	1 (<1%)
Total cholesterol (>240 mg/dL)	30 (7%)	77 (18%)
Triglycerides (>750 mg/dL)	2 (<1%)	15 (4%)
Hyperglycemia (>251 mg/dL)	1 (<1%)	1 (<1%)

* Grade 2-4 in >3% of patients

With laboratory AE's, grade 3-4 ALT/AST elevations were low (>2%) in both arms.

Lipid profile favoured ATZ/r with fewer patients at week 48 having total cholesterol >240 mg/dL (7% vs 18%), and significantly lower changes from baseline for TC, non HDL and TG (all p<0.0001). Lipid lowering drugs were used by 2% and 7% of the ATZ/r and LPV/r arms respectively.

C O M M E N T

The study concluded that atazanavir/r is an appropriate treatment for first line therapy. Regulatory and guidelines committees will hopefully review these data carefully and promptly.

Ref: Molina JF et al. Efficacy and safety of once-daily atazanavir/ritonavir compared to twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine in ARV-naive HIV-1-infected subjects: the CASTLE study, 48-week results. Abstract 37.

<http://www.retroconference.org/2008/Abstracts/31137.htm>

This oral presentation is available to view online from the conference website (Monday 4 February).

Baseline inflammation and coagulation markers and changes over four weeks during a treatment interruption are strongly linked to HIV viraemia and risk of mortality

Simon Collins, HIV i-Base

Lewis Kuller presented further analysis from the SMART study. In summary, this international study randomised around 5,500 patients to CD4-guided treatment interruptions or continuous treatment, was stopped early because of excess death in the intermittent treatment group: with 55 vs 30 deaths over the first 16 months, most not related to opportunistic infections.

Baseline markers of inflammation and clotting as they related to total mortality, the changes of these variables, and how they related to outcome.

Two matched controls for each death prior to January 2006 when the study was stopped, were matched on a variety of variables. Logistic regression analysis was used to estimate odds ratios (OR) for mortality with adjustment for cardiovascular, HIV, co infection risk factors and other demographic factors. Baseline characteristics relating to deaths included lower CD4 counts, and a higher proportion of current smoker, diabetes, treated blood pressure and CVD, in the cases compared to the controls, all of which were adjusted for.

Markers analysed included inflammatory markers: serum amyloid A and serum amyloid P, C-reactive protein (CRP) – acute phase proteins (pentraxins), and IL-6 (a major inflammatory marker and stimulant of CRP and stimulant of release of tissue factor from smooth muscle cells in the endothelium).

The markers of coagulation that were measured were D-dimer (a measure of the breakdown of fibrogenesis that is a powerful risk factor for CVD) and prothrombin fragments 1+2 (F1.2).

All markers have been strongly associated with cardiovascular risk in HIV-negative patients.

Kuller first reported that many of these markers were elevated at baseline and that this was significantly associated with all cause mortality. Adjusted OR (4th vs 1st quartiles) showed an almost 12-fold increased risk associated with elevated IL-6 and a 26-fold increased risk associated with increased D-dimer (both $p < 0.0001$). CRP was associated with a 3-fold risk ($p = 0.03$).

IL-6 and D-dimer, but not the other markers, also increased over 4 weeks in patients not on treatment, compared to those on continuous treatment ($p < 0.0001$). Changes in both markers were strongly correlated with increases in viral load. Change from baseline to week four levels in IL-6 (OR 5.3, 95%CI 1.6-17.1; $p = 0.006$) and D-dimer (OR 5.0, 95%CI 1.3 -18.9; $p = 0.02$) were also strongly correlated with risk of death.

Kuller suggested that activation of coagulation and inflammation markers could impact multiple organs: the association with all cause mortality was stronger than to CVD.

This may occur as a consequence of a challenge to the endothelium. Viraemia affects vascular endothelium, which increases production of tissue factor transcription, which activate the extrinsic clotting pathways. Elevated d-dimer and IL-6 clearly identified patients at highest risk of death, at a level unseen with any other marker in HIV-negative predictive biomarker studies (which report 1-2-fold increased risk). He concluded by suggesting that this opened the questions of whether this may be a useful marker to monitor in patient management.

These findings were initially presented to the IAS conference last July. [2]

References:

1. Kuller L et al. Elevated Levels of Interleukin-6 and D-dimer Are Associated with an Increased Risk of Death in Patients with HIV. Oral abstract 139.
<http://www.retroconference.org/2008/Abstracts/32757.htm>
2. See HTB August/September 2007
<http://www.i-base.info/htb/v8/htb8-8-9/HIV.html>

Restarting treatment after an interruption reduces the risk of serious events but CD4 recovery falls short of baseline levels

Simon Collins, HIV i-Base

Wafaa El-Sadr from the INSIGHT research network, presented an analysis of event rates from the large international CD4-guided treatment interruption study (SMART) that occurred in the 18 month period of follow-up since enrollment was stopped and patients were recommended to restart treatment.

The study was halted following a recommendation by the DSMB in January 2006 after only two of the planned seven years, due to significant benefits in terms of mortality and serious AIDS and non-AIDS morbidity, in favour of continuous treatment.

As well as providing sufficient power to look at the original study question, this trial dataset (5472 patients were randomised) is providing significant insight into other important aspects of HIV management.

Prior to January 2006, patients randomised to the treatment discontinuation arm (DC=drug conservation) spent 34% of follow-up time on treatment compared to 94% patients in the continuous treatment arm (VS=viral suppression). Post-January 2006 this increased to 71% vs 91% respectively, and when the study closed in July 2007, 83% and 95% of patients in each arm were on treatment.

It is important that after the recommendation to restart treatment, the rate of opportunistic infection or deaths all declined in the interruption arm (from 3.4 to 2.1/100 pt yrs) and stayed constant for patients in the continuous therapy group (1.4/100 throughout). This was a significant change in hazard ratio between the pre- and post January 2006 hazard ratios ($p = 0.03$). Rates reduced in inverse proportion to time since restarting treatment.

Although similar trends were reported for other endpoints (death, OI, major CVD renal or hepatic disease) the p-value for the change in hazard ratio pre- and post January 2006 was not statistically significant.

Although the majority of patients in the DC group re-suppressed viral load, mean CD4 count noticeably failed to reach pre-interruption levels. Patients in either arm who had experienced a non-fatal serious event prior to January 2006 (113 in DC and 50 in VS arms) were at 5.8-fold increased risk of death during the follow-up (95%CI 3.2-10.8), $p < 0.0001$.

These differences were not explained by patients in the DC not following the recommendation to restart treatment; an analysis of a subgroup of patients who all restarted treatment confirmed similar results.

Clinics where >85% patients followed the recommendation to restart treatment reported a drop from 3.8 to 1.1 in the DC arm ($p = 0.02$, for difference in HR pre- and post- January 2006). The persistence of increased risk in the DC arm was largely explained by lower mean CD4 count and higher proportion of patients with uncontrolled viraemia.

When looking at the CD4 response to restarting treatment, the researchers found a significant difference between the two groups, even 18 months after restarting treatment: mean 507 vs 648 cells/mm³ in favour of the continuous treatment arm. Baseline CD4 counts in each group was approximately 600 cells/mm³.

This was not explained by patients within the DC group who chose not to restart treatment as an analysis of a sub group of patients who had all followed the recommendation to restart treatment found similar results.

The investigators concluded that these results further strengthened the earlier recommendation not to use CD4-guided treatment interruptions, as this was associated with long-term impact beyond the period of interruption.

C O M M E N T

This provides additional validation for the decision to stop the study early and for the recommendation to restart treatment.

Although the study provides some evidence that long-term clinical outcome may become normalised over time once treatment is restarted, the significantly lower CD4 count, even 18 months after treatment was resumed, was not expected.

Ref: El-Sadr W et al. Re-initiation of ART in the CD4-guided ART Interruption Group in the SMART Study Lowers Risk of Opportunistic Disease or Death. 15th CROI, 3-6 February 2008, Boston. Abstract 36.

<http://www.Retroconference.org:8888/2008/Abstracts/32784.htm>

This oral presentation is available to view online from the conference website

Immediate HAART reduces death and AIDS progression over 48 weeks in patients with acute OIs

Simon Collins, HIV i-Base

Andrew Zalopa from Stanford University and colleagues presented results from ACTG A5164 Phase 4 study which randomised 282 patients to either immediate or deferred use of ARVs in the context of an acute OI diagnosis for which treatment is available (TB was excluded).

Optimal timing of HAART in this context is currently guided more by expert opinion than data from randomised studies, and is difficult due to the advanced illness of study participants.

Patients needed to be treatment-naïve, not to have used ARVs in the previous 8 weeks or not to have used treatment for more than one month if used in the past. Deferred treatment was defined as after OI treatment (at least 4 weeks after randomisation). Randomisation was stratified by OI and CD4 (above and below 50 cells/mm³). Patients with tuberculosis were excluded. The primary week 48 endpoint was an ordered categorical variable of three outcomes: death/AIDS progression; no progression, HIV viral load <50copies/mL; or no progression, viral load <50 copies/mL.

Baseline characteristics included median (IQR) CD4 and viral load counts of 29 (10-55) cells/mm³ and 5.07 (4.71-5.63) log copies/mL. Over 90% were treatment-naïve. Median age was 38 years; 85% men/15% women; 37% black, 36% Hispanic, and 23% white.

OIs included PCP (63%), cryptococcal meningitis (13%), pneumonia (10%), other OI including cryptosporidiosis, toxoplasmosis, CMV and MAC (25%). One third of patients were diagnosed with more than one OI within 30 days.

Immediate and deferred arms started ART with a median (IQR) of 12 (9-13) and 45 (41-55) days, respectively, after treatment for the opportunistic infection had started. 10% of the deferred treatment arm did not start HAART. Choice of ARVs was open with 89% and 85% patients in the immediate and deferred arms respectively, starting with a boosted-PI based regimen.

13% patients were lost to follow-up (18 in each arm). Although there was no significant difference in the composite primary endpoint with both arms achieved similar CD4 and viral load by week 24, the immediate arm had significant clinical benefits. Immediate HAART led to fewer deaths/AIDS progressions (n=20 vs 34, p=0.035), longer time to death/AIDS progression (stratified HR = 0.53, 99% CI 0.25-1.09, p = 0.02), and shorter time to achieving an increase in CD4 counts to >50 and >100 (median 8.1 vs 3.9 weeks and 11.8 vs 4.2 weeks, both p<0.001), respectively.

There was a trend of earlier ART changes in the immediate arm (p = 0.15), but no significant differences in grade 3 or 4 adverse events, adherence, hospitalizations, or immune reconstitution inflammatory syndrome (8 immediate vs 12 deferred).

The clinical benefits from immediate treatment were driven by the more rapid increase in CD4 count, which decreased the period of vulnerability to new AIDS-related infections and death.

C O M M E N T

It is important that the question of HAART timing has been answered in a randomised study. The acknowledgement of patients for participating in this study, many of whom were already “disenfranchised from the US healthcare system”, was particularly deserved.

Ref: Zalopa A, Andersen J, Komarow L et al. Immediate vs Deferred ART in the Setting of Acute AIDS-related Opportunistic Infection: Final Results of a Randomized Strategy Trial, ACTG A5164. Oral abstract 142.

<http://www.retroconference.org/2008/Abstracts/32805.htm>

This presentation is also available as a webcast (Wed 6th Feb).

CROI: MATERNAL HEALTH AND PMTCT

Predictors of mother to child transmission among women initiating HAART in pregnancy in a South African cohort

Polly Clayden, HIV i-Base

There are limited data from Africa describing mother to child transmission (MTCT) in mothers initiating HAART in pregnancy.

A poster authored by Risa Hoffman and coworkers from the Reproductive Health and HIV Research Unit of the University of Witwatersrand and the UCLA Program in Global Health, Los Angeles presented findings from a retrospective analysis from a cohort of women in an antenatal antiretroviral clinic at Johannesburg Hospital looking at factors associated with infant HIV infection.

In this study 689 women indicated for antiretroviral treatment (CD4 <=250 cells/mm³ or WHO stage 4) were referred to the antenatal clinic between August 2004 and February 2007. The women had a mean baseline CD4 of 154 cells/mm³ and 82% received d4T/3TC/NVP. 302 mothers completed 6 weeks postpartum follow up; of these 15/302 (5%) infants had positive DNA PCR.

Using univariate analysis, the investigators found shorter duration of treatment (p=0.001) and lower CD4 baseline (p=0.03) to be associated with MTCT.

Analysis of variance (ANOVA) found a statistically significant difference in duration of gestational HAART in pregnancy among mothers whose infants were positive (n=15), negative (n=287) and of unknown status (n=376), p=0.0005.

Mothers with HIV-positive infants received HAART for a shorter duration than those with negative infants, 5.1 vs 11.2 weeks

(OR, 0.730, 95% CI 0.612-0.879), $p=0.001$. The investigators noted that for each additional week of HAART during gestation, the odds of transmission were reduced by 27%. The transmission rate for women receiving >7 weeks HAART was 0.3%.

Lower CD4 baseline, 148 vs 106 cells/mm³ (OR, 0.991, 95% CI 0.982-0.999, based on change of 25 cells/mm³), $p=0.03$, was also predictive of MTCT in this analysis.

Viral load at baseline and follow up were not predictors of transmission in this analysis but the investigators suggest that this may be due to high variance in viral load and small numbers of women with complete viral load data.

Unsurprisingly, overall women receiving HAART in pregnancy in South Africa have low rates of transmission. The investigators wrote: "Strategies are needed to facilitate earlier treatment of HIV-infected pregnant women with advanced disease".

C O M M E N T

In this cohort, lower CD4 count (ie women with more advanced disease in need of treatment for their own health) was associated with an HIV-positive infant, and this is consistent with the literature, which shows this over and over again.

The authors highlight the need to initiate treatment earlier in pregnancy and this deserves emphasis both for the health of the mother and the baby's HIV status.

The transmission rate of 3-5% at 6 weeks in this cohort of women with advanced disease (almost all with CD4 <250 cells/mm³) is lower than the reported transmission rates for healthier women in South Africa who only have access to single dose NVP or other PMTCT regimens. The cruel irony seems to be that if you want an uninfected baby, you need to be sicker and get treatment.

Ref: Black V, Hoffman R, Sugar C et al. Factors associated with MTCT in South African women with advanced immunosuppression initiated on HAART during pregnancy. 15th CROI, February 2008, Boston. Poster abstract 657.

<http://www.retroconference.org/2008/Abstracts/31294.htm>

Tenofovir plus FTC reduce NNRTI resistance following single dose nevirapine

Polly Clayden, HIV i-Base

Single dose nevirapine (NVP) still remains an important component in prevention of mother to child transmission (PMTCT). With short course AZT and "tail" coverage it is considered to be a reasonable option for women who do not need antiretroviral treatment to protect their own health.

Four presentations at CROI and a recent Lancet paper looked at using tenofovir (TDF) and emtricitabine (FTC) added to single dose NVP to reduce the emergence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI). Two of the presentations describe TDF and FTC maternal and infant pharmacokinetics.

Both drugs have long half-lives (approx 17 hours for TDF and 8 hours for FTC in plasma) and are category B for use in pregnancy.

Reduction in NNRTI resistance with one dose of TDF/FTC

A paper authored by Benjamin Chi and coworkers, published in the November 17, 2007 edition of the Lancet reported findings from a Zambian study to investigate whether the addition one dose of the co-formulation of 300mg TDF and 200mg FTC (Truvada) to single dose NVP in labour would be effective in reducing resistance [1].

