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CONTENTS

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EDITORIAL

Welcome to the September/October issue of HTB.

This issue includes further coverage from the 5th IAS Conference in CapeTown. We review antiretroviral , pregnancy and PMTCT, HSV and TB research presented at this conference.

We also include reports from the excellent HIV Drug Interactions website and from Richard Jefferys weblog.

Our final reports from IAS, including paediatrics and operational research, and studies presented at ICAAC (which concluded as this issue went to press) will be included in the November/December issue, our last HTB for 2009.

CONFERENCE REPORTS

5th IAS Conference on HIV Pathogenesis, Treatment and Prevention

19-23 July 2009, Cape Town

Introduction

We continue with further reports from this important conference.

- Overview of ARV studies at IAS:
  - First results of new integrase compound: GSK1349572
  - Raltegravir in treatment naive patients
  - Nevirapine vs atazanavir/ in naive patients: ARTEN study
  - Darunavir/r monotherapy studies
  - Maraviroc results similar to efavirenz when analysed using more sensitive tropism test
- Lipid and metabolic changes with ARV combinations
- Maximal suppression achieved with three drugs: no additional virological impact of raltegravir intensification
- Tenofovir and renal safety
- Time from seroconversion to treatment in Europe and Africa
- Pharmacokinetics of atazanavir/ritonavir during pregnancy
- Presentation with late stage HIV diagnosis in pregnancy
- Low transmission rates and favourable pregnancy outcomes reported in the DREAM study
- Pregnancy rates and outcomes among women in the DART trial
- Pregnancy outcomes in HAART exposed infants in Johannesburg
- Efavirenz conceptions in Soweto
- Impact of regimen and duration of therapy on risk of mother-to-child HIV transmission in Johannesburg
- A cost-effectiveness analysis of the OCTANE trial
- The PEARL study
- Results from HSV-2 acyclovir studies
- Overview of TB-related studies at IAS

For the first time, webcasts of several sessions are available via the conference website together with searchable online abstracts and PDF files of many or the posters or presentations:

http://www.ias2009.org

The abstract database from the meeting is online at the same site.

5th IAS: ANTIRETROVIRALS

Overview of ARV studies at IAS

Simon Collins, HIV i-Base

The conference included a broad range of important studies that could inform use of currently approved drugs, and first results of a new integrase inhibitor.

First results of new integrase compound: GSK1349572

Three posters at the meeting provided insight into a new compound in development from Shionogi and GSK.

Lalezari and colleagues presented first virological efficacy data from a 10-day Phase IIa dose-finding study (2, 10 and 50mg monotherapy or placebo, all once-daily) of GSK1349572 (GSK572) in 35 treatment-naive patients. [1]

Patients in the 50mg arm showed a mean viral load drop of almost 2.5 logs and 7/10 patients in this arm had viral load reductions to <50 copies/mL.

The 10 mg and 2mg doses reached mean viral load declines of approximately -2.0 and -1.5 logs respectively. No serious side effects were observed and reported events were generally similar to the placebo group.

Two pharmacology studies showed the advantages of limited interpatient variability and an indication that the 50mg dose left a significant safety buffer before activity dropped, and that higher doses were unlikely to increase activity. Median half-life was 15 hours. Steady state geometric mean (CV%) AUC (0-24) and Cmax ranged from 16.7 (15) ug.h/mL and 1.5 (24) ug/mL at 10 mg once daily to 76.8 (19) ug.h/mL and 6.2 (15) ug/mL at 50mg once daily. The geometric mean steady-state C24 at 50mg was 1.5 ug/mL which is ~23-fold higher than the in vitro protein-adjusted IC90. [2, 3]

In vitro results with a broad panel of resistant isolates, suggested minimal cross-resistance to elvitegravir and raltegravir. with high level resistance only developing after serial passaging for 56 and 84 days respectively. [4]

A second resistance poster looking at GSK572 susceptibility to a range of common integrase mutation patterns seen in raltegravir and elvitegravir studies (based on limited in vivo data), suggested that cross-resistance with other integrase inhibitors might be sufficiently likely for GSK572 not to be able to rescue people with previous integrase resistance. For example, although G140S/Q148H resulted in a median fold-change in susceptibility of less than 4-fold (n=7), G140S/Q148R lead to a range of around 8-19-fold changes (n=2). By comparison both these dual mutations confer high-level phenotypic resistance to raltegravir (>87-fold). [5]

Of note, in addition to greater virological impact during a short monotherapy than other currently used drugs, this compound is being developed as a once-daily drug, does not require boosting and PK is unaffected by food.

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Raltegravir in treatment-naive patients

In July 2009, raltegravir was approved in the US as first-line therapy, and also received a positive opinion from the CHMP for a similar indication in Europe, based on 48-week results from the STARTMRK trial. [5, 6]

In summary, raltegravir showed similar virological efficacy compared to efavirenz (86% vs 82% <50 copies/mL at week 48), when used with tenofovir+FTC. [7]

At the IAS conference, longer-term safety data was available from 144-week follow-up from the initial dose-finding study (Protocol 004), where, after the first year, all patients (n=160) were switched to, or continued receiving, raltegravir at the 400mg twice-daily dose. [8]

Viral efficacy remained similar between the two arms (78% vs 76% <50 copies/mL). Drug-related side effects were similar or less frequent in the raltegravir arm, as were grade 3/4 laboratory abnormalities (except pancreatic amylase (>2xULN: 2.5% vs 0) and creatinine kinase (10 xULN: 8.8% vs 2.6%). Lipid changes in combined raltegravir groups were not sgnificant for total cholesterol,

LDL-cholesterol or triglycerides and HDL-cholesterol increased by a mean of +6.6 mg/dL (compared to +11.7 in the efavirenz arm). This meant that there was no significant difference in the total:HDL ratio between the two groups (-0.5 vs -0.4, p=0.451).

C O M M E N T

Although in a limited number of patients, this extended safety and efficacy data are encouraging.

To date, this more favourable lipid profile has not led to differences in body composition. A study presented at ICAAC as HTB went to press that we will report in full in the next issue showed similar DEXA results when compared to efavirenz at 48 weeks. [9]

Given that fat accumulation is one of the principal concerns for patients, and the mechanism is still unexplained, preliminary data should be made available for bone and body fat changes with all new drugs at the same time as other efficacy and safety data.

Ten years after lipodystrophy was identified as a major side effect, it is not acceptable to have wait for years after approval for these results.

However, another study at ICAAC reported encouraging data in respect to raltegravir activity in the CSF. [10]

Currently, access to raltegravir is imited for patients in the UK who could benefit from it's tolerability profile, due to the high cost.

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Nevirapine vs atazanavir/ in naive patients: ARTEN study

A late breaker poster from Soriano and colleagues presented 48-week results from the ARTEN study. This international non-inferiority trial randomised 569 treatment-naïve patients to nevirapine 400mg once-daily (n=188), nevirapine 200mg twice-daily (n=188) or atazanavir/r (300/100mg) once-daily (n=193), all in addition to background tenofovir+FTC. [11]

The lower margin for non-inferiority was -12% and patients were recruited based on with CD4 counts below the upper recommended upper limit (250 and 400 cells/mm3 for women and men respectively).

The primary end-point was suppression to < 50 copies/mL at weeks 48 by Intent-to-treat (ITT) analysis, with a secondary sensitivity analysis looking at time to virological failure (TLOVR).

Baseline demographics and HIV-related characteristics were similar between groups. Mean CD4 and viral load were 183 cells/mm3 and 5.1 log copies/mL, respectively. Although <10% patients had a CD4 count <50 cells/mm3, 64%had viral load >100,000 copies/mL.

In the main analyses, nerirapine was non-inferior to atazanavir/r. For the primary endpoint, by ITT analysis the combined nevirapine groups were non-inferior to atazanavir/r (66.8% vs 65.3%; <50 copies/mL: difference 1.9% [95% CI -5.9% to 9.8%]). Using the TLOVR algorithm, the results were 70% and 74% of NVP and ATZ/r patients, respectively [difference 2.9% (95% CI -10.4% to 4.5%)].

CD4 responses were also similar (+170 vs +185 cells/mm3 in the NVP and ATZ/r groups, respectively).

Although side effects were similar, there were significantly higher discontinuations in the nevirapine arms: 22% in QD, 28% BID and 9% with ATZ/r.

Grade 3/4 events occurred in 12%/5% of NVP and 16%/3% of ATZ/r patients. Rash was reported in 16% of NVP and 12% of ATZ/r patients, but more NVP patients were discontinued due to rash compared with ATZ/r (5% vs 0%). Most nevirapine-associated rashes developed during the lead-in phase, with no Grade 4, SJS or TEN and no deaths due to liver or skin toxicity.

Nevirapine had a better impact on HDL-cholesterol and triglycerides (both p<0.0001) but not for for total cholesterol (p=0.41) or LDL-cholesterol (p<0.011). Overall though, the change in the TC:HDL ratio favoured nevirapine (-0.24 vs +0.13, p=0.0001).

Grade 3/4 increases in liver enzymes occurred in <5% patients but were higher in nevirapine patients, (see Table 1). Although exclusion criteria excluded active HBV or HCV infection, numbers of coinfected patients or response were not reported by this hepatitis status. Only one patient discontinued atazanavir/r due to increased bilirubin.

Table 1: Grade 3/4 liver enzyme elevations at week 48 (%pts)

	NVP QD once-daily		NVP BID twice-daily		ATZ/r	
	G3	G4	G3	G4	G3	G4
ALT	3.2	2.7	4.3	4.3	2.1	0.0
AST	4.3	1.6	4.3	2.7	2.6	0.5
bilirubin	1.1	1.6	2.1	1.6	45.6*	8.8

* only 1 patient discontinued ATZ/r

C O M M E N T

It is reassuring that the high virological failure rate observed in smaller studies when nevirapine was used with tenofovir+FTC [12, 13] and which is highlighted in US guidelines [14], was not seen in ARTEN.

The data also support a reduced risk of nevirapine-associated severe reactions when prescribed to patients within the recommended CD4 thresholds. Although no cases were reported of fulminant liver failure, this remains the main reason for reduced use of nevirapine in Western countries.

The results are important, as nevirapine-based regimens remain widely used as first-line therapy, usually with d4T/3TC.

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Darunavir/r monotherapy studies

Several studies presented results from using darunavir/r monotherapy.

José Arribas and colleagues from the Tibotec sponsored MONET study. This study randomised 256 patients, who had been suppressed on their current HAART (< 50 copies/mL) for at least six months, to switch to darunavir/r 800/100 mg once-daily, either as monotherapy (n=127) or with 2 nukes (n=129). [15]

The primary endpoint was virological suppression at week 48 by TLOVR analysis (time to loss of virologic response) and the study had 80% power to show non-inferiority for the monotherapy arm (lower limit -12%).

Participants generally had responded well to their initial treatments (median CD4 ~570 cells/mm3 with only 12-14% with CD4 counts below 350 cells/mm3. Mean (±SD) prior ARV use was 6.4 (4.0) and 7.4 (4.2) years in the triple and mono arms respectively, with 48% and 35% still on their first NRTI combination. About a quarter of each group were PI-naive at baseline. A lower percentage of patients in the triple therapy arm were coinfected with HCV (11% vs 19%).

At week 48, both the per protocol and ITT analyses by TLOVR <50 copies/mL showed non-inferiority for the monotherapy arm, with 87.8% vs 86.2% (-1.6%; lower limit 95%CI: -10.1%) and 85.3% vs 84.3% (-1%; lower limit 95%CI: -9.9%), in the triple vs mono arms respectively.

CD4 remained stable at baseline levels and tolerability was good and generally similar between the two groups.

As with monotherapy studies using lopinavir/r, patients using darunavir/r monotherapy experienced more blips (n=1 vs 7) but were similarly resuppressed when nukes were added, and PI mutations were rare (in only one patient). Two patients in each arm had viral load rebounding consistently to >400 copies/mL. Nine patients per arm discontinued randomised treatment for either adverse

events or other reasons. No new or unexpected safety signals were detected.

A similar study design was used for the French MONOI study, presented by Cristine Katlama as a late-breaker. [14]

In this study, 242 patients on HAART who were suppressed to < 400 copies/mL for at least 18 months were, after an 8-week induction phase of darunavir/r (600/100 mg bid), randomised to either continuing the triple-drug regimen (2NRTI+DRV/r) or switching to DRV/r monotherapy. Virologic failure was defined as two consecutive viral load results above 400 copies/mL, or modification/discontinuation of study treatment by week 48. The trial had 80% power to show non-inferiority for the DRV/r arm (lower limit = -10%).

Virological responses at week 48 in the Per Protocol and ITT analysis were 99.0% vs 94.2% (difference -4.9% [- 9.0 to - 0.7%]; and 92.0% vs 87.5% (difference -4.5% [-11.2 to 2.1%], for the triple and monotherapy arms respectively.

Therefore, in this study, non-inferiority was only proven for darunavir/r monotherapy in the per protocol and not the ITT analysis (although the lower margin was -10% compared to the commonly used -12%).

C O M M E N T

Even with promising results using either lopinaivr/r or darunavir/r monotherapy, there is limited data on some aspects of this strategy, including the importance of penetration into the CNS and other compartments. For patients in the UK, many of these questions will be answered by the currently-enrolling MRC-sponsored PIVOT study. [17]

This MRC study randomises people stable on first-line HAART to continue on their current treatment or switch to ritonavir-boosted PI monotherapy. Choice of PI is not specified and follow-up continues for five years.

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Maraviroc results similar to efavirenz when analysed using more sensitive tropism test

Several studies provided results that might increase the confidence in using the CCR5 inhibitor maraviroc. Although approved over two years ago, the potential use was has been limited because Phase III studies, using background AZT/3TC, did not shown non-inferiority compared to efavirenz, and it was not approved in Europe as a first-line option.

However, the efficacy of CCR5 inhibitors are dependent on accurately screening and enroling patients who are CCR5-tropic, which in turn is dependent of the accuracy of the available tropism test.

A post-hoc analysis of the 48-week results from the MERIT study (called MERIT-ES), using the recently developed more sensitive Trofile ES tropism test, provided an indication of current results that could be expected based on this change in standard of care diagnostics. [18]

The initial analysis from MERIT also showed poorer responses in patients from the Southern compared to Northern hemispheres and in patients with higher baseline viral load (> vs <100.000 copies/mL.

Virologic results, summarised in Table 1, showed that using Trofile ES, maraviroc produced comparable results to the efavirenz group at any baseline viral load, and for patients in the Northern hemisphere. A difference remains for Southern hemisphere patients that has yet to be explained.

Table 1: MERIT ES: 48-week response rates <50 copies/mL

	MERIT		MERIT ES	
	EFV	MVC	EFV	MVC
Baseline >100,000 c/mL	66.0%	59.6%	62.5%	64.2%
Baseline <100,000 c/mL	71.6%	69.6%	72.1%	71.8%
N. hemisphere	67.8%	68.0%	65.4%	72.0%
S. hemisphere	71.0%	62.1%	71.6%	64.6%

Significantly more patients changed treatment due to side effects in the efavirenz arm (13.6% [49/361] vs 4.2% [15/360]), with changes occurring earlier (78.0% vs 60.0% by week 16) and at higher viral load (69.0% vs 60.0% ≥ 50 copies/mL) before discontinuation.

The sustainability of these results out to week 96, together with a modelled analysis for the impact on the non-inferiority criteria (defined lower limit -12%) were presented by Saag and colleagues, and are summarised in Table 2 (though neither MERIT nor

MERIT ES studies were powered to assess results at this time point). [19]

Table 2: MERIT ES: non-inferiority analysis at week 96: difference* (lower bound of 1 sided 97.5% CI)

	MERIT: original Trofile Diff. (lower limit)	MERIT-ES: new Trofile ES analysis Diff. (lower limit)
<400 copies/mL, %	-3.2 (-10.2)	-0.4 (-7.9)
HIV-1 RNA <400 copies/mL, % (TLOVR)	-2.7 (-9.7)	0.2 (-7.3)
HIV-1 RNA <50 copies/mL, %	-5.8 (-12.8)	-3.9 (-11.5)
HIV-1 RNA <50 copies/mL, % (TLOVR)	-3.2 (-10.3)	-0.3 (-7.9)

* Adjusted for randomisation strata; For descriptive purposes only; TLOVR = time to loss of virologic response.

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Lipid and metabolic changes with ARV combinations

Simon Collins, HIV i-Base

Lipid results can be complicated to interpret, especially between studies, given the lack of consistency in the method of reporting. Changes in lipid parameters, both from baseline and between-arm comparisons can often be statistically significant, for differences that are modest in absolute (and therefore clinical) terms.

While total cholesterol:HDL ratio is most useful in terms of having an impact on Framingham-based calculation of cardiovascular risk, other studies report results by the percentage of patients reaching guideline target for starting lipid-lowering drugs (LLDs). This is further complicated, particularly in treatment-naive studies by a return-to-health effect that reverses earlier HIV-related metabolic changes.

Comparative and detailed results on body composition supported DEXA/CT scaning - probably the most important results for patient currently experiencing lipohypertrophy on existing regimens – are still scarce, even in Phase III studies for the most recently approved drugs.

The MERIT study reported more favourable lipid parameters in patients using maraviroc compared to efavirenz (each with FTC/TDF) evaluated by the percentage of each group that exceeded NCEP guidelines for lipid lowering therapy. At week 96, in the maraviroc vs efavirenz groups respectively, approximately 11% vs 39% for total cholesterol; 6% vs 27% for LDL-cholesterol (>3.4mmol/L), both p<0.0001; and 16% vs 19% triglycerides (NS). [1]

Although the main finding of the ALTAIR study was the under-performance of a 4-nuke arm, the lipid profile of efavirenz produced greater increases in HDL-cholesterol (but also conversely glucose) compared to atazanavir/r. [2]

Metabolic changes were measured by DEXA and CT imaging. This was a three-arm open-label study that compared atazanavir/r to efavirenz and to AZT/abacavir all using FTC/tenofovir, in just over 300 treatment-naive patients. The four-nuke combination was significantly less effective virologically, but also (compared to atazanavir/r) for HDL-cholesterol, LDL-cholesterol, total cholesterol and glucose changes. The inclusion of AZT resulted in significant peripheral fat loss in arm, leg and total body fat and a reduction in the VAT:SAT ratio. Broadly similar responses were seen in the efavirenz and atazanavir/r groups (+0.6% and +1.7%) in limb and total body fat, though efavirenz produced a significantly greater increase in HDL (+0.18 vs +0.09, p = 0.006) and glucose (+0.34 vs -0.03, p<0.001).

The impact of 100mg ritonavir on lipid levels when boosting atazanavir (with background 3TC/abacavir) was shown in the ARIES study. This study randomised 419 patients, who were initially suppressed for 36 weeks on atazanavir/r (300/100mg daily), to either continue on the boosted regimen or switch to unboosted atazanavir (400mg daily). [3]

At 48 weeks after the switch, median total cholesterol, LDL-cholesterol and triglycerides declined in the unboosted group while continuing to increase (slightly) in the boosted arm. HDL-cholesterol remained unchanged in each arm (both slightly higher compared to study baseline: median +10mg/dL). Use of lipid-lowering drugs was similar (16% vs 13% in the boosted vs unboosted groups).

The lipid profile of nevirapine was slightly better when compared to boosted atazanavir, in the ARTEN study, again each with FTC/tenofovir. [4]

Lipid changes at week 48 showed a -0.24% reduction in the TC:HDL ratio in the nevirapine group compared to an increase of

+13% in the atazanavir/r group. This was driven by proportionally greater increases in HDL-cholesterol, as total cholesterol, LDL-cholesterol, HDL-cholesterol all increased in both groups. Although statistically significant ($p \leq 0.0001$) both changes were modest terms in absolute terms. Triglycerides increased by 28mg/dL in the atazanavir/r group but remained similar to baseline levels in the nevirapine group. Previously, in the CASTLE study, ritonavir-boosted atazanavir showed a small improvement in TC:HDL ratio.

