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EDITORIAL

An important focus at CROI this year was the direct impact that current treatment is already likely to be having on reducing transmission.

The results are particularly important given that many treatment programmes in developing countries are under increasing pressure to limit enrollment of new patients, while 70% of people in immediate need of ARVs globally have yet to access them.

When treatment is pitched against prevention for funding, the phase 'we can't treat our way out of the epidemic' is often used, and CROI provided new data challenges this misconception.

Another prominent statement is that 'for every person put on treatment, there are two new infections'.

The CROI data challenges this too, though it has always been flawed logic to link these two unconnected figures.

The numbers accessing treatment are driven by the effectiveness of treatment programmes. Double the programme and the equation equalises. Scale treatment up four times and the impact is reversed: 'for every two people on treatment only one person becomes infected' etc.

When this connection is made it is insidious, because it implies that people on treatment are driving new infections. It is challenging and undermining our right to care. It seeks to connect two broadly different groups of people. New infections are predominantly driven by people who themselves are recently infected but currently unaware of their new HIV status, whereas people on treatment are likely to already have modified risks for onward transmission.

So, post-CROI, based on very conservations data from the PARTNERS and other studies, lets revise the link between treatment and prevention and say clearly that 'every person on treatment prevents at least nine new infections'.

CONFERENCE REPORTS

17th Conference on Retroviruses and Opportunistic Infections (CROI)

16-19 February 2010, San Francisco

Introduction

The 17th Conference on Retroviruses and Opportunistic Infections (CROI), one of the most important annual HIV meetings, was held this year from 16-19 February. As with previous meetings, much of the conference is published online including all abstracts and webcasts of oral presentations including poster discussions.

Making this scientific content available without login or subscription is itself a significant achievement. It is a model for broadening access to medical research to a degree that is currently unmatched by any other meeting.

The webcasts this year include oral presentations, poster discussions, the opening lectures and the pre-meeting set of training workshops for young investigators.

The conference website also includes a searchable abstract database.

We encourage readers to view these lectures directly.

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

http://www.retroconference.org/2010/data/files/webcast_2010.htm

Lectures are also available as audio downloads and podcasts which include slides as audiobooks.

Our first articles covering this meeting are:

- Treatment reduces infections by over 90%: a theme that is here to stay
- ACTG 5205: atazanavir/ritonavir vs efavirenz in treatment naïve patients
- Pipeline compounds and new approaches to treatment
- Clinical benefits of stopping smoking: CVD and CHD risk returns to that of 'previous smoker' in HIV-positive people within three years
- HIV increases the risk of lung cancer, independent of smoking status
- HIV-positive people in the HOPS cohort have 4-fold risk of fracture compared to general population in the US
- Vitamin D deficiencies in HIV management

- OCTANE 2: nevirapine and lopinavir/r are similar when used with tenofovir and FTC in treatment-naïve women
- HIV incidence and retesting in pregnancy
- Efavirenz use in pregnancy and birth outcomes
- Pregnancy outcomes in women using non-AZT HAART in Europe
- When should HAART be initiated in pregnancy to achieve an undetectable viral load?
- Pregnancy outcomes in infants exposed to maternal antiretrovirals in utero
- Maternal TB, HIV and pregnancy

More to follow next issue...

Treatment reduces infections by over 90%: a theme that is here to stay

Simon Collins, HIV i-Base

CROI was important this year because of the profile given to further studies supporting the role of treatment as prevention. Together they support the argument that universal treatment is perhaps the most powerful prevention tool we are likely to have for many years, perhaps with the potential to even eradicate the virus on a population level.

In a lecture prior to the main conference, Brian Williams from the South African Centre for Epidemiological Modelling and Analysis, Stellensbosch, detailed the modeling data for the direct and indirect impact of ARVs on prevention, [1] elaborating on the research paper published last year in the Lancet. [2]

At its most optimistic, this includes the potential for universal treatment to eliminate new infections in South Africa within 5-10 years on a cost neutral budget, at the same time saving millions of lives (and preventing millions of new infections). The science on which the model is based shows an impact on dramatically reducing infections that few can ignore.

The epidemiology for the model included low HIV infectivity (~0.001 per heterosexual encounter), 10-fold individual variability in infectivity, a slow epidemic doubling time (~1-3 years), a long period of potential infectiousness (5-15 years) and an average case reproduction number (~7 additional people infected per case): leading to a calculation showing that virtual eradication of HIV could be achieved if transmission could be reduced by 7-fold.

Viral load is commonly reduced by 10,000 times on treatment, and although infectivity reduces in smaller proportions (roughly in relation to the cube route of viral load), the net impact of treatment on infectivity was estimated to be a 96% reduction.

The impact on reducing TB and for continuous treatment after pregnancy were also included, and for interventions based only on PrEP alone or in combination with ARVs. For South Africa, the model was based on a conservative treatment programme, treating at a CD4 count of 200 cells/mm3, but similar costs and benefits were shown when starting universal treatment at 350, 500 or even at diagnosis. The initial outlay (an adjusted US $60 billion) was compensated by lower cost of hospitalisations and reduced new infections, and saved an additional 3 million lives over 40 years, at stable costs.

The discussion after the presentation stressed the need for pilot operational research on each aspect of a universal treatment model, including willingness to test, virological response rates with earlier treatment, the actual impact on transmission - and the need to develop new heath structures to allow such scale-up.

A first step in confirming treatment reduces HIV transmission in real world settings was shown in results from the Partners in Prevention HSV/HIV Transmission (PARTNERS) Study in over 3400 serodifferent heterosexual couples in seven southern African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia). The HIV-positive partner was a man in 32% and a woman in 68% of couples. [3]

This study previously reported that HSV therapy with daily acyclovir failed to protect against HIV infections, explained by a massive increase in localised CD4 target cells, and persistence for up to two months after the healing of HSV lesions.

All HIV-positive partners entered the study with CD4 counts >250 cells/mm3 and were not on treatment. Over two years, approximately 10% of study participants required HIV treatment for their own care, and this allowed for the HIV transmission rates to be compared by use of ARV treatment. Intensive risk reduction support was supplied throughout the study, to minimise HIV risk for the HIV-negative partners.

People with more advanced HIV at baseline were more likely to start treatment; with higher baseline viral loads (mean 4.4 vs 3.9 log copies/mL, $p<0.001$), and lower CD4 counts (375 vs 540 cells/mm3, $p<0.001$). A higher proportion of men than women (12% vs 9%, $p=0.01$) strated treatment, at slightly lower median CD4 counts (192 vs 204 cells/mm3, $p=0.05$). People starting treatment were also older (mean 35.2 vs 32.7 years, $p<0.001$).

ART was initiated at CD4 counts <200 cells/mm3 in 52% patients, between 200 and 349 cells/mm3 in 33%, and ≥350 cells/mm3 in 15% (30% of this group were for prevention of mother to child transmission).

New HIV infections were detected in 151 of the HIV-negative partners, over 24 months of follow-up, with testing and prevention support provided every 3 months. Phylogenetic analysis suggested that slightly less than one third (43/151) of the infections were not from the relationship partner. Five cases were excluded from the transmission analysis due to uncertain use of ARVs.

This left an overall transmission rate in 103 remaining transmissions of 2.1%.

Of these, 102/103 were in the non-ARV group (102/4558 person years; rate 2.24 95%CI 1.82-2.72) compared to 1/103 from partners using ARV treatment (1/233 person years; rate 0.37 95%CI 0.09-2.04). This produced an unadjusted relative risk of 0.17 (p=0.037), which became even more significant when adjusting for time on study and CD4 count, showing a 92% reduction in risk: RR=0.08 (95%CI 0.002, 0.57, p=0.004).

The single transmission case occurred in someone whose partner started treatment 18 days before the 9 month assessment, when they were still HIV-negative (details on whether this was by HIV-antigen or PCR testing were not provided), but who seroconverted by the month 12 evaluations. Viral load was undetectable at month 12 in the HIV-positive partner.

Details on CD4 count in the HIV-positive partner showed transmissions at all CD4 levels, with a considerably higher risk when the partner had a count <200 cells/mm3 (rate = 8.79 vs 2.79 at 200-350 and 1.7 at 350-500).

This is likely to be an indirect marker of higher viral load relating to more advanced infections, but surprisingly, the presentation provided no further information on viral load levels of the source partner, other than showing that after a median of 7 months treatment (IQR 3-12months) the median viral load dropped to undetectable, indicating excellent responses.

Importantly, and perhaps showing the positive results from the behavioural interventions, the percentage of visits at which people reported unprotected sex dropped from 6.2% to 3.7% at the pre- and post-treatment visits, respectively, with no change in frequency of sex.

Two other studies at CROI, in a largely MSM population in San Francisco, supported the impact of ARVs to reduce transmission.

Moupali Das-Douglas and colleagues from the San Francisco Department of Public Health and the University of California presented results from a model that estimated values for average and total community viral load (CVL) from 2004-2008 and then compared these with the expected and actual number of new diagnoses over the same period. [4]

Average CVL was defined as the mean of the most recent viral load of all reported HIV-positive individuals in a particular population, divided by the number of reported HIV-positive individuals in the population. Total CVL was the sum of the most recent viral loads of all HIV-positive individuals in a particular population.

The context for this study was an effective 'test and treat' programme that from 2004 to 2008 increased the percentage of MSM testing within 12 months from 65% to 72% and within 6 months from 41% to 53%. The percentage of HIV-positive MSM unaware of their status dropped from 24% to 14.5% (comparable UK figures vary from 30-50%). By 2008, 90% of patients in care were on HAART, with 72% virologically suppressed (<75 copies/mL).

The decreases in mean CVL and reductions in actual diagnoses (from 798 in 2004 to 434 in 2008) were both statistically significant (p=0.005), as were the decreases in total CVL (p=0.019) and percentage of virologically suppressed patients (p=0.002). The presentation acknowledged that a limitation in these results is that cases may be diagnosed chronic rather than new infections, which was addressed in methodology for expected and actual incidence rates.

However, using a more conservative meta-regression analysis (different to the reported abstract), the 30% reduction in CVL and almost 40% reduction in incidence (rather than cases) was not significant (p=0.3) due to the degree of imprecision in the estimates.

While this makes it too early to link CVL with incidence, the reductions in newly diagnosed and reported cases, at the same time as increased testing, greater ARV coverage and greater virological suppression strongly support close following of subsequent data from this model.

In a related poster, Edwin Charlebois and colleagues modeled the impact of earlier treatment and broader test and treat programmes in San Francisco, suggesting that HIV prevalence could fall from the current 25% to around 10% by 2030 if the programme shifted to universal test and treat. [5]

As this issue of HTB went to press, a policy shift in San Francisco to offer HIV treatment to all newly diagnosed patients, regardless of CD4 count or viral load, was announced by public health officials. [6]

C O M M E N T

The positive correlation between viral load and risk of transmission for every route, whether sexual, from shared injection equipment, during pregnancy, at birth and from breast milk, and from needle stick exposure to health workers, is now convincingly demonstrated. For some of these transmission routes, antiretroviral treatment to reduce viral load is already widely used to reduce transmission (principally for mother to child transmission, PEP and PEPSE).

Treatment dramatically extends life, reduces morbidity and should now be additionally valued for reducing transmission. An estimated 70% of HIV-positive people globally in need of immediate treatment for their own care are still unable to access it.

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ACTG 5205: atazanavir/ritonavir vs efavirenz in treatment naïve patients

Simon Collins, HIV i-Base

The few randomised clinical trials using currently licensed antiretrovirals worth highlighting from CROI partly stood out because there were fewer comparative studies that at previous CROI meetings. Of these, ACTG 5205, and its metabolic sub-study ACTG 5224s, generated most attention.

ACTG 5205

ACTG 5205 enrolled over 1850 treatment naïve patients from 2005-7 and followed them through to September 2009. The study was designed to compare efavirenz to atazanavir and tenofovir/FTC to abacavir/3TC by randomising equally to one of four groups. Patients were stratified by baseline viral load (above vs below 100,000 copies/mL). [1, 2]

Baseline demographics included 83% men/17% women; 40% white (non-Hispanic), 33% black, 23% Hispanic; median age 38 years median viral load ~50,000 copies/mL, and median CD4 230 cells/mL, Primary efficacy endpoints were time to confirmed virological failure (>1,000 copies/mL) at or after 16 weeks and before week 24 or viral load >200 copies/mL at week 24. Safety endpoints included time to first grade 3/4 event or laboratory abnormality at least one grade higher than baseline (excluding unconjugated hyperbilirubinaemia). Tolerability was assessed as time to change of treatment.

In February 2008, following a DSMB review, patients with baseline viral load >100,000 copies/mL who were using abacavir/3TC were unblinded and recommended to change to tenofovir/FTC due to significantly poorer virological responses. [3, 4]

Interpreting the final results now is further complicated because HLA-B*5701 testing was not available when the study started. Also, and perhaps more surprisingly, baseline resistance testing was performed in less than half the study group. In practice, this means that the most relevant results from the whole study relate to the comparisons between efavirenz vs atazanavir/r.

Using the primary virologic endpoint, there were no significant differences between atazanavir/r and efavirenz with either abacavir/3TC (HR 1.13, 95%CI 0.82–1.56) or tenofovir/FTC (HR 1.01, 95%CI 0.70, 1.46). The differences for the safety endpoint report benefits for atazanavir/r over efavirenz only with abacavir/3TC (HR 0.81, 95%CI 0.66–1.0; p=0.05), probably driven by a caution over management of rash and a potential hypersensitivity reaction when NNRTIs are prescribed with abacavir. This was seen even more in the tolerability analysis (HR 0.69, 95%CI 0.55, 0.86; p=0.0008).

Cardiovascular and renal events, non-AIDS malignancies and bone fractures were broadly similar in each group.

Again, as seen in other PI vs NNRTI studies, patients with virological failure were significantly more likely to develop resistance on the NNRTI compared to the PI regimen (approximately 60% vs 20% of virological failures included ≥1 major mutation in the efavirenz vs atazanavir/r group respectively).

The only signficant differences in CD4 responses were seen when atazanvir/r group was compared to efavirenz, but only when tenofovir/FTC was used as the nucleoside backbone (+252 vs +221 cells/mm3 at 96 weeks, p=0.002).

Lipid differences were more complicated, and while statistically significant for some values, may or may not be of clinical relevance.

In an on-treatment analysis at week 48, efavirenz was consistently associated with significantly greater increases in total cholesterol, LDL and HDL regardless of nucleosides (all comparisons p<0.001, except LDL with TDF/FTC, p=0.002). Increases were also consistently greater with abacavir/3TC compared to tenofovir/FTC. There were no significant differences for triglycerides although there was a trend for greater increases with atazanavir/r compared to efavirenz, when used with tenofovir/FTC (p=0.07). Despite this, there were no significant differences in total cholesterol:HDL ratio in any comparisons.

Finally, creatinine clearance dropped by approximately -3.0 mL/min at week 96 (as-treated analysis) when atazanavir/r was used with tenfovir/FTC compared to slightly higher increases in the other three groups (p<0.001). These differences were described as modest and <5% of patients in any arm experienced changes of greater than 25% decline.

ACTG 5224s

The metabolic substudy ACTG 5224s provided data on bone mineral density (BMD) and limb fat changes in 269 patients in ACTG 5202 (approximately 65 from each of the four comparative regimens). [5, 6]

Exclusion criteria for the substudy included diabetes or other complications including use of medication related to bone or body composition. DEXA evaluations (whole body and bone) were taken at baseline and at 24, 48 and 96 weeks, then annually. CT abdominal scans were taken at baseline and at week 96.

When no interaction was seen between either the RTI component or third drug components, factorial analyses were performed comparing pooled results for each dual RTI, and for atazanavir/r to efavirenz.

Primary endpoints included percentage changes in hip and lumber spine between the two RTI components, and changes of >10% loss of limb fat. Secondary analysis included fracture rates and the same bone and fat changes in the PI vs NNRTI groups.