In this study, conducted at two primary health care facilities in Lusaka, women screened that met WHO maternal criteria for antiretroviral therapy were referred and not enrolled.

All enrolled women received standard of care of AZT from 32 weeks gestation plus single dose NVP in labour. The women were randomised to receive TDF/FTC or no additional intervention above the standard of care.

All infants received single dose NVP plus seven days of AZT. The majority of women opted to breastfeed for six months.

The primary endpoint of the study was maternal NNRTI resistance at 6 weeks post partum. The secondary endpoints were NNRTI resistance at two weeks, other antiretroviral resistance (particularly to TDF, FTC and AZT) at two and six weeks post partum, HIV transmission rates and drug safety.

The investigators reported: 627 women were enrolled in the study, of those 227 were not eligible, 397 women were randomised between March 2005 and February and three others were excluded from the analysis, two due to incorrect dispensing of the study drug according to protocol and the third due to the randomisation envelope being incorrectly opened.

The mean maternal CD4 was 464 cells/mm³ (SD, 208) in the intervention arm ($n=198$) and 490 cells/mm³ (SD, 200) in the control arm. 83% and 79% received antenatal AZT, and the length of time on AZT was 39 (SD, 25) and 34 (SD, 20) days in the intervention and control arms respectively. 28% and 29% of women had a viral load <400 copies/mL at delivery. Among those not suppressed at delivery the mean log viral loads were 3.9 (SD, 0.8) and 3.7 (SD, 0.6) logs in the intervention and control arms.

Using a genotype test with thresholds for detection to detect a mutant viral subpopulation of 20%, they found that women receiving the intervention were less likely than controls to have an NNRTI mutation at 2 weeks post partum: 6/187 (3%) vs 21/169 (12%) (RR, 0.27; 95% CI, 0.11-0.66), $p=0.002$; at 6 weeks, 20/173 (12%) vs 41/166 (25%), (RR, 0.47, 95% CI 0.29-0.76), $p=0.002$ and cumulatively, 22/167 (13%) vs 49/163 (30%), (RR, 0.44, 95% CI, 0.28-0.69), $p<0.0001$.

The investigators noted that when they stratified the women according to maternal viral load at delivery, they found the protective effect was greatest in women whose viral load was >10,000 copies/mL.

They did not detect any mutations associated with resistance to TDF, FTC or AZT.

The overall transmission rate at 6 weeks was similar in the two groups 10/180 (5.6%) and 14/175 (8%) in the intervention and control group respectively, $p=0.403$. This was consistent for in utero, 8/180 (4.4%) vs 10/175 (5.7%), $p=0.635$, and intrapartum/early post partum, 2/127 (1.6%), $p=0.44$.

Serious maternal adverse events were also similar in both groups, 7/198 and 9/199 in the intervention and control groups. The most common was postpartum anaemia, which was reported for four women in each group. 20/198 (10%) of infants in the intervention group and 23/199 (12%) in the control group had a serious adverse event, mostly septicaemia (n=22) or pneumonia (n=8), there was no difference between the groups and none were considered to be associated with the study intervention.

The investigators concluded that addition of a single dose of combined TDF and FTC to the prophylaxis regimen of short course AZT and single dose NVP was associated with a 73% reduction in resistance at two weeks and a 53% reduction at six weeks. They noted that in this setting the intervention did not result in a reduction of mother to child transmission compared to controls.

The frequency of the K103N mutation increased from 2 weeks to 6 weeks postpartum as has been described in other studies. The frequency of Y181C/I remained stable. None of the women in the intervention group developed a mutation at codon 181 and the investigators were unable to explain this finding.

The investigators suggested that further reductions in resistance might be possible with the addition of a second dose of tenofovir and FTC but would also preserve the simplicity of the regimen.

A poster authored by the same group, showed findings from a secondary analysis from this study, in which they evaluated 122 random maternal samples using an oligonucleotide ligation assay (OLA) [2]. This assay can detect a mutant sub-population as low as 5% of circulating virus. Mutations found at codons 103, 106, 181, and 190 were considered to be NNRTI resistant.

Of the 122 maternal samples evaluated, 38 were taken at two weeks post partum (15 in the intervention arm and 23 in the control arm) and 84 were taken at six weeks post partum (43 in the intervention arm and 41 in the control arm). The investigators reported that the median log₁₀ viral load was not different between the study arms at two weeks post partum (3.53 vs 3.67; p=0.27), nor at six weeks postpartum (4.61 vs 4.54; p=0.44).

When NNRTI resistance was assessed by OLA, they found a 69% reduction at two weeks post partum, 2/15 (13%) vs 10/23 (44%), (RR 0.31, 95%CI 0.08-1.21), and a 58% reduction in NNRTI at six weeks post partum, 8/43 (19%) vs 18/41 (44%), (RR 0.42, 95%CI 0.21- 0.87).

The investigators concluded that the efficacy of single-dose TDF and FTC in reducing NNRTI drug resistance by population genotyping was confirmed with the more sensitive OLA. "These findings further emphasise the role of this simple intervention in settings that rely heavily on intrapartum NVP, alone or in combination with other drugs, for perinatal HIV prevention" they wrote.

Further reduction with seven days TDF/FTC postpartum

In an oral presentation, Elise Arrive from the TEmAA French National Agency for AIDS Research (ANRS) 12109 study conducted in Ivory Coast, Cambodia and South Africa presented findings from a similar strategy but using seven days TDF/FTC tail coverage [3].

This is an open label, phase II trial to look at safety in which all HIV-positive pregnant women received AZT from 28-38 weeks of gestation (median 33) single dose NVP at the onset of labour

with two doses of TDF/FTC followed by once daily TDF/FTC for seven days post partum.

All infants received single-dose NVP syrup and AZT syrup for 7 days.

The study enrolled 38 women with a median age of 27, a median CD4 count 450 cells/mm³, and a median viral load of 4.08 log₁₀ copies/mL. The women received TDF/FTC at a median of 4.9 hours before delivery.

The investigators reported 9/38 (24%) women experienced Grade 3/4 biological events (anemia, leucopenia) postpartum. 9/39 (23%) live births (1 set of twins), had serious adverse events, including 4 deaths (meningitis, gastroenteritis, intestinal obstruction, and severe encephalopathy of unknown aetiology) and 2 had transient grade 3 anemia (5%).

They found that the mothers' viral load decreased by a median of 0.90 log copies/mL at 2 days postpartum, and returned to baseline at 4 weeks. 2/39 (5.1%) infants had detectable virus at 3 days (confirmed at 4 weeks), suggesting in utero transmission. No genotypic viral resistance to AZT, NVP, FTC, or TDF was detected in either the mothers or infants in this small study.

The investigators wrote: "A TDF/FTC combination for PMTCT appears to be well tolerated in women and exposed newborns: 7 days of postpartum TDF/FTC exposure seem to extend the suppression of viral replication avoiding NVP-resistance mutations".

Tenofovir and FTC pharmacokinetics

In a pharmacokinetic substudy presented as an oral late breaker, Deborah Hirt and coworkers from the ANRS group evaluated tenofovir pharmacokinetics in pregnant women and in their infants. [4]

In this study, they measured maternal, cord blood, and neonatal tenofovir plasma concentrations.

The authors noted that absorption was faster and greater for women with caesarian section than with vaginal delivery (they suggested this was due to fasting administration of TDF before delivery). Following a 600-mg TDF administration, median population tenofovir AUC, C_{max} and C_{min} in pregnant women were 2.73 mg.L⁻¹.h, 0.31 and 0.056 mg/L, respectively.

They found at delivery, maternal and cord blood median tenofovir concentrations were 0.13 and 0.10 mg.L⁻¹ respectively. Neonatal plasma half-life was 8.3 hours (45%), suggesting low neonatal concentrations quickly after birth.

They concluded: "TDF 600 mg before delivery produces similar concentrations to those of HIV infected people taking 300 mg daily. If time elapsed between maternal administration and delivery is >12 hours, 2 tablets of TDF/FTC should be re-administered. Tenofovir was shown to have good placental transfer. Administering 13 mg/kg of TDF as soon as possible after birth should produce neonatal concentrations comparable to those observed in adults."

A poster from the same group presented findings from a similar pharmacokinetic study with FTC.

They report, after the 400-mg FTC administration, median population AUC, T_{max}, C_{max} and C_{min} in pregnant women were 15.5 mg.L⁻¹.h, 3.0 hours, 1.60 and 0.14 mg/L, respectively. At delivery, median (range) FTC maternal and cord concentrations were respectively 1.02 (0.035 to 2.04) and 0.74 (0.005 to 1.46) mg.L⁻¹.

They conclude: "FTC was shown to have good placental transfer. Administering 2 mg/kg of FTC 12 hours after birth or 1 mg/kg 6 hours after birth should produce neonatal concentrations comparable to those observed in adults."

C O M M E N T

These preliminary studies looking at TDF and FTC are useful in extending the possibilities to reduce the risk of maternal NNRTI resistance following single dose NVP. In the Chi et al study the investigators excluded women with CD4 <200 cells/mm³ (who, quite rightly, received HAART), and 81% of women evaluated received antepartum AZT for a median of about 37 days, with 30% having undetectable viral load at delivery.

In contrast, in TOPS (which looked at AZT/3TC tail coverage and provided evidence for this strategy to be included in the WHO guidelines), there was no AZT and all women received single dose NVP regardless of CD4 [6]. It is possible that the longer TOPS regimens were more successful in reducing resistance (from nearly 60% to 10% vs 30% to 14% in the Chi study) but there is no head-to-head comparison. TEMA also evaluated healthy women who received AZT from a median of 33 weeks so, again, it is difficult to compare results between studies.

Chi's findings suggest that the single dose addition of TDF/FTC would be valuable where the WHO guidelines are being fully implemented ie where those indicated for HAART receive it. But perhaps some will caution, "not yet known" to the question of whether this strategy will be as effective where only single dose NVP is viable. But the simplicity would make it even more attractive for those programmes with very limited capacity.

Shahin Lockman and James McIntyre write in an accompanying editorial to the Lancet paper: "Chi's results do provide strong evidence that addition of single-dose tenofovir/FTC to short-course zidovudine and single-dose nevirapine in women with higher CD4+ cell counts is a new, effective, and feasible approach to reducing maternal nevirapine resistance, and one that should be seriously considered for implementation." [7]

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Response to treatment after single dose nevirapine exposure in women

Polly Clayden, HIV i-Base

In an oral presentation, Paul Weidle showed findings from a prospective cohort study of treatment response to an NNRTI-based regimen in women exposed or unexposed to single dose nevirapine for PMTCT. [1]

The study was conducted in Zambia (n=201), Thailand (n=87), and Kenya (n=67) between May 2005 and January 2007. The investigators looked at treatment failure (viral load \geq 400 copies/mL, not on NNRTI, died) at 6 months after initiation of HAART.

Of the 878 women, 355 were single dose NVP-exposed (including with short course AZT) and 523 unexposed. Single dose NVP-exposed women were younger (29 vs 33 years, $p < 0.001$), had a higher median CD4 (160 vs 139 cells/mm³, $p = 0.007$), and lower median viral load (97,300 vs 142,000 copies/mL, $p = 0.02$).

The investigators reported that at 6 months after initiation of HAART, 186 (21%) women had failed (76 had viral load \geq 400 copies/mL, 51 left the study, 48 died, and 11 had been switched to a protease inhibitor).

In a primary analysis looking at treatment failure at 24 weeks, they found women exposed to single dose NVP \leq 6 months before initiating NNRTI-based HAART, with baseline CD4 0 to 49 cells/mm³ or viral load $> 100,000$ copies/mL responded less well to treatment (see table for odds ratios for treatment failure).

They also reported that women exposed to single dose NVP > 12 months before NNRTI-based HAART did as well as unexposed women at time of analysis.

In a secondary on-treatment analysis, including only those still on NNRTI-based ART at 6 months, they reported similar results.

The investigators wrote: "These data do suggest an increased risk of treatment failure among women with recent single dose NVP exposure, but not with single dose NVP exposure > 12 months before initiation of NNRTI-based ART. Treatment with ART or perinatal HIV prevention strategies other than single dose NVP should be considered for pregnant women who are likely to initiate ART within 1 year after delivery."

Table 1: Odds ratios for treatment failure at 24 weeks, primary analysis

Baseline characteristics (n=878)	Adjusted odds ratio (95% CI), also adjusted for age
Time since exposure:	
Unexposed	Ref
<6 mo	1.9 (1.1-3.1)
7-12 mo	1.6 (0.9-3.0)
>12 mo	0.9 (0.8-2.7)
Country:	
Thailand	Ref
Zambia	2.0 (1.2-3.2)
Kenya	1.5 (0.8-2.7)
CD4 >200 cells/mm ³	Ref
50-199	1.4 (0.9-2.2)
0-49	3.2 (1.9-5.5)
Viral load <10,000	Ref
10,000-99,000	1.9 (0.95-3.6)
>=100,000	2.3 (1.2-4.3)
WHO stage I or II	Ref
III	1.4 (0.85-2.1)
IV	1.7 (0.96-2.8)

C O M M E N T

The failure rates in Africa versus Thailand reported in this study are scary.

Following this presentation John Mellors remarked that, "24 weeks is not long enough for emergence of archived resistance". One problem now seems to be that we could be getting a false sense of security from some of these studies with short follow up and as the "just wait 6 months" school-of-thought gains momentum. [2, 3, 4]

From the early days of denial, the emergence of resistance following single dose NVP to prevent MTCT story has swung past the alarmingly high rates of resistance seen if you looked early enough and hard enough to the most important question of "when does it matter?" Single dose NVP alone should not be given if there are sufficient resources to use more effective strategies. These would include HAART for pregnant women with advanced disease (some would say HAART for all) and short course AZT plus single dose NVP plus cover for the NVP tail for women not eligible for HAART.

Unfortunately, where resources are such that single dose NVP is the only option, the chances of initiating HAART in the mother less than 12 months later seem small.

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CROI: PAEDIATRICS

Response to treatment after single dose nevirapine exposure in infants

Polly Clayden, HIV i-Base

A poster from Linda Barlow-Mosha and coworkers showed findings from an analysis of treatment response to a NVP-based regimen in HIV-positive Ugandan children, who were exposed or unexposed to single dose NVP at birth.

There were 92 children enrolled in this study and they received 3TC/d4T/NVP. The children who had been exposed to NVP cohort were significantly younger than the NVP-unexposed children: median age 1.7 years (range 0.6 to 6.3) vs 7.8 years (range 2.9 to 12.4) (p<0.001).

The investigators reported, both groups showed substantial increases in median CD4 percentage. Baseline 8.5%, 48 weeks 22.5% cells/mm³; Baseline 14.0%, 48 weeks 33.0% cells/mm³ in the unexposed and exposed children respectively (p<0.0001)

The children's median baseline viral load was 650,568 copies/mL in the NVP exposed group and 239,027 copies/mL in the NVP unexposed group. Viral load response was similar in the two groups: 80% of the NVP unexposed and 76% of the single-dose NVP exposed group an undetectable viral load (<400copies/mL) at 48 weeks (p=0.74).

The investigators concluded that their data suggest that prior single dose NVP exposure did not have a negative effect on treatment success for children placed on a NVP-based HAART at a median age of 1.7 years.