The impact of the integrase inhibitor raltegravir on glycemic changes in HIV-negative volunteers, resulted in a more favourable profile compared to lopinavir/r. [5]

Changes in insulin sensitivity and glucose disposal, measured by euglycemic clamps, were recorded in in a 2-phase cross-over study, separated by a 2-week wash-out period, in HIV-negative individuals exposed to either lopinavir/r or raltegravir (each for two weeks). Supporting results from earlier studies, the lopinavir/r group experienced a mean reduction of insulin sensitivity of -16% compared to no changes seen during raltegravir exposure ($p=0.018$). Total cholesterol, LDL-cholesterol and triglycerides all increased significant during lopinavir/r exposure (by about 14%, 15% and 37%, respectively) compared to during raltegravir exposure, when no significant changes were seen. Mean levels of adiponectin, an insulin-sensitising adipokine, also increased in the lopinavir/r groups (by 15%, $p=0.03$ compared to raltegravir) indicating that peripheral fat cells were working harder to become insulin sensitive during lopinavir/r exposure.

Finally, lipid changes for darunavir/r (800mg/100mg once-daily) in the ARTEMIS study were compared to lopinavir/r (in both once- and twice-daily regimens). At 96 weeks, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides all increased from baseline in both arms, although the increases in both total cholesterol and triglycerides were significantly greater for lopinavir/r (TC: +28 vs +35; TG +18 vs 65 mg/dL), with all grade 2-4 lipid changes higher in the lopinavir/r vs darunavir/r groups (~15% vs 8%).

Use of lipid-lowering drugs were similar (darunavir/r: 8% [statins: 7%; fibrates 1%]; lopinavir/r: 11% [statins: 5.5%; fibrates: 3.5%].

Although patients in the darunavir/r arm had greater increases in weight (+2.5kg [IQR -0.2, +6.1kg] versus 1.3kg [-1.0, +5.0kg]; $p=0.006$) and in median BMI (0.9kg/m2 vs 0.4kg/m2; $p< 0.006$) these differences not considered clinically relevant. Symptomatic lipodystrophy changes (fat loss or gain, investigator judged) were reported in <1% of patients in each group.

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Unless stated otherwise, all references are to the Programme and Abstracts of the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention. 19-23 July 2009, Cape Town.

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Maximal suppression achieved with three drugs: no additional virological impact of raltegravir intensification

Simon Collins, HIV i-Base

A late-breaker presentation by Rajesh Gandhi and colleagues from ACTG 5244 provided addtional data that are important for understanding the impact of HAART on the pathogenesis of HIV. [1]

Several small studies have already shown similar results (including Maldarelli et al at last years Resistance Workshop). [2]

This new study benefited from larger patient numbers and intensification with an integrase inhibitor.

The study randomised 53 patients to either add raltegravir or placebo to their combination for 12 weeks. At week 12, patients

crossed over to the alternative arm for a further 12 weeks. The primary endpoint was averaged plasma viral load between weeks 10 and 12. Patients needed to be on HAART for at least one year, with viral suppression <50 copies/mL (but have viral load >0.02 copies/mL at baseline using a more sensitive test).

Median baseline CD4 count and viral load were 589 cells/mm^3 and 1.7 copies/mL (a similar low level has been reported in other studies). The median viral load at week 10/12 did not differ between the raltegravir (n=25) and placebo (n=24) groups (1.1 vs. 1.7 c/mL, p=0.80), nor did the median change in viral load from baseline to week 10/12 (-0.3 and -0.1 c/mL, p=0.52). There was also no significant change from weeks 10/12 to weeks 22/24 during the cross-over study.

Interestingly, there was a trend towards greater CD4 cell count increases from baseline to week 12 in the raltegravir group (+42 vs. -44 cells/mm^3, p=0.08), which reversed after the cross-over.

C O M M E N T

This study supports the hypothesis that effective HAART (that maintains viral suppression to <50 copies/mL) stops onging viral evolution, and that residual HIV originates from recent activation of latently infected cells.

This demonstrates a ceiling of antiretrovial activity that many patients achieve with current three-drug combinations – though treatment-experienced patients may benefit from using additional drugs to overcome drug resistance.

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Tenofovir and renal safety

Simon Collins, HIV i-Base

A couple of posters presented interesting data relating to renal safety associated with tenofovir.

Firstly, and encouragingly, a sub-study from the international DART study suggested that while tenofovir may have a slightly greater renal toxicity compared to either abacavir or nevirapine, this still occured in a small minority of patients. [1]

DART randomised over 3,300 treatment-naive patients in Uganda and Zimbabwe to routine CD4 and labaoratory monitoring or to clinical monitoring (with only grade 4 laboratory results reported in real time). Virological results were reported in the last issue of HTB. [2]

Patients used one of three treatment arms: tenofovir (n=2469, 74%), nevirapine (n=547, 16%) or abacavir (n=300, 9%), each used in combination with AZT/3TC), allowing safety and efficacy to be compared by drug class.

Elevated creatine (>360umol/L(4.1mg/dL) was an exclusion criteria. GFR was estimated by Cockcroft-Gault, and was adjusted for body surface area.

For this renal sub-study, glomerular filtration rate (GFR) severity was defined as mild, moderate and severe if 60-<90, 30-60 and <30 ml/min/1.73m2 respectively. Chronic kidney disease (CKD) was defined as GFR <60 on two tests for > 3 months or a 25% reduction in patients with eGFR <60 at baseline. An analysis also looked at 25% reduction rates in all patients.

Baseline demographics included 65% women; median age 37 years; CD4 86 cells/mm3; and weight 57 kg. Median eGFR was 89: with 48% >90; 45% 60-90; 7% 60 - 30 and 0.2% <30.

By week 216, patients in all three groups had small mean increases in GFR (lowest in the tenofovir group, and a slightly higher incidence of GFR decreases to <30 and <60, and in the percentages of patients with more than a 25% reduction, see Table 1. Renal disease contributed to death in 0.4% (n=13) patients on tenofovir-based therapy.

The incidence of severe reductions (GFR<30) was higher in the clinically monitored group [3.4% (2.7-4.5%) vs 2.3% (1.7-3.1%), p=0.05]. However, the study emphasised that rates were low in all arms.

The main DART study, showed an almost 90% 5-year survival rate without routine laboratory monitoring, and contrasted with <10% survival rates pre-HAART. In this context, the researcher are right to concluded that the study showed supportive safety data for wider use of tenofovir in reseource-limited settings. This is particularly important given the toxicities associated with d4T and AZT.

Table 1: Changes in renal function in DART study

	TDF	NVP	ABC	p
B/line GFR; median (IQR)	90 (75-107)	89 (76-103)	80 (70-98)	
Adj GFR change; mean (95%CI)	+2 (+1, +3)	+7 (+5, +9)	+6 (+3, +9)	<0.001
Renal-associated death	0.7% (0.4-1.1%)	0	0	0.07
Severe GFR decrease (<30)	3.1% (2.5-3.9%)	1.9% (1.0-3.4%)	2.4% (1.2-5.0%)	0.26
CKD (GFR<60)	5.9% (5.0-6.9%)	2.1% (1.2-3.7%)	3.1% (1.6-5.8%)	0.0004
CKD >25% (all pts)	3.4% (2.7-4.2%)	1.1% (0.5-2.5%)	2.1% (0.9-4.5%)	0.01

The second study resented results on the reversibilty of kidney damage associated with tenofovir in 26 adult male patients who either switched from tenofovir (n=24) or dose-reduced (n=2) due to renal impairment.

Median eGFR (using MDRD) was 72 (IQR 60, 88) before starting tenofovir, and fell to 49 (IQR 37, 54) mL/min/1.73m2 prior to the change in regimen. After a median of 15 months, his increased to 56 (IQR 45, 70) mL/min/1.73m2. Howverer, although the changes were only slight and developed slowly, with only 10 (38%) patients reached their pre-treatment level.

Although in small patient numbers, this is one of the first studies to show a potential reversal of reduced kidney function after switching from tenofovir, though the improvements were very modest in clinical terms.

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Time from seroconversion to treatment in Europe and Africa

Simon Collins, HIV i-Base

People who are newly diagnosed with HIV, commonly expect to delay HAART for 5-8 years. However, the UK Register of Seroconverters has previously reported that at least a quarter of patients may need to start treatment within two years of infection. In a review of this cohort published in AIDS in January 2008, the median time from seroconversion to HAART initiation was 5.0 years but the IQR was 2.1 to > 10 years. The 25th percentile of time to starting HAART was 2.0, 2.0, 2.0 and 1.4 years in 1998-1999, 2000-2001, 2002-2003 and 2004-2006, respectively. [1]

This was also a conservative analysis as it excluded patients who started treatment within six months of infection due to complications during seroconversion. This analysis related to the period when UK guidelines recommended starting treatment before the CD4 count dropped below 200 cells/mm3.

At the IAS meeting, two studies from the CASCADE cohort of European seroconverters (which includes the UK data) provided further information on time to progression.

A European analysis, presented by Sara Lodi from the UK's MRC, looked at time to CD4 counts dropping to below 500 cells/mm3, in order to inform policy should guidelines broaden to this higher threshold. [2]

Of over 11,700 adults (age >15 years) who seroconverted after 1992, over half (57%) reached CD4 ≤500 cells/mm^3 during a median of 20 months (95%CI: 19.6, 20.5), with 29% censored at initiation of antiretroviral therapy. The proportion of patients with CD4 counts above 500 at 6, 12, 24 and 36 months after seroconversion was approximately 92%, 72%, 43% and 30%, respectively.

From these results, the authors concluded that 50% of patients would require treatment within 20 months of seroconversion, if future guidelines change the CD4 initiation threshold to 500 cells/mm3.

Increasing age at seroconversion was associated with faster progression (HR, 95%CI: 1.06,1.03-1.09 per 10-year increment). For example, 50% of the patients aged 15-20 still had counts >500 cells/mm3 after two years compared to only 35% of patients who were older than 40 at diagnosis. Unadjusted median times for those aged < 20, 20-29, 30-39, and 40+ years were 25.5, 21.9, 19.8 and 17.6 months, respectively.

No association was found with gender, transmission group and acute infection. Although numbers of patients with sub-type A, C and D were very low, there was an indication that progression may have been faster compared with sub-type B.

A second study from the CASCADE group, presented by Andrea de Luca, reinforced the finding that older age is associated with a shorter time to starting treatment, but also that older age was associated with better virological response (suppression to <50 copies/mL viral load). [3]

Of over 7100 patients who seroconverted after 1993 that were included in the analysis, just under half (48%) initiated antiretroviral treatment. Median time to starting treatment was 3.32, 3.15, 2.64 and 2.08 years for patients aged 15-29, 30-39, 40-49 and 50+ years respectively.

Later calendar period and seroconversion illness, but not age, were found to be independent predictors of CD4 count at ARV initiation. Increasing age was associated with better viral response (HR (95%CI)= 1.17 (1.06, 1.29); 1.30 (1.15, 1.47); and 1.25 (1.07, 1.47) for 30-39, 40-49 and 50+, respectively, compared to 15-29 year olds at seroconversion).

Data on progression rates in an African cohort were presented from the French ANRS 1220 Primo-CI cohort 1997-2008, in patients from Abidjan, Côte d'Ivoire. [4]

This study had a similar design, though it was a much smaller cohort (of 254 adults enrolled, 112 had baseline CD4 >500 cells/mm^3). Baseline characteristics of these 112 patients followed included 65% men, median age was 28 years (IQR 25-34), median time from estimated seroconversion was 7 months and median CD4 cell count was 677 cells/mm3 (IQR 591-800). Median duration of follow-up was 7.1 years (IQR 4.2-9.3; 790 person-years).

The probability of reaching CD4 <500 cells/mm^3 (the guideline for starting PCP prophylaxis) was 0.58, 0.70, and 0.78, at 2, 4 and 5 years, respectively. The probability of reaching CD4 <350 cells/mm^3 was 0.22, 0.47, and 0.49, at 2, 4 and 5 years, respectively. Baseline CD4 count and haemoglobin were associated with a CD4 decrease below 500.

The study concluded that, in this cohort, half of patients reached CD4 <350 within five years of infection. They also reported higher morbidity and mortality at CD4 counts between 350 and 500 (compared to higher CD4 counts). Mortality was 0.9 per 100 patient years and incidence of WHO stage III/IV events was 0.5.

C O M M E N T

Highlighting the significant interpatient variability in the time to starting treatment would give newly diagnosed patients a more realistic understanding of the chance that the optimal time to start may well be within two years. The probability is likely to be over 25% for any setting where the recommended CD4 threshold is now 350 rather than 200.

The association with older age at infection support the BHIVA guidelines recommendation to consider earlier treatment in older patients.

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5th IAS: PREGNANCY & PMTCT

Pharmacokinetics of atazanavir/ritonavir during pregnancy

Polly Clayden, HIV i-Base

Previous reports have shown plasma concentrations of some PIs are reduced in pregnant women.

A late breaker poster authored by Francesca Conradie and coworkers from the A1424182 study showed PK data from women receiving atazanavir/ritonavir (ATV/r) once daily during pregnancy.

This was a multicentre, open label, single arm phase I study with sites in South Africa, Puerto Rico and the USA. Women were enrolled who were between 12 and 32 weeks gestation with CD4 >200 cells/mm3.

This study determined multiple clinical and PK parameters during the second and third trimesters, and post-partum.

ATV was dosed ATV/r 300/100 mg (n=20) or ATV/r 400/100 mg (n=21) in combination with AZT/3TC 300/150 mg twice-daily during the third trimester. Second trimester and post partum dosing was ATV/r 300/100mg.

Third trimester exposures were compared to historical ATV 300/100mg exposures in non-pregnant adults. Foetal:maternal ratio was determined using cord blood samples. Infants were followed up for 6 months.

The investigators reported all mothers had fully suppressed viral load (<50 copies/mL) before or at delivery. At the time of analysis all infants (n=40) were HIV DNA negative. There were no infant deaths.

Maternal drug-related serious adverse events (SAEs) were: hyperbilirubinemia (n=1) and anaemia (n=4). Grades 3-4 hyperbilirubinemia occurred in 6/20 and 13/21 mothers in the 300/100mg and 400/100mg groups, respectively.

Three infants had drug-related SAEs. Infant bilirubins were within normal limits to day 14; 7 had Grade 3 hyperbilirubinemia after day 14 (maximum 8.5 mg/dL at day 15). One infant received 3 days phototherapy from day 3. This infant had other risk factors (low birth weight and prematurity).

For the 300/100mg group, they reported that Cmax and AUC during the third trimester were 27% and 21% lower and C24 was similar to historical data in non-pregnant HIV-positive patients taking ATV/r 300/100 mg once-daily.

For the 400/100mg group they found AUC and Cmax similar to, and C24 39% higher than, historical levels; post partum exposures were also higher than historical. The investigators noted that elevated levels have been observed with other PIs in the post partum period. Levels of ATV appeared to normalise by 16 weeks post partum.

The ATV foetal:maternal ratio was 0.19 and 0.12 for 300/100 and 400/100, respectively. This ratio indicates that ATV, like other PIs, has poor transplacental transfer.

The investigators concluded that this phase I study suggests that no dose modification of ATV 300/100mg once daily is necessary in the third trimester of pregnancy. Clinical outcomes indicate that this dose suppressed HIV viral load effectively in the participating women, and prevented vertical transmission of HIV to their infants, when used in combination with AZT/3TC twice daily. Treatment with ATV/r in the mothers appeared to be well tolerated.

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Presentation with late stage HIV in women diagnosed during pregnancy

Polly Clayden, HIV i-Base

HIV-positive women are frequently unaware of their status prior to antenatal testing.

Late diagnosis of HIV results in some advanced management considerations. The extent to which this occurs in pregnancy in Europe has not previously been quantified, nor have the implications for maternal and child health.

Claire Townsend from the European Collaborative Study presented data from an analysis performed to quantify this occurrence within the cohort, describe management strategies and the impact of late diagnosis on MTCT, prematurity and low birth weight.

The investigators defined late diagnosis as women diagnosed antenataly with CD4 count <200 cells/mm3. The analyses used logistic regression and linear mixed effects models.

Date of first positive HIV test was available for 3605 women, of which 1256 had CD4 data available.

Overall 654 (53%) were white, 499 (41%) black and 73 (6%) were of other ethnicities. Of these 15% (185/1256) had late stage diagnoses. This proportion has increased over time with 12% between 1985-89 and 19% between 2005-2008, p=0.24.

The median baseline CD4 count was 140 cells/mm3 (IQR 90-147) among the late diagnosis women vs 460 cells/mm3 (IQR 333-650) among non-late diagnosis women. Of the late diagnosis group, 11% (n=20) had an AIDS-defining illness in pregnancy.

In logistic regression analysis limited to 613 women enrolled after 1996, the investigators found adjusted late diagnosis rates were positively associated with black African ethnicity vs white ethnicity (OR 2.02; 95%CI 1.17-3.48, p=0.01) and older maternal age (OR 2.17; 95% CI 1.10-4.25, p=0.02) for women aged 30-34 years vs <25 years.

More women with late diagnosis received antenatal HAART than other women 85% (94/110) vs 67% (388/580), p< 0.001. The median duration of HAART was 16.9 (IQR 11.6-20.7) weeks vs 13 (IQR 11.6-20.7) for women with late stage and non-late stage diagnosis respectively.

Adjusting for time of measurement and type and duration of regimen, late stage diagnosis was associated with a significantly higher viral load throughout pregnancy, +0.29 log copies/mL vs non late-stage diagnosis women, p<0.001. The estimated mean viral loads at time of delivery were 2.94 log copies/mL and 2.65 log copies/mL for late diagnosis and non-late diagnosis women respectively.

More infants born to women with late diagnosis were premature, 24.0% (44/183) vs 13.7% (145/1062), p< 0.001 and of low birth weight, 27.5% (46/167) vs 16.1% (165/1022), p< 0.001 than other infants.

In the period 2000-08, MTCT rates were similar, 3.0% (95%CI 0.37-10.5) and 1.5% (95%CI 0.5-3.51), p=0.4 in the late diagnosis and non-late diagnosis groups respectively.

This analysis found that an increasing minority of HIV-positive women in Europe, newly diagnosed through antenatal testing, already has advanced disease. Although these women are more likely to initiate HAART, and to do so earlier, they still have worse pregnancy outcomes than women with better functioning immune systems.

“Barriers preventing timely access of women to HIV testing are important to address, both for the health of the mother and her infant”. Dr Thorne concluded.

Ref: Thorne CN et al. Presentation with late stage HIV disease at diagnosis of HIV infection in pregnancy. 5th IAS Conference, Cape Town, South Africa.19-22 July 2009. Poster abstract TUAC103.

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Low transmission rates and favourable pregnancy outcomes reported in the DREAM study

Polly Clayden, HIV i-Base

Drug Resource Enhancement and Malnutrition (DREAM) is a large HAART programme with sites in sub-Saharan Africa attended by about 75,000 people. A major part of DREAM is nutritional supplementation and prevention of mother-to-child transmission of HIV.

Women in DREAM receive HAART in pregnancy irrespective of their CD4 counts. Those indicated for treatment with CD4 <350 cells/mm3 receive NVP-based HAART from 14 weeks gestation which is continued indefinitely. Women with CD4 >350 cells/mm3 receive HAART from 25 weeks gestation, which is stopped after weaning at 6 months post partum. Women who stop treatment continue to receive AZT/3TC for 21 days to cover the nevirapine PK tail. PCR DNA determines infant infection.