Baseline demographics broadly reflected the main study and were balanced between groups. Of note, baseline rates of osteopenia (T-score <1.0) were 35% at lumbar spine and 23% at the hip.

Mean values for BMD at lumbar spine dropped in all groups over the first year of treatment and then recovered by about 50% over the subsequent year. These declines were more significant in the tenofovir/FTC compared to abacavir/3TC (approximately -3.5%% vs -1.5% at week 96, p=0.004) group and in patients using atazanavir/r compared to efavirenz (-3.2% vs -1.7, p=0.035).

Tenofovir/FTC was associated with a greater drop in hip BMD at 96 weeks compared to abacavir/3TC (-4.0% vs -2.6%, p=0.025) with no difference between atazanavir/r and efavirenz (p=0.59, each approx -3.0%). Early declines in hip BMD did not appear to reverse over time.

Fracture rates were similar in all groups, with an incidence of 1.7 per 100 patient years, all of which were reported as traumatic (ie expected in general life). No difference by regimen was seen in the main study (where 12% of fractures were without trauma).

Changes in fat distribution was complicated by the study decision to select a relatively marginal 10% cut-off for fat loss as the endpoint. No differences were seen between arms using this criteria (approximately -16%), with a post-hoc analysis using >20% reported in <5% patients with no clear RTI or third drug association.

Absolute mean values increased in both RTI arms (approximately +1 kg gain, no statistical difference) but this was higher in the atazanavir/r vs efavirenz groups (approximately +2 kg vs +1 kg; +30% vs +15%, both p=0.008).

Trunk fat increases were similar in each RTI group, but atazanavir/r had greater increases at 96 weeks compared to efavirenz (approximately +2.4 kg vs +1.2 kg, p=0.023).

C O M M E N T

The clearest outcome from these complicated results is likely to be a stronger recommendation for atazanavir/ritonavir as a clinical option in for first-line therapy.

Absolute differences in side effects, tolerability and metabolic differences are more complicated to interpret in clinical terms, even when they are statistically significant, but would be a factor to consider in individual patients at higher risk.

The reductions in bone mineral density in all groups are concerning, especially given the high percentage of patients with low levels at baseline. While fracture rates in this study were low, other studies at CROI suggested that the concern that ageing will uncover reduced BMD as a greater complication in HIV-positive people compared to the general population, may, unfortunately, be well founded.

Fat changes are difficult to interpret given the choice of endpoint for fat loss, although ~5% patients lost >20% fat across all arms. The significant increases in trunk fat, largely interpreted as a return to health effect, were based on DEXA results. The analysis of CT results, not included in the CROI presentation, is needed to determine whether this is an accumulation of visceral or subcutaneous fat.

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Pipeline compounds and new approaches to treatment

Simon Collins, HIV i-Base

There were fewer presentations at this years meeting on either new drugs or comparative studies between existing drugs. While the missing studies were very noticeable, this is probably more due to the recent approval of several new drugs over the last two years.

It may be significant though that most of the notable studies were nearly all included in one oral abstract session. [1]

QUAD, elvitegravir and cobicistat

New clinical data was presented on the integrase inhibitor elvitegravir, in combination with a new pharmacokinetic booster from Gilead called cobicistat (previously GS-9350), both coformulated with tenofovir/FTC in a four-in-one tablet called Quad. [2]

When Quad was compared to Atripla (efavirenz + tenofovir + FTC), over 80% of patients in each group had undetectable viral load (less than 50 copies/mL) after 24 weeks. However, mean baseline viral load was <40,000 copies/mL, and it was only >100,000 copies/mL in 25% of patients. In this Phase 2 study, patients in the Quad group (n=48) became undetectable more quickly than those on Atripla (n=23), as was seen with raltegravir. For example, after 8 weeks, about 80% people were undetectable with Quad compared to about 50% with Atripla.

While Quad was better tolerated in terms of not having efavirenz-related side effects, a caution due to the impact of cobicistat on reducing estimated glomerular filtration rate (eGFR) - but not actual GFR - suggests that management of renal toxicity may have to be handled differently.

Results from a second Phase 2 study were presented in the same oral presentation, this time comparing the new booster (n=50) to ritonavir (n=29), each in combination with atazanavir, tenofovir and FTC. [2]

No differences were seen in efficacy or tolerability between the two boosters. Unlike ritonavir, cobicistat has no antiretroviral activity.

In summary, results were sufficiently encouraging for both QUAD and cobicistat to be taken into larger Phase 3 studies.

Compounds in earlier development

A dose-finding Phase 1 study of a CCR5-inhibitor in development with Tobira Pharmaceuticals under the compound name TBR-652. The compound has a plasma half-life of 35-40 hours allowing once-daily dosing and although metabolised by CYP and non-CYP pathways is neither and inducer or inhibitor of CYP P450. [3]

These first results in 54 HIV-positive patients produced median viral load reductions of 1.7 log with the 50, 75 and 150mg doses after 10 days monotherapy. Although baseline viral load was lower in the 150mg group (median 4.0 logs, compared to 4.5 and 4.6 logs in the 50mg and 75mg groups), all patients using the 75mg dose had >1.0 log reductions. Patients were treatment-experienced (off treatment for at least 6 weeks), CCR5-naïve and CCR5-postive. No dose-related or serious side effects were reported, though the study was only in about 50 people.

Side effects were mild (none reported at the 75mg dose) and included nausea, diarrhoea, headache and fatigue in greater frequency at the 100 and 150mg - although many of these were reported as being associated with one patient with a concomitant infection.

Very little new information was available for the new integrase inhibitor in development with Shionogi and GSK called S/GSK1349572. [4] Although included in the oral session, this was more a product overview, adding no new in vivo data to that presented at the IAS meeting in Cape Town last year. [5]

Results from a pooled analysis of 721 treatment experienced patients in the unfortunately named Victor-E 3 and 4 Phase studies, presented by Joe Gathe, disappointingly found to too little difference compared to placebo for the troubled CCR5-inhibitor vicriviroc to continue to be taken forward for further development. In a modified ITT analysis the percentage of patients with undetectable viral load (<50 copies/mL) at 48 weeks was 64% and 61% in the vicriviroc and placebo groups respectively (p=0.6). [6]

The presentation suggested this was because of more effective background drugs were available for patients to construct optimum background therapy (approximately 65% had ≥3 active drugs), for the third agent to show significant advantages. A prespecified sub analysis showed that 70% of people randomised to the vicriviroc arms who had ≤2 active drugs achieved <50 copies/mL compared to 55% of the placebo group, and an indication that this was significant. As the vicriviroc group had fewer active drugs at baseline, this potentially obscured a difference in activity between the two arms.

While safety was apparently similar, during the questions, we learned that there were 7 vs 0 deaths in the vicriviroc and placebo arms respectively, not apparently significant after adjusting for time on treatment.

Despite the early promise, it looks likely that the development of this compound will now be put on hold. [6]

Preliminary studies looking at a handful of other targets and approaches, including attempts to target latently infected cells were presented as posters.

Frauke Christ and colleagues from University of Leuven, Belgium, detailed potential compounds from a new class of integrase inhibitor, called LEDGINS, that would not bind at the active site, and therefore not be cross-resistance to raltegravir or elvitegravir. These potential molecules, 2-(quinolin-3-yl)acetic acid derivatives, were designed by rational drug design, and identified after screening 200,000 molecules. [7]

Stephen Mason presented preclinical results on two early compounds that could interfere with the assembly and stability of the capsid core, that are in development at Boehringer Ingleheim. These compounds interrupt the process for assembling new virus and were shown to have activity against resistant HIV from other classes.

Many presentations reiterated that eradication with current drugs is not possible, due to the inability to recognise latently infected resting cells. Even after many years of maximally suppressive therapy, it is well established that viral load rapidly rebounds to pretreatment levels, potentially within weeks of discontinuing treatment.

At least five new types of treatment are the focus of research on how to target latently infected cells. These include cellular restriction factors – human proteins that reduce HIV replication and that can help or block infections – such as tetherin, a protein that blocks HIV release, APOBEC3, an immunity gene that has anti-HIV activity, and TRIM5-alpha, a protein that in some monkeys protects against HIV infection, and that gene therapy could perhaps be modified to adapt the related human protein. Zinc finger inhibitors that can knock out CCR5 were included in other presentations, although this potential target that has been on the outer radar of investigative treatment for at least 15 years.

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Clinical benefits of stopping smoking: CVD and CHD risk returns to that of 'previous smoker' in HIV-positive people within three years

Simon Collins, HIV i-Base

An analysis from the D:A:D study, presented as an oral session, reported that HIV-positive people who stop smoking can expert similar direct health benefits to HIV-negative people.

Kathy Petoumenos from the University of New South Wales, Sydney, looked at rates of cardiovascular disease before and after stopping smoking in over 27,500 HIV-positive patients from Europe, the US and Australia, who had smoking status recorded in the prospective D:A:D cohort study.

The group looked at four endpoints: fatal and non-fatal myocardial infarction (MI), a broader definition of coronary heart disease (CHD), cardiovascular disease (CVD) combining CHD and stroke, and all cause mortality. Event rates were calculated for never smokers (n=8,920), ex-smokers at D:A:D study entry (n=6,265), current smokers (n=11,951), and smokers who stopped during D:A:D follow-up (n=8,197).

Current smokers were more likely to be male (77%), white (70%), infected through IV drug use (32%) and HCV-positive (34%), but CD4, viral load, BP, lipids and ARV-exposure were broadly similar between groups.

Incidence rate ratios (IRR) were determined adjusting for age, sex, cohort, calendar year, antiretroviral treatment, family history of CVD, diabetes (men and women), and time updated lipids and blood pressure assessments. Mortality endpoint also adjusted for HCV, HBV, mode of HIV exposure, ethnicity and incidence of CVD during follow-up.

Up to February 2008, there were 432 (MI), 600 (CHD), 746 (CVD) and 1902 (mortality events) endpoints. Crude event rates were 2.85, 3.96, 4.94, and 12.45 per 1000 person years respectively.

With never-smoked as the reference, increased risks rates were 1.73 and 3.40 for previous- and current-smokers respectively. Rate ratios for patients who had stopped smoking for <1, 1-2, 2-3 and >3 years follow-up since quitting, were 3.73, 3.00, 2.62 and 2.07 respectively, compared to never-smokers. This showed significant reductions within a year of stopping that continued to reduce over subsequent years. A similar pattern was seen for CHD and CVD, and although these were not significant at all timepoints, this is likely to be related to the lower number of events in some groups and the lower number of people who stopped smoking more than two years ago. The protective trend here is clear and important (see Table 1).

Although current smokers were at 28% higher risk of mortality, with no difference between never- and former-smokers, no clear reductions were seen during follow-up since stopping, with all confidence intervals crossing 1.0, even in a sub-group at higher risk of CVD-related mortality (in patients older than 50 years).

Table 1: Incidence rate ratios by baseline smoking status and time since quitting

	Never	*Previous*	*Current*	*<1 year*	*1-2 years ago*	*2-3 years ago*	*>3 years ago*
MI	***1.0***	***1.73***	***3.40***	***3.73***	***3.00***	***2.62***	***2.07***
CHD	***1.0***	***1.60***	***2.48***	***2.93***	***2.48***	***1.90***	***1.83***
CVD	***1.0***	***1.38***	***2.19***	***2.32***	***1.84***	***1.60****	***1.49****
Mortality	***1.0***	***0.99****	***1.28***	***1.67***	***1.02****	***1.34****	***1.30****
Mortality >50yo	***1.0***	***1.21****	***1.31***	***1.68***	***1.02****	***1.43****	***1.16****

* Non significant (CI crossed 1.0)

An explanation for the higher rates seen in the most recent (< 1 year) quitters was explained by the likelihood that a medical incident could have been the prompt needed to stop smoking. This group would therefore be at higher risk compared to current smokers (who would have been symptomatic). This was supported by the cause of mortality being more likely to be HIV/AIDS in the never smoked group with higher rates of non-AIDS malignancies seen in the previous and stopped groups.

The study has limitations in the amount and type of data that were collected on smoking (e.g. no start/stop dates or pack-year data). However, the significant reductions on CHD with each year after stopping smoking should support cessation programme for HIV-positive people, a greater percentage of whom smoke than the general population.

C O M M E N T

This is the first time that the clinical benefits of stopping smoking has been reported in HIV-positive people and these findings should not be taken for granted.

Each year, HIV-positive people are advised on the importance of modification of lifestyle for 'healthy options' related to the complicated etiology of cardiovascular health and any study that can show tangible benefits is important.

This is particularly important given the higher rates of lung cancers reported in other studies. Keith Sigel and colleagues reported that HIV is an independent risk factor for lung cancer after adjusting for smoking (IRR 1.80; 95%CI 1.28 2.15). [2]

Edgar Simard from the US National Cancer Institute, reported a 3-fold observed incidence of lung cancer in HIV-positive patients within 3-5 years of an AIDS diagnosis compared to the general population (and increasing cumulative incidence). [3]

Meredith Shiels and colleagues reported that lung cancer was one of the cancers that was being diagnosed at an earlier age in HIV-positive compared to HIV-negative people, and that this 3-4 year difference was statistically significant after adjustment for multiple comparisons (p<0.001). [4]

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HIV increases the risk of lung cancer, independent of smoking status

Simon Collins, HIV i-Base

Keith Sigel and colleagues presented an analysis from the US Veterans Ageing Cohort Study Virtual Cohort (VC) on the relationship between HIV and lung cancer. [1]

The advantages of this database included size, smoking status data from a related health survey and a matched HIV-negative control group, although this was an almost exclusively (98%) male study. Median age was 47 years and ethnicity was approximately 40% white, 40% black. 10% Hispanic and 10% other. Approximately 30% were current smokers, 15% recently quit (< 1 year), 25-50% distantly quit (> 1 year) and 20% of HIV-positive compared to 25% of HIV-negative had never smoked.

The analysis compared over 3,700 HIV-positive and nearly 10,000 HIV-negative patients (contributing 28,500 and 76,800 person-years of follow-up respectively).

Lung cancer was defined using International Classification of Diseases (ICD-9) codes and Incidence Rate Ratios (IRR) were adjusted for age, race, smoking exposure, and Chronic Obstructive Pulmonary Disease (COPD).

The overall incidence of lung cancer per 100 person years was 0.26 compared to 0.16 in the HIV-positive vs HIV-negative groups (unadjusted IRR 1.5, 95%CI 1.2–2.0). Results from the adjusted analysis are detailed in Table 1.

Table 1: Adjusted IRR for lung cancer multivariate model including all covariates

Variable	IRR	95% CI
HIV infection	1.8	1.3–2.4
Age	1.1	1.1–1.1
Race/ethnicity: *		
African-American	0.9	0.7–1.2
Hispanic	0.4	0.2–0.8
Other	0.9	0.5–1.6
COPD	1.5	1.1–2.1
Smoking exposure: **		
Current daily smoker	9.8	4.4–21.4
Current occasional smoker	3.4	1.0–11.6
Recently quit smoking (<1 yr)	9.9	4.4–22.3
Distantly quit smoking (>1 yr)	5.1	2.4–11.2

* Reference = white race; ** Reference = never smoked.

The authors concluded that the incidence of lung cancer was significantly increased in HIV-positive men in their group, even after adjusting for smoking exposure.

C O M M E N T

This study reported slightly lower rates of increased risk of lung cancers in HIV-positive individuals compared to rates that were 2- to 6-fold higher in earlier studies, that also adjusted for smoking status. [2, 3, 4]

While the approximate 2-fold increased risk associated with HIV was significant and is important, the presenter emphasised the 10-fold higher risk for current smokers (that was halved to around 5-fold for former smokers who had quit more than one year earlier).

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HIV-positive people in the HOPS cohort have 4-fold risk of fracture compared to general population in the US

Simon Collins, HIV i-Base

Over the last ten years HTB has reported numerous studies of lower bone mineral density and higher rates of osteopenia and osteoporosis in HIV-positive people compared to rates in age- and gender-matched general population.