C O M M E N T

Data describing infant response to treatment following single dose nevirapine are even scarcer than those for mothers. These are encouraging. Findings from Lockman et al from the Mashhi study were not: 10/15 exposed treatment infants having treatment failure at 12 months vs 1/15 unexposed. But these are tiny numbers. [2]

More studies are ongoing: the NEVEREST (Nevirapine Resistance Study) is evaluating response to treatment in women and children exposed to single-dose NVP; and IMPAACT 1060 is comparing the responses to initiation of NNRTI-based versus PI-based antiretroviral treatment in infants who have and have not previously received single dose NVP. Both are being conducted in South Africa.

This continues to be an area in which we need more data.

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Infant prophylaxis for postnatal transmission

Polly Clayden, HIV i-Base

Two studies looked at giving prophylaxis to breastfed infants of HIV-positive mothers, who were negative at birth.

PEPI

In an oral presentation Taha E Taha showed data from the PEPI trial. PEPI is an open label, controlled phase III trial conducted in Blantyre, Malawi. [1]

In this trial all mothers received single dose NVP for PMTCT. The infants were randomised to one of three arms immediately after delivery: Arm 1 single-dose NVP + 1 week AZT (control arm); Arm 2 the control regimen plus extended daily NVP (ExtNVP) for 14 weeks; Arm 3 the control regimen plus extended daily NVP+AZT (ExtNVP/AZT) for 14 weeks.

The primary endpoint was HIV infection at 9 months in infants who were HIV-negative at birth. This analysis evaluated 3016 infants enrolled before August 7, 2007, HIV negative at birth, for whom information on HIV status were available (1003 control, 1016 ExtNVP, and 997 ExtNVP/AZT).

Mothers were counselled to exclusively breastfeed and wean at 6 months. Mothers' CD4 counts were similar in all three arms: control, median 401 cells/mm³ (IQR 263-587), n=921; ExtNVP, median 379 cells/mm³ (IQR 245.0-570.5), n=924; ExtNVP/AZT, median 400.5 cells/mm³ (IQR 280.0-581.0), n=902.

There was a very high rate of breastfeeding in this study from birth to 6 months. The investigators reported a reduction across all arms between 6 and 9 months (from 91% to 32% in control, 90% to 27% in ExtNVP, and 90% to 29% in ExtNVP/AZT).

At 14 weeks there were substantial differences in probability of infant infection: 8.4% in control arm, 2.8% in ExtNVP and 2.8% in ExtNVP/AZT. The differences continued to 9 months: 10.6% control, 5.2% ExtNVP and 6.4% ExtNVP/AZT. At 9 months the probability of death was 8.9%, 6.8% and 6.3% in the control, ExtNVP and ExtNVP/AZT arms respectively. And the probability of infection or death was 16.8%, 10.6% and 11.2% in the three arms respectively.

The protective efficacy in the extended arms vs the control arm was 67%/66% at 14 weeks in the ExtNVP and ExtNVP/AZT arms declining to 51%/40% at 9 months (and further decreasing over time: 23%/24% at 24 months). In a proportional hazards model, the risk factors for infant infection were ExtNVP vs control HR 0.56 (95% CI 0.41-0.76), p=0.0003; ExtNVP/AZT vs control HR 0.65 (95% CI 0.48-0.88), p=0.006 and maternal CD4 count (decrease of 100 units) HR 1.27 (95% CI 1.99-1.36), p<0.0001. Most deaths were caused by gastroenteritis and pneumonia. There was no difference in grade 2 or higher adverse events across all prophylaxis arms.

SWEN

The Six Week Extended dose Nevirapine (SWEN) study evaluated a similar strategy but of a shorter duration. In an oral presentation, Jayagowri Sastry reported findings from this study. [2]

SWEN is a group of three separate but coordinated, randomised controlled trials conducted in Ethiopia, India, and Uganda to evaluate whether daily NVP given to breastfed infants until 6 weeks of age can decrease HIV transmission through breastfeeding. This presentation was a combined analysis from the three trials.

HIV-positive women breastfeeding their infants were enrolled. There were two prophylaxis arms: Arm 1, single dose NVP to mothers and infants. Multivitamin placebo to the infants from day 8 to 42. Arm 2, the single-dose NVP regimen plus 5 mg NVP daily from day 8 to 42 to the infants (SWEN). This study looked at the risk of HIV infection and death at 6 weeks and 6 months of age in infants HIV-negative at birth.

Maternal baseline CD4 was 397 cells/mm³ in the single dose NVP arm and 394 cells/mm³ in the SWEN arm. This data was from a modified intent-to-treat analysis including 986 single-dose NVP infants and 901 SWEN infants (excluding infants lacking specimens and those with indeterminate or HIV-positive at birth).

The investigators found that 6 weeks of age, SWEN infants had a 46% lower risk of HIV infection than the infants in the single-dose NVP arm (2.5% vs 5.3%; RR 0.536, 95%CI 0.336 to 0.855; p=0.009). At 6 months of age, SWEN infants had a non-significant, 20% lower risk of infection than single-dose NVP infants (6.9% vs 9.0%; RR 0.800, 95%CI 0.584 to 1.096; p=0.164). At 6 months of the mortality risk for the SWEN arm vs single-dose NVP arm was 1.1% vs 3.6% (RR 0.471, 95%CI 0.256 to 0.867; p=0.016).

The combined risks of post-natal HIV transmission or death in the SWEN arm vs the single-dose NVP arm were 3.7% vs 6.8% (RR 0.583, 95%CI 0.391 to 0.870; p=0.008) at 6 weeks and 8.0% vs 11.6% (RR 0.729, 95%CI 0.549 to 0.967; p=0.028) at 6 months, respectively.

The estimated cumulative probability of death or HIV transmission were RR 0.58, p=0.008; RR 0.7, p=0.026 and RR 0.73, p=0.028 at 6 weeks, 14 weeks and 6 months respectively. Serious adverse events were similar in both arms.

Resistance in SWEN

Inevitably this strategy should cause concern about resistance in infants who become HIV-positive despite receiving nevirapine prophylaxis.

In a second oral presentation from SWEN, Anitha Moorthy showed data from the Indian study comparing NVP resistance in infants receiving SWEN vs single-dose NVP by timing of HIV-1 infection and receipt of maternal single-dose NVP. [3]

In this analysis, infant DNA PCR was performed at 48 hours, 1, 2, 4, 6, 10, and 14 weeks, and 6, 9, and 12 months of age. Timing of infection compared 4 groups: in utero (positive by 48 hours; n=22); peripartum/early breastfeeding (positive at week 1 to 6; n=19); late breast-feeding (positive at week 10 to 14; n=18), and very late breast-fed (positive at >=6 months; n=35).

Median maternal CD4 counts were 316 cells/mm³ (IQR 238,454) and 320 cells/mm³ (IQR 194,522) in the single dose NVP

and SWEN arms respectively. 57% Of the women received maternal single dose NVP. 83/89 (93%) infant plasma samples could be genotyped. 76 infants met the inclusion criteria (able to define timing of infection) with sample taken 28 days since HIV diagnosis.

The investigators found higher rates of NVP resistance in SWEN infants infected within 6 weeks of life but lower rates of NVP resistance in infants infected after 6 weeks.

Table 1: Timing of infection

Timing of infection	S/D NVP n=51	ExtNVP n=25
Infected at \leq 6 weeks	38%	92%
Infected at >6 weeks	18%	15%
Infected in utero	50%	88%
Infected 1-6 weeks (Post partum/early BF)	27%	100%

The primary mutations were Y181C across both arms. There was no difference in mutations whether or not the mother had received NVP.

In multivariate analysis, the investigators found infants infected very late (>14 weeks) were 89% less likely to have NVP resistance than those infected earlier (in utero, peripartum, early breastfeeding, late breastfeeding) and these infants had mainly wild type virus.

With infection \leq 6 weeks as reference the adjusted odds ratios for NVP resistance during late or very late transmission (population or clonal level) were: OR 0.75 (95%CI 0.21-2.69), $p=0.658$ and OR 0.11 (95%CI 0.02-0.48, $p=0.004$ for late and very late transmission respectively.

Following this presentation Dr Jeff Stringer remarked that according to his "back of an envelope calculation" of 1000 HIV exposed babies 21 may be HIV-negative but 53 may have NVP resistance and asked whether this was "too high a price to pay."

And a poster authored by Jessica Church and coworkers evaluated resistance in the Ugandan infants. [4]

In this study, samples were available from 49/69 (71%) infants with HIV infection by 6 weeks of age (24 in the single-dose NVP arm; 25 in the SWEN arm). Maternal CD4 cell count, infant viral load, and HIV subtypes were similar in the both arms.

At six weeks NVP resistance was detected using the ViroSeq assay in a greater number of infants in the SWEN arm compared to the SD NVP arm (21/25 84% vs 12/24, 50%, $p=0.01$). A higher percentage of infants in the SWEN arm also had at least one NVP resistance mutation detected using the more sensitive LigAmp assay (19/25, 79% vs 7/24, 35%, $p=0.004$).

In the SWEN arm, NVP resistance was not associated with the number of NVP doses received or the HIV status at birth. Among infants with resistance detected at 6 weeks, only 1 of 6 infants in the single-dose NVP arm had NVP resistance detected by ViroSeq at 6 months. All 7 infants in the SWEN arm still had detectable NVP resistance at 6 months.

Phenotypic resistance results were available for 42/49 (85.7%) of infants evaluated at 6 weeks. There was a higher percentage of infants with phenotypic resistance in the SWEN arm than in the single-dose NVP arm (19/22, 86.3% vs 9 /20, 45%, $p=0.005$).

The Indian and Ugandan analyses were consistent in showing SWEN infants were more likely to have NVP resistance than those who received only single-dose NVP.

C O M M E N T

Isn't this all getting rather over evolved?

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2. Sastry J and The Six Week Extended Dose Nevirapine (SWEN) Study Team. Extended-dose nevirapine to 6 weeks of age for infants in Ethiopia, India, and Uganda: A randomised trial for prevention of HIV transmission through breastfeeding. Oral abstract 43. <http://www.retroconference.org/2008/Abstracts/32811.htm>
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4. Church J, Omer S, Guay L et al. Analysis of NVP resistance in Ugandan infants who were HIV-infected despite receiving single-dose nevirapine vs single-dose NVP plus up to 6 weeks of daily NVP to prevent HIV vertical transmission. Poster abstract 635b. <http://www.retroconference.org/2008/Abstracts/33467.htm>

Immune reconstitution inflammatory syndrome in young children initiating ART

Polly Clayden, HIV i-Base

There has been limited data describing immune reconstitution inflammatory syndrome (IRIS) in infants and children.

In an oral presentation Kelly Smith showed findings from a case note review of children enrolled in NEVEREST 2 (between April 2005 and November 2006), a South African trial in which HIV-positive children <2 years, exposed to nevirapine through PMTCT receive d4T/3TC/LPV/r (or RTV if <6months). Children in this cohort receive BCG vaccination as a matter of routine. Often this occurs prior to HIV diagnosis.

In this study children were monitored for IRIS during the first four months of HAART.

The investigators found 34/162 children initiated on HAART were confirmed to have IRIS. The median time from initiation to first symptom was 16 days (range 7-115 days), with 73.5% of symptoms occurring within 30 days from HAART initiation.

BCG-osis, most commonly BCG injection site inflammation or ipsilateral axillary lymphadenitis with abscess formation, were the most common, 24/34 (70.6%) of all the IRIS events and 14.8% of all children initiating HAART.

Other IRIS events included: TB in 11/34 (32%) children, CMV pneumonia, PCP, seborrheic dermatitis, herpes simplex, S pneumoniae sepsis and pneumonia.

The investigators reported that children with IRIS were younger, 47% <6months vs 25%; had lower CD4%, 56% CD4% <15% vs 34% and had higher baseline viral load, >750,000 copies/mL 45% vs 21% than children with no IRIS.

These children also had lower average weight for age z-score, mean -3.26 vs -2.09 and 82% vs 49% had < -2 SD below the mean (p=0.0004).

See Table 1 for baseline predictors for development of IRIS.

Table 1: Baseline predictors for development of IRIS

Variable	OR	95% CI
Age <6months	4.5	1.73-11.74
CD4% <10% vs >= 20%	5.84	1.72-19.8
Weight for age <= 2 SD from mean	4.13	1.53-11.11

After 24 weeks, response to HAART was lower the children with IRIS, with 28% vs 62% <400 copies/mL and 14% vs 44% <50 copies/mL.

Increase in CD4 percentage was similar between groups, but children with IRIS had lower mean CD4% at 24 weeks, 21.5% vs 29.0%, (p=0.001).

Dr Smith concluded that IRIS, particularly BCG-related disease, was common in this cohort of young children initiating HAART. Children with very advanced disease and low weight for age appear to be at particularly high risk.

Additionally, children with IRIS are less likely to achieve complete viral suppression by 24 weeks.

She added, "Further research is required to understand the pathogenesis and diagnosis of IRIS and determine best practices for prevention and treatment."

C O M M E N T

Diagnosing IRIS in children remains difficult and is an inexact science. BCG reactions are the most clear-cut clinical presentations of IRIS (see also study below). CMV pneumonia, PCP, seborrheic dermatitis, herpes simplex, S. pneumoniae sepsis and pneumonia carry an element of subjective assessment.

Was the decision to call a condition IRIS made by clinicians blinded to the CD4 percentage? There is great potential for bias, if the diagnostic criteria for calling a condition IRIS is based in part on the knowledge that the initial CD4 is low. Also, a child developing a new opportunistic infection within a few days or weeks of starting ART, may have been so profoundly immunosuppressed that they remained at much the same risk of OIs as they had prior to initiating ART. Including such children in the data set further perpetuates the notion that IRIS occurs in children with a low CD4 %.

The conclusion that further research is needed to understand the pathogenesis is entirely correct.

Ref: Smith K, Kuhn L, Coovadia A et al. Immune reconstitution inflammatory syndrome in HIV-infected infants and young children initiating ART. 15th CROI, February 2008, Boston, MA, USA. Oral abstract 75.
<http://www.retroconference.org/2008/Abstracts/31092.htm>

Complications with BCG vaccination in HIV-positive and negative infants: CHER Study

Polly Clayden, HIV i-Base

A poster from the CHER study group looked at Bacille-Calmette-Guerin (BCG)-related complications in this cohort and in a comparator group of HIV-negative infants born to mothers participating in a vaccine trial.

In this study 292 HIV-positive infants 6 to 12 weeks of age were randomised to immediate ART and 125 to deferred ART. The HIV-negative infants in the study were born to HIV-positive (n=125) and HIV-negative mothers (n=125).

All children received BCG vaccination at birth as is standard in South Africa. Signs of local reaction to BCG and other clinical events were compared among the infants.

This was data after a median follow up of 40 weeks.

The investigators reported that the prevalence of regional BCG-adenitis among the HIV-positive infants was 33/417, 7.9% (5.5 to 10.9), of which 13 (10.4%), were in the deferred arm and 20 (6.9%) in the early ART arm (OR 1.6, 0.8 to 3.3; p =0.22). By comparison none of the HIV-negative infants had local BCG-adenitis.

The majority, 31/33 (93.9%) of cases of BCG-related regional adenitis occurred following initiation of HAART, which suggested IRIS. 2 infants in the deferred arm had pre-existing adenitis.

There was no difference in the development of IRIS-related BCG-adenitis between the early-HAART 20/292 (6.8%), p= 0.48 and the deferred HAART 11/125 (8.8%) groups.