In two oral presentations, Leonardo Palombi presented data from Mozambique and Malawi describing transmission rates and infant outcomes. Both analyses were retrospective record reviews.

Rates of transmission and infant mortality

This analysis looked at:

1. HIV free survival at 1 and 6 months
2. Transmission rates by maternal CD4
3. Infant health at 6 months

Between July 2005 and December 2008, there were 3148 live births from 3273 pregnancies. At one month, 93 infants were lost to follow up, 7 had died, and 2,994 had test results. Of these 22/2994 (0.7%) were HIV-infected.

Transmission was 0.9% (26/2,707) in mothers who received at least one dose of HAART before delivery (median viral load 3.55 log) and 5.1% (2/39) in women who did not initiate HAART until delivery (VL 4.51 log), p<0.001. Infant HIV free survival at one month was 97.6%.

At 6 months, a further 143 infants were lost to follow up and 41 had died. Six-month testing found 15/2120 infected infants (5 awaiting confirmation). The cumulative 6-month transmission rate was 1.4-1.9%, the mortality rate was 2.1% and loss to follow up was 7.5%.

The investigators found that duration of antenatal HAART and the combined endpoint of infant infection or death were associated across baseline maternal CD4 counts: 1.3% (16/1231) vs 3.8% (6/157) infants were infected or died who had mothers with CD4 <350 cells/mm3 who received >=30 days and <=30 days HAART respectively, OR 0.33 (95% CI 0.12-0.86). And 0.7% vs 2% infants were infected or died who had mothers with CD4 >350 cells/mm3 who received >=30 days and <=30 days HAART respectively, OR 0.33 (95% CI 0.10-1.09).

In multivariate analysis at one month, adjusted for maternal baseline viral load, CD4, haemoglobin and BMI, there was an association between antenatal HAART-exposure and transmission or death: 2.4% with 1-30 days, 1.1 % with 31-90 days and 0.9% with >90 days, (OR 0.57; 95% CI 0.36-0.88).

At six months, 3.1% vs 8.8% infants were infected or died who had mothers with CD4 <350 cells/mm3 who received >30 days and <30 days HAART respectively, OR 0.33 (95% CI 0.16-0.7). And 1.8% vs 2.1% infants were infected or died who had mothers with CD4 >350 cells/mm3 who received >30 days and <30 days HAART respectively, OR 0.81 (95% CI 0.24-2.83).). That is, at higher maternal CD4 counts the impact of HAART > 30 days vs <30 days was not significant.

In multivariate analysis at 6 months, duration of HAART and maternal viral load were associated with transmission or infant death.

At six months, HIV free survival was 90.9% in infants whose mothers had received <30 days pre-delivery HAART, and 96.6% for those whose mothers received >30 days pre-delivery HAART.

Dr Palombi noted that the effect of HAART observed in DREAM was found across all maternal CD4 counts and that mothers with >350 cells/mm3 comprised 37% of transmissions where they occurred

Overall transmission rate at 6 months was 2% in this cohort.

Outcomes

In the second analysis, the investigators looked at maternal health/mortality, and infant outcomes ie prematurity, spontaneous abortion and stillbirth (defined as foetal death at < or ≥32 weeks gestation respectively).

Overall they reported 42 maternal deaths giving a maternal mortality rate (MMR) of 1.2%. The majority of women in DREAM received longer duration of HAART but 68 women received none and 365 women <30 days HAART. Although infrequent, maternal mortality was significantly associated with HAART (7.4% if no HAART vs 0.7 ≥90 days antenatal HAART) and CD4 count (3.2% vs 0.7% if >200; p< 0.001).

Foetal death included 3.1% stillbirth and 2.1% spontaneous abortion. The prematurity rate was 19.1%.

Duration of antenatal HAART was associated with infant outcomes. The rate of abortion and stillbirth was 5.2% among infants whose mothers received >90 days HAART compared to 26.5% among those whose mothers received no HAART and 7.1% <30 days HAART, p<0.001.

Maternal CD4 was also associated with abortion and stillbirth, with a rate of 16.7% among mother with CD4 <200 cells/mm3.

In this cohort, prematurity was associated with shorter duration or no HAART. The investigators reported a 70.8% reduction (Mantel-Haenszel test) overall, OR=0.16 (95% CI, 0.12-0.21) and within each CD4 strata.

In multivariate analysis, BMI (OR 0.27; 95% CI,0.15-0.50) and viral load at delivery (OR 1.44; CL95% 1.22-1.70) were associated with prematurity (see Table 1). Low birth weight was 11.5% and not associated with HAART duration or CD4 count.

Table 1: Prematurity rates in DREAM

(Table reproduced from abstract)

CD4 count	Antenatal HAART (days)	Premature delivery (n)	%	OR (95%CI)
>500	<30 >30 TOTAL	43/77 121/712 164/789	55.8 17.0 20.8	0.16 (0.10-0.26)
351-500	<30 >30 TOTAL	27/56 94/661 121/717	48.2 14.2 16.9	0.18 (0.10-0.31)
201-350	<30 >30 TOTAL	45/63 124/779 169/842	71.4 15.9 20.1	0.08 (0.04-0.13)
≤200	<30 >30 TOTAL	10/32 85/497 95/529	31.3 17.1 18.0	0.45 (0.21-0.99)

The investigators found low incidence of SAEs: 8.6% women had grade 3/4 anaemia; 6.9% d4T-associated peripheral neuropathy; 2.2% grade 3/4 liver toxicity; and 2.4% grade 3/4 rash. However, Stevens-Johnson Syndrome was reported in 1.2% patients.

They also found no resistance in a small sub-study of women (n=26) who had discontinued HAART after weaning.

They wrote: "HAART was strongly associated with improved pregnancy outcomes including reduction in prematurity, regardless of CD4 strata. HAART is beneficial for PMTCT and protects against unfavorable pregnancy outcomes".

C O M M E N T

The data from DREAM seem impressive and it was suggested that they demonstrate that the low rates of transmission now associated with HAART during pregnancy in resource-rich settings can be reproduced in a large roll-out programme in a resource-poor environment.

However, several things make these data very difficult to interpret including significant loss to follow-up and that the number of infants evaluated at different time points is different.

The data on premature delivery and HAART are curious. The authors conclude that short-duration of HAART is associated with prematurity, and at <30 days with as much as 71.4%, these rates are extremely elevated. But perhaps this finding is not surprising since duration is timed from initiation to delivery, and will inevitably be shorter in those who deliver preterm. Data reported by Karin van der Merwe from Johannesburg (reported on in this issue) looking at HAART vs no HAART and longer vs shorter HAART, found higher rates of preterm delivery with HAART and with longer HAART, completely contradicting the DREAM data.

The extensive use of nevirapine-based HAART in this study, with relatively little toxicity reported, despite use at CD4 counts >250 cells/mm3 is also noteworthy and adds to the extensive literature of uncertainty regarding nevirapine, pregnancy and CD4 cell counts.

So these data raise a lot of questions. It was unfortunate that neither the slides nor the webcast from these sessions were available online to check some of the information presented.

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Pregnancy rates and outcomes among women in the DART trial

Polly Clayden, HIV i-Base

Pregnancy rates and outcomes and outcomes among women participating in DART were shown in a poster authored by Paula Munderi and coworkers on behalf of the DART trial team. [1]

The investigators had previously shown findings from an evaluation of pregnancy at a median of 2.8-years of follow-up, which we reported previously in HTB. [2]

This further analysis was at a median of 4.6 years follow-up from January 2003 to June 2008, and included information on maternal/infant outcomes and infant feeding. Longer-term infant follow-up and documentation of infant outcomes are ongoing in a separate sub-study.

Of the 2156 women enrolled in DART, 1876 (87%) were of childbearing age (<45 years). No women were pregnant at enrollment and pregnancy tests were performed six-monthly. Women in DART were given contraceptive advice, including free condoms, counselled if they wished to conceive, and encouraged to disclose any pregnancy.

If they became pregnant on the trial they continued HAART in their study randomisation, received extra diagnostics as required for pregnancy within the trial, and were referred for routine antenatal care.

Data on infant follow up to 2 weeks of age were analysed for congenital abnormalities, early infant survival, and HIV status if tested.

The investigators reported that 378 pregnancies occurred in 299 women. The majority had one pregnancy (n=235) but 50, 13 and 1 women/woman had 2, 3 and 4 pregnancies respectively.

Multiple pregnancies occurred in 16% women <45 years and 33% women <30 years and this rate was similar across sites.

The overall pregnancy rate in women <45 years was 4.83/100 woman years (95% CI 4.36-5.34). Incidence pregnancy rates peaked at 2-3 years across all age groups and then declined. It was highest in the 18-29 years age group.

The median CD4 count was greater among women who were ever pregnant vs never pregnant 106 (IQR 32-142) vs 87 (IQR 31-141) cells/mm3 respectively, p=0.01.

The majority of mothers (60%) received TDF+AZT+3TC regimens. Of the remaining, 17% received NVP+AZT+3TC; 7% d4T-containing HAART; 6% second-line with LPV/r; 5% ABC+AZT+3TC; 3% were off HAART and 2% received other first line HAART.

Four mothers died, 2 during pregnancy (I due to malaria, 1 due to septic abortion) and 2 peripartum (1 post partum haemorrhage and 1 puerperal psychosis).

There were 206 live births and 26 stillbirths. Any congenital abnormalities were reported in 7 (3%) infants. These were club-foot (3; 2 tenofovir, 1 nevirapine); hydrocephalus (1 tenofovir, died); cardiac anomaly (1 nevirapine); undescended testes (1 nevirapine) and skin tag on neck (1 tenofovir).

Prematurity <37 weeks occurred in 9% live births (16% live and still births). Low birth weight <2.5kg occurred in 17% of live births (13% >=37 weeks). The mean weight in infants >37 weeks was 3.0kg (SD $\pm$0.54).

At two weeks post partum, the investigators reported 9 neonatal deaths, of which 6 occurred within 24 hours; 5 infants were HIV-DNA PCR negative and 4 were not tested. Causes of death were: foetal distress (2), prematurity (1), intestinal obstruction (1), haemorrhagic disease (1) and 4 were from unknown causes.

Only a small number of children (n=15, 7%) were tested by the DART assessment visit at 2 weeks and none were HIV-infected.

The infant follow up sub-study has enrolled 174/206 infants. Of these 152 are known to be still alive. Of the 137/174 (74%) infants with results available, none are HIV-infected.

At two weeks only a minority of women (30%), across all study sites, chose to breastfeed.

The investigators concluded that in this group of women, pregnancy rates increased after the first year and declined from the fourth year on HAART. Rates were higher among younger women with less severe HIV disease.

Rates of foetal loss were high and are consistent over time. They suggest that this may reflect improved reporting within a clinical trial but note that increased foetal loss has been reported in other studies.

The low rates of congenital abnormalities are encouraging and similar to those shown elsewhere: 3.0/100 95%CI 2.4-3.7) among HIV-positive women with first trimester HAART exposure in the Antiretroviral Pregnancy Register (APR) and 2.7/100 live births in the CDC birth defects register.

C O M M E N T

At first sight the preterm delivery rate is encouragingly low, much lower than in most other studies (eg 19% in DREAM see above, 17% in Europe, 18% in North America). Contributing factors may include conception on therapy, negating the effect of HIV infection on preterm delivery, and the regimen prescribed. Conversely the stillbirth rate is high and highly associated with preterm delivery. More data on the gestational age are needed to interpret these findings.

The low rates of congenital abnormalities are also encouraging and this large dataset from women receiving TDF in pregnancy is very useful. These data have been submitted to the Antiretroviral Pregnancy Registry. [3]

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Pregnancy outcomes in HAART exposed infants in Johannesburg

Polly Clayden, HIV i-Base

There are conflicting reports concerning the association between preterm birth or low birth weight and HAART.

Karin van der Merwe and coresearchers investigated the impact of HAART exposure on birth weight and gestational age among infants of South African women with advanced HIV disease attending antenatal antiretroviral clinics in Johannesburg. [1]

This review included 1630 women attending clinics between April 2004 and July 2008. All women had CD4 <250 cells/mm3.

Gestation and birth weight of infants were compared: maternal HAART exposed vs unexposed; early (<28 weeks gestation) vs late (>=28 weeks) and PI-based vs NVP-based vs EFV-based. Multivariate logistic regression was used and included maternal CD4 and infant HIV status (PCR).

The investigators found the median CD4 counts for mothers of infants exposed and unexposed to HAART were 154 (IQR 101-229 and 191(IQR 136-220) cells/mm3 respectively, p<0.001. The two groups were similar for other risks of adverse infant outcomes: smoking, alcohol, hypertension, diabetes, anaemia, syphillis serology and history of previous miscarriage.

Prematurity rates were 6% (8/143) in HAART-unexposed infants vs 14%(129/949) in HAART-exposed infants (p=0.01). The HAART-exposed infants had mothers with a higher rate of previous preterm infants than the unexposed group, 11% vs 6%, p=0.055.

See Tables 1 and 2 for infant outcomes by duration of exposure and HAART regimen.

Table 1: Infant outcomes in women exposed and unexposed to HAART and by duration of exposure

Variables	HAART-unexposed A n=233	HAART-exposed B n=1397	p value (A vs B)	Early HAART-exposed C n=533	Late HAART-exposed D n=427	p-value (C vs D)
Time received HAART Median weeks (IQR)		9.7(5.0-17.6) n=921		18.4 (12.1-42.6) n=412	5.8 (3.3-8.5) n=416	<0.001
Gestation: n (%)	n=147	n=946	0.002	n=389	n=427	<0.001
Extremely preterm	6 (4%)	58 (6%)		40 (10%)	3 (1%)	
Preterm	1 (1%)	80 (8%)		41 (11%)	18 (4%)	
Term/Postdates	140 (95%)	808 (85%)		308 (79%)	406 (95%)	
Birth weight (kg): n	n=224	n=1003	0.008	n=388	n=407	0.39
Mean (SD)	2.8 (0.6)	2.9 (0.6)		2.9 (0.6)	2.9 (0.5)	
0.75-1.49	10 (4%)	16 (2%)		8 (2%)	2 (0%)	
1.5-2.49 >2.5	50 (22%) 164 (73%)	199 (20%) 789 (79%)	0.015	82 (21%) 298 (77%)	74 (18%) 331 (81%)	0.071

Table 2. Infant outcomes in women exposed to HAART by regimen

Variables	Early HAART-exposed			p	Late HAART-exposed			p
	PI-based HAART	NVP-based HAART	EFV-based HAART		PI-based HAART	NVP-based HAART	EFV-based HAART	
Time taking HAART	n=139	n=192	n=81		n=290	n=107	n=19	
Median weeks (IQR)	17.1 (13.7-23.1)	15.6 (10.7-25.8)	62.7 (33.1-86.4)	<0.001	6.1 (3.3-8.7)	5.1 (3.0-7.8)	5.2 (3.9-9.4)	0.38
Gestation: n	n=131	n=167	n=91		n=290	n=116	n=21	
Extremely preterm (%)	13 (10%)	15 (9%)	12 (13%)	0.048	0 (0%)	3 (3%)	0 (0%)	0.024
Preterm	6 (5%)	25 (15%)	10 (11%)		9 (3%)	8 (7%)	1 (5%)	
Term/Postdates	112 (86%)	127 (76%)	69 (76%)		281 (97%)	105 (91%)	20 (95%)	
Birth weight (kg): n	n=135	n=158	n=95		n=284	n=103	n=20	
Mean (SD)	3.0 (0.6)	2.9 (0.5)	2.7 (0.6)	0.002	2.9 (0.5)	2.9 (0.5)	2.8 (0.5)	
0.75-1.49	5 (4%)	0 (0%)	3 (3%)		2 (1%)	0 (0%)	0 (0%)	0.59
1.5-2.49	18 (13%)	31 (20%)	33 (35%)		46 (16%)	23 (22%)	5 (25%)	
>2.5	112 (83%)	127 (80%)	59 (62%)	<0.001	236 (83%)	80 (78%)	15 (75%)	0.50

The investigators concluded that, in this analysis, any HAART exposure was associated with preterm birth between 34-37 weeks gestation. This was strongest when HAART was initiated before 28 weeks gestation. However, they did not find an increased risk of extremely preterm birth (<34 weeks gestation).

Overall, they found neither low birth weight nor very low birth weight to be associated with HAART exposure. In this cohort, infants unexposed to HAARTwere more likely to have low birth weight.

PI exposure was not a risk factor for preterm or low birth weight. But, of the three regimens, early EFV exposure was associated with low birth weight. The investigators suggested that higher levels of TB among this group of women could be confounding, as EFV is frequently used in South Africa in pregnancy in the presence of HIV/TB coinfection. TB is a risk factor for preterm birth and low birth weight.

They added that these findings could help guide PMTCT policies in South Africa.

C O M M E N T

As the investigators suggest, the observation that there was an association between early efavirenz exposure and low birth weight may be subject to confounding due to TB.

They included two useful tables (see Tables 3 and 4) showing published studies that looked at HAART exposure and preterm delivery or low birth weight. Data from Africa is slowly emerging.

Table 3: Major studies showing a link between preterm birth or low birth weight and HAART exposure

Study	Year of publication	Population	Findings
European Collaborative and Swiss Mother and child HIV cohort study [2]	1998	3920 mother-child pairs in Europe	Protease inhibitor exposure linked with preterm birth
European Collaborative study [3]	2004	4372 live births in Europe	HAART-initiation pre-pregnancy associated with preterm birth especially extreme preterm birth
Miami study, Cotter et al [4]	2006	1337 women in Miami	Protease inhibitor exposure associated with preterm birth
National Population-based surveillance study, Townsend et al [5]	2007	4445 pregnancies in UK and Ireland	HAART exposure associated with preterm birth especially extreme preterm birth

Table 4: Major studies showing no link between preterm birth or low birth weight and HAART exposure

Study	Year of publication	Population	Findings
US combined cohort [6]	2002	3266 women in the US	No association between LBW or preterm birth and HAART exposure
WITS [7]	2005	2543 women in the US	Preterm birth decreased in association with HAART exposure
Szyld et al [8]	2006	681 women in Latin America and the Caribbean	PI-exposure not significantly associated with LBW or preterm birth compared to NNRTI exposure
Paediatric Spectrum of Diseases [9]	2007	11 321 infants in the US	HAART not significantly associated with preterm birth

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Efavirenz conceptions in Soweto

Polly Clayden, HIV i-Base

A poster from the Perinatal Research Unit in Soweto, South Africa, showed findings on the rate of miscarriages and still births from a retrospective review of women receiving efavirenz (EFV) in pregnancy. [1]

Although EFV is FDA category D, increasingly women are conceiving while already receiving this antiretroviral.

In this review, the investigators looked at records of 886 women receiving HAART between August 2004 and March 2008. Among this group, 117 pregnancies were recorded and 83 women (70.9%) had conceptions that were EFV-exposed for a mean duration of 97.05 days (range 12-343 days). Of these, 3/83 (2.6%) miscarried, 1/83 (1.2%) was a stillbirth, and 28/83 (33.7%) were electively terminated.

The remainder of HAART exposed conceptions, 34/117 (29.1%), were EFV-unexposed; of these 5/34 (14.7%) miscarried, 1/34 (2.9%) were stillbirths, and 2/34 (5.9%) were electively terminated.

The investigators found that compared to live births, elective termination of pregnancy (TOP) rates were significantly higher among EFV-exposed than non-EFV exposed, p=0.00418.