While some research groups cautioned that their findings might not translate into higher fracture rates, most others suggested that ageing was likely to compound this risk and that it would be only a matter of time before the additional impact of HIV might be seen.

Two studies at CROI unfortunately suggest that these concerns are likely to be real.

Christine Dao from the US CDC in Atlanta and colleagues presented an analysis of fracture rates from 1994-2008 in over 8,400 HIV-positive patients followed in the HIV Outpatients (HOPS) Cohort and compared this to rates from non-HIV US inpatient (NHDS) and outpatient (NHAMCS) surveys that were weighted to make inferences to the US general population.

Only first fractures were included from HOPS and adjusted Hazard Ratios (AHR) were calculated controlling for age and gender. As fracture data were not comprehensively collected in HOPS prior to 2000, the presentation focused on fractures from around 5800 patients seen at least annually over the last eight years.

Baseline characteristics at first visit included: 79% male; 52% non-Hispanic white, 38% non-Hispanic Black; median (IQR) age 40 years (34-46), median BMI 24.4 (22.3-27.4); median time since diagnosis 5.3 years (1.3-9.9). Three-quarters of patients were treatment-experienced with median viral load (for the cohort) of 1,300 (<400-35,560) copies/mL.

Approximately 4% patients (236/5826) experienced a fracture at median age 45 years (38-51), roughly in proportion to baseline characteristic of race and gender, although only 51% of fractures were in treatment-experienced patients.

Gender-adjusted rates were restricted to patients aged 25-54, representing most HIV-positive individuals and showed not only an increase in fracture rates over time from about 55 to 85/10,000 PY, p=0.01 (compared to stable rates at around 30/10,000 PY in general population outpatient data). The rate in HIV-positive people was stable from 2002-2008 (and was approximately 4-fold higher).

Fractures at fragility sites (wrist, vertebra, femoral head) occurred at higher rate in both HIV-positive men and women compared to the general population, and are detailed in Table 1.

Factors independently associated with increased risk of fracture (adjusted HR: 95%CI) included: age >47 years (1.6; 1.0–2.5, p<0.05); nadir CD4 <200 cells/mm3 (1.6; 1.1–2.3, p=0.04); HCV coinfection (1.6; 1.1–2.3, p=0.01); diabetes (1.6; 1.0–2.6, p<0.05); and history of substance use (1.5; 1.0–2.3, p<0.05).

Limitations of the study included the use of different data collection systems for the HIV-positive and general population groups, no data linking bone mineral density to fracture risk, and whether this increase was due to an increase in events or a potential improved reporting.

Table 1: Percentage of fractures by anatomic site in adults 25-54 years old (HOPS 2000-2008)

	HOPS	*NHAMCS-OP*	*P (vs HOPS)*
Men	***n=146***	***n=1,705,433***	
Wrist	***9%***	***3%***	***<0.05***
Vertebra	***10%***	***1%***	***<0.05***
Femoral head	***3%***	***2%***	***NS***
Non-fragility site	***78%***	***94%***	***<0.05***
Women	***n=45***	***n=1,136,788***	
Wrist	***4%***	***8%***	***NS***
Vertebra	***18%***	***4%***	***<0.05***
Femoral head	***7%***	***1%***	***<0.05***
Non-fragility site	***71%***	***86%***	***<0.05***

Importantly, they also stressed that the actual event rate remained low, even though the relative rate was significantly higher.

Nevertheless, the researchers concluded that HOPS patients experienced higher rates of fracture compared to the general US population, that this rate increased over time and included a higher percentage of fragility fractures; and that in addition to known risk factors, low CD4 nadir was also associated with increased fracture risk.

Julie Womack and colleagues from the Veterans Ageing Cohort Study (VACS) presented results from men in the largely male VA cohort, focusing on the prevalence and incidence of fragility fractures (ie associated with minimal or no trauma, and with low bone mineral density). [2]

The VACS is a prospective observational cohort of about 40,000 HIV-positive veterans matched 1:2 by age, sex and site to around 80,000 HIV-negative controls. This analysis only included first fracture. Wrist fractures and compound fractures were excluded because of the higher likelihood of being related to trauma.

Multivariable models were adjusted for HIV status, race, enrollment date, age, coinfection, BMI and corticosteroid use, with additional adjustment for baseline CD4 and ARV use in HIV-positive patients.

During a median follow-up of 8 years (range 4-11), 952 fractures (644 hip and 308 vertebral) fractures were recorded, with an unadjusted incidence of 16 vs 11/10,000 PYFU in the HIV-positive vs HIV-negative groups. Fractures occurred at a mean age of 55 years (SD$\pm$11).

Prevalence results showed that across all ages only hip fractures occurred at a significantly higher rate in the HIV-positive vs HIV-negative groups ($p<0.0001$), with a difference developing and widening from age 40 onwards. Although vertebra fractures were generally similar in both groups, the rate in HIV-positive men increased significantly in men over 70 years who were HIV-positive.

After adjustment for cofactors (AHR; 95%CI), including Caucasian race (1.79; 1.57–2.03), BMI <19 (2.50; 1.54–4.05), alcohol use (H1.79; 1.47–2.18), pulmonary disease (1.38; 1.10–1.73), cerebrovascular disease (2.16; 1.54–3.02), and peripheral vascular disease (1.64; 1.10–2.44), the HIV effect was reduced, though still significant (1.38; 1.18–1.60). Similar ratios applied for the full model and HIV-positive only model.

The presentation also discussed management and this was picked up in the question session afterwards. Prevention is stressed for all patients. Clinical assessment for fracture risk was recommended for patients aged 40-50 and DEXA indicated when HIV is not the only risk factor.

Several members of the audience commented that they would encourage broader use of DEXA scans, especially given the high rates of other risk factors, including higher rates of smoking, alcohol use and low testosterone.

Although ARV use was not found to be significant in this study, another question from the audience suggested that this was unlikely to be a reliable conclusion, as the study defined exposure by baseline use of d4T, tenofovir, PIs or NNRTIs, rather than looking at cumulative exposure more commonly adopted in most studies.

Finally, a third presentation in the same oral session reported fracture incidence in a retrospective analysis in about 2400 women (approxiamtely 1700 HIV-positive, 700 HIV-negative) in the Women's Interagency HIV Study (WIHS). Of note, this study also collected data on smoking, opiate/cocaine use and vitamin D/calcium supplementation.

Fractures occurred in 148 (9%) HIV-positive women vs 47 (7%) HIV-negative women producing incidence rates of 1.79 vs 1.41/100 PY, respectively ($p=0.13$ NS). Analysis by fracture site also showed no significant difference in rates by HIV status. In the multivariate analysis, HIV status remained non-significant, with only age, race (being Caucasian), HCV coinfection and serum creatinine only showing positive relationship to increased fracture rate. The only determinants of time to fracture in HIV-positive women were age (per 10 years older HR 1.2; 95%CI 1.0–1.5, $p=0.047$) and previous AIDS defining illness (HR 1.9; 95%CI 1.3–2.7, $p=0.0008$), but not CD4 count or ARV use.

Although no impact of HIV was seen over five years of follow-up the limitations of this study was that this was broadly a pre-menopausal patient group and in a modest sample size. Also, approximately 50% women had high BMI which is associated with protecting bone density and strength.

The conclusion included recognition that fracture risk could increase in HIV-positive post-menopausal women, given that oestrogen has a protective effect and other studies have already highlighted the lower levels of bone mineral density in HIV-positive women.

References

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Vitamin D deficiencies in HIV management

Nathan Geffen, TAC

HTB has run several articles on vitamin D deficiencies in previous issues in relation to bone problems, tenofovir and efavirenz. There is increasing concern and research about vitamin D deficiency in people with HIV, especially with regard to African immigrants and people of African descent living in the cold climates of North America and Europe. There were several posters on this topic at CROI 2010 and so a themed discussion on it was held, chaired by discussants Peter Reiss of the University of Amsterdam and Michael Yin of Columbia University. Reiss started the session by giving a clear explanation of the basic science of vitamin D. [1-3]

Background

Vitamin D is a group of fat soluble prohormones that mainly originate in the skin where ultraviolet radiation interacts with 7-dehydrocholesterol to form pre-vitamin D3 and then vitamin D3. This process is harder in people with darker skins. Some vitamin D3 is also consumed from diet and supplements. The main purpose of vitamin D is to increase the flow of calcium in the bloodstream.

Vitamin D3 is hydroxylated by the enzyme 25-hydroxylase into hydroxylated vitamin D, 25(OH)D, in the liver. An alternative pathway to hydroxylated vitamin D is via vitamin D2 acquired from diet, but this is considered a less important source.

The hydroxylated vitamin D, 25(OH)D is then further hydroxylated in the kidneys to one-alpha-hydroxylated-vitamin D (1α-25(OH)2D) which is the active metabolite. The enzymes involved in this process belong to the cytochrome p450 family, which is a catalyst for some antiretrovirals. There is also speculation that HIV itself affects the production of vitamin D (discussed further below).

Even though 1α-25(OH)2D is the active metabolite, for diagnostic purposes the amount of its precursor, 25(OH)D is measured. This is because if there is a deficiency in 25(OH)D, an auto-regulatory mechanism upregulates the manufacture of 1α-25(OH)2D. So a person can have sufficient amount of the active metabolite, but still have a deficiency of vitamin D.

Clinical consequences of vitamin D deficiency

Widely accepted criteria for clinically sufficient, insufficient and deficient levels of vitamin D are given in Table 1. However, as Reiss pointed out, by this definition, 40 to 100% of elderly people are deficient in vitamin D and the criteria do not account for ethnic differences. Moreover optimum levels of vitamin D for skeletal and extra-skeletal health have not been established neither in the general population nor for specific ethnic groups. As is clear from the presentations described in Table 1 below, these criteria are not standardised.

Julian Falutz of McGill University has compiled a table of studies examining vitamin D levels in people with HIV (Table 2). They cover a wide range of countries, seasons, CD4 count ranges and levels of ARV uptake, giving a diverse range of proportions of people categorised as sufficient, insufficient or deficient.

Table 1: Criteria for clinical definitions of 25(OH)D3 in blood (Reiss [3])

	European (SI) measurement (nanomoles per litre)	US measurement (milligrams per millilitre)
Sufficient	>=75 nmol/L	>=30 ng/mL
Insufficient	50–75 nmol/L	20-30 ng/mL
Deficient	<50 nmol/L	<20 ng/mL

Table 2: Vitamin D studies in people with HIV (Falutz)

Study	N	Sex/race	Age	CD4	ARV (%)	Season	25(OH)D Low (%)	25(OH)D Insufficient (%)	25(OH)D Normal (%)
Stephensen (US) 2000	238(+) 121(-)	72%F, 75%B	20	?	?	86% Spring-Summer	?	87	?
Seminari (Italy) 2002	68	80%M, all W	41	150	100	Nov-Jun	?	81	?
Bang (Sweden) 2004	115	M, all white	44	480	62	Autumn-Winter	23	36	40
Rubin (NYC) 2005	62	M, 34% white	48	540	92	Autumn-Winter	42	34	24
Rodriguez (Boston) 2005	57	77% M, 60% W	46	430	81	Winter-Spring	48	?	?
V. der Ven (Holland) 2006	254	75% M, 73% W	41	420	79	Jan-Aug	29	?	71
Wetz (London) 2008	47	60% M, 60% B	41	455	88	30% Autumn-Winter	74	17	9
Garcia-Aperico (Spain) 2008	30	100% M and W	38	550	56	Oct-Jun	86	?	?
Falutz	41	83% M	54	549	100	Autumn	5	55	40

The role of HIV and its treatment in vitamin D regulation is speculative and complex. HIV might affect dietary intake in sick people which in turn might affect levels of vitamin D. HIV might also affect the 1-alpha hydroxylation step and thereby inhibit synthesis of the active metabolite. Vitamin D might also be used by maturing and proliferating T-cells. With their increased production during HIV infection, there might be greater utilisation of vitamin D. The utilisation of cytochrome p450 enzymes by NNRTIs and protease inhibitors might also affect levels of vitamin D. The hydroxylation step in the kidney takes place in the proximal tubular cells, which are also affected by tenofovir, and this might impact on vitamin D levels. On the other hand ritonavir inhibits 1α-hydroxylase and consequently this might lead to an accumulation of unconverted 25(OH)D in the kidneys.

Vitamin D receptors are found on nearly all cells and deficiency of it is associated with many diseases such as osteomalacia (softening of bones), inflammatory conditions, hypertension, cardiovascular disease, insulin resistance, renal disease, prostate and colon cancer, greater risk of bacterial infection, cognitive dysfunction and frailty.

The SUN study

Christine Dao of the CDC presented results of the SUN study. This study assessed levels of vitamin D (measured by 25(OH)D, as with all other studies presented here) from 2004 to 2006 in the United States in 672 adults with HIV. Insufficiency was defined as less than 30ng/mL. The study found 72% of participants were vitamin D insufficient. Black race, Hispanic ethnicity, lower ultraviolet exposure, hypertension, lack of exercise and efavirenz exposure were independently associated with insufficiency. On the other hand renal insufficiency (GFR<90) and ritonavir exposure were independently associated with lower odds of insufficiency. In question time, Dao stated that 9% of participants were deficient, defined in this study as a 25(OH)D less than 10ng/mL (which is different from the definition of deficiency given above). [4]

Italian cohort

Antonella d' Arminio Monforte from the University of Milan presented the results of an observational cohort with retrospective analysis in vitamin D in stored plasma samples of 852 patients contributing 1,498 measurements. Of these, 262 measurements were taken before and 1,236 after ART initiation. Insufficiency was defined the same way as the European measurement in Table 1, but deficiency was defined as less than 30 nmol/L. [5]

Insufficiency was found in 804 measurements (54%), while deficiency was found in 98 (7%). In 116 patients measured pre- and post-ART initiation in the same season, there was a non-significant drop of vitamin D levels (average of 7.57 nmol/L per year; p=0.11).

The following were significantly associated with deficiency versus normal values (adjusted odds ratios):

- Age (per 10 years older) (OR 1.53; 95%CI 1.11–2.09; p=0.009)
- Non-Caucasian origin (OR: Caucasians were 0.17 times as likely to have deficiency; 95%CI 0.07–0.42; p=0.0001)
- Lower CD4 count (per 100 cells/mm3) (OR: Higher CD4 count was 0.9 times as likely to have deficiency; 95%CI 0.82–0.99; p=0.04)
- Lower BMI (OR: for each unit higher, 0.9 times as likely to have deficiency; 95%CI 0.83–0.98; p=0.01)
- NNRTI vs PI use (OR: participants on PI regimens were 0.47 times as likely to have deficiency; 95%CI 0.27–0.84; p=0.01)
- Season: (with summer as reference: OR of autumn: 1.24; 95%CI 0.51–3.05; p=0.64; winter: 4.84; 95%CI 2.07–11.33; p=0.0003; spring: 8.3; 95%CI 3.61–19.09; p=0.0001)

During questions, d'Arminio Monforte stated that they had found that deficiency was associated with clinical events, in particular cardiovascular ones, but the direction of any causal effect, if any, was unclear. She also pointed out that in the HIV-negative population obesity is associated with deficiency, while in this cohort the opposite occurred: lower BMI was associated with deficiency.

Swiss cohort

Christoph Fux of University Hospital, Bern presented data on vitamin D deficiency in 211 patients in the Swiss HIV cohort, half of whom were measured in spring and half in autumn. As with the Italian cohort, insufficiency was defined the same way as the European measurement in Table 1, but deficiency was defined as less than 30 nmol/L. [6]

At baseline before ART initiation, there was 14% deficiency in autumn and 42% deficiency in spring. After 12 months of ART - at which point all patients were virologically suppressed - this was virtually unchanged (47% in spring, NS). White race was associated with significantly higher vitamin D levels than Asian, Hispanic and black race.