Out of the 33 infants with BCG-adenitis, 3 died (2 in the deferred arm and 1 in the early ART group). One of the deaths (in the deferred arm) was considered to be associated with BCG disease.

The investigators noted that the infants in the deferred arm received more concomitant therapy than in the early ART group (7/13 infants vs 4 /20 for TB treatment). Of 8 infants that received prednisone, 7 were in the deferred arm (53.9%) and 1 in the early ART group (0.5%).

The percentage of local BCG reactivity to BCG was similar (>50%) regardless of HIV status.

In the discussion section of this poster the investigators explained that in May 2007, the WHO revised its guidelines for BCG vaccination for children born to HIV-positive mothers. WHO recommended that it should not be given to children known to be HIV-positive. By that time, the CHER trial was fully recruited.

The investigators concluded:

- HIV-positive infants receiving BCG at birth have a high risk of BCG-associated IRIS.
- Associated factors are lower CD4 count/percentage and low WAZ.
- In infants with baseline CD4 >=25%, early ART is associated with significantly less IRIS than deferred ART
- Children in the deferred arm developed IRIS sooner after ART initiation with longer time to resolution

- TB drugs +/- steroids did not improve the time to resolution.

They wrote: "Early ART is associated with a significant reduction in BCG-associated IRIS, probably by limiting the degree of CD4 depletion."

Ref: Rabie H, Violari A, Madhi S et al. Complications of BCG vaccination in HIV-infected and -uninfected children: CHER Study. 15th CROI. February 2008. Boston, USA. Poster abstract 600.
<http://www.retroconference.org/2008/Abstracts/33235.htm>

The association between clinical characteristics and HIV-infection in very young infants

Polly Clayden, HIV i-Base

There are very few descriptions of characteristics of very young HIV-positive and HIV-exposed infants (<60 days). In settings with no access to PCR or CD4% quantification where clinical presumptive diagnosis is often used, these data could guide diagnostic algorithms for infants.

In an oral presentation, Heather Jaspen from the Faculty of Health Science, University of Stellenbosch, Cape Town, South Africa reported findings from an evaluation of the clinical and immunological parameters of HIV-positive infants and clinical characteristics of exposed, uninfected (EU), and unexposed, uninfected (UU) infants aged 4 to 10 weeks.

HIV-positive infants in this study were enrolled from the CHER study (n=540), and EU (n=125) and UU (n=125) infants were from a vaccine study in Cape Town and Soweto.

The median age of all infants was 44 days (range 28 to 78 days).

The investigators found weight below the 10th centile, oral thrush, lymphadenopathy and hepatomegaly to be significantly associated with HIV-positive status in infants in this study (all $p < 0.001$). Nappy rash, was also more likely in infants with HIV ($p < 0.05$).

Anaemia, neutropenia, gastroenteritis and gastric reflux (GERD) were also associated ($p < 0.005$).

When the investigators looked at clinical characteristics and severe immunosuppression ($\leq 25\%$) in the HIV-positive infants only weight (OR 1.6, 95% CI 1.1-2.4) and lower respiratory tract infection (OR 0.3, 95% CI 0.1-0.7) were associated in an age adjusted analysis.

So the study largely focused on the association between clinical characteristics and HIV infection.

After age adjustment, the investigators found weight in the lowest 10th percentile (OR 3.3, 95% CI 1.6-6.6), oral thrush (OR 5.6, 95% CI 3.0 to 10.2), any lymphadenopathy (OR 8.9, 95% CI 3.8 to 29.8), generalized LAD (OR 9.2, 95% CI 2.9-29.8) and nappy rash (OR 2.4, 95% CI 1.5-4.0) were associated with HIV infection.

When the investigators performed a sensitivity analysis including the following symptoms: oral thrush, any LAD, hepatomegaly, splenomegaly, GERD and weight below the 10th percentile,

presence of one symptom gave a sensitivity of 49.6% and specificity of 78.4%. Increasing the cut off to two or more symptoms decreased sensitivity but rapidly increased specificity. Two symptoms gave a specificity of 97.6% with 25% sensitivity. Three or four symptoms gave 100% specificity with 10.2% and 5.6% sensitivity for three and four symptoms respectively.

Dr Jaspen remarked that this is at least as good as the IMCI and WHO algorithms for diagnosis in older children. But, she explained, "Many HIV-infected children will still be missed, therefore PCR in resource limited settings is essential." She added that these findings need to be validated in different populations before an algorithm can be developed.

C O M M E N T

A previous small study from the Cote d'Ivoire [Rouet et al. AIDS 2002, 16:2303 – 2309] described a mononucleosis-like syndrome, dermatitis, and generalised lymphadenitis as independent factors associated with acute infection in breast fed infants. Generalised lymphadenopathy had a specificity of 96% and a sensitivity of 32%.

The negative and positive predictive values depended on the MTCT rate: the higher the rate of transmission, the higher the PPV but the lower the NPV. Clinical algorithms are no substitute for affordable sensitive and specific tests, when it comes to decision-making about starting ARVs.

Ref: Jaspen H, Myer L, Violari A et al. Clinical and immunological characteristics of very young infants with HIV infection: Children with HIV Early Antiretroviral Study. 15th CROI, February 2008, Boston, MA, USA. Oral abstract 76, 2008.

<http://www.retroconference.org/2008/Abstracts/31111.htm>

Paediatric pharmacokinetic studies

Polly Clayden, HIV i-Base

Correct dosing of antiretrovirals in HIV-positive children is complicated due to age-dependent changes in pharmacokinetics (PK) and the scarcity of data.

There were a number of posters at CROI showing PK data of old and new antiretrovirals in children from different age groups, and settings and with varying treatment experience.

Lopinavir/ritonavir in young infants

Data from the CHER study demonstrated a 76% reduction in early mortality in very young infants starting antiretroviral therapy (ART), regardless of clinical status, CD4 percentage or viral load. [1]

Since this finding, US guidelines (and others are expected to follow) recommend initiation of ART as soon as possible after birth for all infants age <12 months. [2]

Infants started on LPV/r 300 mg/m² before 6 weeks of age have low LPV exposure after two weeks of treatment. The clinical relevance of these low concentrations depends on how rapidly infants acquire therapeutic LPV exposure.

Edmund Capparelli and co-workers from the USA and Brazil evaluated longitudinal PK and response to treatment in young infants initiated on LPV/r-containing regimens.

This was a prospective, phase I/II, open-label, dose-finding study using a dose of 300/75 mg/m² twice daily + 2 NRTI in young infants ≥ 2 and < 6 weeks of age.

Infants had a 12-hour PK evaluation after 2 weeks of treatment and a second PK evaluation at approximately 1 year of age. Trough LPV concentrations and viral load were assessed regularly during the first year of treatment.

Doses were modified to maintain LPV pre-dose (C-pre) > 1 ug/mL and AUC < 170 ug.hr/mL based on week-2 pharmacokinetic results.

10 infants were enrolled in the study before 6 weeks of age (median 5.6 weeks) with median viral load of 5.9 log copies/mL. Of these, 9 infants had evaluable PK at 2 weeks and 7 had repeat evaluations at 1 year of age.

The investigators reported that during the first year of treatment the overall median LPV C-pre was 2.3 ug/mL; 20% of levels were sub-therapeutic (< 1 ug/mL). In individual infants, C-pre < 1 was observed in 0% to 50% of levels. 9/10 and 7/10 infants had viral loads < 1000 copies/mL at 16 weeks and 48 weeks, respectively.

Table1: LPV exposure increase during the first year of life

	2 week	1 year	p value
LPV dose (mg/m ²)	267 (246 to 296)	331 (305 to 331)	0.047
C-pre (ug/mL)	1.81 (1.54 to 2.67)	8.19 (4.79 to 10.8)	0.031
Cmax (ug/mL)	4.76 (3.30 to 7.06)	14.2 (10.6 to 15.6)	0.031
AUC (ug*h/mL)	36.6 (28.6 to 62.0)	134 (87.9 to 137.6)	0.016
CL/F (L/h/m ²)	5.64 (4.30 to 9.98)	2.44 (2.34 to 3.47)	0.016

They found that infants with viral blips > 1000 copies/mL between 8 and 48 weeks were more likely to have sub-therapeutic C-pre, ($r = 0.73$, $p = 0.016$).

The investigators concluded that LPV/r exposure is initially low in infants < 6 weeks of age but increases dramatically during the first year of life. But despite the low initial LPV exposure, most infants achieved viral load < 400 copies/mL at 48 weeks.

They noted that viral loads > 1000 copies/mL at 8 weeks and later, seen more frequently in infants with intermittently low LPV concentrations, suggested a link with difficulties in drug administration or adherence.

Recommended dose of lopinavir/ritonavir too low in protease inhibitor-experienced children

Lopinavir/r is approved for paediatric use in children aged 6 months and older at a dose of 230 mg/m² twice daily, with a maximum of 400 mg/dose.

In adult PI-experienced patients, a target trough LPV concentration of < 5.7 mg/L is associated with less likelihood of an undetectable viral load.

Natella Rahmanina and coworkers from the US reported findings from a study using modelling to determine whether this target is relevant in children, and can be achieved at the current recommended paediatric dose. [3]

Over 52 weeks, the investigators evaluated 50 PI-experienced children (4 to 17 years) receiving LPV/r-based therapy (single PI). Baseline resistance tests and 12-hour PK evaluations were performed (at second visit); viral load and adherence were assessed throughout the study.

Using multiple logistic regression, trough LPV concentration, adherence, and resistance were modelled as predictors of virologic outcome. PK data were fitted to candidate PK models. The model with the highest log-likelihood was used to simulate 5000 children to find the percentage with trough LPV concentration < 5.7 mg/L after standard dosing.

The investigators found LPV resistance at baseline ($p = 0.003$) and trough concentrations < 5.7 ($p = 0.03$) were significant predictors of never achieving viral load < 400 copies/mL during the study period. In this model adherence did not predict virological outcome. LPV trough was < 5.7 in 40% of the 5000 children simulations from this model.

The investigators wrote: "In this validated paediatric population pharmacokinetic model of LPV/r, the currently recommended dose of LPV will fail to consistently achieve this target in a large percentage of children. Further studies on therapeutic drug monitoring of LPV/r in children are warranted."

Therapeutic drug monitoring of lopinavir and saquinavir in Thai children

Torsak Bunupuradah and coworkers from Thailand and the Netherlands looked at drug levels of PIs in a group of 50 Thai children. [4]

This was a prospective, open-label single-arm study of children receiving LPV/r and saquinavir (SQV) at standard doses.

Pre-dose plasma concentrations (Cmin) were taken at weeks 12, 24, 36, 48, 60, 72, 84, and 96. Children with Cmin < 0.1 mg/L for LPV or 0.02 mg/L for SQV were excluded from the analysis because of suspected nonadherence.

Doses were adjusted according to clinical, growth, and Cmin. Cmin above the 50% inhibitory concentration (IC50) of > 1.0 mg/L for LPV and > 0.28 mg/L for SQV were targetted.

The children in this study had a median age at baseline of 9.3 years (IQR 7.1 to 11.2). For each time-point, 42 to 48 samples were available for analysis (348 for LPV and 353 for SQV).

The investigators found the overall mean (SD) of the C_{min} were 5.52 (3.85) and 1.37 (1.24) mg/L for LPV and SQV, respectively. They reported no significant change over time for the C_{min} levels.

At week 96, 5.5% and 3.7% had C_{min} >IC₅₀ for LPV and SQV respectively. The average dose for SQV decreased from 43 mg/kg at baseline to 34 mg/kg at week 96. The LPV dose remained almost the same: 228 mg/m² and 229 mg/m², at the same time-points.

The median intravariability over 96 weeks was 55% (IQR 41 to 76) and 67% (IQR 54 to 85) for LPV and SQV, respectively. The median intervariability was 69% (IQR 60 to 74) for LPV and 81% (IQR 76 to 94) for SQV.

The investigators noted that despite the dose reduction of 32% from standard dosing for SQV at week 96, the plasma levels indicate that further dose reduction is possible and that the high LPV C_{min} suggests that dose reduction is reasonable. "Further research is warranted to establish a more appropriate dose for this Asian population", they wrote.

Nevirapine exposure with WHO paediatric weight band dosing

Nevirapine (NVP) is dosed according to body surface area (150 to 200 mg/m²) or weight and age (7 mg/kg <8 years and 4 mg/kg ≥8 years). These dosing guidelines are far too complex for implementation in resource-limited settings and are themselves inconsistent. World Health Organisation (WHO) has developed a simple weight-band tables based on body surface area calculations of appropriate dose of key antiretroviral drugs for use in these settings. To date dosing of NVP (or other drugs) in this way has not been validated.

Edmund Capparelli and coworkers presented combined data from several paediatric trials of nevirapine PK and NVP exposure. PK values were modeled and comparisons made between values expected from dosing according to WHO guidelines to Food and Drug Administration (FDA) approved method (per kg). [5]

NVP PK data from 5 Pediatric AIDS Clinical Trials Group (PACTG) studies conducted in the United States were combined with data from Zambia (CHAPAS) and Thailand (IMPAACT P1056). Data from 565 children were included.

The AUC and C_{min} with WHO dosing using 50-mg or 60-mg NVP (as part of FDC baby tablets with 3TC and d4T ie NVP/3TC/d4T of 50/30/6mg or 60/30/6mg) were assessed from the ratio of doses (parameter x WHO Dose/Study Dose). The frequency of sub-therapeutic concentrations (C_{min} <3 ug/mL or AUC <48 ug.h/mL) and supra-therapeutic concentrations, 120 ug.h/mL (2x average) were determined.

The investigators performed a Monte Carlo simulation using a population PK model that included age, weight, ritonavir (RTV) use, and CYP 2B6 genotype. Using weight-band dosing, 7720 paediatric NVP concentration profiles were simulated.

The investigators found NVP AUC and C_{min} were similar across the 3 countries (ie no difference in PK in the much more malnourished Zambian children). 94 children receiving

RTV and 88 who were outside the WHO dosing weight groups (<5 or >30 kg) were excluded from the analysis.

The median, C_{min} and AUC were 174 mg/m² (IQR 162 to 187), 5.7 ug/mL (IQR 3.8 to 8.0), and 77.7 ug.h/mL (IQR 55.8 to 107.2) for WHO weightband dosing using 50/30/6mg ratios (based on the principal that NVP doses never go below 300mg/m² and 153 mg/m² (IQR 112 to 172), 4.6 ug/mL (IQR 3.0 to 6.9), and 62.2 ug.h/mL (IQR 45.1 to 90.8) for FDA dosing (4 or 7mg/kg). WHO dosing exceeded C_{min} and AUC targets in 85% and 84% of children. The FDA dose met these targets in only 75% and 72% of children. The frequency of AUC >120 was higher with WHO than FDA dosing (18% vs 10%).

Increasing the ratio of NVP in FDCs (from 50mg to 60 mg NVP to be combined with 30mg 3TC and 6mg d4T) reduced the frequency of sub-therapeutic levels by 5%, but increased supra-therapeutic levels (>120%) by 12%. Monte Carlo simulation exceeded target AUC and C_{min} in 77% of simulated patients.

The investigators concluded:

- The recommended WHO weight band dosing of NVP will result in therapeutic concentrations in approximately 80% of children without incurring a high frequency of excessive NVP exposures.
- The WHO weight band dosing of NVP achieves target exposure in a greater portion of children than the FDA dose of 4-7 mg/kg.
- Monte Carlo simulations produced similar NVP exposure to observed results from multiple clinical trials and can be used to help to optimise dose recommendations.
- The 50mg NVP tablet strength (50/30/6mg of NVP/3TC/d4T in FDC tablets used according to WHO weightbands) maximises the therapeutic index compared to other potential tablet strengths (such as 60/30/6 mg).
- WHO weight band dosing should be adopted in resource limited settings.