They also note that South African public sector surveillance reports a miscarriage rate of 6.3% (2001), a stillbirth rate of 2.4% (2006-07), and an elective termination of pregnancy rate of 13.6% (2001).

They suggest that this high rate of TOP in women receiving EFV-containing HAART may reflect provider teratogenicity counselling. Additionally, they suggest that it reflects provider choice to initiate EFV-containing regimens for women not expressing the desire to have children. They note that they did not find an increase in miscarriage or stillbirths in women receiving EFV compared with the general population.

C O M M E N T

The investigators explained that this evaluation was performed in response to findings from Brazil showing a higher rate of miscarriage among EFV-exposed pregnancies. [2]

In our comments concerning the Brazilian data [3] we wrote:

"These data should be treated with extreme caution. The miscarriage rate reported from this notes review is extremely low (1.38%). It is generally thought that approximately 30% of conceptions are miscarried. The potential for biased reporting is very high and this is more likely to be seen with efavirenz than other antiretroviral drugs. Although the congenital anomaly rate is reported to be more than twice the background for Rio de Janeiro (2.2% v 0.8%) the later figure is only about one third of the normally cited of congenital malformations and 2.2% is a more realistic figure."

This South African review did not find a higher rate of miscarriage or stillbirth among women receiving EFV at conception.

However, the high rate of termination of pregnancy among women taking efavirenz is striking and the investigators suggest that this may reflect provider teratogenicity counselling. FDA category D states that there is evidence that the drug is associated with teratogenicity in humans. This is a relative contraindication and this FDA classification also states that the benefits may outweigh the potential risk (category X states that the drug should not be prescribed in pregnancy because of the risk). Despite this categorisation, the Antreroviral Pregnancy Registry, which now has sufficient numbers of first trimester efavirenz exposures to detect at least a two-fold increase in risk of overall birth defects, report no such increase to date, 14/477, 2.9% (95% CI, 1.6-4.9%). [4]

The data from DART above show that even in a clinical trial with pregnancy counselling 4.8% of women conceived per annum. In this cohort from Soweto 13% of the women on HAART conceived with the majority (71%) taking an efavirenz-based regimen.

So, as the investigators suggest, consideration needs to be given both to provider antiretroviral choice and to provider counseling with women of child-bearing age who may or do become pregnant.

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Impact of regimen and duration of therapy on risk of mother-to-child HIV transmission in Johannesburg

Polly Clayden, HIV i-Base

There are limited data describing the effects of HAART on mother-to-child transmission among HIV-positive women in Africa with CD4 counts <250 cells/mm3.

A poster authored by Risa Hoffman and coworkers showed an analysis of the impact of HAART regimen and duration of treatment on risk of transmission in women attending antenatal clinics in Johannesburg. [1]

This group had looked at transmission among women initiating HAART in pregnancy in an earlier analysis from this cohort. They found that for each additional week of HAART, the odds of transmission were reduced by 27%. We reported this study previously in HTB. [2]

In this more recent analysis they included both women who became pregnant while receiving HAART and those initiating HAART

during pregnancy. The authors used chi square tests and logistic regression to evaluate the effects of regimen and duration on transmission. An infected infant was defined as having a positive DNA PCR at 6 weeks.

A group of 1115 women were followed from April 2004 until July 2008. At baseline the women were a mean age of 31 years and their mean CD4 count was 159 cells/mm3. Most women (97.3%) received a nucleoside backbone of d4T/3TC. Similar proportions received LPV/r (448; 40.2%) and EFV (469; 42.1%); and a smaller group of women received EFV (198; 17.8%).

Data for initiation of therapy were available for 874 women. Of these, 16.0% became pregnant while already receiving HAART. For those already on HAART the mean duration was 93.4 weeks. For those initiating HAART in pregnancy the mean duration was 10.7 weeks of therapy.

The investigators reported an overall transmission rate for women with known date of initiation of 4.7% (43/874). They found no significant differences between HAART regimens. This finding remained with or without adjustment for prior single-dose NVP.

Women who became pregnant on HAART had significantly lower transmission rates than women who initiated HAART during pregnancy, 0.7% vs 5.7%, p=0.01.

Women initiating HAART during pregnancy (n=553) had higher transmission rates with shorter duration of therapy: 9.3%, <4 weeks; 5.5%, 4-16 weeks and 3.5%, 17-32 weeks. There were no transmissions among women receiving >32 weeks of HAART. Each additional week of HAART reduced the odds of transmission by 8%, OR 0.92, p=0.02, CI 0.87-0.99.

"To improve rates of MTCT, strategies are needed to facilitate earlier identification of HIV-infected pregnant women", they wrote.

C O M M E N T

Data continues to accumulate to support early identification of HIV-positive women in pregnancy and timely initiation of treatment.

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A cost-effectiveness analysis of the OCTANE trial

Polly Clayden, HIV i-Base

The Optimum Combination Therapy After Nevirapine Exposure (OCTANE)/ACTG5208 trial found superior outcomes among women exposed to single dose nevirapine (NVP) receiving lopinavir/ritonavir (LPV/r)-based HAART compared to those receiving NVP-based regimens. [1, 2]

In OCTANE, women with CD4 <200 cells/mm3 exposed to NVP as PMTCT prophylaxis a median of 17 months prior to HAART initiation were randomised to receive either LPV/r- or NVP-based HAART. Over a median of 73 weeks follow up, women in the LPV/r arm had significantly lower risks of virological failure or death compared to those in the NVP arm. We covered these findings in previous issues of HTB.

However, the difference in cost between the two drugs is quite considerable: LPV/r is12 times more expensive than NVP.

Andrea Ciaranello presented an analysis that examined the cost-effectiveness of first line LPV/r based HAART, compared to first line NVP-based HAART, for women with prior single dose NVP exposure in South Africa. [3]

This analysis utilised the Cost-effectiveness of Preventing AIDS Complications (or CEPAC) computer simulation model. The model included incidence, prophylaxis, and treatment of opportunistic infections in South Africa, CD4 count, viral load and HAART efficacy. The investigators used data for the modeling from OCTANE and from published South African cohorts, including natural history data from the Cape Town AIDS Cohort.

They projected two year and lifetime outcomes associated with first line HAART strategies for women with prior single dose NVP exposure. These projections included risk of opportunistic infections, deaths, and per-person HIV-related costs.

Dr Ciaranello explained that cost-effectiveness analysis a method of comparing alternative health care strategies. This method uses an incremental cost-effectiveness ratio (ICER). To calculate the ICER, the number of additional health care resources needed for one strategy compared to another is determined. This is divided by the additional health benefits gained by this strategy compared to the other.

Currency per year of life saved (YLS) is the most common unit for an ICER. A lower ratio, when less money is needed to produce a health benefit, shows a more cost-effective intervention.

To determine whether an intervention is cost effective, WHO compare ICER to per-capita GDP. ICER <1xGDP/YLS is considered to be "very cost effective" and ICER <3x GDP/YLS is "cost effective". South African GDP (2006) is $5400.

Three strategies were evaluated in this analysis:

1. No HAART (comparitor)

2. First line NVP/TDF/FTC (Second-line LPV/r/ddI/AZT)

3. First line LPV/r/TDF/FTC (Second-line NVP/ddI/AZT).

Following second line failure, women were assumed to receive a maintenance regimen of LPV/r and 3TC, which was common practice at OCTANE sites.

Baseline data for the women were used from the OCTANE cohort and included median: 31 years of age; CD4139 cells/mm3; viral load, 5.15 log copies/mL and 17 months since exposure to single dose NVP.

The efficacy of each regimen was modeled on that observed in the OCTANE trial. Efficacy was defined as achieving viral load suppression <400 copies/mL at 24 weeks after initiation of HAART.

With a median time from single dose NVP exposure of 17 months, efficacy of the first line NVP regimen was 84.6%, and the efficacy of the first-line LPV/r regimen was 96.7%.

The investigators noted that these data are slightly different from those previously presented, as a composite endpoint of virologic failure or death was shown.

There are very few data on the efficacy of NNRTI-based second-line regimens. For the model data were extrapolated from two studies to give an estimate of 43% virologic suppression at 24 weeks for second-line NVP. Data for second-line PI-based HAART are more common and, using multiple sources, an estimate of 72% suppression was used.

The investigators assumed that routine viral load tests were not available and that HAART was switched for severe opportunistic infection, 50% CD4 decline or toxicity.

They used HIV-related healthcare costs derived from the South African Health Systems Trust. These included the cost of a day in hospital of $221, the cost of an outpatient clinic visit of $11 and the cost of a CD4 test of $9.

For drug costs, they used prices from the Clinton Foundation HIV/AIDS Initiative. Annual drug costs were $38 for NVP and $444 for LPV/r. For the nucleosides, the figures were $142 for TDF/FTC and $238 for ddI/AZT.

Projecting outcomes for the entire cohort at two years revealed that with no HAART, 41.7% of women would survive at a per-person cost of $2650. Using a NVP-based first-line regimen survival was 96.1% at a per-person cost of $2450, and providing LPV/r-based HAART first-line, survival was 97.1% at a per-person cost of $2780. Compared to first-line NVP, LPV/r gave a 26% risk reduction in mortality at an additional per-person cost of $330.

Projecting long-term outcomes showed live expectancy of 1.8 years at a per-person cost of $3540 if the cohort were untreated. With NVP-based first line survival increased by 13.6 years to 15.4 years at a per-person cost of $14,040 for an ICER of $770/YLS. Using LPV/r-based first-line gained a further 1.1 years survival (16.5 years) at a per-person cost of $16,180 for an ICER of $1970/YLS. So using LPV/r first-line would be ”very cost effective” compared to NVP according to WHO criteria for South Africa.

Additionally, the investigators then conducted a sensitivity analysis. They evaluated many model inputs parameters and assumptions. Dr Ciaranello presented estimates for parameters of particular importance.

Importantly, they evaluated the efficacy of second-line NVP, for which there are few data (in the range of 16-45%). The investigators looked at 0-100% efficacy and found that LPV/r remains “very cost effective” by WHO criteria unless the efficacy of second-line NVP is less than 15%.

They also looked at the influence of NNRTI resistance at the time of initiation of HAART. Among the OCTANE cohort, 86% of women had no detectable NNRTI resistance using standard genotype assay at the time of starting treatment. For this group of women the efficacy of first line NVP was greater than for the cohort overall, 89% vs 85% (97% for LPV/r first line). For women with no resistance the ICER of first line LPV/r compared to NVP was $10,990/YLS, and no longer a “very cost-effective” intervention in South Africa.

OCTANE also included stratification by time from NVP exposure to initiation of HAART. Looking at cost effectiveness according to these strata, the investigators found LPV/r was “very cost effective” with 6-24 months between NVP exposure and treatment, at an ICER of $2000/YLS. However, >24 months the ICER reached the WHO threshold for South Africa at $5400. They noted that LPV/r first-line became less cost effective as time from NVP exposure increased.

Dr Ciaranello acknowledged that the limitations to these estimates include some input data from cohorts of both men and women; costs and cost effectiveness thresholds that are specific to South Africa and results are sensitive to data that are not yet available from the OCTANE trial.

She stressed that reducing the impact of NNRTI resistance related to single dose NVP is particularly important in order for women to benefit from available classes of antiretrovirals in the treatment of their own HIV.

She also emphasised the importance of HIV and CD4 testing of pregnant women in order to initiate HAART in eligible women before delivery, both improving maternal health and reducing mother-to-child transmission.

However she added: “Despite these efforts, many of the single dose NVP-exposed women living in resource-limited settings are likely to need to initiate HAART soon. The choice of optimal first-line HAART for these women will require important data about

long-term outcomes, particularly outcomes of second-line HAART. Such outcomes can only be observed after the conclusion of most clinical trials. OCTANE, cohort studies, and HAART programme monitoring and evaluation efforts will be crucial sources of these data".

C O M M E N T

This cost-effectiveness analysis is useful to demonstrate that for NVP-exposed women, particularly those with an interval since exposure of <24 months, using LPV/r-based HAART first-line is very cost-effective.

However, it would be better to avoid risk of resistance in the first place by early identification and treatment for women indicated for their own health (with CD4 <350 cells/mm3), and more complex PMTCT regimens for healthier women (short course PI based HAART, AZT plus single dose NVP plus tail coverage).

As the investigators suggest, the future options for NVP-exposed women for second-line treatment are unclear in resource-limited settings.

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The PEARL study

Polly Clayden, HIV i-Base

David Coetzee from the University of Cape Town presented data from the PEARL study. This study was a four-country evaluation of the effectiveness of PMTCT programmes in Africa. [1]

PEARL evaluated 43 sites in Zambia, Cote D'Ivoire, South Africa and Cameroon. The primary outcome was coverage ie the proportion of mother-child pairs with HIV antibody-positive cord blood with confirmed receipt of maternal (detectable NVP in cord blood) and infant (documented) NVP. The study also evaluated AZT and 3TC where appropriate.

All PMTCT sites used a minimum intervention of single dose NVP. Some also used short course AZT plus single dose NVP and/or HAART.

Cord blood was collected anonymously from every delivery between April 2007 and October 2008 and tested for HIV (there was an excellent collection rate of about 98% of consecutive deliveries). If the result was positive, the presence of NVP (AZT and 3TC if applicable) was determined by high performance liquid chromatography.

The investigators also used documented information collected anonymously from patients' notes including infant ingestion of NVP.

The investigators collected 28,060 cord blood samples of which 3250 were HIV-positive.

Evaluating both sets of information together they described the "coverage cascade" (see Table 1), where coverage is defined as maternal and infant ingestion of nevirapine.

Table 1: Coverage cascade

Intervention	%
Positive cord blood	100
Information in folder	92
Offered HIV test	84
HIV tested	81
Result in folder	74
Maternal receipt NVP	71
NVP in cord blood	57
Coverage	50

They reported wide variation in coverage across different sites (17%-69%).

Reasons for failed coverage included: no offer of HIV test; HIV test declined; testing declined; test result not given; NVP not dispensed; mother did not adhere and infant not dosed.

The risk of failed coverage increased with younger age: ≤20 years adjusted OR 1.58 (1.23-2.02) vs >30 years. The association

also increased with fewer antenatal visits: 0-1 visits AOR 2.92 (2.22-3.84) vs >6 visits.

Risk of poor maternal adherence was significantly higher in the 26-30 years age group, adjusted OR 1.42 (1.04-1.93) vs >30 years; with greater gravidity, OR 1.62 (1.12-2.34), 4 vs 1; fewer antenatal clinic visits OR 2.98 (2.07-4.48), 0-1 vs >6 visits; vaginal delivery OR 1.51(1.11-2.05) vaginal vs caesarean; and AZT plus NVP prophylaxis, OR 1.42(1.04-1.93) vs NVP alone (HAART was not significantly associated with poorer maternal adherence). All rates are adjusted.

The study included an analysis of PMTCT in the Western Cape, where guidelines have recommended HAART for women with CD4 <200 cells/mm3 and short course AZT plus single dose NVP with CD4 >200 cells/mm3 since 2007.

In this province 12% women received HAART (the investigators used detectable 3TC as a surrogate for HAART) and 47% AZT plus NVP, so overall 59% received standard of care. However, 6% received only NVP, so 65% received "at least NVP"; 8% received AZT alone and 27% of pregnant women received nothing at all. The investigators noted that CD4 data was not collected in this study (so they would not be able to estimate how many women should have received HAART).

The investigators concluded that failures in the "cascade" of interventions occur at every step of the way, giving only 50% coverage overall across sites.

Even in settings with two-drug prophylaxis and HAART over a quarter of women are not covered by PMTCT prophylaxis (so also not receiving HAART for their own HIV if indicated).

"Interventions must systematically target better performance at each step to maximise their benefits", they wrote.

C O M M E N T S

These data provided an important reality check and show that despite interventions that benefit maternal health and/or prevent transmission to their infants, inadequate roll out and coverage is the norm.

The PEARL Study's primary outcome variable is uptake of PMTCT interventions. As such, PEARL measures programme coverage, but does not assess programme effectiveness at preventing or treating HIV infection. During the conference, reports on national roll out of PMTCT protocols were notable for the absence of infrastructure to detect infant HIV infection, and therefore the effectiveness of PMTCT interventions in practice. Early detection of paediatric HIV is belatedly but rapidly becoming a priority in many countries. We will report on research presented on infant diagnostics in the next issue of HTB South.

WHO PMTCT consultations have also used PMTCT cascades and Lynne Mofenson showed estimations from these in her plenary at the paediatric meeting preceding the IAS conference. [2] In a "typical" scenario they estimate that of 1000 mothers, 90% (900) will attend ANC; of these 70% (630) will be counselled and tested for HIV and 50% of this group (315) receive ARVs. If 685 women receive no ARVs, that will mean 25% (172) of their infants will be infected.

In this estimation, overall transmission rates, if all women with CD4 <200 cells/mm3 receive HAART and the remainder receive either single dose NVP, short course AZT plus single dose NVP or HAART, would be 19.7%, 18.1% and 17.6% respectively.

With improved uptake, if 96% (960) mothers attended ANC, 99% (950) were counselled and tested and 98% (931) received ARVs, that would mean 69 mothers receive no ARVs and 17 infants would be infected. In this estimation the overall transmission rates would be 9.1%, 4.5% and 3.1% for single dose NVP, AZT plus single dose NVP and HAART respectively.

Coceka Mnyani and coworkers showed data from January to December 2008 from the Soweto programme on which the improved figures were based. [3] In March 2008 short course AZT was introduced in addition to single dose NVP for women with CD4 >200 cells/mm3. During this period, 30180 women attended ANC of which 99% (29968) accepted HIV testing and 29% (8774) tested HIV-positive. Of these 5704 mothers and 6641 infants received AZT plus single dose NVP and 96% (8137/8514) elected to formula feed. A total of 324/5572 infants were HIV-infected giving a transmission rate of 5.8%. The transmission rate was 7.2% during the period when single dose NVP was used alone and 4.4% using AZT plus NVP, OR 1.67 (95%CI, 1.24-2.3), p=0.0004.

As Lynne Mofenson explained, "Programme efficacy is as much related to the PMTCT cascade as the specific regimen."

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Results from HSV-2 acyclovir studies

Nathan Geffen, TAC

Acyclovir studies at IAS 2009

Connie Celum, the principal investigator on the HPTN 039 trial, together with Jai Lingappa, the medical director, and other members of the Partners in Prevention HSV-HIV Transmission Team presented findings at IAS2009 on a counterpart trial to HPTN 039. This study, in HIV serodiscordant couples, looked at whether suppressing HSV-2 in people dually infected with HSV-2 and HIV infections could reduce HIV transmissions to their HIV-negative partners. [1]

HPTN 039 was a double-blind placebo controlled trial of standard doses of acyclovir for HSV-2 suppression (400 mg twice daily) to prevent HIV acquisition among over 3200 African women and MSM in Peru and the United States who were HIV-negative and HSV-2 positive. HTPN 039 found that acyclovir suppression did not reduce HIV incidence compared to placebo. Results were reported at CROI2008 and subsequently in the Lancet. [2]

Celum presented the main results of this new double-blind placebo controlled trial, conducted at 14 sites in sub-Saharan Africa, including South Africa, Kenya, Zambia, Botswana, Tanzania, Rwanda and Uganda.

Of 6544 heterosexual HIV discordant couples screened, 3408 were enrolled. The inclusion criteria for the coinfected partner included a CD4 cell count ≥250/mm3. The other partner could be either HSV-2 positive or negative, but had to be HIV-negative. HIV-positive participants could not be eligible for ART at trial entry according to their country guidelines.

The HIV-positive partners were randomised to receive either 400mg acyclovir twice-daily or placebo twice-daily. Couples were followed for a maximum of 24 months. Participants were provided with ART if they became eligible for it according to country guidelines.