Interestingly, measurements of 1α-25(OH)2D were also taken and it was found that there was some compensation, ie when 25(OH) D levels were lower, there was a higher ratio of the active metabolite to 25(OH)D.

In multivariate analysis, white race (14.1 umol/L higher; p=0.001) and, surprisingly, duration of HIV by 10 years (6.4; p=0.02) were associated with higher 25(OH)D levels. While BMI (-0.7; p=0.05), active IDU (-11.2; p=0.02), spring (-17.7; p<0.001) and NNRTI use (-8.2; p=0.002) were associated with lower levels. Sex, age, HCV positivity, cGFR <60mL/min, previous AIDS, CD4 count and tenofovir use were not significantly related to lower levels.

Interestingly, for 1α-25(OH)2D levels, the results were different. Neither race nor season were significant. BMI was positively associated with vitamin D levels (1.7; p<0.001), as was tenofovir use (7.8; p=0.02). HCV positivity was negatively associated (-9.1; p=0.04) as was previous AIDS (-11.6; p=0.007) and CD4 count by 100 cells (-2.6; p=0.003).

Tanzanian cohort

Saurabh Mehta of Harvard Medical School presented data from Tanzania on the association between vitamin D levels and wasting, acute respiratory infections and thrush. They defined low vitamin D level as less than 32 ng/mL. Vitamin D levels were measured in 884 pregnant Tanzanian women who were followed up for a median of 70 months. In January, this research group published an article in PloS One showing that low vitamin D levels are associated with increased HIV disease progression (RR 1.25; 95%CI 1.05–1.5) and anemia (RR 1.46; 95%CI 1.09–1.96). Women in the highest vitamin D quartile had a 42% lower risk of all-cause mortality (RR 0.58; 95%CI 0.4–0.84). This group has also previously published a widely cited study showing that a vitamin supplement delayed disease progression and mortality in this cohort, but the supplement did not contain vitamin D [7-9].

In this study, low vitamin D was associated with a 45% higher risk of wasting (BMI <18kg/m2; p=0.03), a higher incidence of acute respiratory infections (RR 1.28; 95%CI 1.05–1.55) and a much higher incidence of thrush (RR 2.92; 95%CI 1.43–5.96). They also found a linear relationship between any vitamin D level and wasting.

During questions, Mehta pointed out that no association was found with seasonal factors (Tanzania is near the equator). He also said that they found no association between vitamin D and TB, but did find an association between children born to mothers with deficiency and TB. When asked to comment on which way the association between wasting and vitamin D went, Mehta explained that the vitamin D level was measured at baseline when women with wasting were excluded from analysis and that the wasting in this cohort came subsequent to the vitamin D measure.

WIHS cohort

Audrey French of Rush University Medical Centre presented data from a cross-sectional sub-study of the Womens' Interagency HIV Study (WIHS), whose objective was to see if there was an association between vitamin D deficiency and bacterial vaginosis. WIHS is a longitudinal multi-site study of about 3,000 women with and without HIV. The substudy is from Chicago and New York City and includes 480 HIV-positive and 122 HIV-negative participants.

Bacterial vaginosis was diagnosed using the Amsel criteria. Vitamin D insufficiency was defined as 20-30ng/mL and deficiency as less than 20ng/mL. Prevalence of deficiency was 60% and insufficiency was 24%. Black race was the only predictor of deficiency in an analysis using demographics, socioeconomic status and HIV associated variables including HIV status. Factors associated with bacterial vaginosis in multivariate analysis were black race (OR 6.08; 95%CI 2.66–13.9), number of recent sexual partners (OR 2.3; 95%CI 1.12–5.06) and vitamin D deficiency (OR 2.3; 95%CI 1.02–5.19). The correlation co-efficient between vitamin D and bacterial vaginosis was -0.14 (p<0.001).

During question time, it was stated that vitamin D status was not associated with bone mineral density. Two researchers indicated that in their US cohorts of HIV-positive and HIV-negative people, they had not found an association between HIV status and vitamin D status. But another researcher indicated that a Swiss study had found a difference.

The need for a clinical trial

Michael Yin summarised the session, emphasising the many unanswered questions, lack of data and need for clinical trials of vitamin D. Study participants to consider include people initiating ART especially efavirenz, people who are ageing and people in resource limited high TB prevalence areas. Study endpoints to consider are bone density, muscle mass, fall risk, insulin resistance, cardiovascular disease, CD4 count, HIV progression, opportunistic infections and other measures of innate and adaptive immunity. He suggested a vitamin D supplement dose of 1000–2000 IU per day was a reasonable dose. [10]

He also described unanswered questions about screening. He asked if there should be universal screening (adopted by European AIDS Clinical Society) or targeted screening aimed at older people, black race people, people with previous fractures or low bone mass density, people who are frail or have sarcopenia and patients on efavirenz. He suggested that a target in patients of 40–60 ng/mL or 100–150 nmol/L should be aimed for.

During questions, Yin was asked about the risk of high dosages. He described a study that looked at vitamin D and its correlation with calcium levels. Hypercalcaemia was only seen at levels of 200-240 nmol/L, which was far higher than could be reached with the doses he was proposing. Another questioner asked whether clinical or surrogate end point markers should be the endpoint of a vitamin D trial. Reiss responded that a trial looking at clinical endpoints would have to be too large and consequently surrogate endpoints would have to be used.

C O M M E N T S

These studies contribute to our understanding of vitamin D deficiency in people with HIV. However, there remain many unanswered questions relating to the clinical implications of vitamin D deficiency, how and what to measure and appropriate target levels in different populations, if supplementation is indicated.

In the absence of data from clinical trials, most HIV guidelines defer to national protocols for management of bone disease, recommending supplementation for patients with deficient levels.

While a Cochrane review found statistically significant evidence for prescribing vitamin D to patients taking systemic corticosteroids, other reviews found insufficient evidence to show supplementation prevents fractures in older people, or during pregnancy or to treat chronic kidney diseases or children with cystic fibrosis.

Peter Reiss noted that the size and cost of an adequately powered randomised trial probably makes this unlikely. Management should therefore also include lifestyle changes, such as greater exposure to sun and improved diet and that this may be sufficient for some patients.

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OCTANE 2: nevirapine and lopinavir/r are similar when used with tenofovir and FTC in treatment-naïve women

Polly Clayden, HIV i-Base

In an oral presentation, James McIntyre showed data from the OCTANE/A5208 trial. This trial, conducted in seven African countries, was designed to evaluate which of two antiretroviral regimens is more effective in women previously exposed to single dose NVP and whether single dose NVP compromises subsequent NVP-containing HAART. [1]

OCTANE was composed of Trial 1 and Trial 2. Trial 1 women (n=243) were NVP exposed at least six months prior to the study and those in Trial 2 (n=502) were unexposed. Women in each trial were randomised to receive either NVP or lopinavir/ritonavir (LPV/r) in regimens with tenofovir (TDF) and emtricitabine (FTC). Women with CD4 <200 cells/mm3 were eligible.

The time from randomisation to death or virologic failure (defined as plasma viral load <1 log copies/mL below baseline 12 weeks after treatment initiation, or ≥400 copies/mL at or after 24 weeks) was the primary endpoint in both studies.

Trial 1 was stopped by the DSMB in October 2008 at a median of 66 weeks, after an interim analysis, which found LPV/r to be significantly more effective than NVP and associated with fewer side effects. We reported this data in previously in HTB. [2, 3]

It is notable that in this study the LPV/r arm performed extremely well with only 8% of women meeting an endpoint vs 26% in the NVP arm (adjusted HR 3.6; 95% CI 1.7–7.5).

Trial 2 was designed to assess equivalence (defined as 95% CI for the HR: 0.5–2.0) between the two treatment arms. As in Trial 1, women were followed for ≥48 weeks. This was an intent-to-treat analysis of 500 women (2 excluded): 249 in the NVP arm and 251 in the LPV arm.

Baseline characteristics were similar in both arms, median: age 34 years, CD4 121 cells/mm3 and viral load 5.15 log copies/mL. One woman in the LPV/r arm had received single dose NVP but was included in the analysis. In a random sample of 119 women, baseline NVP resistance was detected in 1% of women. The median duration of follow-up was 118 weeks; 14 women in the NVP and 6 in the LPV/r arms were lost to follow-up.

Dr McIntyre reported that 42 (17%) women in the NVP arm and 50 (20%) in the LPV/r arm reached the primary endpoint (HR 0.85; 95%CI 0.56–1.29). These results met the criteria for equivalence. The as-treated analysis results were similar (HR 0.71; 95%CI 0.45–1.13).

When the investigators broke down the composite endpoint to look at virologic failure and death separately, they found 15% vs 17% experienced virologic failure and 2% vs 3% died in the NVP and LPV/r arms respectively.

Overall, 93 women discontinued NVP or LPV/r permanently, 70 (28%) in the NVP arm and 23 (9%) in the LPV/r arm, HR 3.4 (95% CI 2.2-5.5). Of these, 35 (14%) in the NVP arm and 0 in the LPV/r arm discontinued due to adverse events, p<0.0001.

Grade 3 or 4 signs/symptoms while receiving NVP or LPV/r were reported in 75 (15%) women (14% in NVP, 16% in LPV/r arm), and 26% and 22% (respectively) had grade 3/4 laboratory test abnormalities. Dr McIntyre noted that the protocol took a conservative approach to adverse events for women receiving NVP but events in the LPV/r arm could be managed without a protocol-mandated switch in therapy.

In conclusion, the study reported that NVP+TDF+FTC and LPV/r+TDF+FTC were equivalent in treatment-naïve women. This suggests that the previously reported inferiority of NVP in Trial 1 was related to NVP resistance from single dose NVP exposure.

C O M M E N T

James McIntyre remarked that these data are reassuring for programmes using nevirapine, particularly in Africa where it is a mainstay of antiretroviral regimens.

What remains unexplained is why the LPV/r arm in Trial 1 performed so well whereas in Trial 2 what we are seeing is similar to general experience.

When this was questioned after the presentation Dr McIntyre remarked that this raises "intriguing possibilities" and there may be some plausibility that nevirapine-induced mutations could have some effect on gag/pol cleavage causing conformational changes which may make protease enzymes less effective. If so, protease inhibitors would have less to inhibit, so would work better. He added that he knew of no evidence to support this!

It is perhaps worth noting that equivalence in this study is powered with an equivalence range from 0.5 to 2 - ie requiring a doubling or halving of the risk is still defined as 'equivalent'.

When looking at absolute rates at other studies that use a tighter range, differences of up to 12% are typically viewed as being 'non-inferior'. Using a doubling/halving in risk is stretching this even further.

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HIV incidence and retesting in pregnancy

Polly Clayden, HIV i-Base

Several groups have documented high rates of HIV acquisition during pregnancy and breastfeeding.

Two oral presentations at CROI showed findings from investigations into HIV incidence and retesting among women in high prevalence settings in Africa.

John Kinuthia from the University of Nairobi, Kenya presented data from a study looking at HIV incidence among mothers accompanying their infants for routine 6-week immunisation at 6 maternal–child health clinics in Nairobi and Nyanza Province of Western Kenya. [1]

In this study, mothers completed a questionnaire, before their HIV test, that assessed sociodemographic characteristics, obstetric history, HIV risk perception, and participation in PMTCT programmes during their last pregnancy. The investigators compared characteristics of HIV-negative women who seroconverted during pregnancy and immediately post partum to those who did not.

Dr Kinuthia reported that 2035 out of 2135 (95.3%), mothers who had tested HIV-negative in pregnancy, accepted a repeat HIV test at the immunisation visit. Of these, 53 (2.6%) were HIV-positive, giving an overall estimated HIV incidence of 6.8 (95%CI 5.1–8.8) per 100 woman-years.

The mean age of the mothers was 23.7 years. Of these 86.8% were married, 7.1% in polygamous marriages and 29.4% were employed.

Mothers who seroconverted were more likely to be employed (45.3% vs 29.0%, p=0.01), married (96.2 vs 86.6%, p=0.04) and from a higher HIV prevalence region (60.4% in Nyanza vs 28.8% in Nairobi, p<0.001).

Married women, in a polygamous relationship were significantly more likely to seroconvert (19.6% vs 6.7%, p<0.001). Age, educational level, HIV risk perception, history of physical assault, and economic status were not associated with seroconversion. In multivariate analysis, region (OR 3.6; 95%CI 2.1–6.4, p<0.001) and employment (OR 1.9; 95%CI 1.1–3.3, p=0.03) were independent predictors of seroconversion.

Dr Kinuthia suggested that the limitations of the study included no data on the timing of the mothers' initial HIV test, nor their partners' status.

He concluded that repeat HIV testing in early postpartum was highly acceptable and resulted in detection of substantial HIV incidence. He noted that the incidence in pregnancy and early postpartum in this study compared to that among cohorts of sex workers and women in discordant relationships. He stressed the need for an urgent review of services for negative pregnant women in regions with high HIV seroprevalence and interventions such as couple counselling and testing, the promotion of safer sex in pregnancy and awareness of the risk of infection and in turn MTCT.

Following on from this was a presentation from Mary Pat Kieffer from the Elizabeth Glaser Pediatric AIDS Foundation, showing data from a study in which retesting in maternity facilities was used to provide interventions for women who became infected late in pregnancy. [2]

Swaziland has a very high rate of HIV prevalence among pregnant women (42%) and a high uptake of PMTCT.

The primary objective of the study was to evaluate the effectiveness of a provider focused intervention in increasing ARV coverage at time of delivery. As secondary objectives the investigators sought to determine HIV incidence in late pregnancy and the number of newly-indentified HIV-positive women in maternity. They also looked at whether provision of nevirapine to women who refused testing increases coverage.

Maternity staff received an extra one-day training based on the women's status on arrival. This included:

- Testing women with unknown status and offering nevirapine (NVP) to those who declined.
- Routine HIV retesting as standard of care for women who tested negative three months or more earlier (Swazi guidelines).
- Ensuring all newly identified women receive ARV treatment or prophylaxis.

Women received antiretrovirals in accordance with Swazi national guidelines (NVP+3TC+AZT for women meeting criteria for treatment or short course AZT plus single dose NVP and AZT+3TC "tail" prophylaxis for healthier women).

Sampling used 6 public maternity sites, matched as pairs and randomised within the pair to intervention or control.

Data on testing and ARV prophylaxis were collected through questionnaires and MoH registers.

Cord blood samples were collected as dried blood spots (DBS) and tested for HIV. All positive DBS were tested for NVP. Coverage was defined as number of cord bloods with detectable NVP.

The investigators found 1398/2444 (62.3%) women enrolled in the study had previously tested negative in pregnancy.

Overall NVP was detected in 75% cord bloods, this was significantly higher in the intervention than the control groups, 80% vs 69%, p=0.0001. Dr Kieffer noted that the only group of women for whom there was no significant improvement was those who already knew their status and had taken their ARV prophylaxis at home (p=0.23).

The most critical finding of this study was the high level of HIV incidence in pregnancy: 4.4% women who were HIV negative in ANC were positive at time of delivery giving a rate of 16.75 new infections per 100 person-years. Dr Kieffer suggested that, like the previous data from Nyanza, this rate is similar to cohorts of sex workers and IDU.

She compared these rates to earlier data from Rakai that showed 1.1 per 100 person years incidence in non-pregnant women vs 2.3 in pregnant women per 100 person years.

The second critical finding was that ARV provision almost doubled for women who seroconverted during pregnancy (n=58), 26% vs 54% in control vs intervention groups respectively (p=0.03).

Dr Kieffer explained that this was still only reaching about half those that seroconverted. Control sites had retested 14% (135/ 959) HIV-negative women, compared to 45% (528/1185) women at intervention sites p<0.0001; relative risk 3.17 (95%CI 2.67–3.74). The primary reason for this was the Swazi guidelines only recommend retesting after 3 months or more, but a significant proportion of women (38%) had been previously tested for HIV earlier than this so were not eligible for retesting.