Nevirapine PK in Thai children receiving either an adult or paediatric fixed-dose combination of d4T, 3TC, and NVP

HIV-positive Thai children frequently receive a divided adult fixed-dose combination of stavudine (d4T)/lamivudine (3TC)/nevirapine (NVP) (30/150/200 mg/tablet).

A new chewable fixed-dose combination tablet of d4T/3TC/NVP (7/30/50 mg/tablet) for children has recently been introduced by the Thailand Government Pharmaceutical Organisation (GPO). (These are the same ratios as in the Zambian Chapas trial 6/30/50 mg).

Kulkanya Chokephaibulkit from Thailand and the United States looked at NVP PK in Thai children receiving either adult (GPOvir S30) or paediatric (GPOvir S7) fixed-dose combinations [6].

In this study, NVP concentration data from 44 children (age 8.6±2.9 years and weight 24.3±8.3 kg) was combined from two clinical trials. Results from 9 children enrolled in IMPAACT P1056, an ongoing PK study comparing GPOvir S7 with the standard liquid formulations, who had intensive PK sampling pre-dose, and 0.5, 1, 2, 4, 8, and 12 hours post-dose were combined with data from a separate study of 35 children who

received GPOvir S30 and had PK sampling pre-dose, and 2, 6 hours post-dose.

The investigators used a 1-compartment model and population approach to analyse the data. They found median NVP clearance was 0.081 L/h/kg and volume of distribution 1.79 L/kg across both formulations.

Children receiving NVP GPOvirS30 showed a slower absorption rate ($p < 0.001$), but had comparable bioavailability ($p > 0.20$) to those receiving GPOvirS7. The average NVP AUC was 75.5+/-40.5 and 81.1+/-34.7 ug.hr/mL for GPOvir S30 and GPOvir S7, respectively. Median pre-dose NVP concentrations were higher with GPOvirS30 compared to GPOvirS7, 6.0 ug/mL (3.4 to 24.0) vs 4.3 ug/mL (3.0 to 10.0), $p = 0.06$. All children achieved a pre-dose NVP concentration above the recommend target of 3.0 ug/mL.

The investigators concluded: "NVP pharmacokinetic parameters in Thai children using fixed-dose combination tablets containing either NVP 200mg or 50mg were within the range observed in prior paediatric studies." They observed no clinically significant differences in NVP concentrations between the two formulations.

PK of etravirine (TMC125) in HIV-positive children between 6 and 17 years of age

Thomas Kakuda and coworkers from Tibotec showed findings from a study to determine the weight-based dose of etravirine that will achieve exposures in children comparable to those in adults. [8]

This study enrolled HIV-1-positive children between 6 and ≤ 17 years of age on a stable (at least 2 consecutive viral loads < 50 copies/mL) on a LPV/r –containing regimen. Etravirine 4 mg/kg twice daily was added for 7 days followed by a morning dose, and 12-hour PK assessment on day 8. Both 25 and 100-mg tablets were used. The 25mg tablet is currently only available for research purposes.

TMC125 PK was assessed using non-compartmental analysis; C_{min} and AUC_{12h} were compared to PK parameters in adults receiving 200 mg twice daily on a LPV/r-containing regimen.

PK assays were available for 16/17 children. 10 children were aged between 6 and < 12 years, and 6 between ≥ 12 and ≤ 17 years. The mean (SD) C_{max} and C_{min} in 16 children were 555.2 (514.6) ng/mL and 233.2 (237.9) ng/mL, respectively.

Mean (SD) AUC_{12h} was evaluable in 15 children and was 4788 (4459) ng.h/mL.

The investigators reported, relative to adults, the least square means ratio for C_{min} and AUC_{12h} was 1.08 (90% CI: 0.69 to 1.69) and 1.11 (90% CI: 0.76- 0.62), respectively.

They found interpatient PK variability was greater in children than adults, primarily as a result of 1 outlier. When the outlier was removed range of exposures in children was similar to that in adults. Exposure was not associated with age or body surface area (BSA).

There were no serious adverse events. 12 children reported at least 1 adverse event, mostly grade 1 or 2; 2 children (12%) developed a rash on treatment (grade 1 and 2, respectively), both on day 8 and resolving after 5 to 6 days; the AUC_{12h} in these children were 7408 and 1826 ng.h/mL, respectively.

The investigators concluded:

- Etravirine at 4mg/kg bid following a meal provides comparative exposure in children age 6-17 to 200mg bid in adults.
- Etravirine was generally safe and well tolerated. Two patients developed mild to moderate transient rash (with no apparent association with etravirine AUC_{12h}).

As antiretrovirals are frequently under-dosed in children (in part because of increased variability), stage II of this trial with 30% higher dose 95.2mg/kg bid) is underway. A phase II trial to determine safety and efficacy in treatment-experienced children will begin after final dose selection.

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CROI: WOMEN'S HEALTH

The unmet need for contraception services for women receiving ART

Polly Clayden, HIV i-Base

Two oral presentations clearly highlighted the importance of contraception services for HIV positive women receiving ART and PMTCT services.

DITRAME Plus

Valeriane Leroy presented findings from a study of the ANRS 1201-1202 Ditrane Plus Cohort in Abidjan, Côte d'Ivoire, looking at the incidence of a new pregnancy among HIV-positive women followed postpartum over 24 months after a PMTCT intervention, who chose either replacement or breast feeding. The study hypothesis was that non-breastfeeding women are exposed to a greater risk of unwanted pregnancy.

The analysis included all women in the Abidjan cohort between March 2001 and July 2003, age <49 years, who received a short course ARV prophylaxis regimen (AZT + single-dose NVP+/-3TC), delivered a live infant and initiated one of the two infant feeding options offered (replacement feeding or exclusive breastfeeding for 4 months).

Contraceptive methods were promoted and provided free of charge according to the infant feeding option: replacement feeders used oral or injectable contraception; breast feeders followed the lactational amenorrhea method for 4 months, then injectable or oral contraception. Condoms were provided to both feeding groups.

The study evaluated the occurrence of first new pregnancy within the 24 months follow-up period. The start of pregnancy was estimated using the reported date of last menstrual period and the gestational age as assessed by ultrasound.

724 women were assessed, 332 (46%) replacement feeders, and 392 (54%) breast feeders. Use of a contraceptive method was similarly high in both groups: formula feeders, 78.1% vs. 77.5% breast-feeders ($p=0.87$).

The investigators reported 79 new pregnancies over 24 months. At 12 months, the incidence of a new pregnancy was similar between the two groups: 4.4% (95% CI: 2.7-7.2%) in breast-feeders and 4.1% (CI: 2.4-7.0%) in formula-feeders. They found correlates of incidence of a new pregnancy within 12 months were an advanced WHO clinical stage 3-4 vs 1-2 (adjusted relative risk: 0.2; 95% CI: 0.1-0.8, $p=0.02$) and the death of the last-born child (adjusted RR: 6.6; 95% CI: 2.6-16.6, $p<0.0001$)

At 24 months the incidence of a new pregnancy was significantly lower in formula feeders than in breast feeders, 10.0% vs. 16.5% (adjusted RR: 0.5; 95% CI: 0.3-0.9, $p=0.02$). Factors associated with pregnancy at this time point were: the follow-up clinic, the number of live-born children and the death of the last-born child (adjusted RR: 3.5; 95% CI: 1.4-8.7, $p=0.008$).

The investigators concluded: "Replacement feeding is not responsible for a greater incidence of pregnancy in this urban West African population. Our results highlight the public health importance to deliver appropriate family planning services for HIV-infected women".

HBAC

Jaco Hornsy then showed findings from a cohort of 733 HIV-positive women enrolled in the Home Based AIDS Care (HBAC) study in Uganda and receiving HAART.

This was a prospective cohort study of women age 18-49 who initiated HAART from March 2003 – June 2006, in which trends and predictors of pregnancy, desire for children, and use of family planning were analysed.

Women were counselled on the effect of HAART on restoring fertility and sexual activity, HIV prevention and family planning. They received free condoms on request.

The investigators conducted detailed social and behavioral questionnaires in the women's homes. These were quarterly the first year after initiating HAART, and every 6 to 12 months thereafter.

There was no provision or referral for termination of pregnancy in this study; abortion is illegal in Uganda. However, women who aborted were asked about their experiences and treated for any complications.

The analysis included 708 women with a median follow-up of 2.05 years (IQR 2.0 to 2.1). After initiation of HAART, 120 (16.9%) women had 140 pregnancies (20 repeat pregnancies). The median time to conception was 12.4 months (IQR 7.9-18.0). There were 144 pregnancy outcomes (4 sets of twins); 106 live births (74%), 4 (3%) miscarriages, 8 (5%) still births and 26 (18%) induced abortions.

The investigators reported an increased incidence in pregnancy from 3.46/100 person-years in the first quarter of HAART to 11.71/100 person-years in the fourth quarter ($p=0.0001$). They noted that this paralleled an increase in the proportion of women reporting sexual activity in the past 3 months from 24.4% to 32.5% over 24 months of follow-up, $p=0.001$.

Predictors of pregnancy were: age (per 10 year decrease) (adjusted HR 2.7, 95% CI 1.9-3.8, $p<0.001$), having a body mass index >18.5 (adjusted HR 1.1, 95% CI 1.0 to 1.1, $p=0.02$), and inconsistent condom use (adjusted HR 1.8, 95% CI 1.0 - 3.2).

Despite 93% to 97% of all women in this study reporting that their pregnancies were unwanted or unplanned, only 14% and 13% of women used permanent or semi-permanent family planning methods and 3.5% and 4.3% used dual contraception at 18 and 24 months respectively.

The investigators recommended:

- Family planning services should be an integral part of HAART interventions in Africa.
- Counselling is critically needed to explain the restorative effect of HAART on fertility and sexual activity.
- Younger women and their partners should be particularly targeted.
- Dual contraceptive services should be available to all for free.

C O M M E N T

The first part of the conclusion from the Abijan study was curious; the effectiveness of the lactational amenorrhea method of contraception has been well documented and is reported to be 98% effective "with perfect use".

Surely any differences in pregnancy incidence between the two feeding groups would be masked by the high rate of uptake of contraception by all the women in this study, which at 78% is to be applauded and is considerably higher than the background rate in Cote d'Ivoire (<10%) and most African countries.

As Karen Beckerman remarked following the presentation, "free contraception and counselling works, it contributes to pregnancy spacing and, if offered, women will take up this life saving intervention".

With regards to the finding that women with WHO stage 3-4 vs 1-2 were more likely to become pregnant within 12 months, it would be useful to know if these women were receiving HAART (baseline variables in this study included maternal eligibility for HAART but these data were not presented).

In the second study, the HBAC investigators describe an “unmet need” for family planning services as part of ART programmes. The rate of unwanted pregnancy (93% - 97%) in this cohort was scary - even within the Ugandan setting with a fertility rate of 6.7 children.

This presentation ended with quotes from HBAC women, which made uncomfortable listening, and included: “I wanted to abort so badly. I tried all the methods I was told locally but I failed. And there was no way I could ask the doctors to do an abortion. That is why I carry the pregnancy today...”

Policy makers and healthcare providers have responsibilities to include contraception services alongside ART and PMTCT programmes, and the need becomes even greater in settings where termination of pregnancy is illegal.

Although not really discussed in either study, it deserves mentioning that, in addition to considerable advantages to women’s health, even a minimal reduction in unplanned pregnancies can have the equivalent impact to PMTCT interventions in reducing infant infection. One previous study suggested that in Kenya and Zambia, lowering the pregnancy rate by 5.6% and 6.6%, respectively would have the equivalent impact to providing single dose nevirapine. [3]

These two studies highlight both the need for and the potential uptake of such services.

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Valacyclovir decreases plasma and genital viral loads in HSV-2/HIV-1 co-infected women

Polly Clayden, HIV i-Base

A poster authored by Jared Baeten and coworkers from the University of Washington, Seattle, US; Assn Civil Impacta Salud y Educacion, Lima, Peru; and Fred Hutchinson Cancer Reserach

Centre, Seattle, WA, US showed findings from a study to assess whether HSV-2 suppressive therapy reduces HIV-1 plasma and genital viral loads. [1]

This was a randomised, placebo-controlled, cross-over trial of 500 mg valacyclovir received orally twice daily by 20 HSV-2/HIV-1 co-infected women in Lima, Peru who had CD4 counts >200 cells/mm³ and were not receiving ART.

The women were randomised to receive valacyclovir or placebo for 8 weeks. Then following a 2-week washout period, they received the alternative regimen for a further 8 weeks.

Plasma samples were taken weekly and endocervical swabs were collected three times a week for measurement of HIV-1 viral load. Additionally, the women collected genital swabs themselves daily for HSV DNA PCR. The women’s median CD4 count was 372 cells/mL (range 229- 850).

The investigators reported detection of genital HSV on 3.7% of days receiving valacyclovir versus 22.1% of days receiving placebo (p<0.001). HIV-1 plasma viral load was significantly lower during the valacyclovir arm compared to the placebo arm, 4.34 vs 4.61 log copies/mL, p<0.001; a difference of -0.27 log copies/mL, (95%CI -0.34 to -0.20). Cervical HIV-1 was detected at 54.3% of visits while receiving valacyclovir versus 71.1% of visits while receiving placebo, p<0.001. Cervical HIV-1 levels were significantly lower while receiving valacyclovir vs placebo, 2.87 vs 3.23 log copies/swab, p<0.001; a difference of -0.35 log copies/swab, (95% CI -0.46 to -0.25).

The investigators concluded: “Daily valacyclovir therapy (500 mg twice daily) for HSV-2 suppression significantly reduced plasma and genital HIV-1 concentrations among HSV-2/HIV-1 co-infected women. Suppressive HSV-2 therapy has the potential to reduce HIV-1 infectiousness and the rate of disease progression; these outcomes are under evaluation in ongoing clinical trials.”

C O M M E N T

Results from the HPTN 039 study conducted by the same group were also presented at this conference [2]. This was a randomised, placebo-controlled trial to determine whether HSV-2 suppression with twice-daily acyclovir reduces the risk of HIV acquisition among women in Africa and men who have sex with men (MSM) in the Americas (n=3251).

This study found that acyclovir did not reduce HIV acquisition among women with HSV-2 and MSM, despite evidence from multiple epidemiologic studies that HSV-2 infection increases HIV susceptibility by 2- to 3-fold, even with excellent retention and adherence among the trial participants. The investigators wrote “..acyclovir (400 mg twice daily) suppresses HSV-2, but does not prevent HIV acquisition. Further research is needed to elucidate the disparity between extensive data on epidemiologic and biologic interactions between HSV-2 and HIV and these trial results.”

Although the investigators suggest that suppressive HSV-2 therapy with valganciclovir has the potential to reduce HIV-1 infectiousness and the rate of disease progression, the results from ongoing research with valganciclovir are needed

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HPV genotypes in HIV-positive women in Zimbabwe and Uganda

Polly Clayden, HIV i-Base

Two posters evaluated HPV genotypes in HIV-positive from Zimbabwe and Uganda. HIV is known to be risk factor for human papillomavirus (HPV) prevalence and persistence. Both current HPV vaccines however are only known to be effective against types 16 and 18 of HPV.