The primary endpoint was HIV infection in the HIV-negative partners. The secondary endpoints included plasma and genital HIV viral load in the HIV-positive partners, and HIV disease progression. The trial was set up so that if 88 'linked' HIV transmissions (i.e. the virus transmitted from the enrolled partner to the seroconverting partner was determined by molecular sequencing to be linked) were observed, the trial would have high statistical power (90%) to see a 50% reduction in HIV transmissions in the acyclovir arm.

Baseline characteristics of the group included:

- 67% of HIV-positive partners were female;
- 65% of volunteers were ≤35 years old;
- average partnership duration was five years;
- 90% were cohabiting;
- a median of five sex acts were reported in the month prior to baseline measurements:
- 29% reported unprotected sex;
- 22% of the HIV-positive partners reported genital ulcer disease (GUD) in the prior three months;
- 4% of HIV-positive and 7% of HIV-negative partners reported outside partners respectively;
- median CD4 count was 460 cells/mm3 and median plasma HIV viral load was 4.2 log.

Monthly follow-up visits included medication provision, pill count and adherence support and individual and couple HIV risk reduction counselling. Every three months, HIV-positive partners were examined for GUD and plasma viral load and HIV-negative partners were tested for HIV and given risk reduction counselling. CD4 cell counts were taken every six months.

Retention was high. At 24 months, 92% of HIV-positive and 84% of HIV-negative participants were still in follow-up. Adherence measured by pill count was also high: 88% of all bottles were dispensed and 97% of dispensed bottle doses were taken.

No significant differences in incidence

There were 136 seroconversions at a rate of 2.8/100py (95% CI: 2.3-3.3), one after an incorrect drug kit was dispensed. Of the remaining 135, 68 occurred on the acyclovir arm and 67 on the placebo arm (HR: 0.92; 95%CI 0.60-1.41; p=0.70).

In a modified intention to treat analysis, 43 transmissions were linked by viral sequencing technology to partners on the acyclovir arm and 47 were linked to partners on the placebo arm. However, two in the acyclovir arm and four in the placebo arm were excluded from analysis because the study drug was withheld during pregnancy. Here too, there were no significant differences between the two arms. The sequencing methodology for this study was explained in a late breaker poster from Mary Campbell. [3]

Benefits of acyclovir

There were fewer GUD events in the acyclovir arm (217 vs 550; RR: 0.39; 95% CI: 0.32-0.48; p<0.001). HSV-2-positive GUD as determined by DNA PCR was also lower in the acyclovir arm (92 vs 336; RR: 0.27; 95%CI 0.2-0.36; p<0.001).

The acyclovir arm also had a 0.25 log reduction in plasma viral load (95%CI: 0.22-0.29).

A novel component of this study was evaluation of herpes suppression on HIV disease progression, an important secondary endpoint of the Partners in Prevention trial. In a separate analysis presented by Jairam Lingappa, 3,381 of the HIV-positive participants were followed up until a composite endpoint of first of CD4 cell count <200 cells/mm3, ART initiation, or death from non-trauma causes. [4]

In the acyclovir arm, 284 participants reached this endpoint versus 325 in the placebo arm (HR 0.83; 95%CI: 0.71-0.90; p=0.03). Similar reductions were found for each component of the composite endpoint analysed separately. However, Lingappa's team further calculated that for every 43 people treated with the trial dose of acyclovir for a year, only one person would be prevented from attaining the composite endpoint. (We have previously reported findings demonstrating acyclovir and its pro-drug, valacyclovir's effect on HIV plasma RNA levels, in the October 2006 and July/August 2008 issues of HIV Treatment Bulletin, but this is the first report documenting impact of herpes suppression on HIV disease progression.)

Among participants with CD4 counts ≥350 cells/mm^3 at enrollment, acyclovir delayed the time to CD4 < 350 cells/mm3 (HR 0.81; 95%CI 0.71-0.93; p=0.002). Here, 20 people would need to be treated to prevent one person from progressing to a CD4 count < 350 cells/mm3.

Acyclovir effect on genital viral load

A late breaker poster by Jared Baeten et al presented the results of a substudy that examined genital HIV RNA concentrations as a surrogate marker for HIV infectivity. [5]

Endocervical and semen samples were collected from 2,521 (1,805 women and 716 men) of 3,408 HIV-positive participants. For 1,797 of these, plasma was concurrently taken. For the remainder a plasma viral load within six months was available. Since the genital samples were taken only once during the study, the genital viral load was analysed as a time-independent variable.

HIV was detected in 60% of endocervical swab samples and 57% of semen samples. The median endocervical HIV concentration was 3.2 log (IQR 2.08-3.87) overall. Genital HIV-1 concentrations were significantly lower among those randomised to acyclovir (median 2.98 vs 3.29 for endocervical swabs; p<0.001 and 2.38 vs 2.76 for semen; p=0.008). The key finding of the study was that genital HIV concentrations were higher among HIV transmitting couples, where transmission was genetically linked to the partner (3.44 vs 2.49 log copies/mL for semen, p<0.001 and 3.91 vs 3.18 log copies/swab for endocervical swabs, p<0.001). Each log increase in genital HIV-1 RNA concentration was associated with 1.85-fold increased odds of HIV transmission for semen (p<0.001) and 2.03-fold increased odds of transmission for endocervical swabs (p<0.001). The study found no significant difference in genital HIV concentration for participants whose partners acquired HIV from outside sexual partners versus those who did not transmit HIV.

However, despite a 73% reduction in GUD and 0.25 log decline in plasma HIV levels and an approximately 0.3 log decline in genital HIV levels, acyclovir conferred no reduction in HIV transmission. The authors interpret the overall results of the trial to indicate that the plasma and genital tract HIV viral load reduction from herpes suppression with standard doses of acyclovir is too small to confer a protective effect against HIV transmission.

Future acyclovir trials

Nevertheless, given the promising effect of acyclovir on HIV viral load, Steve Reynolds described an ongoing double-blind placebo controlled trial in Rakai, Uganda. [6]

The purpose of the trial is to evaluate the effect of suppressive HSV-2 therapy among HIV-1/HSV-2 co-infected individuals on progression to AIDS, defined as CD4 count < 250 cells/mm^3 or WHO stage IV disease. Volunteers with CD4 counts between 300 and 400 cells/mm^3, not on ART, without WHO III/IV symptoms and no history of opportunistic infections, other than mucocutaneous Kaposi Sarcoma, candida or treated TB were eligible for inclusion. Enrollment was completed in November 2008. The trial assumes that 40% of individuals in the placebo arm will progress to CD4 counts <250 cells/mm^3 or AIDS over 24 months and is powered to detect at least a 20% reduction in HIV disease progression in the intervention arm.

C O M M E N T

These studies show that a standard dose of acyclovir for HSV-2 suppression does not reduce HIV transmission. These are disappointing findings for an HIV prevention strategy that is already available.

A mechanism for the lack of protection has been suggested by Laurence Corey and colleagues in a recent paper in Nature Medicine. [7] By analysing regular skin biopsies taken during acute lesions and over 20 weeks follow-up, they indentified a 'massive localised infiltration' of CD4 and CD8 cells, thereby increasing the targets for HIV infection. Eight weeks after lesions healed, these levels were still 8-fold higher (655 and 618 cells/mm2 of skin, respectively, compared to 68 and 55 cells/mm2 in unaffected skin samples).

This paper is reported in detail in the Basic Science section of this issue of HTB. [8]

It has been conventional wisdom that wider availability of acyclovir for patients with genital herpes outbreaks would reduce HIV transmissions. We now know this is incorrect, at least with the doses of acyclovir (400 mg twice daily) used in these trials. However, efforts to make acyclovir widely accessible should continue because herpes is a debilitating, unpleasant disease which acyclovir effectively treats and because HSV-2 in widely prevalent in both HIV-negative and HIV-positive people. One of the barriers to its accessibility remains its high price in many developing countries.

Despite the negative findings, this trial and its substudies have set a high standard for the testing of future HIV prevention interventions. Furthermore, modeling studies using the data from this trial provide a potential threshold of HIV plasma viral load reduction in HIV-infected persons that will be needed to impact HIV transmission.

We now need to know whether a therapeutic dose of acyclovir could delay the time until initiation of HIV treatment, and whether this would be cost effective. The trial in Rakai described by Steve Reynolds using 400 mg twice-daily dose will provide complimentary information to the Partners in Prevention trial.

Studies with higher doses of valacyclovir will evaluate whether greater reduction in plasma HIV levels is feasible compared to acyclovir 400 mg twice daily. However, this research could be overtaken by new developments in ART management, if guidelines recommend earlier treatment.

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Overview of TB-related studies at IAS

Nathan Geffen, TAC

Some useful TB research has been published since the last issue of HTB. With approximately 120 TB-related abstracts at IAS2009, we summarise some of the most important.

Epidemiology

The most interesting TB research presented at the IAS conference dealt with the epidemiology of TB/HIV co-infection.

A presentation by Keren Middelkoop and colleagues analysed the association between the introduction of HAART in a community and active TB rates. [1]

They collected TB notification data, prior to HAART (1998 to 2004) and after HAART was introduced (2004 to 2008), in Masiphumelele township in Cape Town. HIV prevalence was estimated to be 23% in the township. Pre-ART adult TB notifications increased by an average of 212 cases per 100,000 people per year (p =0.005 for trend). Post-HAART, adult cases decreased by 116 per 100,000 people per year (p=0.16, NS for trend).

TB rates in HIV-negative people did not change substantially over the period and averaged 697 cases per 100,000 per year. TB rates in HIV-positive people increased by an average of 826 cases per 100,000 per year over the same period (p value for trend 0.08), but after the introduction of HAART, declined by 600 cases per 100,000 per year (p=0.16, NS for trend). For HIV-positive people not on HAART, the average decline in the post-HAART era was 421 cases per 100,000. For people on HAART, it declined

by 1,394 cases per 100,000 and this trend was significant (p=0.05). The authors concluded that wide-scale HAART implementation and the community's well-functioning TB programme were associated with modest TB declines.

Masiphumelelo's population is only 20 to 30,000 which might explain a lack of power to detect statistically significant trends. But another study in Masiphumelelo also conducted by Middelkoop and colleagues makes the argument for the effect of ART on a declining TB rate more compelling. [2]

In 2008 they repeated a randomly sampled cross-sectional survey that was first performed in 2005. About 30% of HIV-positive adults were estimated to be on HAART in 2008. Two sputum samples were obtained from each participant. Participants also filled in questionnaires on TB history. Those who were not being treated for TB and had two TB-positive sputum or culture tests were considered to have undiagnosed TB. The survey measured a significant decline in the TB rate in HIV-positive people since 2005 (all testing was anonymous), including a significant decline in undiagnosed TB in this group. No such decline was seen in HIV-negative people. The study also found that after adjusting for age, sex and HIV status, the overall 2008 TB prevalence was significantly lower than the overall 2005 prevalence (p=0.02). See Table 1.

Shortly after the conference, members of this research group published an article in AIDS that examined the association between current CD4 count and risk of TB. [3]

Table 1: Results of surveys in 2005 and 2008 in Cape Town township

	HIV-positive			HIV-negative		
	2005	2008		2005	2008	
	n=174	n=310	p	n=584	n=949	p
On treatment TB (%)	4.00%	1.30%	0.19	0.70%	1.20%	1.0
Undiagnosed TB (%)	5.20%	1.60%	0.01	0.50%	0.80%	0.7
TOTAL	9.20%	2.90%	0.01	1.20%	2.00%	0.81

Table 2: TB incidence by CD4 count strata (from Lawn et al.)

CD4 count (cells/mm3)	Unadjusted TB incidence (per 100py)
0-100	16.8
101-200	9.3
201-300	5.5
301-400	4.6
401-500	4.2
>500	1.5

They analysed TB incidence in 1480 patients receiving ART for up to 4.5 years. Updated CD4 cell counts were measured 4-monthly. During 2785 person-years of observation, 203 cases of TB were diagnosed, giving an overall incidence of 7.3 cases/100 person-years. TB incidence by CD4 count strata is described in Table 2 (p<0.001).

The authors found that updated CD4 cell counts were the only patient characteristic independently associated with long-term TB risk. They concluded that updated CD4 cell counts were the dominant predictor of TB risk during ART in this low-resource setting. They also found that among those with baseline CD4 cell counts less than 200 cells/mm3, the excess adjusted risk of TB during the first four months of ART was consistent with unmasking of disease missed at baseline screening. They noted that TB incidence at CD4 cell counts of 200-500 cells/mm3 remained high and concluded that TB prevention would be improved by ART policies that minimised the time patients spend with CD4 cell counts below 500 cells/mm3.

These studies provide evidence that widespread ART implementation can reverse the growth in active TB rates in Southern Africa.

A study by Van Rie and colleagues analysed risk factors for TB in patients who had been on HAART for greater than six months in a prospective cohort from the Themba Lethu clinic in Johannesburg. [4]

This study provided quantitative data on TB incidence and its relationship to patients failing treatment. Of 5934 adults, 217 (4%) developed TB after six months. Median time to TB was 418 days (IQR: 276-672, incidence of 2.3 cases per 100py). The incidence was four times lower than in the first six months of ART. Significant risk factors associated with active TB were BMI <18.5 compared to BMI ≥25 (HR: 6.52, 95%CI: 3.60-11.80) history of TB treatment (HR: 1.50, 95%CI: 1.09-2.50), current viral load >10,000 copies/mL (HR: 2.44, 95%CI: 1.57-3.79) and CD4 count ≤ 50 cells/mm3 (HR=0.84, 0.45, and 0.34, for CD4 51-100, 101-200, and 201-350 respectively).

In a study from Khayelitsha, Pepper and colleagues examined patients in their cohort who had clinical deterioration. [5]

They enrolled 298 people with who had initiated TB treatment from June to August 2008 and then followed them for six months. In this group, 209 (71%) were HIV-positive, with a median CD4 count of 129 cells/mm3 (IQR: 62-277). At TB diagnosis, 35 (17%) HIV-positive patients were receiving HAART. This rose to 112 (54%) on HAART six months later.

Within 6 months, 117 patients (39%) experienced 208 episodes of clinical deterioration. Of these, patients, 71% were HIV-positive. There was an escalating risk of clinical deterioration in HIV-positive patients as CD4 counts decreased (CD4>350: RR:1.4; 95%CI=0.7-2.9; CD4 200-350: RR:2.0, 95%CI: 1.1-3.6; CD4< 200: RR=3.0, 95%CI=1.9-4.8).

AIDS-defining illnesses (n=30), TB-IRIS (n=22) and MDR-TB (n=10) were important causes for clinical deterioration. The number of deaths was 17, of whom 15 were HIV-positive with a CD4 count <200 cells/mm3 at TB diagnosis. The authors also noted that health-care use was significantly higher in HIV-positive patients with low CD4 counts. They pointed out that starting HAART initiation at higher CD4 counts is likely to reduce this clinical burden.

De Bruyn and colleagues presented data from Soweto that showed an association between ART and neutrophil count. [6]

They explain that neutrophil granules contain antimicrobial peptides that kill M.tuberculosis. In HIV-negative people exposed to TB, neutrophil count is inversely associated with risk of latent TB infection and positively associated with ability to contain mycobacterial growth in vitro. However, neutrophil functional defects occur in HIV-positive patients. The authors therefore examined the association of incident TB with neutrophil count.

They followed a prospective cohort of almost 2700 HIV-positive adults for over 5500 person-years. Median age was 32. Women comprised 79% of the cohort. Median CD4 count was 282 cells/mm3. The median neutrophil count was 2.46 copies/nL. TB incidence was 5.2/100py (95%CI: 4.6-5.8). ART was associated with a reduced risk of TB (HR: 0.26; p<0.001), as was increasing CD4 count. Increasing neutrophil count was also associated with increased risk of TB (HR: 1.18; p=0.02). For patients on ART, there was a trend showing that risk of TB was reduced by 75% per nL increase in neutrophil count (HR: 0.25, p=0.08).

The authors conclude that the association between neutrophil count and risk of tuberculosis in HIV-positive adults varies according to whether HAART is administered. Their results suggest that HAART critically influences the relationship between neutrophils and the risk of TB.

C O M M E N T

The potential role of earlier ART in reducing the epidemiological impact on TB is encouraging.

This supports the recommendation to start HAART at CD4 counts over 350 cells/mm3 in patients coinfected with TB.

Drug resistance

Research on drug-resistant TB continued to be a concern.

A study by Max O'Donnell and colleagues who have produced excellent data on the drug-resistant TB epidemic, found that health care workers in Kwazulu-Natal had a much higher incidence of TB than the general population. [7]

Based on data from King George V Hospital, MDR-TB incidence was 58.9 per 100,000 people for the province's health workers and 10.7/100,000 for the province's general population (OR: 5.53; 95%CI; 4.70-6.50). XDR-TB incidence was 4.0/100,000 among health workers and 1.0/100,000 in the general population (OR: 3.89 95%CI: 2.02-7.11). There were 235 cases of health workers with drug-resistant TB and 3,391 cases for non health-workers at the hospital. About half of drug-resistant patients were HIV-positive and this did not differ between health workers and the general population. The high incidence amongst health workers is clearly related to occupational exposure. The researchers therefore conclude that screening and controlling occupational exposure among health workers is critical to limit nosocomial spread of drug-resistant TB.

In another Khayelitsha study, Helen Cox and colleagues reported on the prevalence of drug-resistant TB. [8]

This team conducted a representative cross-sectional survey of clients attending two clinics suspected of having pulmonary TB between May and November 2008. Of 1,850 TB suspects surveyed, 536 (30%) were culture-positive. HIV status was known for 427 (80%) cases with 261 HIV-positive (61%). Rifampicin resistance was found in 4% of new cases and 10% of previously treated cases (p=0.003), and in 8.0% of HIV-positive and 4.8% of HIV-negative cases (p=0.18). They estimated rifampicin resistance in Khayelitsha to be 50 to 72/100,000 people per year. They concluded that there is extremely high prevalence of drug-resistant TB in the township. Moreover, that it is high amongst HIV-negative people too.

PACTG 1041 was a double-blind placebo controlled trial to test isoniazid preventative therapy (IPT) in perinatally HIV-exposed infants. The primary endpoint was TB disease, infection or death. The DSMB stopped the trial because of futility. Partial results were reported at ICAAC 2008 (covered in HTB Nov/Dec 2008) and CROI 2009. At IAS2009 a poster by Anneke Hesseling and colleagues reported the results of an analysis of the 22 culture-confirmed cases of TB in the trial. [9]

Of these, 18 were sent for drug-susceptibility testing. Five were drug-resistant (one to INH, four MDR-TB). The authors conclude that the high rate of drug-resistant TB in the trial is consistent with the growth of the adult drug-resistant TB epidemic and has potential consequences for the programmatic implementation of IPT.

C O M M E N T

The growing evidence of a rising drug-resistant TB epidemic that might undermine the benefits of IPT, particularly in infants, is concerning. So too are the high rates of drug-resistance in HIV-negative people beyond nosocomial infection in Khayelitsha. The South African government is still not demonstrating adequate commitment to co-ordinating and prioritising infection control measures and contact tracing. For example, it would be useful to have a project to revamp clinic waiting rooms (along similar lines to the waiting room at the Ubuntu clinic in Khayelitsha, which has heaters and a roof, but no walls allowing a continuous flow of air). A public information campaign to keep windows open in public places (e.g. buses and taxis) is also important.

Izoniazid preventative therapy (IPT)

One concern about community-wide IPT is that it will result in higher isoniazid resistance. A study by Halsema and colleagues provides promising data that will help allay, albeit not completely, this fear. [10]

The Thibela TB study is a large cluster-randomised trial to study IPT strategies in South African gold mines. Individual mine shafts are randomised to receive either standard TB control (IPT to miners with silicosis or HIV infection) or the intervention (IPT to everyone in the mine, from miners to executives).