"Reaching women who become infected late in pregnancy cannot be an afterthought for PMTCT programmes" she said.

Like the previous study these data highlight the need for interventions to identify and provide ARV prophylaxis to women who seroconvert in pregnancy and prevention strategies to enable HIV-negative women to remain negative.

C O M M E N T

This issue is important and was also raised by Lu et al at CROI last year. [3]

The question of poor test performance discussed by Black et al in AIDS was also discussed following the presentation. [4]

Whether these transmissions can be attributed to HIV incidence in pregnancy or poor test performance, unidentified HIV positive women in pregnancy remain a barrier to the eradication of paediatric HIV.

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Efavirenz use in pregnancy and birth outcomes

Polly Clayden, HIV i-Base

Of all the antiretrovirals, efavirenz attracts the most controversy with regard to use in pregnant women. Two posters at CROI looked at birth outcomes among mothers who received efavirenz in pregnancy. [1, 2]

Daniel Westreich and colleagues analysed prospective data from Themba Lethu Clinic in Johannesburg. They examined the risk factors for pregnancy after initiation of HAART using Cox proportional hazards regression and looked at birth outcomes in women receiving efavirenz.

The investigators reported that of 5011 women initiating HAART between April 1 2004 and March 31 2007, 351 (7%) became pregnant giving a rate of 4.1 pregnancies per 100 woman years (95% CI 3.7–4.5).

They found that this was less among older women (>35 years) and those with lower CD4 counts or employed.

The investigators noted that although women who initiated HAART with efavirenz based regimens were less likely to become pregnant that than those starting with nevirapine, HR 0.6 (95% CI 0.4–0.8), 68% (n=238) of pregnancies occurred in women receiving efavirenz.

The investigators looked at 136 of the women receiving efavirenz for pregnancy outcome. They reported three maternal deaths, 39 women lost to follow up and one who refused to be interviewed. In addition 12 women were still pregnant at the time of analysis.

Out of 81 pregnancies analysed, 8 were voluntarily terminated and 13 miscarried. Of the remaining 60 live births, 41 were examined using the Denver Development Screening Test. According to this scale, 30 infants were classified as "within normal limits" and 11 (>25%, 95% CI 14–43) were "suspect" for developmental delay. The investigators did not find any congenital abnormalities among the infants examined.

The investigators rightly suggested that further study including a comparison group is required to evaluate whether suspected neurodevelopmental delays or miscarriages are associated with efavirenz use. And they wrote, "These results suggest that the risk of efavirenz in pregnancy may be less catastrophic than feared".

A related poster authored by Daniel Conway and colleagues reported findings from an analysis of prevalence of congenital abnormalities among antiretroviral-exposed infants in IMPAACT P1025. This US cohort study enrolled all women and infants in P1025 born between 2002 and 2007 (n=1306) during pregnancy or up to two weeks post-partum. No information was provided regarding prospective or retrospective enrollment, that is, whether any women/infants could be enrolled after an anomaly had already been diagnosed.

A total of 1112 infants were eligible for analysis. Infants were examined for congenital anomalies and reviewers were blinded to in utero antiretroviral (individual drugs and classes) exposure. In utero exposure was classified as 1st, 2nd/3rd trimester and unexposed. The investigators used logistic regression to estimate the relationship between congenital anomalies and antiretroviral exposure.

The investigators reported 80 congenital anomalies among 61 infants, a rate of 5.49/100 live births (95%CI 4.22–6.99). These were broken down into organ systems involved: cardiovascular (n=33), genitourinary (n=7), renal (n=8), musculoskeletal (n=15, including accessory digits of hand or foot, n=7), craniofacial (n=3), central nervous system (n=3), chromosomal (n=3), eye (n=3), gastrointestinal (n=5).

This study reports that first trimester exposure to efavirenz was associated with a significantly increased risk of congenital anomalies (OR 2.89; 95%CI 1.15–7.25) compared to 2nd/3rd trimester exposure. No information was provided regarding the types of anomalies associated with efavirenz exposure.

They did not find any other classes of antiretrovirals nor individual drugs (only data for efavirenz and AZT were shown) to be associated with increased risk of anomalies. Covariates including ethnicity, maternal age and substance use (tobacco, alcohol and recreational drugs) were not significantly associated with increased risk of congenital anomalies.

C O M M E N T

Because of the uncertainties about efavirenz use in pregnancy, all new information on this subject is worth reporting.

Unfortunately neither of the posters summarised here showed enough data to make their interpretation straightforward and both studies seem underpowered.

The Themba Lethu Clinic analysis does not report baseline data and has high loss to follow up. Only the abstract is on the conference website so it was not possible to double-check these data.

The P1025 numbers are also small, about 1/10 of the APR, including those with efavirenz first trimester exposure (47 vs 501). [3] They do not report what the 6 anomalies with first trimester efavirenz exposure were, which seems very important in view of the monkey data. The only other antiretroviral they report on individually is AZT.

Some of the P1025 data are already in the APR though it is not clear which, and not all women were enrolled into this study before

pregnancy outcome was known which would make them ineligible for the APR. Retrospective observations of birth defects cannot be used to determine birth defect prevalence, because of differential reporting bias, that is, that a foetus or infant with a birth defect would be more likely to be enrolled than one with an unknown or normal outcome.

Good data to guide recommendations in this area are urgently needed including other important outcomes such as spontaneous abortion and termination of pregnancy.

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Pregnancy outcomes in women using non-AZT HAART in Europe

Polly Clayden, HIV i-Base

AZT is the only antiretroviral licensed for use in pregnancy. In resource rich settings AZT-containing regimens are becoming less and less common and in turn increasing numbers of women are becoming pregnant while receiving non AZT-containing HAART, or initiating non-AZT-containing HAART in pregnancy.

A poster at authored by Shema Tariq and colleagues reported findings from an investigation into the risk of detectable maternal viral load (VL) at delivery, congenital abnormality and mother to child transmission (MTCT) in pregnancies among women receiving HAART containing and not containing AZT. [1]

This analysis combined data from the National study of HIV in Pregnancy and Childhood (NSHPC) and the European Collaborative Study (ECS).

All live singleton births from 2000 to 2009 with ≥14 days of HAART in pregnancy were included. The investigators used logistic regression to estimate adjusted odds ratios (AOR).

A total of 7353 (6310, NSHPC and 1263, ECS) pregnancies were included, of which 1199 (15.8%) were exposed to non-AZT HAART. Of this group, 23.2% and 71.3% were on HAART prior to conception in the AZT and non-AZT groups respectively. Exposure to non-AZT HAART increased over time: 2000–2002 19.6% vs 17.1%, 2006–2009 41.4 vs 58.7% women received AZT vs non-AZT HAART respectively, p<0.01.

Tenofovir and abacavir was the most commonly used non-AZT drug in this cohort; approx 45% and 35% respectively.

In multivariate analysis the investigators found no evidence of associations between non-AZT HAART and detectable viral load at delivery, risk of congenital abnormalities (including in a sub-analysis of pregnancies with 1st trimester exposure or rate of MTCT, see Table 1.

Table1. Maternal and infant outcomes AZT vs non-AZT HAART multivariate analysis, AOR (95% CI)

	Detectable maternal VL at delivery	Congenital abnormalities (all pregnancies)	Congenital abnormalities (1st trimester HAART exposure)	MTCT
n	4212	7353	1930	6111
AZT HAART (ref. group)	1	1	1	1
Non-AZT HAART	0.90 (0.73-1.11); p=0.33	0.95 (0.64–1.41); p=0.80	0.76 (0.46–1.25); p=0.28	1.81 (0.77–4.26); p=0.18

The investigators noted that information on maternal VL at delivery was missing for 45% of pregnancies however the proportions of missing data were similar for both groups. Additionally HIV status was not yet reported for 20% of infants, mainly those born recently. They suggested that this is unlikely to introduce bias.

The investigators described these results as reassuring and that continued monitoring of pregnancy outcomes and longer term consequences of in utero exposure to these antiretroviral drugs is required.

Ref: Tariq S et al. Pregnancy outcomes in HIV-infected women using non-zidovudine HAART in Europe: 2000 to 2009. 17th CROI, San Francisco, 2010. Poster abstract 895.
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When should HAART be initiated in pregnancy to achieve an undetectable viral load?

Polly Clayden, HIV i-Base

Women who do not need treatment for their own HIV in resource-rich countries generally receive a short course of HAART in pregnancy to prevent mother to child transmission (MTCT).

It is considered a safe option for women with low or undetectable viral loads (VL) to choose vaginal delivery. BHIVA guidelines recommend a cut off of <50 copies/mL and the US guidelines <1000 copies/mL.

However the optimum timing to initiate short course HAART and achieve an undetectable viral load is uncertain.

A poster authored by Phillip Read and colleagues showed findings from a retrospective UK study across five centres in London and the South East, conducted to provide data for clinicians for the timing of short course HAART in pregnancy.

All available data were included for women commencing boosted PI, NNRTI or triple NRTI based HAART from 2000 onwards

In this study demographics, gestation, drug class, CD4 count, and VL results were collated. VL data were right-censored at delivery date and drug regimen analyses were intent-to-treat. Survival curves for reaching a viral load <50 copies/mL were stratified by VL at initiation of HAART. Cox's proportional hazards regression model adjusted for demographics and immuno-virological parameters.

In this study, 439 pregnancies met the inclusion criteria and 378 had sufficient data for analysis.

Of those evaluated, 70% of women were of black African origin and their mean age at conception was 29.9 (range 14.7–49.8) years. Median pre-treatment CD4 and viral load was 330 cells/mm3 (IQR 195–470) and 8243 copies/mL (IQR 2341-32,640).

For their regimen, 246 women (65%) started PI-, 129 (34%) NNRTI-, and 3 (1%) NRTI-based HAART, initiated at a median of 23.2 weeks gestation (IQR 20.4 to 26.3).

By their delivery date (mean 38 weeks), 292 (77%) women achieved VL <50 copies/mL after a median of 58 days. Pre-treatment VL was associated with both the time taken and the proportion achieving a VL <50 copies/mL at delivery, p<0.001.

A baseline viral load of <10,000, 10,000 to 50,000, 50,001 to 100,000, and >100,000 resulted in 91%, 73%, 54%, and 37% of women achieving <50 copies/mL at delivery, respectively.

In multivariate analysis, the hazard ratio (HR) for a NNRTI regimen achieving a viral load <50 copies/mL compared to a PI was 0.7 (95% CI 0.52 -0.94). If VL was >10,000, 58% of PI and 66% of NNRTI regimens achieved <50 copies/mL.

When baseline VL was <10,000 copies/mL, gestation at initiation of HAART did not significantly change the probability of a VL <50 copies/mL at delivery. With a baseline VL of 10,000–50,000 copies/mL, the HR for a VL <50 copies/mL declined to 0.51 if HAART was initiated after 23.3 weeks (p<0.01) while if viral load was >100,000, starting HAART before 20.4 weeks gave a HR of 0.2 (p <0.01) compared with 0.1 if started after 20.4 weeks (p <0.01).

The investigators concluded with four key messages:

- Women with a VL >10,000 copies/mL should commence HAART by 20.4 weeks
- Women with a VL >100,000 copies/mL should commence HAART without delay
- If the VL is <10,000 copies/mL, HAART may be deferred to 26 weeks
- If the VL is >10,000 copies/mL NNRTI-based HAART, where appropriate, may be more successful

And they noted: "Final decisions on mode of delivery often depend on the VL at 36 weeks gestation and this needs to be taken into account when starting HAART based on these data".

C O M M E N T

This analysis provides useful data to guide when to commence short course HAART in pregnancy.

Presumably, a larger proportion of women would commence long term treatment if they were starting according to current guidelines, as the median baseline CD4 count in this data set was 330 cells/mm3 (IQR 195–470), and previous guidance used a 200 CD4 cells/mm3 threshold at which to start HAART.

Ref: Read P et al. When Should HAART be initiated in pregnancy to achieve an undetectable viral load? 17th CROI, 16-19 February 2010, San Francisco. Poster abstract 896.

http://www.retroconference.org/2010/Abstracts/37418.htm

Pregnancy outcomes in infants exposed to maternal antiretrovirals in utero

Polly Clayden, HIV i-Base

Several posters at CROI 2010 showed findings from studies looking at outcomes in infants exposed to maternal antiretrovirals in utero.

Tenofovir exposure in DART

Enniie Chidziva and colleagues from the DART trial evaluated infants born to women mainly receiving tenofovir (TDF) based HAART in Uganda and Zimbabwe from 2004 to 2009. [1]

We have reported earlier results from the DART trial and pregnancy outcomes in previous issues of HTB. [2, 3]

During DART there were 223 live births with 6 infant deaths; 217 infants were alive two weeks after birth. Of these 129 (59%) were exposed to TDF in utero. Infants were evaluated in DART and in a separate follow up study.

The investigators reported that congenital abnormalities occurred in 7/217 (3%) of infants overall and 4/129 (3%) with TDF exposure. The abnormalities were: talipes 3 (2 with TDF exposure), cardiac 1, hydrocephalus 1(with TDF exposure), skin tag 1 (with TDF exposure) and undescended testes 1.

The majority 182/217 (84%) of infants were enrolled in the infant follow up study. At their last visit they were a median age of 26 months (IQR 13–39); 69% were <12 months of age. The investigators noted that infants who were not enrolled in the follow up study were likely to have been born during the earlier part of the trial.

Prophylaxis was given to 152/182 (84%) of infants (single-dose nevirapine 44%, AZT 18%, sd NVP+AZT 23%, other 15%)

Of the 182 infants, 73 were ever breastfed for median 92 days (range 5-1186 days). Unadjusted HR for currently BF vs never BF 0.45 (95% CI 0.05–3.62) and for stopped vs never BF 0.7 (95% CI 0.19–2.57, p=0.59).

Of the 171 children tested, all were HIV-negative, 3 were lost to follow up and 8 died before testing. Fourteen children died at a median age of 9.4 months, giving 6% 12-month mortality. Of these, 8 had in utero TDF exposure, 6 were HIV-negative and 8 untested.

Only 4/386 creatinine and 7/310 phosphate measurements were abnormal, all were grade 1 and confined to 7 children of which 4 were exposed to TDF in utero (3 throughout pregnancy and one 61% of time in utero). There was no evidence of an effect of TDF in utero on growth after 48 weeks (p=0.31) and there were no bone fractures.

Additionally, an Italian cohort study reported by Alessandra Vigano and colleagues showed that exposure to TDF during the second and third trimesters of gestation, when bone formation occurs, does not impair bone mass and bone metabolism in HIV-negative children born to HIV-positive women. [2]

Mashi and Mma Bana

Two studies with data combined from the Mashi and Mma Bana PMTCT trials in Botswana looked at infant anaemia and birthweight respectively. [5, 6]

We have reported on both trials in previous issues of HTB. [7, 8, 9, 10, 11]

Scott Dryden-Peterson and colleagues compared the incidence of severe and life-threatening (grade 3 or 4, DAIDS 2004 toxicity tables) anaemia in breastfed (BF) infants exposed to HAART in utero with BF and formula fed (FF) infants exposed to AZT in utero in these trials.

Endpoints were incidence of first severe anaemia from birth to 7 months and the analyses used scheduled measurements of first born uninfected infants.

A total of 1788 infants met the inclusion criteria (1096 Mashi, 692 Mma Bana). Of this group, 743 were exposed to maternal HAART (AZT+3TC+LPV/r or AZT+3TC+NVP), one month of post natal AZT and BF (categorised as HAART+BF; 517 to in utero AZT, 6 months of post-natal AZT, and breastfeeding (AZT+BF); and 528 infants to in utero AZT, 1 month of post-natal AZT, and formula feeding (AZT+FF).