David Hill and coworkers (from Stanford University School of Medicine, Wake Forest University Baptist Medical Centre, Caradon Consulting San Carlos and University of California), looked at HPV genotypes in HIV-positive pregnant Zambian women with subtype C HIV-1 and assessed cervical HPV infection and HIV-1 virus shedding. [1]

In this study, women were evaluated for HIV and HPV infection by assays of cervical swab samples. For HPV, real-time polymerase chain reaction (RT-PCR) was performed followed by a generic HPV probe using DNA hybridisation. Positive samples were re-probed for 29 individual HPV types and a probe mixture of 10 types. Cervical HIV RNA was measured using RT-PCR.

119 women were enrolled (5 were excluded from HPV analyses due to insufficient DNA).

The investigators found, 82% (94/114) of samples were HPV-positive. Re-probing revealed 27 unique HPV types in 72 women. 58% (66/114) of women had high cancer risk genotypes: HPV 58 in 19 women, followed by HPV 66, in 14 women.

Additionally, HIV cervical virus was detected in 88% (46/52) of cervical samples tested. The median cervical viral load was 3.54 log copies/mL.

The investigators found no correlation between HIV-1 shedding and the presence of HPV, or specific HPV types in cervical samples tested.

The investigators wrote: "A high proportion of HIV-positive pregnant women in Zimbabwe shed HIV-1 RNA and carried high risk cervical HPV types associated with increased cervical cancer risk. However, only 16 of 94 (17%) were infected with HPV-16 or -18, types against which current vaccines are known to be protective."

They added: "These data suggest that current HPV vaccines may not prevent HPV infections or provide protection against the high risk HPV types prevalent among HIV-infected women in Zimbabwe."

In the Ugandan study Janis Taube and coworkers from Johns Hopkins Medical Institute, Baltimore, MD, US; Makerere University, Johns Hopkins University Research Collaboration, Kampala, Uganda; and Makerere University, Kampala, Uganda looked at HPV genotype prevalence in HIV-positive and

HIV-negative women in Kampala. Additionally they wished to determine which genotypes are associated with cervical pathology in this population. [2]

200 women aged 18 to 30 years were recruited to the study at 4 to 12 weeks post-partum at Mulago Hospital. The women underwent rapid HIV testing and a pelvic exam. Cervical cytology samples were collected and processed.

Among these women, the investigators reported an HIV prevalence of 19% and an HPV prevalence of 65%. The most frequent high-risk HPV genotypes were 16 (9%), 33 (9%), 35 (6.5%), 45 (6.5%), and 58 (6%). The most frequent low-risk genotypes were 62 (22%), 61 (11%), 81 (11%), 70 (10%), and 53 (10%). The prevalence of HPV 6, 11, and 18 was 2.5%, 1%, and 4%, respectively.

They found there was no significant difference between the presence of HPV 16 or HPV 18 in HIV-positive or HIV-negative women (13.9% vs 7.3%, $p=0.20$ and 3.7% vs 5.6%, $p=0.64$, respectively). HIV-positive women were more likely to have other HPV genotypes (both high and low risk) than HIV-negative women (72.2% vs 40.9%, $p<0.001$ and 63.9% vs 36.6%, $p=0.0046$, respectively).

They also found HIV-positive women had a greater median number and range of HPV genotypes vs HIV-negative women (median of 2, range 0-8 vs median of 1, range 0-6, $p<0.001$). HIV-positive women were significantly more likely to have an abnormal Pap smear vs HIV negative women (43% vs 11%, $p<0.001$). And HPV prevalence was 58% in women with normal cytology and 97% in women with abnormal cytology. They noted that HPV 16 and 18 prevalence in women with normal cytology was 9.9% and in women with abnormal cytology was 28%.

They concluded: "Our results show that while HPV types 16 and 18 may be seen in association with cervical pathology, preventative, or therapeutic vaccines will need to target a broad-spectrum of HPV genotypes to effectively combat cervical disease in this population".

C O M M E N T

Both these studies and another from Zambia [3] highlight the question of whether current HPV vaccines will be effective in populations with a significant diversity and multiplicity of HPV types. HPV vaccine development of the future needs to consider a broader range of HPV types if these advances are to have a wider global impact.

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CROI: SCALE UP

Utility of routine viral load, CD4 count and clinical monitoring among HIV-positive adults in rural Uganda

Polly Clayden, HIV i-Base

In an oral presentation, Alex Coutinho from TASO and Infectious Disease Institute, Kampala, Uganda presented findings from a randomised trial to evaluate the utility of laboratory vs clinical monitoring in rural Uganda.

This study was part of the Home Based AIDS Care (HBAC) programme for people with HIV, in which ART is provided to all eligible household members. In this programme lay workers delivered ART to participants' homes each week and there were no scheduled clinic visits after enrollment.

HIV-positive adults with a CD4 count of <250 cells/mm³ or World Health Organisation (WHO) stage 3 or 4 received ART and were randomised to 1 of 3 monitoring groups: arm A, clinical monitoring and quarterly CD4 cell counts and viral loads; arm B, clinical monitoring and quarterly CD4 cell counts; or arm C, clinical monitoring alone.

Participants received NVP+3TC+d4T (EFV if receiving TB treatment) for first-line. Second-line could include LPV/r, ddI, AZT and TDF.

Lay workers collected data on illness and mortality, and referred participants to the study clinic for care. Quarterly CD4 cell counts and viral loads were performed for all participants. Clinicians received results as described in the study protocol.

Clinical failure was defined as, unintentional weight loss of >10%, CDC category 4 illness, diarrhea or fever for >1 month or new or recurrent oral, oesophageal or vaginal candidiasis.

In this study 1116 ART-naïve participants were randomised and 1094 started ART, their median baseline CD4 cell count was 130 cells/mm³. The median follow-up was 3 years.

From the time of randomisation, there were 126 deaths (11.2%) and 148 new AIDS-defining illnesses; 47% of deaths and 57% of AIDS-defining illnesses occurred in the first three months of receiving ART. 61 (5.8%) of participants had virologic failure (defined as 2 consecutive viral loads >500 copies/mL) after the first 6 months of ART. 28 (2.7%) of participants changed to second line drugs.

The investigators found, in an intent-to-treat analysis from the date of starting ART, adjusting for age, sex, baseline CD4 count, viral load, body mass index, and Center for Epidemiologic Studies Depression Scale (CESD) score, the rate to new AIDS-defining event or death was higher in arm C than arm A (HR 1.88, p=0.002) or B (HR 1.47, p=0.047). They found no difference between arms B and A (HR 1.28, p=0.26). The study had 80% power to detect a rate ratio of 1.75 at p<0.05.

Although overall mortality in arm C during the 3 years of ART was low (13%), there was a non-significant trend towards higher mortality between arm C and arms A (HR 1.58, p=0.07) and B (HR 1.38, p=0.18). There was no difference in mortality between arms B and A (HR 1.14, p=0.6).

When the investigators looked at specific disease morbidity they found the incidence risk ratio (IRR) for TB, PCP, cryptococcal diseases and KS was significant for arm C vs A, across all four diseases: 1.7 (p=0.045), 8.7 (p=0.01), 2.3 (p=0.04) and 3.3 (p=0.07) respectively. For arm C vs B the IRR was significant for all but KS: 1.7 (p=0.045), 17.2 (p=0.009), 3.1 (p=0.013) and 1.6 (p=0.39) respectively.

Similar numbers of participants experienced virologic failure in all three arms, A:16, B:26 and C:19, and this was associated with increased severe morbidity or mortality (18% vs 10%, p=0.049). Overall 90% of participants had an undetectable viral load at one year. Of those participants experiencing virologic failure, 28 switched to second line regimens: 7/16, 4/26 and 2/19 in Arms A, B and C respectively. The total number of participants that switched in each arm were, 7, 4 and 17, of these 7, 4 and 2 switched to second line with detectable viral load in Arms A, B and C respectively.

Dr Coutinho noted that in Arm C, "15 people were substituted on clinical grounds even though they did not have a detectable viral load."

He suggested that arms A and B did better not just because of the earlier switch (only <50% with viral load <500 copies/mL changed to second line drugs the remainder of the participants achieved subsequent suppression after adherence interventions), but using laboratory monitoring made it possible to identify problems with adherence before the occurrence of severe morbidity or mortality. "Clinical criteria were poorly sensitive and poorly specific to detect adherence challenges", he explained.

He concluded: "Clinical monitoring alone was associated with increased rate of new AIDS-defining events and a trend towards increased mortality." This study showed no benefit to adding quarterly viral load measurements to CD4 counts in the first three years of ART.

"However there is need to determine long term outcomes and cost effectiveness of CD4 and viral load monitoring", he added.

C O M M E N T

This study was interesting but hard to interpret and like the Phillips et al study summarised on page 24 highlights the need for more data particularly the anticipated results from DART.

Ref: Alex Coutinho et al, Mermin J, J Ekwaru J et al. Utility of Routine viral load, CD4 cell count, and clinical monitoring among HIV-infected adults in Uganda: A randomised trial. Oral abstract 125. <http://www.retroconference.org/2008/Abstracts/30881.htm>

Implementation of more complex regimens for prevention of mother-to-child transmission of HIV in Rwanda

Polly Clayden, HIV i-Base

In September 2005, the Rwandan national HIV programme introduced ART for women indicated for treatment and a multi drug regimen for women not indicated for treatment for the prevention of mother-to-child-transmission (PMTCT).

Prior to this women received single dose NVP as PMTCT prophylaxis.

In addition, the new guidelines included routine HIV counselling and testing for all pregnant women and CD4 testing for all HIV-positive women.

A poster from Landry Tsague and coworkers described the experience of the International Center for HIV/AIDS Care and Treatment Programs (ICAP) of providing technical and clinical support in delivering more complex ART regimens for PMTCT in 18 health facilities in Rwanda.

In accordance with new national guidelines (2006), ICAP developed strategies to implement more complex regimens including AZT from 28 weeks gestation with single-dose NVP + 7 days' AZT + 3TC "tail" or HAART (AZT + 3TC + NVP) for pregnant women with CD4 <350 cells/mm³.

The investigators described the main barriers to rapid expansion of PMTCT services and implementation of the new guidelines as: limited number of CD4 machines at district level; weak linkages between PMTCT and ART programmes and a limited number of nurses trained on the new PMTCT protocol.

In order to address these barriers, CD4 capacity was decentralised to two districts and a coordinated "district CD4 system" was introduced to all PMTCT sites with a district laboratory. In order to facilitate same day diagnosis and CD4 testing, first antenatal clinic visits were scheduled to the day of CD4 blood taking at each centre. Nurses or social workers began escorting women to ART services and doctors were sent to PMTCT sites to help strengthen the link between services.

Training on the new PMTCT protocols was introduced for all appropriate staff, ICAP PMTCT field workers gave clinical mentorship to nurses and regular assessments of the quality of care were made.

In this programme AZT was initiated by nurses for women not indicated for treatment and HAART was initiated by a doctor. In ART/PMTCT sites without doctors, district hospital doctors initiated HAART during weekly visits.

The investigators reported, from July 2006 to September 2007 CD4 testing for HIV-positive women increased from 60% (140/234) in the fourth quarter 2006 (Q4-06) to 82% (136/166) in Q3-07 (p<0.0001). Those getting CD4 testing and receiving their results increased from 43% (100/234) in Q4-06 to 82% in Q3-07 (p<0.0001). The percentage of women with CD4 <350 cells/mm³ increased from 11.4% (16/140) in Q4-06 to 20% (928/136) in Q3-07 (p=0.004).

Women receiving single dose NVP only decreased from 48% (34/71) in Q3-06 to 1% (2/175) (p<0.0001). The proportion initiating more complex ARV regimens increased from 52% (37/71) in Q3-06 to 99% (173/175) in Q3-07 (p<0.0001). And since Q-3-06 93% (762/819) of HIV-positive pregnant women received any ARV drug in pregnancy.

ICAP demonstrated within a short period, the feasibility of implementing more complex regimens for PMTCT at multiple sites in a resource-limited setting.

The investigators highlighted the main challenges:

- Reorganising services to ensure same-day HIV and CD4 testing, which required strong collaboration between ART, PMTCT and laboratory staff and took 1-2 months to accomplish at each site.

- Nurses are not yet allowed to initiate HAART in Rwanda.
- Active referral to the nearest ART site from PMTCT sites with no ART services is time consuming for nurses/social workers escorting patients.
- More complex regimens for PMTCT require strong support for HIV-positive women and their families (for example support groups), which is insufficient at most sites.
- The provision of comprehensive HIV/AIDS care for mother/infant pairs post-partum

They wrote: "Increasing CD4 count testing capacities at the district level and providing close mentorship to health providers are critical to quickly expand the scope of PMTCT services and facilitate the implementation of potent multidrug regimens for HIV-positive pregnant women."

Ref: Tsague L, Tene G, Adje-Toure C et al. Rapid Implementation of More Efficacious ART Regimens for the Prevention of Mother-to-Child Transmission of HIV in Rwanda. 15th CROI. February 2008. Boston, USA. Poster abstract 830.

<http://www.retroconference.org/2008/Abstracts/31688.htm>

The estimated cost of switching from d4T to TDF in South Africa

Polly Clayden, HIV i-Base

The majority (70%) of patients in resource limited settings starting antiretroviral therapy (ART) do so with a d4T containing regimen. d4T is associated with high rates of toxicities including lactic acidosis, lipodystrophy and peripheral neuropathy and is responsible for the majority of drug switches.

Many countries are considering replacing d4T with tenofovir (TDF), which, although currently more expensive than d4T, is associated with fewer adverse events.

A poster from Ian Sanne and coworkers from the University of the Witwatersrand, Johannesburg, South Africa and Boston University, MA, US, reported findings from an analysis using a Markov model to estimate the cost of switching from d4T to TDF in South Africa's first line regimen.

The model used existing prices of d4T and TDF and also estimated the incremental cost per quality-adjusted life year (QALY) gained from the switch. This analysis then determined the prices of TDF at which the switch would become highly cost-effective and budget-neutral.

The investigators modelled both the ARV and toxicity management costs of treating a hypothetical cohort of 1000 adult patients for two years with the current first-line regimen of d4T/3TC/EFV (d4T scenario) and compared them with corresponding cost estimates for a regimen of TDF/3TC/EFV (TDF scenario).

They used data from the patient database at a public hospital in Johannesburg to estimate rates of toxicities, associated drug switches and management for the d4T scenario. They estimated corresponding rates and resource use parameters for the TDF scenario from the literature.

In the model, events defined for the analysis attributed to d4T were: peripheral neuropathy, hyperlactatemia/lactic acidosis, lipodystrophy, and pancreatitis. Renal failure was the only toxicity attributed to TDF.

Resources used for estimates for toxicity management included hospital admissions, outpatient visits, laboratory tests, and drugs.

They used the current public sector price for d4T (\$3.15/month) and the Clinton Foundation HIV/AIDS Initiative (CHAI) price for TDF (\$12.42/month).

The investigators reported, in the d4T scenario, 50.5% of patients experienced a confirmed or suspected d4T-related toxicity and 16.2% were switched to a different drug (mainly AZT) by the end of two years. Hyperlactatemia (64%) and peripheral neuropathy (26%) accounted for the majority of d4T toxicities. In the TDF scenario, only 2.5% of patients experienced a TDF-related toxicity and were switched to AZT. The average toxicity management costs ranged from \$45 for mild hyperlactatemia to \$5506 for lactic acidosis.