In this case-controlled study, drug susceptibility data from TB cases among people who received IPT in the Thibela TB intervention clusters were compared to two groups: (1) TB cases in the control clusters and (2) a subset of patients from a laboratory substudy confined to the first TB episodes in the control clusters. The comparison cases were restricted to the same calendar period as the intervention cases. The Thibela TB intervention began in July 2006 and the study included all TB cases in the intervention clusters up to mid-February 2009.

The intervention group included all participants receiving IPT who attended at least one follow-up visit and were subsequently treated for TB, unless they did not have positive TB cultures. Of the 126 individuals who met the inclusion criteria in the intervention arm all but one were male. The median age was 43 years. Of 103 patients with known HIV status, 89 (86.4%) were HIV-positive. Median CD4 cell count was 196 cells/mm3 (n=51). The median time from starting IPT to TB treatment was 316 days (IQR: 174-491). For 75% people (n=94) this was their first TB episode and 25.4% (n=32) were retreated. TB was pulmonary for 87 (69.0%), extra-pulmonary for 22 (17.5%) and disseminated for 17 (13.5%).

Amongst the intervention cases, 96 outcomes had been documented at the time of the analysis: 39 (41%) were cured, a further 23 (24%) completed treatment, 8 (8.3%) died, there was one treatment interruption, one treatment failure, 11 (11.5%) transferred out or were lost-to-follow-up and for 13 (13.5%) cases the outcomes were unknown.

The authors concluded that TB disease after IPT may be largely due to re-infection in this high HIV prevalence group.

Data on drug susceptibility was presented for 58 people in the intervention group, 182 in the control clusters and 32 in the laboratory substudy. Table 3 presents the results of their analysis.

Table 3: Drug-resistance in three groups from Thibela TB study

	TB after IPT group (n=58)	Control clusters (n=182)	Laboratory substudy (n=270)
Isoniazid resistance	7 (12.1%)	12 (6.6%)	32 (11.8%)
MDR	1 (1.7%)	6 (3.3%)	21/269 (7.8%)

There were no significant differences between the groups in any of these outcomes. However, the authors noted the very wide confidence intervals (depicted graphically on their poster). In their discussion, they explained that if IPT is more effective at treating isoniazid susceptible latent TB, then an increased proportion, but not absolute numbers, of isoniazid resistant TB cases would be expected among those who have taken IPT. They concluded however, that the proportion of TB episodes in the intervention groups did not differ from the controls, and that these data do not support concerns about IPT induced resistance.

TB treatment

The standard model for the management of TB patients that is promoted by the WHO involves directly observed treatment (DOT). In this model, patients come daily to their health facilities to take their pills under the supervision of a health worker.

Atkins et al. described an alternative model piloted from April 2007 to March 2008 in five health facilities in Cape Town. [11]

In this intervention, adult TB patients received adherence counselling. They also selected a treatment buddy. Lay health workers supported patients' self-supervised treatment.

Using information stored in a routine electronic TB register, TB data from these five clinics was compared against another five

clinics that use DOT. Across the five intervention clinics 75% of new patients were treated using the new model. In these clinics, treatment success was 72.4% (95%CI: 67.4-77.4) and in the control clinics it was 75.9% (95%CI: 70.8 to 80.9), a non-significant difference.

In the previous issue of HTB South, we reported on the results of the CAPRISA trial that compared immediate versus deferred HAART in patients coinfected with TB. It showed significant reduced mortality in the immediate arm. We commented on the importance of integrating TB and HIV services to make this intervention easier to implement. Further evidence of the benefits of integrating TB and HIV treatment comes from a Malawian study.

Malawian TB case notifications have risen dramatically over the last two decades. Chan and colleagues described what happened when the Zomba Central Hospital ART Clinic, which opened in 2004, began integrating TB services. [12]

Zomba district has a population of 670,000 (80% rural). HIV prevalence amongst 15 to 49 year-olds is estimated to be 16.5%. Routine national TB programme data shows that 69% of TB patients are HIV-positive.

Integration of services began in September 2007 through monthly HIV/TB integration days. By April 2008, services were fully integrated with a daily TB/HIV Integration clinic where all patients registered for TB were also tested for HIV and referred for HIV care in the same physical area. Ministry of Health TB patient records and HAART records from September 2007 to December 2008 were reviewed to assess uptake of HAART. Following integration, HAART uptake increased dramatically from 4% to 33% in HIV monoinfected patients and from 25% to 50% in patients with HIV/TB coinfection. See Table 4.

Table 4: Numbers of patients (%) in HAART uptake following integration of TB and HIV clinics at Zomba Central Hospital , Malawi

	New TB	TB/HIV co-infected	Already on HAART n (%)	Need to start HAART	Started HAART	% uptake new HAART	% uptake all co-infected
Q3 2007	464	307	67 (22%)	240	9	4%	25%
Q4 2007	482	312	60 (19%)	252	25	10%	27%
Q1 2008	518	325	48 (15%)	277	28	10%	23%
Q2 2008	593	384	75 (20%)	309	84	27%	41%
Q3 2008	650	334	81 (24%)	253	77	30%	47%
Q4 2008	556	212	68 (32%)	144	47	33%	50%

The CARINEMO-ANRS 12146 Trial is a randomised, open-label non-inferiority study comparing 48 weeks virological suppression and safety of nevirapine (400mg daily without leading dose) vs efavirenz (600mg daily) co-administered with rifampicin. The other ARVs in the study regimen were d4T and 3TC. HAART was started four to six weeks after TB treatment. Bhatt and colleagues presented preliminary safety data, covering the period November 2007 to December 2008. [13]

By the end of this period, 236 patients with CD4 counts <250 cells/mm3 and who were co-infected with active TB had been randomised. Of these, 11 (4.7%) discontinued the study (6 due to death, 3 withdrew consent, 1 lost-to-follow-up and 1 other).

Follow-up included weekly clinical assessments for the first eight weeks of HAART and monthly assessments thereafter. Patients also had aminotransferase (ALT) measurements every two weeks during the first eight weeks followed by monthly measurements. 204/236 patients (86.4%) presented at least one adverse event. There were 26 serious adverse events, of which six resulted in death. None of the deaths were drug-related.

Skin-related adverse events were reported in 47 patients (19.9%), but none were severe. Also, 11 (4.7%) patients had an ALT increase (≥ grade 3). Five patients (2.1%) interrupted treatment due to hepatitis. However, there were no cases of severe rash. The researchers concluded that this plus the relatively low number of cases of severe hepatitis and treatment interruptions due to adverse events were reassuring but needed to be confirmed. Final results are expected at the end of 2010. A study by Kamateeka and colleagues of children taking rifampicin and nevirapine is also reviewed in this issue of HTB.

A study from a Uganda found that efavirenz is associated with a greater decline in TB incidence than nevirapine. Hermans and colleagues reported data from their large cohort of ART patients (n=7,648). [14]

Between May 2002 and January 2009 they identified TB events in patients who had been on HAART for two years or less.

At baseline, median CD4 was 111 cells/mm3 (IQR: 38-179) in the cohort and 85 cells/mm3 (IQR: 30-149) in patients with TB coinfection. For the whole cohort, 30% were in WHO stage I or II, 40% in stage III and 30% in stage IV (the TB patients had similar proportions).

In the first two years of HAART (almost 13,600 PYFU), there were 360 (4.7%) new TB events (2.65 per 100PY; 95%CI: 2.39 ¬ 2.94). Incidence rates declined with time on HAART. For 0-3, 3-6, 6-12 and 12-24 months they were 9.91 (95%CI: 8.51-11.55), 5.14 (95%CI: 4.11-6.44), 2.16 (95%CI: 1.66-2.82) and 0.82 (95%CI: 0.64-1.05), respectively.

In a multivariate analysis, baseline CD4 count <50 cells/mm3 (HR 1.58; 95%CI: 1.10-2.27; p=0.01) and male sex (HR 1.43; 95%CI: 1.15-1.77; p=0.001) were significantly associated with increased risk for TB.

A key finding of the study is that 100 patients out of 2842 receiving AZT/3TC/efavirenz versus 227 out of 3974 using d4T/3TC/

nevirapine developed TB (832 used other regimens). Compared to the d4T/3TC/nevirapine regimen, the HR for the AZT/3TC/efavirenz was 0.7 (95%CI: 0.53-0.89; p=0.003).

This difference could not be explained by differences in baseline CD4, calendar year starting HAART or immune restoration status after 14 months of HAART. In a multivariate analysis, the HR was 0.67 (95%CI: 0.53-0.86; p=0.002). The researchers further point out that this association occurred despite clinician bias towards prescribing efavirenz to patients with any TB symptoms to avoid subsequent switching due to interactions between nevirapine and rifampicin. This has not been previously described.

Is therapeutic drug monitoring needed in people with MDR-TB taking ofloxacin? This was a question that arose in a small proof of technology study reported by Mugabo and colleagues at Brooklyn Chest Hospital in Cape Town. [15]

Previously, PK values for ofloxacin have been obtained primarily using high performance liquid chromatography (HPLC) from cohorts in rich country. This study tested liquid chromatography coupled with mass spectrometry and found it to be simple, specific, accurate, sensitive and reproducible.

The inclusion criteria for their study included adult patients (18-65 yrs old) on ofloxacin therapy for at least two weeks who had TB that was resistant to isoniazid and rifampicin but sensitive to second line anti-TB drugs (i.e. strict definition of MDR-TB). Pregnant or breastfeeding women, patients intolerant of ofloxacin or patients on any drugs, other than ARVs, known to interact with ofloxacin PK were excluded.

They researchers found that the PK values of their eight patients with MDR-TB on ofloxacin differed from previous studies, with reduced AUC and Cmax, and prolonged T1/2 and Tmax.

Five patients were HIV-positive (one was female and four male). The woman and two men were on HAART (d4T, 3TC and efavirenz). All eight patients received kanamycin, ethambutol, ethionamide and pyrazinamide. None were on capreomycin, aminosalicylic acid and terizidone.

Obviously this is a very small study, but the results are concerning because they suggest MDR-TB patients are receiving sub-optimal doses of ofloxacin. The authors therefore recommend ofloxacin plasma monitoring in order to maintain therapeutic plasma levels. Larger studies of patients with MDR-TB taking ofloxacin are also needed to ensure that optimal dosages and timing are determined, taking into account the effects of HIV, liver and kidney dysfunction.

Bhaijee and colleagues reported on a drug-induced life-threatening condition related to the commonly prescribed anticoagulant warfarin. [16]

The incidence of warfarin induced skin necrosis is low (estimated 0.01-0.1%), and by 2000, only 300 cases had been reported. Most of these were in patients receiving treatment for venous thromboembolism. This study was a retrospective review of six cases that occurred in GF Jooste Hospital in Cape Town from April 2005 to July 2008. This is a high concentration at one facility for such a rare condition. All patients were HIV-positive women (aged 27 to 42) with venous thrombosis and with active TB coinfecton. Four died, likely from systemic sepsis when resistant bacteria infected their wounds and one of the survivors underwent bilateral mastectomies and extensive skin grafting at a specialist centre. Median time from skin necrosis to death was 43 days (range 23-45).

No common pattern was detected: three were on HAART, two had TB-IRIS, two had previous TB. While five had low nadir CD4 counts (range 10-56), one of these (on HAART) has a CD4 count of 396 cells/mm3 at the time of the necrosis. The site of skin necrosis included breasts, buttocks, and thighs.

The authors made four recommendations: (a) active prevention and appropriate management of venous thromboses, (b) parallel heparin therapy for at least the first four days of warfarinisation in patients with venous thrombosis (which they suggest may limit the occurrence of skin necrosis), (c) effective infection control measures, and (d) expedited referral to specialist centres for surgical review for patients who develop this warfarin induced skin necrosis.

Wilkinson and colleagues prospectively analysed their cohort to find immunological differences in drug-sensitive and drug-resistant patients with TB IRIS. [17]

They compared 12 rifampicin-resistant cases (nine had MDR-TB) to 27 case controls. They found no significant differences in the median duration of IRIS, days of HAART to development of IRIS, baseline CD4 count or days of TB treatment prior to HAART between drug-resistant and drug-sensitive groups. They also found no difference between the IFN-gamma spot forming cells/million PBMCs in response to several M. Tuberculosis antigens (ESAT-6, Acr1, Acr2, 38kDa, PPD and heat killed H37Rv). C reactive protein was elevated in both groups, but without significant difference from each other. The authors concluded that both drug-sensitive and drug-resistant TB-IRIS, are clinically and immunologically indistinguishable, and that the occurrence of TB-IRIS is an opportunity to screen for previously undetected drug resistance.

C O M M E N T

While news on TB treatment is hardly breathtaking, some of the studies described above are important and merit further comment.

The model of care described by Atkins, based on the HAART model, demonstrated that there are workable, more affordable and more convenient alternatives to DOT that give patients greater autonomy. It deserves further study, and ideally a randomised trial.

The increased uptake of HAART following TB/HIV integration at Zomba Central Hospital offers further evidence of the importance of

integration. Although the data from this study can be used for advocacy, one caution should be noted: increased uptake could also have been linked to the general improvements in the facility over time.

The Hermans data is important. One limitation of the study is that a complex and potentially error-prone method was used to merge two separate databases containing patient data to determine the number of TB events. Nevertheless, this data offers evidence that efavirenz and AZT reduced the risk of TB compared to d4T and nevirapine. Their findings are worth testing in clinical trials and perhaps the CARINEMO-ANRS 12146 trial will provide more insight, at least regarding nevirapine versus efavirenz. Furthermore, if d4T-including regimens offer less protection against TB, it is another reason to limit their use in southern African countries.

Diagnostics data at IAS were more disappointing. Data on several methods were presented, including, but not limited to, acid-fast stain, urine lipoarabinomannan and the quantiFERON-TB Gold In-Tube assay. In the last of these, one study found an association between indeterminate results and increased risk of disease progression, but these patients also had lower median current and nadir CD4 counts, which are both, probably, better predictors. [18]

However, no studies at IAS showed algorithms with a combination of high speed, sensitivity and specificity.

The problem is global. One Cambodian study analysed sensitivity and specificity of smear and culture of urine, stool and lymph node aspirate as well as blood culture. It found they added little additional value. The authors aptly concluded, "In HIV settings, there is an urgent need for simple methods for mycobacterial cultures to detect earlier smear-negative tuberculosis." [19]

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TREATMENT ACCESS

FDA approval of generic ARVs: over 100 formulations now approved

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

Drug and formulation	Manufacturer, Country	Approval date
3TC tablets 150mg and 300mg	Strides, India	6 August 2009
efavirenz/FTC/fenofovir fixed dose tablet 600mg/200mg/300mg	Matrix, India	12 August 2009
efavirenz/3TC/tenofovir FDC tablet 600mg/ 300mg/300mg	Matrix, India	3 September 2009

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

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 101 since the programme started. An updated list of generic tentative approvals is available on the FDA website:

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

Source: FDA list serve:

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm122951.htm

ANTIRETROVIRALS

CD4 responses after viral suppression for more than 7 years on HAART

Simon Collins, HIV i-Base

An important study published earlier this year, looking at long-term immunological responses after long-term HAART treatment, provided important quantitative data on the limits in CD4 responses experienced by a significant proportion of patients. Median follow-up in the study was 7.5 years (IQR 5.5-9.7) with over 20% patients followed for over 10 years. [1]

This was a study in five US clinic cohorts, that included 366 patients who had maintained viral suppression for at least four years (defined as viral load consistently <1000 copies/mL). Kaplan-Meier analyses were determined by baseline CD4 quartile, with the primary endpoint of time to 'immune restoration' defined as ≥2 CD4 counts higher than 500 cells/mm3.

The median CD4 cell count at the time of starting treatment was 201 cells/mm3 (IQR 72–344) with roughly 25% patients starting with very advanced HIV and 25% starting based on current guidelines (at 350 cells/mm3). The median age was 47 years and 17% were women.

The majority (71%) of patients initiated HAART with a protease inhibitor–based regimen. Approximately half of the cohort was treatment-naive when they started their first HAART regimen. Twelve percent of the population were coinfected with HCV.

Most patients responded well to treatment: the median CD4 cell count after four years of HAART was 560 cells/mm3 (IQR, 390-776).

However, 151 patients (41%) had a CD4 cell count that was less than 500 cells/mm3 at year 4, of whom 61 eventually had a confirmed increase to >500 cells/mm3. Many of the remaining patients remained below this threshold through 10 years of observation.

Results strongly correlated with baseline CD4 count: 95%, 75% and 56% of patients who started treatment at >300, 100–200 and <100 cells/mm3 respectively, were able to achieve a CD4 cell count >500 cells/mm3. Baseline CD4 count also correlated with time to reaching CD4 >500 and inversely with magnitude of the changes in CD4 count.

In multivariate analysis, age was the only factor consistently associated with CD4 cell count increases, with younger patients having greater increases than older patients. HCV coinfection, sex, and pre-HAART nucleoside use were not statistically significant predictors of CD4 cell count increases.

C O M M E N T

One concern with this study was the use, largely for historical reasons, of a high virological cut-off for the definition of virological success (<1000 copies/mL). An analysis using a <50 copy/mL cut-off may show greater long-term benefits as it would be looking at patients with greater suppression, who are also closer to the current standard of care.

These data are nevertheless important at highlighting that baseline CD4 count is closely linked to immunological response. It also supports the widespread recommendation to start treatment prior to CD4 counts dropping <350 cells/mm3.

Although some patients starting at lower levels still achieve strong responses, a minimum CD4 threshold of 300 cells/mm3 optimised the chance of normalising CD4 counts. Many patients starting at <200 cells/mm3 did not achieve counts over 500 cells/mm3, even after 10 years sustained virological suppression on HAART.

Ref: Kelley CF et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment.

Clin Infect Dis. 2009;48:787–794. doi: 10.1086/597093.

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Raltegravir approved in Europe for treatment-naive patients

On 15th September 2009, raltegravir (Isentress) was been granted an expanded licence from the European Union Commission for use in combination with other antiretroviral (ARV) medicinal products for the treatment of HIV-1 infection in adult patients, including adult patients starting HIV-1 therapy for the first time (treatment-naive), as well as treatment-experienced adult patients.

The safety and efficacy of the drug has not been established in patients below 16 years of age.

The EU Commission's decision is applicable to the 27 Member States of the European Union (EU), including France, Germany, Italy, Spain and the United Kingdom as well as to Iceland and Norway.

Source: Merck press release

50mg and 100mg ritonavir doses achieve similar levels of saquinavir in Thai patients

hiv-druginteractions.org

There has long been interest in the possibility of reducing the boosting dose of ritonavir from 100 mg to 50 mg. If the boosted PI exposure remains comparable with a lower dose ritonavir, then there will be potential toxicity benefit as well as economic benefit.

This was a PK study conducted in 20 HIV-infected Thai patients stable for at least 3 months on a regimen containing saquinavir/ritonavir (1500/100 mg once daily) plus 2 NRTI with a viral load <50 copies/ml. A 24-hour PK profile was initially obtained when patients were on 1500/100 mg and then subsequently after 7 days on a reduced ritonavir dose (i.e. 1500/50 mg once daily, ritonavir in liquid formulation). There was no difference in saquinavir PK parameters between the 2 PK days, whereas exposure to ritonavir was significantly reduced due to the dose reduction. The short-term reduction in ritonavir did not show a toxicity benefit.