The investigators reported there were 126 infants with severe anaemia by 7 months with a cumulative incidence of 12.6 % (n=89) in HAART+BF, 5.4 % (n=26) in AZT+BF, and 2.3 % (n=110 in AZT+FF.

Severe anaemia occurred more frequently among HAART+BF infants than either AZT+BF infants (OR 2.51, 95% CI 1.59-3.95), or AZT+FF infants (OR 6.11, 95% CI 3.2-11.6), both p<0.0001.

In multivariate analysis, predictors of severe anaemia (AOR; 95%CI) were: HAART+BF (2.4; 95%CI 1.5–3.8 and 5.7; 95%CI 3.0–10.7) compared to AZT+BF and AZT+FF, respectively; low birth weight <2.5 kg (2.4; 95%CI 1.5–3.9); and male sex (1.5; 95%CI 1.0–2.2). Maternal CD4, VL, haemaglobin, education, income, study site and gestation at delivery were not significantly associated with severe anaemia.

Birthweight <2.5kg occurred in 103 (13.97%), 43 (8.4%) and 31 (5.9%) of infants in the HAART+BF, AZT+BF and AZT+FF groups respectively.

The investigators reported no differences in infant anaemia according to maternal HAART regimen. Microcytosis or hypochromia

occurred in 39/89 (43.8%) infants in the HAART+BF group, with severe anaemia.

Patients with severe anaemia were treated with iron/multivitamin supplementation, and 10 infants (7.9%) received transfusions. Of those who improved to grade <3 with iron/multivitamin supplementation alone this occured in ≤30 days in 43 (34%), 31–90 days in 50 (39.7%) and >90 days in 18 (14.3%) infants. Three (2.4) infants died while grade 3–4 and 2 (1.6) were lost to follow up.

The investigators concluded: "The clinical implication of this finding requires further investigation to ensure that the established benefits of using HAART for MTCT prevention are maximised for all infants."

The same research group looked at the impact of HAART and short course AZT on longitudinal growth in a subset of Mashi and Mma Bana infants. They noted that HAART for PMTCT may lead to lower birth weight but longitudinal effects of in utero exposure on infant growth have not been previously reported.

In this analysis, Kathleen Powis and colleagues evaluated breastfed, HIV-uninfected infants born ≥37 weeks and exposed in utero to at least 2 weeks of either HAART or AZT. Infants in the HAART-exposed group received postnatal AZT for 1 month. Infants in the AZT-exposed group received 6 months of AZT-prophylaxis during breastfeeding.

The investigators calculated gender-based weight-for-age, length-for-age, and weight-for-length z-scores were using WHO Child Growth Standards. They compared mean z-scores using the Student's t- test and analysis of response profiles.

This analysis included 437 AZT-exposed infants from Mashi, and 592 HAART-exposed infants from Mma Bana.

Median maternal baseline CD4 counts were 393 and 337 cells/mm3 (p=<0.001) and median viral load 4.34 and 4.19 log copies/mL (p=0.04) for Mashi and Mma Bana women, respectively Demographics were similar between cohorts.

The median time of in utero AZT exposure was 5.7 weeks (range 2.0–10.9 weeks), and median in utero HAART exposure was 12.1 weeks (range 2.6–22.3 weeks).

Median birth weights were 3.1kg in AZT-exposed and 3.0kg in HAART-exposed (p<0.001). HAART exposed infants had significantly lower mean weight-for-age, length-for-age, and weight-for-length z-scores (p<0.001, p = 0.02, and p= 0.007, respectively).

However, the investigators reported that by 3 months of age the infants' median weight was no longer different by exposure group, and their weight remained similar to 6 months. Mean weight-for-age differed over time by exposure group (p <0.001). Length-for-age remained lower in the HAART-exposed group to 6 months of age, but weight-for-length improved significantly over time compared with AZT-exposed infants (p<0.001).

They noted that the proportions of infants with z-scores >2 standard deviations below the mean were not different between exposure groups.

These early developmental comparisons are useful and longer-term comparisons are planned. The investigators wrote: "The early correction of birth weight differences among HAART exposed infants is reassuring for programmes utilising maternal HAART for treatment and PMTCT."

C O M M E N T

Both DART and the Botswana group continue to provide urgently needed and excellent data on maternal /infant health and outcomes.

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections, 16-19 February 2010, San Francisco.

1. Chidziva E et al. Outcomes in infants born to HIV-infected mothers receiving long-term ART in the DART trial, 2004 to 2009. Poster abstract 924.
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3. Pregnancy rates and outcomes among women in the DART trial. HTB, October 2009.
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4. Vigano A et al. Exposure during gestation to HAART, including tenofovir, does not impair bone status and metabolism in HIV-positive children born to HIV-positive mothers. Poster abstract 926.
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9. Breast milk, HIV suppression and decreased mother to child transmission. HTB, October 2005.
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10. Response to nevirapine containing HAART following single dose nevirapine for PMTCT. HTB, February 2007.
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http://i-base.info/htb/4466

Maternal TB, HIV and pregnancy

Polly Clayden, HIV i-Base

Two posters looked at maternal TB in HIV-positive pregnant women.

Amita Gupta and colleagues from the SWEN India Study Group assessed the effect of maternal TB (prevalent or incident) between pregnancy to 12 months post-partum on risk of HIV MTCT. [1]

The SWEN trial compared the use of extended NVP to single dose NVP among breastfed infants to reduce MTCT of HIV. [2] A secondary objective of the trial was to look at maternal and infant morbidity and risk factors for MTCT.

Maternal VL, CD4, duration of breastfeeding, type of ART intervention and maternal hepatitis coinfection are well known to be factors associated with HIV MTCT. The role of maternal TB however has not been well characterised.

The investigators used multivariable logistic regression to determine the impact of maternal TB on HIV MTCT. They used WHO criteria to define TB cases and manual methods for AFB smear and culture.

They found, out of 783 mothers, with a median duration of follow up of 365 days (IQR 346-368), median CD4 472 cells/mm3 (IQR 317-667; 7% <200 cells/mm3), 3 had prevalent TB diagnosed in pregnancy and 30 had incident TB by 12 months post partum.

When they looked at maternal TB and HIV transmission, they found among mothers with any TB the HIV transmission rate was 30.3% (10/33) compared to 11.6% (87/750) among mothers without TB (OR 3.3 95%CI 1.5–7.2, p=0.02). When they restricted the analysis to maternal TB diagnosed before HIV transmission this gave a transmission rate of 20.7% (6/29) among mothers with TB compared to 12.3% (91/754) among mothers without, (OR 1.9 95% CI 0.8–4.8, p=0.17).

Mothers with TB had a higher baseline viral load than mothers who did not (85,651 copies/mL vs 37,639 copies/mL, p<0.01).

In multivariate analysis, maternal TB was associated with an OR 2.4 (95%CI 1.0–5.98), for HIV transmission adjusting for maternal factors (viral load, CD4, AZT, NVP, HAART) and infant factors (breastfeeding duration, infant NVP, gestational age, birth weight) associated with MTCT of HIV.

The investigators acknowledged that this analysis had limitations including that as a secondary trial endpoint it was likely to be underpowered, not all TB diagnoses were culture confirmed so some misclassification bias was possible and unmeasured confounders could possibly explain this finding.

However they concluded that maternal TB appears to be an important risk factor associated with HIV MTCT but that, "larger studies are needed to confirm this and to understand the pathogenesis since this appears to be independent of maternal viral load and CD4".

Celine Gounder and colleagues from the Perinatal HIV Research Unit performed a cross sectional study across six antenatal clinics in Soweto to look at provider initiated screening for TB among pregnant women.

The study included all pregnant women >18 years of age presenting to the clinics, who gave verbal consent to participate. Women presenting with obstetric complications or medical emergencies, who declined or were unable to provide verbal consent, and prisoners were excluded.

Regardless of their HIV status, women were screened for symptoms of active pulmonary TB ie, cough for ≥2 weeks, sputum production, fevers, night sweats or weight loss.

Information on their demographics, HIV status, CD4 count, and prior TB and HIV history was also collected at the time of symptom screening.

Any woman with any symptom of active TB was then asked to provide a single sputum specimen, which was sent for sputum smear microscopy, mycobacterial culture and identification, and INH/RIF drug-susceptibility testing.

The investigators reported that 3970 pregnant women were enrolled in the study between December 2008 and August 2009 who had a median age of 26 years (range 18-49).

Of these women, 1492 (36%) were HIV-positive. The percentages of women with CD4 count in the following strata at diagnosis were: 2% (0–50), 17% (51–00), 30% (201–350), 22% (351–500), 19% (>500), and 9% unknown (the investigator noted that 49%

had a CD4 count of ≤350 cells/mm3). Additionally, 5% had a prior history of TB disease, and 21% had previously been exposed to someone with active pulmonary TB.

The investigators reported that the prevalence of active pulmonary TB was 696/100,000 among HIV-positive pregnant women (10/1492 cases), and 200/100,000 among HIV-negative pregnant women (5/2478 cases). They did not identify any cases of MDR-TB.

The investigators wrote: "Provider-initiated TB screening among HIV-infected pregnant women is a high yield intervention, and should be integrated with PMTCT services."

They added: "Given that 49% of the women had CD4+ T cell counts ≤350 cells/mm3, both ART and IPT should be considered in high TB/HIV prevalence settings."

References

1. Gupta A et al. Maternal TB is associated with increased risk of HIV mother-to-child transmission. 17th Conference on Retroviruses and Opportunistic Infections (CROI), 16-19 February 2010, San Francisco. Poster abstract 899.
http://www.retroconference.org/2010/Abstracts/37899.htm
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http://www.retroconference.org/2010/Abstracts/37899.htm

ANTIRETROVIRALS

Non-refrigerated ritonavir tablet approved in Europe and the US

On 25 January in Europe and on 10 February 2010 in the US, the EMA and FDA, respectively, approved the new tablet formulation of ritonavir (Norvir) that does not require refrigeration. The previous capsule formulation was less heat-stable and required refrigerated storage.

This will affect patients using ritonavir as a booster for other protease inhibitors.

Differences in the labels for the new formulation includes new information on food. Unlike the capsule formulation, ritonavir tablets must be taken with meals. This is the current recommendation for all currently boosted protease inhibitors.

The US product label includes the following information about pharmacokinetics:

- Ritonavir tablets are not bioequivalent to ritonavir capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a single 100 mg ritonavir dose was administered as a tablet compared with a capsule, AUC (0-inf) met equivalence criteria but mean Cmax was increased by 26% (92.8% confidence intervals: ↑15 -↑39%).
- No information is available comparing ritonavir tablets to ritonavir capsules under fasting conditions
- A food effect is observed for ritonavir tablets. Food decreased the bioavailability of the ritonavir tablets when a single 100 mg dose of ritonavir was administered. Under high fat conditions (907 kcal; 52% fat, 15% protein, 33% carbohydrates), a 23% decrease in mean AUC (0-inf) [90% confidence intervals: ↓30%-↓15%], and a 23% decrease in mean Cmax [90% confidence intervals: ↓34%-↓11%]) was observed relative to fasting conditions. Under moderate fat conditions, a 21% decrease in mean AUC(0-inf) [90% confidence intervals: ↓28%-↓13%], and a 22% decrease in mean Cmax [90% confidence intervals: ↓33%-↓9%]) was observed relative to fasting conditions.
- However, the type of meal administered did not change ritonavir tablet bioavailability when high fat was compared to moderate fat meals."

C O M M E N T

Final sign off by the European Medicines Agency (EMA) is expected in April, and this new formulation is expected to be available for patients in the UK from June/July 2010.

Sources:

1. Abbott press statement. (25 January 2010).
http://www.abbott.com/global/url/content/en_US/40.45:45/general_content/General_Content_00517.htm

2. FDA list serve. (10 February 2010).

FDA safety review of saquinavir (Invirase) and possible association with abnormal heart rhythms

On 23 February 2010, the FDA issued notice about an ongoing safety review of the protease inhibitor saquinavir (Invirase) in combination with ritonavir (Norvir) in relation to cardiovascular risk in some patients.

The safety announcement for healthcare professionals is published below.

FDA Safety announcement

The U.S. Food and Drug Administration (FDA) is reviewing clinical trial data about a potentially serious effect on the heart from the use of saquinavir (Invirase) in combination with ritonavir (Norvir). The data suggest that together the two drugs may affect the electrical activity of the heart.

The changes to the electrical activity of the heart possibly associated with these drugs, known as prolonged QT or PR intervals, can be seen on an electrocardiogram (ECG). A prolonged QT interval can increase the risk for abnormal heart rhythms, including a serious abnormal rhythm called torsades de pointes. A prolonged PR interval can cause the electrical signal responsible for generating a heart beat to slow or even stop; this is known as heart block and can affect how fast the heart is able to beat.

Saquinavir and ritonavir are antiviral medications given together to treat HIV infection. Ritonavir is given at a low dose with saquinavir in order to increase the level of saquinavir in the body. This is a process known as "boosting."

FDA's analysis of these data is ongoing. However, healthcare professionals should be aware of this potential risk for changes to the electrical activity of the heart. Saquinavir and ritonavir should not be used in patients already taking medications known to cause QT interval prolongation such as Class IA (such as quinidine,) or Class III (such as amiodarone) antiarrhythmic drugs; or in patients with a history of QT interval prolongation.

Patients should not stop taking their prescribed antiviral medications. Patients who are concerned about possible risks associated with using saquinavir and ritonavir should talk to their healthcare professional.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs. The agency will update the public as soon as this review is complete.

Additional information for patients

Patients currently using saquinavir should:

- Not stop taking saquinavir without talking with their healthcare professional.
- Discuss any questions or concerns they have about saquinavir with their healthcare professional.
- Review their cardiovascular medical history and current medications with their healthcare professional to determine if they should continue using saquinavir.
- Report any side effects with saquinavir to FDA's MedWatch programme.

Additional information for healthcare professionals

FDA recommends that healthcare professionals:

Not use saquinavir in patients with a history of QT interval prolongation, preexisting conduction system disease, ischemic heart disease, cardiomyopathy, or underlying structural heart disease.

Not use saquinavir in patients who are currently using Class IA (such as quinidine) or Class III (such as amiodarone) antiarrhythmic drugs or other drugs that may prolong the QT or PR interval.

Report any adverse events associated with the use of saquinavir to FDA's MedWatch programme.

Data summary

The study data were submitted by Roche, the manufacturer of saquinavir, based on FDA's request that all manufacturers of protease inhibitors, including saquinavir, conduct a thorough QT study to evaluate the effect these drugs have on the QT and PR intervals.

The preliminary data show that when saquinavir boosted with ritonavir (1000mg/100mg) was given to healthy patients, ages 18 to 55 years, there was a dose-dependent prolongation of the QT and PR intervals. The magnitude of the effect and clinical implications of QT and PR interval prolongation are still being reviewed by FDA.

These findings suggest that some patients using saquinavir boosted with ritonavir may be at an increased risk for developing abnormal heart rhythms. In particular, this risk may be increased in patients using other medications known to cause QT interval prolongation such as Class IA and Class III antiarrhythmic drugs or in patients with a history of QT interval prolongation.

Source: FDA Drug Safety Communication: Ongoing safety review of Invirase (saquinavir) and possible association with abnormal heart rhythms. (23.03.2010)

http://www.fda.gov/Drugs/DrugSafety

FDA updates US label for darunavir (Prezista)

On 27 January 2010, the FDA approved revisions to the darunavir (Prezista) product labeling to include the 96 week data from two trials; one trial in treatment-experienced patients (TMC114-C214) and one trial in treatment-naïve patients (TMC114-C211).

Additional revisions included:

- Updating the contraindications to include for alfuzosin
- Adding drug hypersensitivity, angioedema and urticaria as less common adverse reactions
- Adding a new section to identify osteonecrosis as an Adverse Drug Reaction (ADR).
- Including redistribution of body fat and toxic epidermal necrolysis as potential side effects (from post-marketing reports).
- Updating maraviroc drug interaction data. In summary maraviroc concentrations are increased when co-administered with darunavir/ritonavir, requiring a dose reduction of maraviroc to 150 mg twice daily.
- Additional resistance data and baseline genotype and phenotype virologic analyses and cross-resistance data were also included.