They found, after two years, the total cost of the TDF scenario was 15% greater than that of the d4T scenario. The average cost increase per patient treated was \$89/year. Savings on toxicity management offset 41% of the higher price of TDF compared to d4T.

The investigators also looked at the question: "What if d4T is responsible for a proportion of observed loss to follow up?"

They found, if 10-20% of observed loss to follow is a result of d4T-related toxicities, then TDF would be "very cost effective" at only slightly less than the modelled price of \$17/patient/month.

The investigators noted that their analysis was limited by data quality, model constraints, and time frame. Also the assumptions used "were conservative and likely underestimated the costs of d4T-related toxicities".

But from this model they concluded:

- If TDF was priced at \$17/patient/month, the reduced costs for managing d4T-related toxicities would offset about 20% of the higher price of TDF.
- For the switch to TDF in first-line regimens to be cost-neutral for the South African government, TDF will need to be priced at approximately \$6/patient/month.
- For patient welfare (QALYs), the switch will be highly cost-effective at a TDF price of \$13/patient/month.
- If 10-20% of observed loss to follow up is attributable to d4T-related toxicities, then switching to TDF is very cost effective even at currently available prices.

Ref: Sanne I, Long L, Fox M et al. The cost of switching from stavudine to tenofovir in first-line ARV regimens in South Africa. 15th CROI. February 2008. Boston, USA. Poster abstract 989.

<http://www.retroconference.org/2008/Abstracts/31042.htm>

CONFERENCE REPORTS

14th Annual BHIVA Conference

23-25 April 2008, Belfast

Monitoring patients on antiretroviral therapy in resource-limited settings with viral load, CD4 count, or clinical observation alone

Polly Clayden, HIV i-Base

The majority of roll out programmes in resource-limited settings will introduce antiretrovirals using clinical monitoring without viral load and often without monitoring of CD4 cell counts.

One of the more controversial presentations was from Andrew Philips who presented results from a paper recently published in the *Lancet* that used a model of HIV progression and the effect of antiretroviral therapy to determine the consequences of using different monitoring strategies on survival and development of resistance. [1, 2]

The investigators used a model (HIV Synthesis) that was originally developed for well-resourced settings. This is a stochastic computer simulation model, which tracks data on the progression of HIV and the effect of antiretroviral therapy on simulated patients.

The model generates information that includes, age, viral load and CD4 count. Each patient's data are updated every three months showing the current number of active drugs in the regimen, the viral load and the level of adherence. For each antiretroviral, the model keeps track of current use, past virological failure, previous use, past stopping due to toxicity, and resistance to the drug.

The model was adapted to reflect the situation in resource-limited settings and the modifications included:

- WHO stage 3 and 4 events in place of CDC grade B and C disease, particularly to model pulmonary TB.
- Increased risk of non-HIV mortality.
- Use of single dose NVP in a proportion of women for mother-to-child transmission prophylaxis (assumed to result in NVP resistance).
- Interruptions in drug supply.

The model only included adult patients. Patients were eligible for antiretrovirals according to WHO guidelines and received a first-line regimen of d4T, 3TC, and NVP. The second-line regimen was AZT, ddI and LPV/r. Switching due to treatment failure was determined by monitoring strategy; some individual drug substitutions due to toxicity were assumed.

The investigators simulated outcomes of using different strategies for 6-monthly monitoring of antiretroviral therapy to determine when to switch to second-line therapy. 1. Viral load, with virological failure >500 copies/mL or 10 000 copies per mL, occurring after more than 6 months continuously on antiretrovirals. 2. CD4 cell

count, with failure defined as 50% decline from peak during the current period of continuous treatment or by a 33% decline over a 6-month period. Additionally the CD4 cell count must be <200 cells/mm³, and the patient must have been on antiretroviral therapy continuously for over 9 months. 3. Clinical events, with failure defined by a new WHO stage 3 or 4 event, or by two new WHO stage 3 events or a WHO stage 4 event (multiple WHO stage 3/new WHO stage 4 event), or by a new WHO stage 4 event. The patient must have been on antiretroviral therapy for more than 6 months.

Using the model, 58% of patients generated at the time of start of ART were women with a median age of 30 years and median baseline CD4 and viral load of 66 cells/mm³ and 5.4 log₁₀ respectively. 32% of patients had TB previously and 13% had received single dose NVP for mother to child transmission prophylaxis.

Estimates of the risk of virological failure using viral load >500 copies/mL were 16% by 1 year, 28% by 5 years, 37% by 10 years, and 51% by 20 years.

Comparing this criterion with other switch criteria, at 1 year: 87% patients if viral load >10,000 copies/mL; 26% if CD4 decline from peak; 25% if current CD4 decline; 32% if new stage 3/4 event; 19% if multiple stage 3 events or new stage 4 event and 10% if new stage 4 event would meet criteria to switch. These proportions continued similarly up to 5 years.

A small proportion of patients met the CD4 count or clinical switch criteria before viral load >500 copies/mL. Of the patients who met the viral load >500 copies/mL criterion first the proportion fulfilling the other viral load criterion (10,000 copies/mL), CD4 count and clinical criteria by one year from fulfilling viral load 500 copies/mL criterion was assessed. This was 87% if viral load >10,000 copies/mL; 26% if CD4 decline from peak; 25% if current CD4 decline; 32% if new stage 3/4 event; 19% if multiple stage 3 events or new stage 4 event and 10% if new stage 4 event, would meet criteria to switch. The median time to meet CD4 count criteria was approximately 4 years.

Using viral load >500 copies/mL as switch criterion 83% of patients had resistance to NVP, 85% to 3TC, and 26% had any thymidine analogue mutation at the time of switch. When the multiple WHO stage 3/new WHO stage 4 event criterion was used, 90% had resistance to nevirapine, 90% to lamivudine, and 55% had thymidine analogue mutations at the time of switch.

These mutations meant that the mean number of active drugs in the second-line regimen was 2.71 in those switched according to viral load and 2.37 in those switched according to clinical events.

When the investigators looked at survival, this was greatest in patients switched according to viral load >500 copies/mL but differences compared to other criteria were modest.

Survival was estimated as mean life years lived over each time period. The investigators found that death rates were not constant over each period and were much higher in the first year. At 5 years, mean person years of potential life were: 4.14 (83%), 4.09 (82%) and 4.09 (82%) using viral load >500 copies/mL, CD4 decline from peak and multiple stage 3/new stage 4 criteria respectively. At ten years these values were: 7.74 (77%), 7.52 (75%) and 7.53 (75%) and at 20 years: 13.46 (67%), 12.76 (64%) and 12.71 (64%) for the same criteria respectively.

The proportion of life-years spent with viral load <50 copies/mL was highest for viral load monitoring: 73%, 74% and 69% at 5, 10 and 20 years using viral load >500 copies/mL and 69%, 68% and 63% using WHO stage 3/new WHO stage 4 event criterion.

When the investigators looked at the risk of transmission of resistant virus and the proportion of life-years in patients with resistance who also had viral load over 1000 copies/mL, (as these patients will be more infectious) they found lower percentages of life-years with resistance to some drugs when the switch criterion was a viral load >500 copies/mL than with other criteria.

In their discussion in the Lancet article, the investigators wrote: "Although viral load monitoring provided a moderate improvement in survival compared with other monitoring strategies, and would be predicted to reduce resistance accumulation and the ability to transmit resistant HIV to others, at around \$3500 per life-year gained (compared with a strategy of new WHO stage 3/4 events), at current costs such monitoring is unlikely to be cost effective in most resource-limited settings."

They explained that since resistance to NVP and 3TC is almost always present at the time of virological failure of the WHO first line regimen, it is largely resistance to d4T and AZT at the start of the second regimen that will be different between the viral load and other monitoring strategies. They found the mean number of active drugs in the second-line regimen was only moderately lower when the multiple WHO stage 3/new WHO stage 4 strategy was used than with use of viral load monitoring, even though the clinical monitoring strategy allows the virus to accumulate thymidine analogue mutations over more than 4 years.

They noted that data on resistance has been largely based on patients in the north with subtype B virus.

They predict that if d4T is replaced with tenofovir in first line regimens (as is increasingly happening in resource limited settings), their overall conclusions are unlikely to differ.

Additionally, if second-line regimens are used that are different to that in the model (including abacavir, ddI, and LPV/r or tenofovir, ddI, and LPV/r), these do not include AZT and so the investigators predict they would be, if anything, less sensitive to the accumulation of thymidine analogue mutations during first-line failure. Therefore their conclusions would probably hold for alternative second line regimens.

They concluded: "In summary, our results suggest that use of antiretroviral therapy without monitoring of viral load or CD4 cell count does not have marked detrimental effects on patient survival or on development of resistance. This finding is particularly relevant in view of the limited array of antiretroviral combinations available to the developing world. Access to antiretroviral therapy should be expanded to all settings as rapidly as possible; lack of access to laboratory monitoring should not be allowed to hinder this process."

C O M M E N T

In an accompanying editorial to the Lancet article David Moore and Jonathan Mermin from HBAC (see CROI reports) write, "These results might seem surprising to clinicians familiar with HIV treatment in high-income countries, where the value of laboratory monitoring has been accepted since the introduction of highly active antiretroviral therapy in the mid-1990s."

They rightly point out that the results from DART, which are anticipated next year, will further inform the question.

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CONFERENCE REPORTS

XVII International Resistance Workshop

10-13 June 2008, Sitges

Integrase inhibitor resistance and cross-resistance: weighing viral fitness and the option to benefit from second-generation compounds

Simon Collins, HIV i-Base

Several research groups presented results on generally small groups of highly treatment experienced patients who are no longer responding to raltegravir-based regimens.

The key questions for these patients who already have limited options involves identifying when the risks of remaining on a less than suppressive treatment outweigh any residual benefits from treatment.

Do integrase inhibitors (INIs) have class properties that are stronger than individual drug profiles (generally like NNRTIs or PIs)?

Does resistance accumulate slowly enough for reduced viral fitness to have a clinical benefit?

Does the risk of accumulated mutations compromise the future option to benefit from second generation INIs?

An understanding of the integrase resistance, first reported at last years meeting, emphasised that primary resistance follows two main pathways – based on either Q148H/R/K or N155H, leading to >10-fold resistance, with one group this years reporting that these mutations are not found on the same genome. Indeed, four distinct pathways appear to develop, with different implications for viral fitness. This year Y143R/C emerged in several studies as a further primary mutation.

While resistance generally has an impact on reducing viral fitness, and immunological benefits were reported as continuing 3 and 6 months after treatment failure, questions were asked to each presenter about the degree to which patients maintained on a failing integrase-based regimen may be compromising their options to use second-generation integrase compounds.

This issue will not be resolved until they are greater data available on the viral responses of patients who stop integrase treatment – and this is currently limited to single case reports.

Michael Miller presented Merck's longitudinal genotyping and cloning analysis from 35/133 patients (28%) failing raltegravir at 48 weeks in their Phase II study. [1]

Three additional patients had showed no INI changes. Of the 35, 2 subsequently resuppressed their viral load, leaving 33 patients with a second genotype. Of these, a further 2 resuppressed and 4 were lost to follow-up, 4 remained stable with Q148H and G140S and 23 provided data from a third genotype.

At first failure only 9 patients had single mutations, with most having 2 or more, and these increased in number over time.

The genotype at first failure showed 20 patients with mutations at Q148 + combinations and 14 with N155 plus combinations. No patients failed with mutations at both these key sites. One patient failed with Y143R alone.

Over time, four pathways were reported: i) a consistent preference for the Q148H at each stage, including Q148H/G140S (n=13) that remain stable; ii) patients with N155H alone, which generally developed to Q148 (n=5); iii) mixed N155H/Q148H viral populations that resolved to Q148H over time, often with G140S (n=7); and iv) patients with other mixed patterns including N155H but who accumulated additional mutations but not Q148 (n=7).

Q148 viruses, especially with secondary mutations, displayed the greater levels of resistance and the least benefit from impaired fitness.

Addressing this small dataset, without details on the time of sampling, Miller was optimistic that second generation Merck compounds would be active against Q148 and N155, but also did not expect to see pharmacologically acceptable formulations available for at least several years.

Most importantly, he also recognised that there were no data to support maintaining raltegravir in patients who were virologically failing treatment.

Signe Fransen and colleagues from Monogram, also working with the Merck team presented results from a subset of 69 samples from the Phase III Benchmrk studies. [2]

Nine patients had mutational changes at both Q148 and N155, but the changes at each point were mixtures and they were never found on the same genome. Secondary mutations - E92Q with N155H, and G140S(A) with Q148R(H/K) – were related to the primary resistance pathway. A few patients were reported with E92Q but without changes at N155 or Q148.

Four patterns in this analysis broadly followed the Miller study: i) Q148R(H/K) with or without additional changes including N155H and Y143R/C; ii) N155H with or without additional mutations, including Q148R(H/K) and Y143R/C; iii) Y143R/C with or without changes at N155 or Q148; and iv) 1 patient with no primary mutations.

Clonal analysis from these patients showed a variable impact of mutation patterns on viral fitness. Both Q148 and N155 reduced replicative capacity and this was either further reduced or, in some cases improved, depending on the secondary mutation pattern.

However, there is unlikely to be any significant clinical relevance from what are likely to be transitory changes in fitness, especially if a trend to developing Q148 is confirmed, as this mutation has little impact on fitness.

Clinical experience from raltegravir use was also provided by several independent research groups.

Steven Deeks group from University of San Fransisco, presented results from 13 patients who remained unsuppressed on raltegravir-containing regimens. [3]

These were multiple experienced and advanced patients (baseline CD4 count was 66 cells/mm³) followed for a median of over 12 months. Most notably, CD4 increases persisted despite virological non-suppression (with increases of +37 and +71 cells/mm³, at 3 and 6 months respectively).

Three patients with intermittent adherence in this group lacked mutations, but otherwise G140S+Q148H and T97A+Y143R patterns were seen, and they were associated with high-level phenotypic resistance.

One patient, who only showed isolated N155H, interrupted only the raltegravir component of treatment while maintaining their background regimen. Plasma levels initially remained stable, suggesting an effect of viral fitness, but they subsequently rebounded by over 1 log as the proportion of raltegravir-associated mutations declined in the absence of selective drug pressure.

Christine Katlama from Pitié-Salpêtrière Hospital, Paris, reported on a cohort of 50 treatment-experienced patients who started raltegravir between September 2006 and November 2007. 34 patients successfully suppressed viral load to <40 copies/mL by week 24. 11 patients had low-level viraemia >40 - <400 copies/mL and 3 had persistent viraemia >400 copies/mL.

4/13 patients with genotype results showed integrase mutations: G140S+Q148H (n=2), N155H (n=1) and a switch from N155H to G140S+Q148H (n=1).

Several studies also addressed cross-resistance between raltegravir and elvitegravir, and no researchers either directly involved in these studies or in the general discussions expected patients who fail on one of these drugs to benefit from subsequent use of the other.

Olivia Goethals and colleagues from Tibotec used selected *in vitro* emergence of resistance to raltegravir and elvitegravir and site directed mutagenesis of selected mutations against a panel of integrase inhibitors. [5]

Q148R was selected by both raltegravir and elvitegravir and conferred resistance to other compounds. The researchers concluded that Q148H, together with E92Q and T66I, which were both also selected by elvitegravir, should be considered to confer class-wide resistance.