C O M M E N T

These data are important and highlight the need for a 50 mg ritonavir tablet or capsule rather than the liquid formulation. Additional studies in other patient populations would clearly add weight to the dose reduction strategy.

Source: www.hiv-druginteractions.org

Ref: Van der Lugt J et al. Reducing the boosting dose of ritonavir does not affect saquinavir plasma concentrations in HIV-1-infected individuals. AIDS, 2009, 23(9): 1176-1178.

Etravirine (Intelence) label change in the US due to severe hypersensitivity reactions

In August, Tibotec in cooperation with the U.S. Food and Drug Administration, issued a Dear Healthcare Professional letter to relay important, updated prescribing information for etravirine (Intelence). This relates to an important safety update regarding severe skin and hypersensitivity reactions.

The Dear Health Professional Letter is online at:

http://www.tibotectherapeutics.com/tibotectherapeutics/documents/INTELENCE_DHCP.pdf

The text of the letter appears below:

IMPORTANT DRUG WARNING

August 2009

Dear Healthcare Professional:

Tibotec Therapeutics, in cooperation with the U.S. Food and Drug Administration, would like to inform you of an important safety update to the Severe Skin Reactions WARNINGS AND PRECAUTIONS section (5.1) of the etravirine tablets prescribing information.

Specifically, the existing Warning and Precaution regarding Severe Skin Reactions has been strengthened to reflect that there have been postmarketing reports of:

- fatality due to toxic epidermal necrolysis (TEN)
- hypersensitivity reactions, sometimes accompanied by hepatic failure

Additionally, Guidance has been added that etravirine should be immediately discontinued when signs and symptoms of severe skin or hypersensitivity reactions develop. Given the clinical relevance of these adverse reactions, the following information regarding severe skin and hypersensitivity reactions has been included in the etravirine Prescribing Information:

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. In Phase 3 clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving etravirine compared to 0.2% of placebo subjects. A total of 2% of HIV-1-infected subjects receiving etravirine discontinued from Phase 3 trials due to rash [see Adverse Reactions (6)]. Rash occurred most commonly during the first 6 weeks of therapy.

Discontinue etravirine immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction.

In addition, the following sections of the etravirine Prescribing Information have been updated to include this new information.

Clinical Trials Experience

In Phase 3 studies, the most frequently reported adverse drug reaction of at least Grade 2 in severity was rash (9.0%). Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme were reported in < 0.1% of subjects during clinical development with etravirine. In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy, and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy. A total of 2% of HIV-1 infected subjects in Phase 3 trials receiving etravirine discontinued due to rash.

Overall, the cases referenced above within clinical and post-marketing experience illustrate the importance of clinical vigilance and familiarity with the signs and symptoms of severe skin rash and hypersensitivity reactions. Additionally they also underscore the **importance of immediate discontinuation of etravirine in cases where severe rash or hypersensitivity reaction is suspected.**

Enclosed, [see] the updated Prescribing Information as well as the Patient Package Insert.

Please see etravirineIndication and additional Important Safety Information included on page 3 and page 4 of this letter.

Tibotec Therapeutics is committed to ensuring that etravirine is used safely and effectively and providing you with the most current information for our products.

Should you have any questions, require further information on product safety, or wish to report adverse patient experiences, please contact Tibotec Therapeutics Medical Information.

Please the full Prescribing Information for more details.

Source: FDA list serve (26 August 2009)

http://www.fda.gov

DRUG INTERACTIONS

Raltegravir trough levels reduced by etravirine may require use of TDM

www.hiv-druginteractions.org

Several pharmoacokinetic studies have reported a negative impact on raltegravir trough concentrations when used in combinations that include etravrine.

A letter published in the 27 April 2009 issue of the publication AIDS, from Amélie Ménard and colleagues, detailed four cases where significant reductions in trough levels of raltegravir were identified in patients who added or included etravirine in their antiretroviral combination. [1]

These cases suggest that TDM should be used for patients using both drugs together and that the significance of the interaction may be clinically important in some patients.

The Liverpool HIV drug interaction group [2] summarised these cases:

"The first case had raltegravir trough concentrations of 189 and 313 ng/ml on two occasions whilst on darunavir/ritonavir, enfuvirtide and raltegravir. After switching enfuvirtide for etravirine, raltegravir trough concentrations decreased to 10 ng/ml and then to 5 ng/ml one month later. The second case started a combination of tenofovir/emtricitabine, etravirine and raltegravir. Tenofovir trough concentrations were in the expected range, but raltegravir trough concentrations were considered low (30 ng/ml). Increasing raltegravir from 800 mg/day to 1200 mg/day resulted in an increase in trough concentration (67 ng/ml). The third case had low raltegravir trough concentrations on two occasions (12 and 9 ng/ml) whilst receiving darunavir/ritonavir, etravirine and raltegravir. The final case switched to tenofovir, etravirine and raltegravir. Etravirine trough concentrations were within the normal range, but raltegravir trough concentrations were low (29 ng/ml).

In all these cases, raltegravir concentrations were below the mean trough concentration previously observed in initial clinical trials (63 ng/ml, range 29-118 ng/ml. [3]

In two of the cases, concentrations were below the in vitro IC95 for raltegravir of 14.6 ng/ml.

An interaction study in healthy volunteers showed that coadministration of raltegravir and etravirine decreased raltegravir trough concentrations by 34%, with minimal effect on AUC and Cmax (~10% decrease). In this study the authors concluded that no dose adjustment for either drug was necessary. [4]

However, given the wide inter-individual variability in the pharmacokinetics of raltegravir and these reports from HIV-positive subjects, a more cautious approach may be required.

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Lopinavir/r affects PK exposure of some antimalarial drugs

www.hiv-druginteractions.org

This study investigated the pharmacokinetics (PK) of the antimalarial combination artemether/lumefantrine when administered with lopinavir/ritonavir (LPV/r) in HIV-uninfected healthy volunteers. Ten participants completed having received standard 6-day treatment courses of artemether/lumefantrine (80/480 mg twice daily) on days 1-4 and 28-31. LPV/r (400/100 mg twice daily) was administered on days 16-41 after a 2-week washout period. Plasma concentrations of lumefantrine, artemether, dihydroartemisinin (DHA, artemether metabolite), lopinavir, and ritonavir were measured.

The PK of lumefantrine was influenced by LPV/r resulting in 2-3-fold increases in AUC (AUC0-264, 413 versus 931 h.μg.mL; AUC0-inf, 456 versus 1073 h.μg.mL). For artemether, a trend towards an AUC decrease (42.7-62.0 versus 25.9-40.5 h.ng.mL) was noted during coadministration. For DHA, a decrease in AUC (190-198 versus 104-109 h.ng.mL) was observed during coadministration without changes in DHA:artemether AUC ratios. The pharmacokinetics of lopinavir or ritonavir were not affected by artemether/lumefantrine.

These are important data for a complex interaction. Overall the authors conclude that coadministration of artemether/lumefantrine and LPV/r can be carried out for patients coinfected with malaria and HIV. Indeed, they suggest that the increase in lumefantrine AUC may be beneficial in the treatment of malaria. However, formal safety analysis of concomitant therapy should be addressed by future studies among individuals living in malaria-endemic regions.

Source: www.hiv-druginteractions.org (July 2009)

http://www.hiv-druginteractions.org/new/Content.asp?ID=441

Ref: German P et al. Lopinavir/ritonavir affects pharmacokinetic exposure of artemether/lumefantrine in HIV-uninfected healthy volunteers. J Acquir Immune Defic Syndr. 2009, epub ahead of print.
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Darunavir/r increases exposure to nevirapine

www.hiv-druginteractions.org

Dailly and colleagues used data from a TDM program and a population PK approach to examine the influence of coadministered drugs on nevirapine pharmacokinetics. The cohort was small (51 patients) but in the final one compartment model there was relationship between nevirapine clearance and the presence of darunavir in the regimen.

In summary, there was a significant decrease in clearance (CL/f, 3.84 ± 0.92 vs 2.76 ± 1.00 L/h) and an increase in the mean nevirapine trough plasma concentrations (3.68 ± 1.69 vs 5.35 ± 3.20 mg/L) in combination with darunavir.

The limitations of the study are that it is TDM data and small numbers. The advantage is that these are results obtained with the recommended twice daily dose of darunavir/ritonavir (600/100 mg) rather than the lower doses (300/100 or 400/100 mg) used in the early interaction studies.

Source: www.hiv-druginteractions.org (July 2009)

http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=441

Ref: Dailly E et al. Influence of darunavir coadministration on nevirapine pharmacokinetics in HIV-infected patients: a population approach. HIV Med, 2009, epub ahead of print.
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Interaction between Ginkgo biloba and efavirenz

www.hiv-druginteractions.org

Data on interactions with antiretrovirals and herbal preparations are scarce and it can be difficult to predict whether there will be a clinical effect from in vitro studies.

This case report describes a possible interaction with efavirenz and *Gingko biloba*. The patient had been on an antiretroviral regimen of tenofovir/emtricitabine and efavirenz for two years and had achieved an undetectable viral load. However, virological failure developed and upon questioning it was found that the patient had been taking *Gingko biloba* for several months. Efavirenz concentrations were determined in stored plasma samples and showed decreasing concentrations that coincided with increasing

viral load. The patient was successfully switched to alternative antiretrovirals.

Although the exact mechanism of the interaction remains unresolved, the authors propose that *Gingko biloba* extract (principally the terpenoids) may lower efavirenz plasma levels by the induction of CYP3A4 and P-gp.

Gingko biloba is a widely used herbal drug and is commonly used because of its assumed beneficial effects on concentration, memory, dementia and depressive disorders.

Source: www.hiv-druginteractions.org (June 2009)

http://www.hiv-druginteractions.org/new/Content.asp?ID=438

Ref: Wiegman DJ et al. Interaction of Ginkgo biloba with efavirenz. AIDS, 2009, 23(9): 1184-1185.
http://www.ncbi.nlm.nih.gov/pubmed/19451798

Use of raltegravir in HIV-positive transplant recipients

www.hiv-druginteractions.org

Tricot and colleagues performed a retrospective review of the outcomes of 13 HIV-infected transplant patients treated with a raltegravir (RAL) and two nucleoside reverse transcriptase inhibitor (NRTI) regimen. Tolerability, ARV efficacy (plasma viral load, CD4 cell count), drug interactions, raltegravir pharmacokinetics and transplant outcome were assessed.

Thirteen patients with liver (n=8) or kidney (n=5) transplantation were included. RAL was initiated (400 mg twice daily) either at time of transplantation (n=6), or after transplantation (n=7). Median raltegravir trough concentration was 507 ng/ml (range, 176-890), which is above the in vitro IC95 for wild type HIV-1 strains (15 ng/ml). Target trough levels of tacrolimus or ciclosporin were obtained with standard doses. There were no episodes of acute rejection and HIV infection remained controlled. After a median follow-up of 9 months (range, 6-14), all patients were alive with satisfactory graft function.

There was no evidence of an interaction between raltegravir and the immunosuppressants, and therefore, the use of an raltegravir + two NRTI-based regimen is a good alternative in HIV-infected patients undergoing solid organ transplantation.

Source: www.hiv-druginteractions.org (July 2009)

http://www.hiv-druginteractions.org/frames.asp?new/Content.asp?ID=442

Ref: Tricot L et al. Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. Am J Transplantation, 2009, 9: 1-7.
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BASIC SCIENCE

Recent basic science updates from Richard Jefferys excellent web log.

Trends in Immunology: free access issue on immune senescence

Richard Jefferys, TAG

The journal Trends in Immunology has published a special issue on immune senescence. [1]

Access to all articles is being offered free of charge thanks to the sponsorship of the National Institutes of Health (www.nih.gov). The parallels between immune senescence in uninfected elderly individuals and people with HIV are increasingly well-recognised and include.

- Depletion of naive CD4 and CD8 T cells
- Involution of the thymus and decreased thymic output
- Skewing of the CD4:CD8 T cell ratio
- Accumulation of dysfunctional CD8 T cells lacking the CD28 co-stimulatory molecule
- Decreased responses to new immunisations
- Decreased recall (memory) T responses to common antigens

Research into immune senescence and its association with illness and mortality has gained considerably more attention recently, and may have the potential to offer important insights into the pathogenesis of HIV infection. Additional background on the topic, along with a link to a webcast presentation by immune senescence expert Rita Effros, can be found in a post from January of this year: “Accelerated Aging of the Immune System in HIV Infection”.

Source: TAG basic science project (13.08.09).

http://tagbasicscienceproject.typepad.com

Ref: Trends in Immunology, Volume 30, Issue 7, 7 July 2009.

http://www.cell.com/trends/immunology/issue?pii=S1471-4906(09)X0007-4

Low viral loads in elite controllers

Richard Jefferys, TAG

Several years ago, Bruce Walker and colleagues from Partners AIDS Research in Boston launched the largest ever effort to research immunological control of HIV infection, the international HIV controllers study. [1]

The project is now proceeding under the aegis of the new Ragon Institute of Massachusetts General Hospital, created recently thanks to the generous support of the Ragon family. [2]

The HIV controllers study is collecting blood samples from both elite controllers, defined based on having a viral load less than 50 copies in the absence of any treatment, and viremic controllers, defined based on a viral load of between 50 and 2000 copies/mL in the absence of treatment. A number of papers have been published already describing results from the study, and the latest has just appeared online in the Journal of Infectious Diseases.

The purpose of this investigation was to quantify the level of viral load among elite controllers using an ultra-sensitive assay that can measure down to a single copy/mL of HIV RNA. [3]

Among 90 individuals studied, the median viral load level was 2 copies/mL. A longitudinal analysis of a subset of 31 participants demonstrated that 2-5-fold fluctuations in viral load were common. For the first time, the researchers were also able to document a significant inverse correlation between the breadth and potency of neutralising antibody responses against HIV and the level of viral load detected; previous studies using less sensitive viral load assays did not reveal this association. The breadth and magnitude of HIV-specific CD8 cell responses, as measured solely by interferon-gamma production, did not show a correlation with viral load at these low levels.

An analysis of the relationship between viral load and the slope of CD4 decline was also conducted. The median time for which multiple CD4 measurements were available was 3.6 years (range 1 – 17.3), and the median number of measurements per person was seven. Although immune activation has previously been associated with CD4 cell declines in elite controllers, [4] in this analysis the median value of the slope per year was +11 cells/mm3.

Due the limited duration of follow up and number of measurements, the researchers note that in many cases the values were not significantly different from zero, indicating CD4 T cell counts were essentially stable over time. To try and get a better sense of which participants might be experiencing significant changes in CD4 counts, the researchers subsequently focused on individuals whose slopes were statistically different from zero. These analyses revealed that 5 out of 27 individuals (19%) with viral load levels less than 1 copy/mL experienced significant CD4 cell count increases over time. The same was true for only 3 out of 50 individuals (3%) with HIV viral loads greater than 1 copy/mL. Conversely, 8 individuals experienced significant CD4 cell declines, and all showed viral load levels over 1 copy/mL. An overall examination of the link between viral load level and CD4 cell count slope showed a weak but significant correlation, with higher viral loads associated with CD4 cell decline (r=-0.23; p=0.04).

Overall, the results suggest that the use of a viral load assay that is 250-fold more sensitive than those currently commercial available can reveal important information regarding elite control of HIV.

Source: TAG Basic Science web log (11.08.09)

http://tagbasicscienceproject.typepad.com

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Immune surveillance below the radar: study offers explanation for acyclovir's failure to reduce HIV risk

Richard Jefferys, TAG

In a recent post on the Merck vaccine trial, I mentioned a new study from Larry Corey's research group addressing the relationship between HSV-2 infection and enhanced susceptibility to HIV. [1]

The data were presented by Corey at the Keystone conference in March and were published online by Nature Medicine on 2 August 2009. [2]

The background to the work is that HSV-2 infection has been consistently associated with a 2 to 3-fold increased risk of acquiring HIV; a meta-analysis published in 2006 reported a relative risk of 3.1, 2.7 and 1.7 for women, heterosexual men and men who have sex with men, respectively. [3]

Recently analysed data from the Merck vaccine trial are consistent with these findings in that HSV-2-infected participants were found to have approximately double the risk of acquiring HIV infection during the study.

The mechanism by which HSV-2 infection increases HIV acquisition risk is not so clear, however, and has been the subject of debate. The general view is that local inflammation and damage to the integrity of the genital mucosa are plausible ways that HSV-2 infection may increase the chances of HIV transmission. This view led to the logical proposition that suppressing HSV-2 with chronic acyclovir treatment might be a means to also reduce the risk of HIV acquisition. Several large trials have now explored this hypothesis and, while acyclovir treatment was effective at reducing symptomatic HSV-2 reactivations, it did not reduce the incidence of HIV infection.

The new study from Larry Corey's laboratory set out to try and shed light on these trial results. The same group of researchers has previously shown that immune surveillance of HSV-2 is a far more active process than many had surmised. In a 2007 paper in the Journal of Experimental Medicine, they demonstrated that HSV-2-specific CD8+ T cells gather at sites of subclinical HSV-2 reactivation in the genital skin and persist for at least several months after HSV-2 DNA is no longer detectable. [4]

A year later in the Journal of Infectious Diseases, they published results of an intensive study in which participants took oral and anogenital swabs four times a day for 60 days. Analysing the swabs for HSV-2 DNA, the researchers found that subclinical reactivations were frequent and typically lasted less than 12 hours, showing that there is an ongoing and dynamic effort on the part of the immune system to keep HSV-2 suppressed. [5]

These findings led the researchers to suspect that perhaps elevated levels of activated HSV-2-specific CD4 T cells would be present in the genital mucosa even during chronic acyclovir treatment, and this is exactly what they report in the Nature Medicine paper. The study initially took biopsies of genital skin during an acute, clinically symptomatic lesion and 2, 4 and 8 weeks after healing. Four participants subsequently initiated chronic suppressive acyclovir treatment at the start of their next symptomatic episode and had biopsies taken at 2, 4, 8, 16 & 20 weeks after healing. In all cases, control biopsies were obtained from an unaffected area of genital skin at each timepoint. [2]

During an acute HSV-2 lesion, the researchers found a "massive localised infiltration" of cells. Mean numbers of CD4 and CD8 T cells per mm2 of skin were 655 and 618, respectively, compared to 68 and 55 per mm2 of the unaffected skin sample. Although follow-up biopsies documented gradual clearance of HSV-2 and a decline in inflammation, elevated numbers of CD4 and CD8 T cells remained present locally for months. Eight weeks after healing, a median of 8-fold more CD4 T cells were present at the affected versus the unaffected site. Furthermore, even after 20 weeks of acyclovir treatment, the number of CD4 T cells remained significantly elevated. Additional analyses illustrated that the majority of these CD4 T cells expressed CCR5 and their presence was also associated with a significant increase in the numbers of DC-SIGN-expressing dendritic cells. The enrichment of CCR5-expressing CD4 T cells and DC-SIGN-expressing dendritic cells at the former lesion site was not significantly altered by chronic acyclovir treatment.

The researchers acknowledge in the conclusion to the paper that the number of participants was small, but nevertheless state: "we feel that our central finding – that HSV reactivation leaves a residual inflammatory response not appreciated clinically – is typical of HSV-2 genital lesions." They also note that "the wide anatomical distribution of HSV-2 in the male and female genital tract underscores the importance that these localized reservoirs of inflammatory cells are likely to have in HIV acquisition."