The updated labeling will be posted to the FDA website at:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda

Source: FDA list serve (27 January 2010)

FDA safety announcement about ddI and non-cirrhotic portal hypertension

On 29 January 2010, the US FDA alerted healthcare professionals and patients about a rare, but serious, complication in the liver known as non-cirrhotic portal hypertension in patients using ddI or ddI EC (didanosine, tradenames Videx and Videx EC).

Non-cirrhotic portal hypertension (portal hypertension that is not caused by cirrhosis of the liver) is rare in the United States. It occurs when blood flow in the major vein in the liver (the portal vein) slows down. This slowed blood flow can lead to the development of severely enlarged esophageal veins (varices) in the gastrointestinal system. Because oesophageal varices are thin and portal hypertension increases the pressure of blood flow in these veins, oesophageal varices can break open. This can result in serious bleeding and, in some cases, death.

FDA became aware of cases of non-cirrhotic portal hypertension through adverse event reports submitted to FDA's Adverse Event Reporting System (AERS). Based on these reports, FDA has revised the didanosine drug label to include information about non-cirrhotic portal hypertension to help ensure the safe use of this drug.

FDA believes the clinical benefits of didanosine for certain patients with HIV continue to outweigh its potential risks. The decision to use this drug, however, must be made on an individual basis between the treating physician and the patient.

Data summary

FDA's decision to revise the drug label for ddI is based on post-marketing reports of patients developing non-cirrhotic portal hypertension while using ddI. Other liver adverse events such as lactic acidosis, hepatomegaly with steatosis, and liver failure have been reported with the use of ddI alone and in combination with other antiviral drugs.

Of the 42 post-marketing cases of non-cirrhotic portal hypertension in patients using ddI:

- Twenty-six were males, 14 were females, and in two no gender was specified.
- Ages ranged from 10 years to 66 years.
- Duration of ddI treatment ranged from months to years before development of non-cirrhotic portal hypertension.
- Definitive cases of non-cirrhotic portal hypertension were confirmed by biopsy and had no alternative etiology for the diagnosis.
- Medical interventions described in the reported cases included:
- Banding/ligation of oesophageal varices in 8 patients.
- Transjugular intrahepatic portosystemic shunt (TIPSS) procedure in three patients.
- Liver transplantation in 3 patients.

There were four deaths in total in the 42 reported cases. The cause of death in the four patients was due to:

- Hemorrhage from oesophageal varices in two patients.
- Progressive liver failure in one patient.
- A combination of multi-organ failure, cerebral hemorrhage, sepsis, and lactic acidosis in one patient.

The only patients who have been reported as fully recovered are the three non-cirrhotic portal hypertension patients who received a liver transplant.

A causal association is difficult to determine from postmarketing reports alone. However, based on the number of well-documented cases and exclusion of other causes of portal hypertension such as alcohol-related cirrhosis or hepatitis C, FDA concludes there is an association between use of didanosine and development of non-cirrhotic portal hypertension. Because of the potential severity of portal hypertension, including death from hemorrhaging esophageal varices, FDA has revised the *Warning and Precautions* section of the didanosine drug label to assure safe use of the medication.

The labeling for the ddI EC and ddI paediatric powder for oral solution have been revised to reflect this new information and will be posted to the FDA website at:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda

Source: FDA Data Safety Announcement (29 January 2010)
http://www.fda.gov/Drugs/DrugSafety

FDA label change for lopinavir/r (Kaletra)

On 29 January 2010, the FDA revised the Kaletra (lopinavir/ritonavir) package insert to include drug-drug interaction information with inhaled medicines such as salmeterol or salmeterol in combination with fluticasone propionate (Serevent, Advair) and sildenafil (Revatio).

Specifically, sildenafil (Revatio) when used for the treatment of pulmonary arterial hypertension is listed under Contraindications (Section 4, Table 3) because a safe and effective dose has not been established when used with Kaletra. There is an increased potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erections and syncope. Additionally, in Section 7 Drug Interactions, Table 9 was revised to include this information and differentiate use of PDE5 inhibitors for pulmonary arterial hypertension and for erectile dysfunction

Section 7 Drug Interactions Table 9 was revised to include the following information on salmeterol.

Concurrent administration of salmeterol and Kaletra is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

Section 17 Patient Counseling Information was revised to state:

If they are receiving sildenafil, tadalafil, or vardenafil they may be at increased risk of associated adverse reactions including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor

If they are taking or before they begin using Serevent (salmeterol) and Kaletra, they should talk with their doctor about problems these two medicines may cause when taken together. The doctor may choose not to keep someone on Serevent (salmeterol)

If they are taking or before they begin using Advair (salmeterol in combination with fluticasone propionate) and Kaletra, they should talk to their doctor about problems these two medicines may cause when taken together. The doctor may choose not to keep someone on Advair (salmeterol in combination with fluticasone propionate).

The revised label will be posted to the FDA website at:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda

Source: FDA list serve (29 January 2010)

FDA notice about drug interactions with etravirine (Intelence)

FDA recently updated Intelence (etravirine) label to include drug-drug interaction information between etravirine and fluconazole, voriconazole, lopinavir/ritonavir tablets and clopidogrel. The major changes to Section 7 Drug Interactions are summarised below.

In additon the magnitude of the interaction for etravirine in the presence of fluconazole, voriconazole and lopinavir/ritonavir tablets can be found in section 12.3 Pharmacokinetics.

Etravirine - fluconazole and voriconazole: Co-administration of etravirine and fluconazole or voriconazole significantly increased etravirine exposures. The amount of safety data at these increased etravirine exposures is limited; therefore, etravirine and fluconazole or voriconazole should be co-adminstered with caution. No dose adjustments of etravirine, fluconazole or voriconazole is needed.

Etravirine - lopinavir/ritonavir tablets: Intelence and Kaletra (lopinavir/ritonavir) tablets can be coadministered without dose adjustment.

Etravirine - clopidogrel: Activation of clopidogrel to its active metabolite may be decreased when clopidogrel is co-administered with etravirine. Alternative to clopidogrel should be considered.

Please also refer to the full lable available online:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda

PDF link:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022187s003lbl.pdf

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
Tenofovir DF, 300mg tabs	Hetero, India	06 April 2010
Nevirapine tablets for oral suspension, 50 mg, for children weighing ≥5 kg	Aurobindo, India	24 February 2010
Efavirenz cross-scored tablets, 200 mg (to be broken into two 100 mg or four 50 mg doses for paediatric dosing.	Strides Arcolab, India	12 February 2010

"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 108 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

Waiting lists grow in the US

Due to the poor economy and increased HIV testing efforts, the US public assistance programme called ADAP (AIDS Drug Assistance Programmes) across are facing unprecedented growth and severe funding shortages and placing people on waiting lists, cutting eligibility and removing drugs from their formulary. The HIV/AIDS community is asking for a $126 million emergency appropriation from President Obama and the Congress.

On 10 April 2010, the 859 individuals currently on ADAP waiting lists by state were: Idaho (25), Iowa (62), Kentucky (191), Montana (17), North Carolina (356), South Carolina (33), South Dakota (32), Tennessee (55), Utah (74) and Wyoming (14).

Cost-containment strategies instituted over the last years included reducing formularies, lowering the level of financial eligibility, using a CD4 threshold of <350 cells/mm3, initiating waiting lists, capping enrollment and capping use of T-20.

For an update on the states with waiting lists and other cost containment measures go to the ADAP Watch update at:

http://www.nastad.org/

South African antiretroviral treatment guidelines updated

Polly Clayden, HIV i-Base

The South African Antiretroviral Treatment guidelines have finally been updated. [1]

These have been long-awaited as the last full edition was in 2004.

Important revisions include the use of tenofovir (TDF) in first line treatment (replacing d4T), more complex prophylaxis regimens and earlier treatment for pregnant women and universal treatment for infants <12 months of age.

The treatment guidelines are also summarised in an abridged version with a series of tables incorporating key recommendations from all three documents.

Management of adults and adolescents

When to start?

Antiretrovirals should be started in all HIV-positive patients with CD4 ≤200 cells/mm3 irrespective of clinical stage.

People with TB/HIV and pregnant women should start antiretroviral treatment at CD4 ≤350 cells/mm3. People with WHO stage 4 or DR TB should start treatment irrespective of their CD4 count.

What to start?

The recommended first line regimens for all new patients are:

- TDF+3TC or FTC+EFV
- TDF+3TC or FTC+NVP

Already receiving d4T-based regimen

If d4T is well tolerated patients should remain on this regimen. An early switch is recommended for any toxicity. People at high risk for toxicity (high BMI, low Hb, older female) should switch d4T for TDF.

Fast track

Pregnant women indicated for treatment, people with very low CD4 (<100 cells/mm3) and stage 4 with CD4 count not yet available and those with MDR/XDR TB, should be fast tracked ie start ART within two weeks of being eligible.

When to switch

Virlogical failure (>1000 copies/mL) over 3 months despite adherence interventions.

Second-line ART

Failing on d4T-based regimen:

- TDF+3TC or FTC +LPV/r

Failing on a TDF-based regimen:

- AZT+3TC+LPV/r

Third-line ART

Specialist referral where possible, but maintain on a failing regimen.

C O M M E N T

That these guidelines did not adopt <350 cells/mm3 as the threshold for starting treatment for all, in line with the WHO, the Southern African Clinicians Society and many national guidelines, has raised much discussion. [2] Arguably this consideration may be largely academic in a country where the median CD4 count at initiation is still about 100 cells/mm3 despite a massive scaling up of testing. [3]

However, now that the SA Ministry of Health is about to launch a campaign to test 15 million people by June next year, this situation is likely to change. Earlier treatment for select groups and fast track for those most at risk however are very welcome.

An important change is the replacement of d4T with TDF for first-line regimens. As well as following guidance to avoid the more dramatic effects of lactic acidosis, hopefully "well tolerated" and "early switch" will be interpreted in the very best interests of patients who have endured peripheral neuropathy or lipoatrophy associated with this drug. Equally dropping ddI from second-line regimens, though not affecting such large numbers of people, is a vast improvement.

Prevention of mother to child transmission

These guidelines make recommendations for pregnant women both eligible and ineligible for treatment and for infant feeding.

When to start?

As above, CD4 <350 cells/mm3.

What to start?

TDF+3TC or FTC +NVP

Women already receiving ART should substitute EFV with NVP if in first 12 weeks of pregnancy. Women contraindicated to TDF should receive AZT+3TC+NVP.

Prophylaxis for women CD4 >350 cells/mm3

AZT from 14 weeks + single dose NVP + AZT three hourly during labour; TDF+FTC single dose post delivery.

Infant regimens

Breast fed or formula fed infants of mothers on HAART: NVP at birth and daily for 6 weeks.

Breast fed or formula fed infants of mothers receiving prophylaxis: NVP at birth and daily for 6 weeks if formula fed or until cessation of breast feeding.

C O M M E N T

Guidance for pregnant women is broadly similar to WHO recommendations. However, the approach to use of efavirenz is far more cautious. Whereas the WHO interpreted the low quality, conflicting evidence for the risks of in utero exposure to confine the contraindication to the first trimester, these guidelines do not recommend its inclusion at all in pregnancy. From an operational point of view this will make treatment of pregnant women a bit more complicated and inconsistent with general adult recommendations. Efavirenz has a number advantages where simplification is important, it can be taken once daily in a fixed dose combination with TDF and FTC, unlike nevirapine there is no extra monitoring for rash and/or hepatoxicity risk and it can be used in conjunction with TB treatment.

The choice of a single dose of TDF/FTC "tail" coverage is an interesting one, whereas the WHO recommend 7 days of 3TC/AZT and this has been adopted by several national programmes, some have suggested that this may be too complicated to implement.

Chi et al showed a reduction in resistance using a single dose of TDF/FTC from approx 30% to 14% among women with CD4 cell counts of about 475 cells/mm3 receiving single dose nevirapine (women with CD4 <200 cells/mm3 were excluded and received HAART), of which approximately 80% received antepartum AZT for a median of about 37 days, and 30% had undetectable viral load at delivery. [4]

It is likely that a treatment threshold of <350 CD4 cells/mm3 will further exclude women most at risk for NNRTI resistance and this approach may offer a reasonable compromise between reduction of resistance risk and ease of implementation.

Management of HIV in children

When to start?

- Universal treatment for infants <12 months old.
- Clinical stage 3 or 4 or CD4 ≤25% or absolute CD4 <750 cells/mm3 for children age 1-5 years.
- Clinical stage 3 or 4 or CD4 ≤ 350 cells/mm3 for children ≥5 years to 15 years.

What to start?

- Infants and children <3 years old: ABC+3TC+LPV/r.
- Children >3 years old: ABC+3TC+EFV.

Second line

Children >3 years old failing ABC+3TC+EFV: AZT+ddI+LPV/r

Children >3 years old failing an AZT- or ddI-based regimen: ABC+3TC+LPV

Children failing a LPV/r-based regimen and/or <3 years old who are failing first-line require specialist referral.

C O M M E N T

Universal treatment for infants <12 months old and initiation at CD4 350 cells/mm3 for children >5 years old reflects current international consensus. Treatment for children between 1 and 5 years has little data to guide us, and WHO and national guidelines all give slightly different recommendations.

That the threshold for initiation for children and adolescents between 5 and 15 years old is 350 cells/mm3 for all differs from adult recommendations, where a considerable number of people will not be eligible for treatment until CD4 drops to 200 cells/mm3.

References

1. SA Dept of Health. The South African Antiretroviral Treatment Guidelines, 2010. http://www.sanac.org.za/resources/art-guidelines
2. WHO. New HIV recommendations to improve health, reduce infections and save lives. (01 December 2009). http://www.who.int/mediacentre/news/releases/2009/world_aids_20091130/en/index.html
3. Geffen N. Guidelines on when to start treatment in resource poor settings. HTB, October 2009. http://i-base.info/htb-south/190
4. Chi BH et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. Lancet. 2007 Nov 17;370(9600):1698-705. Epub 2007 November. http://www.ncbi.nlm.nih.gov/pubmed/17997151

Tenofovir registered in Russia

On 30 March 2010, the Russian healthcare authorities registered a generic formulation of tenofovir 300 mg, manufactured by Hetero Drugs Ltd, India, to be distributed by MakizPharma in Russia.

However, although tenofovir will now be available, this is only through commercial individual purchase because it has yet to be included in either the national HIV treatment standards, or in the list of the government procurement for 2010.

Source: Russian Community of PLHIV
http://www.positivenet.ru

MSF criticise Abbott over new ritonavir formulation

MSF press statement

Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration have recently approved the long-awaited heat-stable 100mg tablet version of ritonavir, the antiretroviral booster drug produced by Abbott Laboratories.

The market authorisation of a heat-stable version of ritonavir as a separate pill finally ends both the stranglehold by Abbott on the treatment options available to people living with HIV/AIDS and the medical double standards the company has promoted by failing to prioritise the development of safer versions of its medicines. Protease inhibitors (PIs) are the cornerstones of second-line AIDS therapy, as set out in World Health Organization (WHO) guidelines.

PI-based regimens recommended in the guidelines include a booster drug, to be taken in conjunction with the PI, in order to make the regimen more effective. Ritonavir is still the only approved booster in existence.

Although Abbott has been marketing the heat-stable version of ritonavir since 2005, this has only been as a fixed-dose combination with its own protease inhibitor, lopinavir - not as a separate heat-stable pill. Until now, 'standalone' 100mg ritonavir was only available in a soft-gel formulation that requires refrigeration, making it extremely ill-suited for use in developing countries. This in turn severely restricted the choice of protease inhibitors for people on antiretroviral treatment, particularly in the developing world, as the use of all PIs other than Abbott's own lopinavir came with refrigeration constraints.