The discussions on cross-resistance were closely tied to interest in second-generation integrase inhibitors, and awareness of the pipeline is important for patients who have already developed integrase resistance. Merck say they have already designed molecules with activity against 148 and 155 mutations - and that rational drug design should also be able to overcome changes at position 143. The bottleneck is overcoming pharmacokinetic problems of delivery and tolerability though, and Daria Hazuda also estimated that they are still likely to be at least 2-3 years away from clinical studies.

Finally, a study from Anne-Genviève Marcelin and colleagues from Pitié-Salpêtrière Hospital, Paris, compared integrase sequences from 72 clade-B and 66 CRF02-AG strains for the difference in naturally occurring polymorphisms. [6]

While several studies have reported that polymorphisms in subtype B infection are not limiting responses in integrase-naïve patients, including two studies at this workshop [7, 8], there are little data from non-B subtypes.

They found 13 amino acid changes that could affect the functional properties of integrase with clustering suggesting these may include compensatory mutations, concluding that virological response to integrase inhibitors by viral sub-type should be studied in clinical trials.

C O M M E N T

This focus on resistance should be seen against the background of raltegravir also producing some of the strongest treatment responses in multiple-experienced and advanced patients.

For patients failing integrase-based treatments though, these questions are critical. Documenting resistance history for selection of future drugs is important. The limited data, and expert opinion from the researchers involved with these compounds suggest no specific benefit from remaining on integrase inhibitors once viral load has rebounded, and that the risk of accumulating mutations will compromise use of future INIs and that this risk should be taken seriously.

The data on viral fitness suggests any benefit is likely to be short term, and unlikely to outweigh the risk from accumulating further resistance, especially once Q148 changes have occurred.

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Pipeline antiretrovirals: IDX899, CHX157 and beviramat

Simon Collins, HIV i-Base

IDX899: an NNRTI in development with Idenix

An oral presentation by Rob Murphy [1] summarised two posters at the workshop that presented information on a new NNRTI being developed by Idenix. [2, 3]

Antiviral activity was shown in results from a seven-day Phase I/IIa dose finding study in Argentina, 40 treatment-naïve patients were

randomised 8:2 to once-daily monotherapy with 800mg, 400mg, 200mg or placebo. All patients switched to 28 days monotherapy or started HAART at the end of the study period.

Results were available for all but two patients in each of the 200mg and placebo arms. Viral activity was similar in each of the active drug groups which saw steady, linear viral load reductions reaching -1.8 log at day eight (using COBRAS AmpliCor 1,5) from mean baseline of approximately 4.3-4.6 log copies/mL.

No clear relationship was seen between drug exposure and response and although the current formulation only has 50% bioavailability, all doses achieved drug trough concentrations that exceeded the protein adjusted EC50 by greater than 10-40 fold (with individual ranges from 5-140 fold).

Mean CD4 count increased by around +65 cells/mm³ in all groups compared to a reduction of -85 cells/mm³ in the placebo arm.

Side effects occurring in > 2 patients were mild, infrequent and distributed equally between the placebo and active drug groups, with no clear dose-related toxicity, and no grade 3/4 laboratory changes. There were no cases of rash, which commonly do not show after only 7 days, but also no cases of CNS disorientation which would be expected, if induced. Toxicity has not been seen in preclinical animal studies.

A second poster presented by Jocelyn Jakubik expanded on the likely resistance and cross-resistance profile of IDX899 in a set of in vitro studies. [2]

IDX899 was shown to remain sensitive (<4 fold change from wild-type) to 20/23 single, double and triple site directed mutations, with greater resistance seen to Y181C (14 fold), E138K/Y181I (11 fold) and E138K/Y181I/M230L (900 fold). It also retained sensitivity to viral pools selected through exposure to efavirenz and etravirine (TMC-125), and retained greater sensitivity to each pool compared with efavirenz, etravirine or TMC-278 (rilpivirine)

High level resistance to IDX899 was selected in vitro after >29 passages with two independent pathways initiated by mutations at either E138K or V90I/Y181C.

While showing potential benefits of IDX899 against NNRTI-resistant virus, the results also tentatively suggested that naïve patients failing IDX899 might retain sensitivity to efavirenz.

This poster expanded on the first presentation of these studies at the Retrovirus Conference earlier this year. [4]

Idenix are still in negotiation with potential companies to take forward the clinical development programme of IDX899 in 2009, based on an improved formulation and possibly also a 100mg dose.

C O M M E N T

These promising early results should help start the Phase III studies. Although the in vitro data support potentially different resistance patterns to both existing NNRTIs and other pipeline drugs, this also needs to be studied in the clinical programme.

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CHX157: a prodrug similar to tenofovir-DF

Randall Lanier, formerly with GSK and now with Chimerix, presented results on hexadecyloxypropyl tenofovir (CMX157), a new compound similar to Gilead's tenofovir disoproxil fumarate. [1]

Differences claimed for this new compound include activity against K65R and that this prodrug is less efficiently cleaved to free tenofovir in plasma, which should increase tenofovir diphosphate levels in target cells, lower the apparent IC50 and reduce the rate of secretion into the kidney (and related toxicity). The primary elimination pathway is thought to be hepatic,

IC50s for CMX157 were determined against a panel of 30 NRTI single and multiple isolates including K65R, M184V, TAMS, K70E, Q151M and 69-SXX insertion and are detailed in Table 1.

Similar results were also reported against a separate panel of 14 NRTI-resistant and wild-type clinical isolates in PBMCs.

Table 1: Examples of IC50s for CMX157 and tenofovir-DF against NRTI-resistant isolates

	CMX157	tenofovir-DF
L74V/M184V	0.66nM	227nM
T69SSG/M184V/L210W/T215Y	57nM	~17,000nM
M41L/L210W/T215Y	6.3nM	2,240nM
M41L/L210W/T215Y/M184V	2.2nM	770nM

The poster reported that tenofovir diphosphate levels were 33-fold higher in PHA/IL-2 stimulated human PBMCs after 24 hours compared to tenofovir-DF and that no toxicity has been observed in rats administered up to 100mg/kg/day for 7 seven days.

Ref: Lanier ER et al. Hexadecyloxypropyl tenofovir (CMX157) has enhanced potency in vitro against NRTI resistant HIV relative to tenofovir and a favorable preclinical profile. XVII IHDRW 2008, Sitges. Poster 4.

Beviramat (PA-457): baseline gag polymorphisms determine treatment response

Scott McCallister from Panacos presented an analysis of the impact of baseline Gag polymorphisms together with individual drug exposure levels on virological response to the maturation inhibitor beviramat. [1]

Results of early studies were complicated by formulation difficulties and disappointing virological responses. In fact, the latest virological information from ongoing Phase IIb results has only trickled out in a series of company press statements containing 'forward-looking statements'. [2, 3]

The analysis at this years workshop was from 44 treatment-experienced patients on currently failing treatment who added beviramat in escalating dose groups as functional monotherapy for 14 days.

Table 1: Virological responses to beviramat

	Responders >0.5 log reduction	non-responders <0.5 log reduction
N	20	24
Trough >20ug/mL	19/20	19/24
Mean VL response	-1.26 log	-0.05 log
Baseline Gag polymorphisms	5.9	7.3

Viral responses by presence of baseline polymorphisms in Gag at positions 369, 370 or 371 were -0.16 (n=9), -0.24 (n=22) and -0.32 logs (n=11) respectively. Patients with absence of the same mutations had viral responses of -0.69, -0.79 and -0.73 respectively. Patients with no changes at 369-371 had a reduction of -1.08 logs.

Panacos are now planning to restrict future research to patients without baseline Gag polymorphisms at the three points, citing the approximate 60% naïve patients from the 567 patients in the University of British Columbia database as guide to proportion of patients likely to be eligible. They will also plan to restrict studies to patients who achieve minimum trough levels >20ug/mL.

C O M M E N T

Predefining a patient group likely to benefit from beviramat is similar to use of a tropism assay prior to prescribing CCR5 inhibitors and should not be a block to future drug development, especially if it can reliably result in a -1.2 log drop in viral load.

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Lack of virological impact of treatment intensification in suppressed patients supports latent viral reservoir as source of residual viraemia

Simon Collins, HIV i-Base

Frank Maldarelli from the US HIV Drug Resistance Programme, and colleagues, presented results from a small treatment intensification study looking to clarify the source of residual viraemia in patients with viral load suppressed to <50 copies/mL. [1]

This group has previously reported that long term suppression < 50 copies/mL still results in 80% patients have viraemia >1 copy/mL (when tested on an assay with this sensitivity), but that median levels are only 3.1 copies/mL once patients have been on stable treatment for 60 weeks, and that no further suppression occurred from week 60 to 120. This study also found that the level at week 60 correlated with pre-treatment viral load but not with choice of treatment regimen. [2] They concluded that “these data suggest that the persistent viraemia on current antiretroviral therapy is derived, at least in part, from long-lived cells that are infected prior to initiation of therapy”.

The new study intensified treatment for 30 days in 6 patients who had been suppressed to <50 copies/mL for at least the previous year on standard 3-drug regimens but who still had detectable virus using a 1 copy/mL assay. The four patients on PI-based therapy intensified with efavirenz and the two patients on NNRTI-based therapy added lopinavir/r. Doses were modified appropriately to allow for ARV drug interactions.

These patients (5 men, 1 woman) had been diagnosed a mean 9 years (range 4-16) and on treatment for a mean of 4 years (range 1-10). Mean baseline viral was 4.5 copies/mL.

No significant changes occurred in viral load or CD4 count over the 30 day intensification period, and treatment was well tolerated with no serious side effects reports. Mean viral load during and after intensification were 5.2 and 5.3 copies/mL respectively, showing no impact of the intervention. This was supported by individual responses of the 6 patients that were all included in the poster.

The researchers concluded that failure to find a decrease from intensification in this study was inconsistent with the idea that persistent viraemia at low levels was the result of ongoing complete cycles of replication and that the results supported the source being from latently infected reservoirs.

C O M M E N T

This study supports research first presented at the resistance workshop several years ago by Lisa Frenkel, who found that 8/11 children with generally suppressed viraemia had no evolution of viral divergence since starting treatment, implying ongoing viraemia was seeded from latently infected cells rather than a partially activated reservoirs as suggested by others.

This has been one of the theoretical foundations behind the drive to achieve suppression to <50 copies/mL, rather than at any higher (or lower) level. The absence of viral evolution shows effective treatment stopping, rather than slowing, HIV progression, with a clearly different and more important impact on clinical outcome.

References

1. Maldarelli F et al. Intensification with efavirenz or lopinavir/r does not reduce residual HIV-viraemia in patients on standardised ARV therapy. XVII IHDRW 2008, Sitges. Abstract 72.
2. Maldarelli F et al. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viraemia. PLoS Pathogens 3(4): e46. doi:10.1371/journal.ppat.0030046.
3. Tobin NL, Frenkel L et al. Evidence that low-level viraemias during effective HAART result from two processes: expression of archival virus and replication of virus. J Virology, Aug. 2005, p. 9625–9634.

NNRTI resistance in infants prophylaxed with single-dose nevirapine varies by the timing of infection

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Ana Blanco and co-workers from the Mozambique Ministry of Health, Health Alliance International, Seattle, University of Washington, Seattle and Seattle Children’s Hospital Research Institute showed findings from an evaluation of infants infected with HIV despite receiving single dose nevirapine (sdNVP) prophylaxis.

The investigators hypothesised that the timing of nevirapine selective pressure relative to when the HIV first infects infants, effects the selection and persistence of NVP resistant virus. They suggest that:

- NVP pressure during “acute” (peri-partum) infection will result in transmission or significant selection of mutations that will populate long-lived viral reservoirs and mutations will persist over time.
- NVP pressure during “established” (in utero) infection will select mutations, however, as HIV-1 reservoirs are already established, fewer will be archived so mutant population will fade over time.

This report was from a prospective observational cohort study of 741 infants of whom 100% received single dose NVP (73% mothers). The investigators estimated the timing of infection using nested PCR for HIV-1 pol in dried blood spots, collected by heel stick, at birth and every 2 weeks for the first 2 months of life, and then every 4-8 weeks until one year of age.

Concentrations of resistant virus were determined using quantitative PCR oligonucleotide ligation assays (OLA) for K103N, V106M, Y181C and G190A.

HIV infection was detected by PCR in 53 infants followed between 0-8 weeks of age. 29 were infected in utero (HIV detected at birth), all had wild type virus and 23 had high and stable viral load at birth ie “established” infection, and 6 had low viral loads that later increased, suggesting “acute” infection at the time of birth.

The investigators reported that the selection and decay of NVP-resistant HIV-1 varied by timing of infection.

Infants with “established” infection had frequent selection of NVP-resistant HIV-1 (87%, 95%CI 66-97%).

Postpartum infant AZT+sdNVP vs. NVP decreased NVP-resistant

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HIV-1 (3/6 vs. 0/17, $p=0.013$). NVP-resistant viruses decayed rapidly compared to infants with peri-partum infection.

Compared to “established”, infants with “acute” in utero infection (ie low viral load at birth) had infrequent (33%) selection of NVP-resistant HIV-1, $p=0.01$. In this group of infants NVP-resistant HIV-1 appeared to decay more slowly.

Among infants with peripartum infection ($n=24$) there was infrequent selection of NVP-resistant HIV-1; (38%, 95%CI 19-59%) compared to “established”, $p=0.001$. Few infants with NVP-resistance, initially had exclusively wild-type viruses vs. “established” (2/9; 22%, 95%CI 3-60% vs. 21/21 ; 100%, 95%CI 84-100%), $p<0.001$.

Also, most infants had 100% NVP-resistant HIV-1 in the first sample with detectable resistance vs. “established”, (6/9; 67%, 95%CI 30-93% vs. 0/22 ; 0%, 95%CI 0-15%), $p<0.001$.

The investigators noted a non-significant trend for less NVP-resistance when mothers did not take sdNVP (0/5 vs. 9/19, $p=0.12$).

They summarised:

- With “established” in utero infection, viral replication in utero generates mutations that are selected by sdNVP. AZT appears to reduce the selection of NVP mutations, “theoretically by increasing the genetic barrier and decreasing viral replication”. Rapid decay of NVP-resistant virus suggests that after an (undefined) interval, NVP-based HAART may be effective.
- With “acute” in utero infection there is frequently too little viral replication in utero to generate mutations, so there are no NVP-resistant mutations to select. But if selected NVP-resistant HIV-1 decays slowly suggesting that it populates long-lived reservoirs.
- With peri-partum infection, infections with 100% resistant virus suggests transmission of NVP-resistant HIV-1. Persistence of mutations at high concentrations suggests it populates reservoirs. Persistence of mutations suggests that NVP-containing HAART may fail.

The investigators noted a low rate of mother-to-child transmission among infants whose mothers received pre-partum AZT in addition to sdNVP. But this was only a minority of women and access needs to be improved.

Ref: Miceck MA, Blanco AJ, Beck IA et al. The selection, transmission and persistence of drug-resistant HIV-1 in infants prophylaxed with single dose nevirapine varies by the timing of infection. XVII IHDRW 2008, Sitges. Abstract 71.

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:

- Do you believe Dr Fauci’s claim for a cure from early treatment?
- Why was I not infected after first exposure?
- Shall I avoid ritonavir?
- Do I really need to take my medications with/without food?
- Shall I have another test?
- Should I start treatment now?
- Do I need to test my baby again?
- Can I drink alcohol with ARVs?
- My CD4 cell count is 122. How do I boost them to get a higher count?

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>



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