Source: TAG Basic Science web log (03.08.09)
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Low-level HIV replication versus latency: identifying the source of viral rebounds during treatment interruption

Richard Jefferys, TAG

In HIV research, there is a persistent and vigorous debate around the question of whether or not viral replication persists in the face of successful antiretroviral therapy. During a plenary session at the International AIDS Conference in Mexico City in August 2008, Bob Siliciano made a compelling argument that, in most cases, antiretroviral therapy completely shuts down virus production. [1]

Now, a paper in PNAS provides additional support for this view. [2]

Beda Joos and colleagues evaluated a staggering 1,753 genetic sequences from the envelope region of HIV, sampled over the course of a treatment interruption trial known as SSITT (Swiss-Spanish Intermittent Treatment Trial). The study design involved a series of two-week treatment breaks followed by a prolonged interruption (therapy was subsequently reinitiated according to the CD4 and viral load thresholds used in current treatment guidelines).

The researchers used the sequence data to plot the relationships between the different viruses, using a technique called phylogenetic analyses. For each study participant analysed, the sequences were used to define "the most recent common ancestor" (MRCA), which is an approximation of the ancestral virus sequence from which all the others derived. Viruses that appeared during treatment interruptions (TIs) were then compared to the MRCA, to see if the sequences suggested that there had been ongoing replication and evolution while the study participants were on ART. The results showed that the rebounding viruses during TI were actually more distant from the MRCA than the viruses detected when the participants first entered the study. The researchers conclude: "the striking lack of a temporal relationship between rebounding virus and pretreatment viruses strongly suggests that rebounding virus originates from reactivated, latently infected cells rather than from a cellular pool or compartment engaged in low-level replication."

Source: TAG Basic Science web log (20.11.08)

http://tagbasicscienceproject.typepad.com

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C O M M E N T

Although this paper and the blog summary was published at the end of last year this is one of the most important, yet least appreciated, aspect of treatment, so data from another study is very helpful.

Although not reported in these studies, it also implies that HIV isn't being seeded from CNS or genital compartments - ie for most people it may also be controlled in these sites.

BHIVA

Detention and removal of HIV-positive people in the UK

In June 2009, BHIVA launched a new resource, produced with National AIDS Trust, called 'Detention, Removal and People Living with HIV'.

This resource provides best clinical practice guidance to support high-quality care for detainees living with HIV in Immigration Removal Centres (IRCs). The booklet, attached, was developed in collaboration with IRC healthcare managers, GUM clinicians that work with local IRCs and community organisations that work with detainees.

The booklet is a useful resource for anyone supporting the HIV treatment, care and support needs of detainees while in detention and during the removal process.

In producing this resource, NAT and BHIVA state that they are not endorsing the policies of detention or removal of HIV positive asylum seekers from the UK. Instead they are aiming to ensure that when detention or removal does occur, the needs of detainees are taken fully into account and the best possible care is provided.

NAT continues to oppose the removal of HIV positive asylum seekers to countries where HIV treatment is not accessible.

PDF download:

http://www.nat.org.uk

For print copies please contact Jane Hillier at NAT:

jane.hillier@nat.org.uk

CORRESPONDENCE

To the editor:

Following the publication of the editorial in the July/August 2009 edition of HIV Treatment Bulletin (Vol 10, No. 7/8), we would like the opportunity to respond to the content and also some of the comments made.

Firstly, the flow diagram (referred to as Example 2: Flow Diagram B) included in the editorial, is not the version that is currently being used by our Directorate. The flow diagram was designed to assist in the triage of patients who contacted our unit by telephone, within the context of increasing demand during an emerging influenza pandemic. It is not being used for patients who have actually attended our unit, all of whom are seen by a clinician and undergo assessment and diagnostic testing where appropriate.

Furthermore, the flow diagram represents only part of our pandemic (H1N1) 2009 clinical guidance package for our HIV clinicians. Thus, without including our clinical guidelines 'which clearly remind clinicians to consider pandemic (H1N1) 2009 infection whilst not attributing all presentations of flu-like or non-specific febrile symptoms to infection with influenza virus' the triage tool can be taken out of context and perhaps appear to oversimplify the assessment of such patients.

In comparison with the Birmingham Heartlands Hospital flow diagram (Example 1), we elected not to include a history of contact with a case of 'swine flu' in our flow diagram. In line with national and international guidelines during a period of sustained transmission of pandemic (H1N1) 2009 in the community, the absence of contact with a known or suspected case is no longer considered to be helpful in assessing the likelihood of a patient being infected with pandemic (H1N1) 2009. At out unit, only one patient in our existing cohort of patients with confirmed pandemic (H1N1) 2009 had an appropriate contact/exposure history.

We feel that the comment „a caution with this option is that a patient with a life-threatening condition who thought they had flu could end up going down the left-hand "no further action route", is inaccurate and may alarm our patients. Every endpoint in our telephone triage flow diagram results in the patient obtaining medical advice, rather than "no further action". Potentially life-threatening conditions that are not flu-related can occasionally present with early symptoms suggestive of uncomplicated influenza, and this is a risk associated with existing local, national and international pandemic influenza management algorithms, including both of the flow diagrams published in the editorial. In the context of an established pandemic, for our patients who make contact by telephone and don't have risks for, or symptoms of, severe pandemic (H1N1) 2009 disease, but in whom uncomplicated influenza is thought to be a possibility, we advise them to contact their GP or the National Pandemic Flu Service for further assessment, with the additional advice that they should attend hospital if they deteriorate or fail to improve.

The risk factors for developing severe pandemic (H1N1) 2009 disease are not yet completely defined; therefore we chose to adopt the list of medical conditions used by the Department of Health and several other health advisory bodies around the world. Such lists are subject to change as more information on cases from the first wave becomes available. For example, although pregnancy and asthma appear to be significant risk factors, reanalysis of initial data from the United States, which suggested that morbid obesity is a significant risk for severe pandemic (H1N1) 2009 infection, demonstrates that morbid obesity may not in fact be a significant risk in their population overall. As accurate risk identification is often a retrospective exercise, we chose to follow the best available

evidence and consensus expert opinion on possible risk factors for severe disease during the first wave of the pandemic.

Algorithms such as these are difficult to develop and are subject to review in order to adapt to an evolving pandemic with predicted separate waves of varying disease activity. They are designed to facilitate the rapid assessment of a potentially large number of patients presenting with symptoms that may be consistent with pandemic influenza, whilst recognising that the same symptoms can also occur with many conditions seen in HIV-infected individuals. As we come to the end of the first wave of the pandemic, we have managed to assess the majority of our patients presenting with flu-like symptoms in person. However, the situation may clearly change during the predicted second wave, which is expected to affect a greater proportion of the UK population and place significantly increased demands on healthcare services. As such, we would fully support the refinement of existing guidelines and algorithms, along with a collaborative effort to pursue a uniform and safe approach to the assessment of possible pandemic (H1N1) 2009 infection in HIV-infected patients across the UK.

Yours Sincerely,

Dr Jake Dunning and Professor Brian Gazzard

Department of HIV and Genitourinary Medicine

Chelsea and Westminster Hospital Foundation Trust.

.....

editor's reply

The inclusion of the C+W diagram was only included as an example of a telephone triage tool for other clinics to start from, and was seen in context by Professor Gazzard in draft form prior to publication.

The provision of two examples was not meant to reflect any difference in clinical responses resulting from the two different solutions, and we are sorry if this impression was given. They were both included to highlight how two clinics, both with expertise in HIV and the swine flu epidemic, interpreted differently the limited available data.

It would clearly be preferable for clinics to agree on one protocol, with appropriate caveat where difference remain, and we hoped this might have been possible prior to this issue of HTB going to press. This would be the most useful outcome for HIV-positive patients on a national level.

The latest version of the C+W diagram is posted to the i-Base website at:

http://www.i-base.info

ON THE WEB

Conference reports and online abstracts:

5th IAS Conference on HIV Pathogenesis, Treatment and Prevention

19-23 July 2009, Cape Town

The conference website includes all abstracts and many PDF or powerpoint slides of posters and oral presentations, together with a limited amount of webcasts.

http://www.ias2009.org

Reports and journals:

Access to HCV treatment in Eastern Europe

A new report on access to hepatitis treatment in Eastern Europe and Central Asia, "Shining a Light on a Hidden Epidemic", was published on 18 August 2009 by the Open Society Institute.

The publication aims to raise awareness and promote advocacy among patients, civil society groups, government officials, multilateral organisations and funding mechanisms (such as the Global Fund), and the pharmaceutical industry.

The report is online and available in English and Russian language editions from the Harm Reduction website:

In English:

http://www.harm-reduction.org/images/stories/documents/links/hepc_osi_en.pdf

In Russian:

http://www.harm-reduction.org/images/stories/documents/links/hepc_osi_ru.pdf

Community resources and publications:

Guide to HIV and hepatitis B coinfection

The Guide To Hepatitis B For People Living With HIV is now available. This guide provides information on the prevention, care, and treatment of HBV, and the impact of HBV on HIV disease. It is designed to be accessible to people with no medical training. Where medical terms are used, they are explained in detailed but simple language.

English and Spanish versions of the Guide are available on-line, at:

http://treatmentactiongroup.org/publication.aspx?id=3174

Hard copies of the Spanish and English versions are available at no charge. They can be ordered on-line at:

http://treatmentactiongroup.org/form.aspx?ekfrm=94

Please send any comments to:

Lei.Chou@treatmentactiongroup.org

TAG pipeline report

TAG's annual Pipeline Report surveys the developments in medicines and diagnostics most likely to improve the lives of people living with HIV, viral hepatitis, and tuberculosis within the next few years.

The report also identifies critical gaps where research is falling short of the need for better tools to manage these diseases.

http://www.treatmentactiongroup.org/publication.aspx?id=3212

Medical resources:

New TB website and resource

The Stop TB Partnership have launched a new website resource focussed on eEvidence-based Tuberculosis diagnosis:

http://www.tbevidence.org

Several agencies, groups and individuals have contributed to the development of the site that provides a comprehensive single source of evidence syntheses, policies, guidelines and research agendas on TB diagnosis. It provides access to published systematic reviews on TB diagnostics (grouped by various test types or platforms), the relevant policies, guidelines and research agendas on TB diagnosis, and several reports, monographs and training modules and slide presentations on TB diagnostics.

The website also provides guidance on how to conduct and report diagnostic TB research, on how to perform systematic reviews of diagnostics, tools on guideline development, including GRADE, and documents on improvement of laboratory quality and practice. Up to date information on the current TB diagnostics pipeline is also provided, along with SOPs and package inserts for several tests, and specimen banks and databases. All information is provided as open access, with no registration or fee requirements.

This new website resource addresses a long-standing need for a single portal that compiles all critical evidence on TB diagnosis, along with relevant policies and guidelines for clinicians, health professionals and policy makers.

Patient resources:

HIV and the kidneys

An excellent new overview of side effects and complications with HIV and the kidneys is included in the July edition of the CATIE Treatment Update (Number 174).

http://www.catie.ca/tu.nsf
Sections include:

- The kidneys
- Drugs and the kidneys
- HIV and the kidneys – a look over time
- Cystatin C for monitoring kidney health
- Comparing viruses – HIV and hepatitis C in mostly men
- The kidneys and hep C in women
- Age, tenofovir and the kidneys
- A large study looks at tenofovir and kidney health

Video news: online resource

TheBody.com has developed a new format TV-news style resource to supplement it's other non-technical resources.

http://www.thebody.com/content/art53518.html
The September issue includes:

- H1N1 (swine flu) and HIV news and predictions
- Why drinking heavily may be particularly risky for HIV-positive people.
- Why even treated genital herpes sores can increase HIV risk.
- How Senator Edward M. Kennedy contributed more to the fight against HIV/AIDS than any other politician.

FUTURE MEETINGS

2009/10 conference listing

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

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

8-9 October 2009: BHIVA autumn meeting, London.

http://www.bhiva.org

26-28 October 2009: 11th Intl Worshop on Adverse Events and Lipodystrophy, Philadelphia, USA.

https://lipo09.events-register.com

29 October-1 November 2009: 47th IDSA, Philadelphia.

http://www.idsociety.org

11-14 November 2009: 12th EACS, Cologne.

http://www.eacs-conference2009.com

16-19 February: 17th CROI

http://www.retroconference.org/2010

8th European Drug Resistance Workshop

17-19 March 2010, Sorrento, Italy

http://virology-education.com

11th International Workshop on Clinical Pharmacology of HIV Therapy

7-9 April 2010, Sorrento, Italy

http://virology-education.com

6th International Workshop on HIV and Hepatitis Co-Infection

June 2010, Israel. The date and venue tbc.

http://virology-education.com

5th International Workshop on Hepatitis C - Resistance and New Compounds

and 5th International Workshop on Clinical Pharmacology of Hepatitis Therapy

June 2010, Boston, USA. The dates and venue tbc.

http://virology-education.com

5th International Workshop on HIV Transmission - Principles of Intervention

15-16 July 2010, Vienna, Austria. Venue tbc.

http://virology-education.com

2nd International Workshop on HIV Pediatrics

16-17 July 2010, Vienna, Austria, Venue tbc.

http://virology-education.com

3rd International Workshop on Clinical Pharmacology of Tuberculosis Drugs

September 2010, USA. Date and venue tbc.

http://virology-education.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Board (UK-CAB), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

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

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

RSS news feed has been introduced for HIV Treatment Bulletin for web and PDA access - we welcome your feedback on this new way to provide treatment updates.

A section on Education, Advocacy and Training includes our training manual for advocates with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 6000 pages are served from the site each day.

i-Base announcements list

A free email News and Announcements list. By subscribing you can be kept up-to-date on new and revised publications from i-Base. This is an announcement only list with low traffic, mainly to announce new and updated publications and services. Messages will contain a link to a PDF file of the publication and/or a link to the web version.

To subscribe please fill out the form at this link:

http://www.i-base.info/forms/newssub.html

Training manual – revised, updated and now fully online

This established training resource has been revised and updated and is now online in new format.

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

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

Additional support material is included on how to understand aspects of science that might be new to a lay reader.

http://www.i-base.info/manual/en/index.html

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to antiretrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. Clinical trial design and the role of advocates

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

Generic clinic forms

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.

These PDF files include record sheets to track CD4 and viral load results, cardiovascular risk, hepatitis, first patient visit, patient update, day case and summary notes.

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

Please contact the i-Base office if you would like help adding your own hospital or Trust logo to these forms.

Report assessing the treatment information needs African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://www.i-base.info/pdf/africantreatmentneeds.pdf

i-Base Book: "Why we must provide HIV treatment information"

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over six years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A recent meeting, held in Cape Town earlier this year, focused on how to raise the profile of treatment literacy. One result from the meeting is a publication "Why we must provide HIV treatment information".

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting since 2002. It now includes over 300 members form over 100 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. Membership is free,

http://www.ukcab.net

World CAB - reports on international drug pricing

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online.

Both are available to download as a PDF file from the i-Base website.

http://www.i-base.info/wcab/index.html

Introduction to combination therapy

June 2009 edition

This non-technical patient guide to treatment explains combination therapy, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance.

Printed and/or PDF versions of earlier versions of this booklet are available in other languages.

Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support

March 2009 edition

This is a new i-Base guide. It is a non-technical patient guide to Hepatitis C and coinfection with HIV.

This booklet mainly covers treatment related aspects of coinfection including transmission, natural history, tests and monitoring, HCV treatment and side effects, research into new drugs and living with coinfection. It also includes contributions from a wide range of people with direct experience of coinfection. The online version of this guide includes additional text.

Guide to changing treatment: what to do when your treatment fails

September 2008 edition

This is a non-technical patient guide to changing treatment, drug resistance and what to do if treatment fails. It is updated to include recent advances in new treatments and strategies, especially in relation to use of new and expanded access treatments.

This booklet helps patients in discussions with doctors, and covers what can be done if viral load starts to rise, and the importance of considering or finding out why the current combination failed, treatment strategies and new pipeline treatments.

Guide to HIV, pregnancy & women's health

January 2009 edition

Updated and revised, this patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether on therapy or not and includes information for the mothers health and for the health of the baby.

The guide gives information on medication, Caesarean section and breastfeeding, as well as details of other sources of help. It is aimed at people in a wide range of circumstances including positive women thinking about having children and pregnant women who have recently been diagnosed HIV-positive.

Guide to avoiding & managing side effects

May 2008 edition

This is a comprehensive 72-page A5 guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on all information.

http://www.i-base.info/about/downloads.html

Languages currently include:

Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian and Spanish.

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published 10 times a year in a printed version, in a pdf file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

HTB South

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

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

ARV4IDUs

An electronic publication, produced in English and Russian language editions, to provide an overview of research related to antiretroviral treatment and IV drug use.

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

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Online Q&A service

An online 'question and answer' service that now has over 900 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- Worried about facial lipoatrophy, what shall I do?
- Is it OK to take probiotic cultures with HIV meds?

- Is d4T+3TC+EFV good enough?
- Can I take zyban pills to stop smoking if im on HIV treatment?
- Could Hunt's syndrome have affected my CD4 count?
- What would happen if somebody starts with 0 CD4 count and on entry inhibitor?
- Is it safe for a man to give oral sex to a woman?
- Can this person receive free treatment in the UK?
- Do I have a natural resistance to HIV?
- Questions about HIV and swine flu in the UK
- Can I fast?
- Is this AIDS dementia?
- Can I use minoxidil 5% scalp solution if I'm on HIV treatment?
- Could melanotan injections have stopped my ARVs from working?
- Do melanotan injetions interfere with my ARVs?
- Will Immunoxel and dermavir patches be available in the UK?
- How to remove genital warts?
- Is it OK to use muscle gain powder?

Find HTB on AEGiS

AEGiS.org - the longest established and largest global resource of online HIV information - includes HTB in the regular journals that it puts online. You can find us at:

http://www.aegis.org/pubs/i-base/2009

The AEGiS daily email news service also carries i-Base conference reports.

Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

http//www.i-base.info/forms

Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), HTB South, Treatment 'Passports' and all our guides to managing HIV and additional reports.

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website: http://www.i-Base.info; by fax or post using the form on the back page by sending an email to: subscriptions@i-Base.org.uk

Editor: Simon Collins

Contributing Editor: Polly Clayden

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

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

HIV i-Base
Third Floor East
Thrale House
44-46 Southwark Street
London SE1 1UN
T: +44 (0) 20 7407 8488
F: +44 (0) 20 7407 8489

http://www.i-Base.info

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HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

However, any donation that your organisation can make towards our costs is greatly appreciated.

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(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA, Sort Code 60-12-14. Account Number: 28007042)

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I do not wish to make a regular donation but enclose a one-off cheque in the sum of _____ instead.

I wish to make a one of donation (minimum £12.50 inc p&p) for the Treatment Literacy Photogrpahy Book £ _____.

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If your employer operates a Give-As-You-Earn scheme please consider giving to I-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit www.giveasyouearn.org

REFUNDS FROM THE TAX MAN

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

Whichever of the above schemes you might chose to donate to i-Base we would like to thank you very much for your support.

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Third Floor East, Thrale House, 44-46 Southwark Street, London SE1 1UN
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HIV 'Treatment Passports' - Booklets for patients to record their own medical history

1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other _____ _____

Guide To HIV, Pregnancy and Women's Health *(January 2009)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

NEW: Introduction to Combination Therapy *(June 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Changing Treatment - Guide to Second-line and Salvage Therapy *(September 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Guide To Avoiding and Managing Side Effects *(May 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Guide To HIV and hepatitis C coinfection *(May 2007)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Translations of earlier treatment guides into other languages are available as PDF files on our website

Phoneline support material *(pls specify required number of each)*

A3 posters _____ *A5 leaflets* _____ *A6 postcards* _____ *Small cards* _____

Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

1 Sheet ☐ **1 pad** ☐ **5 pads** ☐ **10 pads** ☐ **Other** ☐ _____ _____

Please fax this form back, post to the above address, or email a request to HIV i-Base:

020 7407 8489 (fax) subscriptions@i-Base.org.uk