By failing to move faster on creating a separate ritonavir tablet, the company therefore built a market advantage for its own PI lopinavir, and made the use of other life-saving protease inhibitors less practical.

Abbott's delay extends to promoting medical double standards. The soft-gel version of ritonavir comes with more side effects and more dietary restrictions than the heat-stable version. In fact in 2007, the EMA raised this as a public health concern with Abbott. The absence of a heat-stable ritonavir also restricted the possible use of second-line AIDS drugs for patients co-infected with tuberculosis.

As a result of Abbott's inaction, many people living with HIV have therefore been deprived of additional, improved and vital treatment options.

Looking ahead, one particular area of need is the development of a heat-stable combination of atazanavir and ritonavir, one of the two PIs (with lopinavir/ritonavir) recommended by WHO for second-line treatment. A fixed-dose combination of atazanavir/ritonavir would in fact present considerable advantages over lopinavir/ritonavir, as it will reduce the pill burden from four to one pill a day.

Other PIs that require boosting with ritonavir are darunavir (which WHO indicates may form part of a future third-line antiretroviral therapy), and nearly all other PIs are more effective when used with a ritonavir booster. But to date, Abbott has not allowed manufacturers to produce any of these PIs in a fixed-dose combination with ritonavir.

It is hoped that generic manufacturers in developing countries will move forward with the development and registration of such boosted heat-stable PIs as fixed-dose combinations. Where there are potential patent barriers that prevent them from doing so, use should be made of safeguards in patent laws to ensure these are overcome.

MSF calls on Abbott to:

- Register heat-stable ritonavir tablet widely in developing countries.
- Ensure that the price is affordable to patients in all developing countries (Abbott's discounted price of US$83 per person per year for the heat-stable and soft-gel versions of ritonavir is only available for the absolute poorest countries).
- Develop a more adapted heat-stable paediatric formulation of lopinavir/ritonavir (such as soluble granules or sprinkles) for young children who can not swallow the existing tablet.
- Facilitate access to more affordable versions of ritonavir and fixed-dose combinations containing ritonavir by putting the patents on ritonavir into the Patent Pool for HIV medicines currently being set up by UNITAID.

Source: Médecins Sans Frontières - Campaign for Access to Essential Medicines press statement. MSF press statement "Approval of heat-stable ritonavir ends years of neglect by Abbott: years of medical double standards and stranglehold by Abbott come to an end". (12 February 2010).
http://www.msfaccess.org

BHIVA GUIDELINES

BHIVA draft guidelines for the treatment of opportunistic infections: online for comment

The 2010 British HIV Association guidelines for the treatment of opportunistic infection in HIV-positive individuals are now posted to the BHIVA website for comment.

Advances in the treatment of HIV infection with antiretroviral therapy have led to dramatic reductions in opportunistic infections and death. However, late presentation of HIV remains a problem and is a significant contributory cause to death in HIV-positive persons in the UK. Furthermore, a recent UK Health Protection Agency (HPA) analysis showed that of 46,700 patients with diagnosed HIV, 19% had CD4 counts <200 cells/mm3 and therefore remain at significant risk of opportunistic infection.

These guidelines have been drawn up to help physicians investigate and manage HIV-positive patients suspected of, or having an opportunistic infection (OI). The early chapters consider the most common presentations of OI disease such as respiratory, gastrointestinal and neurological disease. Then follow specific organisms such as Candida spp, herpes simplex virus and varicella zoster virus. Finally, special circumstances including pregnancy, the use of the intensive care unit, fever of undetermined origin and management of imported infections, are also addressed.

Each section contains information on the background, epidemiology, presentation, treatment and prophylaxis of OIs. Further information on the role of antiretroviral therapy is also discussed (see below).

The Guidelines Writing Group is grateful for all comments, which will be reviewed before publication.

http://www.bhiva.org

BASIC SCIENCE

Early predictors of disease progression

Richard Jefferys, TAG

Recent research involving SIV-infected macaques has suggested that the early loss of a particular type of memory CD4 T cell (known as a “central memory” T cell or Tcm) may be a key predictor of the subsequent pace of disease progression. Tcm are a long-lived subset of memory T cells that can proliferate robustly in response to antigen. Tcm proliferation generates a fleet of T cells belonging to a shorter-lived subset called “effector memory” (Tem) cells. Tem are generally viewed as first-responders that can rapidly execute anti-pathogen functions, while Tcm provide a stem-cell like renewal source for new Tem if their numbers need to be bolstered. Studies in HIV-infected people have consistently shown a loss of Tcm and increase in Tem (which equates to a decrease in long-lived resting T cells and an increase in short-lived activated T cells), but whether changes in the numbers of different T cell subsets during early infection can predict disease progression has not been thoroughly evaluated.

A new study published in the Journal of Infectious Diseases set out to answer the question of whether quantifying Tcm in early infection provides prognostic information. To provide sufficient statistical power to ensure confidence in the findings, a total of 466 individuals were studied, among whom 101 progression events occurred.

It turned out that the proportion or absolute number of Tcm did not correlate with subsequent disease progression (defined as the time to AIDS or death), but several other parameters did. These included the proportion of naïve CD8 T cells, with a greater proportion being strongly associated with slower disease progression ($p<0.001$); this correlation remained significant after adjustment for CD4 T cell count. The numbers of CD8 T cells expressing the IL-7 receptor (CD127) were also linked to the rate of progression; having fewer of these cells correlated with a faster disease course.

Immune activation was assessed by measuring the proportion of CD4 and CD8 T cells expressing the proliferation marker Ki67. In both subsets, higher proportions of Ki67-expressing cells equated to faster progression, and for CD8 T cells this relationship held up after adjustment for baseline CD4 T cell count, age, and viral load. The median time to AIDS or death among subjects with the highest levels of Ki67-expressing CD8 T cells (based on dividing participants into quartiles) was 4 years for those in the top quartile compared to 10 years for those in the lowest.

Finally, measures of cell-associated viral load (CAVL: the proportion of CD4 T cells containing HIV DNA) were correlated significantly with progression in those participants sampled within 225 days of their estimated date of seroconversion (225 days was the median time after the estimated date of seroconversion that samples were obtained). Among participants sampled later, CAVL was not significantly correlated with rate of progression, suggesting an important impact of the early spread of HIV among CD4 T cells on subsequent disease course. The researchers also evaluated CAVL in different CD4 T cell subsets: naïve, central memory, transitional memory and effector memory. To their surprise, naïve CD4 T cells showed relatively high rates of infection, albeit around 10-fold lower than the memory subsets. Because resting naïve CD4 T cells are known to be very resistant to HIV, the researchers speculate that the infected naïve cells may have been rendered susceptible by immune activation (naïve CD4 T cells have been shown to become susceptible to R5-using HIV after they receive activation signals).

The authors conclude by stating: "we find that quantification of Tcm cells in early infection does not provide predictive power for progression. However, measures of homeostasis and activation, including CD127 expression and Ki-67, do provide such information and should be studied further to determine their role in clinical monitoring of HIV-1 progression…Future efforts to identify markers of subsequent progression should focus on measures of activation and homeostasis during the earliest stages of infection."

Source: TAG Basic Science Blog. (13 Jan 2010).

Ref: Ganesa A et al. Immunologic and virologic events in early HIV infection predict subsequent rate of progression. J Infect Dis 2010;201:272–284. doi: 10.1086/649430.

http://www.journals.uchicago.edu/doi/abs/10.1086/649430

Sex and the single microbicide

Richard Jefferys, TAG

The levels and distribution of an anti-HIV microbicide in the genital tract are likely to be critical factors in determining potential efficacy. Up until now, research studies have typically assessed microbicide levels in sexually abstinent women, which neglects to consider the potential impact of sexual activity. A new study in PLoS One looks at whether the physical act of sex and the introduction of semen into the genital tract affects the microbcide candidate 0.5% PRO 2000 gel. The study was conducted and completed before the recent announcement that 0.5% PRO 2000 gel had failed to show efficacy in preventing HIV infection in a large randomized clinical trial.

The results showed that 0.5% PRO 2000 gel levels were significantly lower after sex, and this correlated with a reduced ability of cervicovaginal lavage (CVL) from gel-treated women to inhibit HIV and HSV-2 in vitro. It was noted, however, that lower gel concentrations did not fully explain the reduction in antiretroviral activity; additional experiments revealed that seminal plasma also had an independent effect.

The researchers acknowledge that their study has limitations, including a small sample size and a single-dose approach that may underestimate microbicide levels compared to repeat dosing. Nevertheless, they suggest that "the current paradigm of microbicide development should be modified to include postcoital sampling following single and repeated dosing with both active and placebo products and should be expanded to include both CVL and biopsies to more fully define the pharmacokinetics and pharmacodynamics of lead candidates prior to embarking on large-scale efficacy trials."

Source: TAG Basic Science Blog. (29 Jan 2010).

Ref: Keller MJ et al. Postcoital bioavailability and antiviral activity of 0.5% PRO 2000 gel: implications for future microbicide clinical trials. PLoS ONE 5(1): e8781. doi:10.1371/journal.pone.0008781.

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0008781

Baseline naïve CD4 T cell numbers predict the immunological response to ART

Richard Jefferys, TAG

The loss of naïveté that comes with getting older is familiar to just about everyone. Somewhat less familiar is the fact that this is also true immunologically; our repertoire of naïve T cells and B cells – vital to responding to pathogens that have not previously been encountered, and keeping up with evolving chronic infections – steadily diminishes. For T cells, the loss is associated with declining output from the thymus, which also shrinks in size over time. It has been appreciated for many years that chronic infections can accelerate the pace of naïve T cell decline, but the effects of HIV far exceed those of any other chronic virus; progression to AIDS is typically associated with an almost complete loss of naïve CD4 and CD8 T cells.

Recent studies of long-term immune reconstitution on antiretroviral therapy (ART) have identified the ratio of naïve T cells to memory T cells as an important factor predicting the extent of CD4 T cell repopulation after 7+ years of treatment. [1]

A study from Timothy Schacker at the University of Minnesota now addresses the question of whether baseline measures of naïve CD4 T cell numbers can predict the potential for immune reconstitution on ART. [2]

The results of an analysis of 348 participants in AIDS Clinical Trials Group (ACTG) trials show that, indeed, baseline naive but not total CD4 T cell counts strongly predicted the magnitude of CD4 T cell increases after ART initiation. Lower naïve CD4 T cell levels at baseline were also associated with greater time spent with low CD4 T cell counts on ART, which is known to be associated with a greater risk of clinical events. The study findings suggest that measurements of naïve CD4 T cells could help optimize timing of ART initiation and lessen the incidence of poor immune reconstitution despite HIV suppression.

Source: TAG Basic Science Blog (01 March 2010)

References:

1. Immune recovery on antiretroviral therapy. TAG Basic Science Blog (04 February 2009).
2. Schacker TW et al. Measurement of naive CD4 cells reliably predicts potential for immune reconstitution in HIV. J Acquir Immune Defic Syndr. 2010 Feb 24. [Epub ahead of print]

http://journals.lww.com/jaids/Abstract/publishahead/Measurement_of_Naive_CD4_Cells_Reliably_Predicts.99039.aspx

Has poor CD4 T cell reconstitution in the gut been exaggerated?

Richard Jefferys, TAG

In recent years, loss of CD4 T cells from the gut of HIV-positive people has become a major research focus. Gut CD4 T cell depletion happens rapidly after infection, and many studies have suggested that recovery of these cells is typically limited even after prolonged antiretroviral therapy (ART). However, the bleakest data has been obtained by measuring the percentage of CD4 T cells in the gut relative to other lymphocytes, and this can produce misleading results because CD8 T cell numbers are increased in the setting of HIV infection.

A new paper from Irini Sereti's laboratory at NIAID reports that the picture is far more encouraging when absolute numbers of CD4 T cells are measured. Taking samples from both the colon and terminal ileum, the researchers show that absolute CD4 T cell numbers among people on long-term (>5 years) ART with viral loads less than 50 copies are comparable to uninfected controls. The numbers are expressed as CD4 T cells per gram of tissue and the results for the ART-treated vs. control group were as follows: $3.9x10^6$ vs. $3.6x10^6$ (colon) and $1.0x10^6$ vs. $1.6x10^6$ (terminal ileum). The researchers note that in some prior papers, "the persistence of a high proportion of CD8 T cells in HIV-infected patients appeared to result in an underestimation of CD4 T cell reconstitution… our findings are in agreement with recent studies using both immunohistochemistry and flow cytometric analyses; some of these have suggested that gut CD4 T-cell reconstitution may even exceed what occurs in peripheral blood."

The researchers also write: "It has also been proposed that initiating ART therapy during acute infection may result in more rapid and complete reconstitution of the CD4 T-cell population in the gut. Three of the four patients in this study who reconstituted their CD4 T-cell counts in the colon to values higher than the median of the HIV-uninfected group had peripheral nadir CD4+ T-cell counts of less than 250 cells per microliter. This suggests that CD4 T-cell restoration may occur despite substantial disease progression before ART initiation."

Source: TAG basic science blog. Have Rumors of Poor Gut CD4 T Cell Reconstitution Been Greatly Exaggerated? (24 March 2010).

Ref: Ciccone EJ et al. Cycling of gut mucosal CD4+ T cells decreases after prolonged anti-retroviral therapy and is associated with plasma LPS levels. Mucosal Immunology (2010) 3, 172–181; doi:10.1038/mi.2009.129; published online 2 December 2009
http://www.nature.com/mi/journal/v3/n2/abs/mi2009129a.html

ON THE WEB

Journal articles

PLoS Medicine

http://www.plosmedicine.org

Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study - Myer L et al.

A multicountry cohort study in sub-Saharan Africa by Landon Myer and colleagues reveals higher pregnancy rates in HIV-infected women on antiretroviral therapy (ART).

Pretreatment CD4 cell slope and progression to AIDS or death in HIV-infected patients initiating Antiretroviral Therapy—The CASCADE Collaboration: A Collaboration of 23 Cohort Studies - Wolbers M et al.

Analysing data from several thousand cohort study participants, Marcel Wolbers and colleagues find that the rate of CD4 T cell decline is not useful in deciding when to start HIV treatment.

Effectiveness of Non-nucleoside Reverse-Transcriptase Inhibitor-Based Antiretroviral Therapy in Women Previously Exposed to a Single Intrapartum Dose of Nevirapine: A Multi-country, Prospective Cohort Study - Stringer JAS et al.

In a comparative cohort study, Jeffrey Stringer and colleagues investigate the risk of ART failure in women who received single-dose nevirapine for PMTCT, and assess the duration of increased risk.

Causes of Acute Hospitalization in Adolescence: Burden and Spectrum of HIV-Related Morbidity in a Country with an Early-Onset and Severe HIV Epidemic: A Prospective Survey - Ferrand RA et al.

Rashida Ferrand and colleagues show that HIV infection is the commonest cause of hospitalisation among adolescents in a high HIV prevalence setting.

FUTURE MEETINGS

2010 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.

45th International Liver Congress (EASL)

14-18 April 2010, Vienna

http://www2.kenes.com/liver-congress/pages/home.aspx

2nd Joint Conference of BHIVA with BASHH

20–23 April 2010, Manchester

http://www.bhiva.org

6th Intl Workshop on HIV and Hepatitis C Coinfection

31 May–2June 2010, Tel Aviv

http://www.virology-education.com

5th International Workshop on Clinical Pharmacology of Hepatitis Therapy *and* 5th International Workshop on Hepatitis C - Resistance and New Compounds

23–24 June and 24–25 2010, Boston

http://www.virology-education.com

5th International Workshop on HIV Transmission - Principles of Intervention

15-16 July 2010, Vienna

http://www.virology-education.com

2nd International Workshop on HIV Pediatrics

16-17 July 2010, Vienna

http://www.virology-education.com

XVIII International AIDS Conference (AIDS 2010)

18-23 July 2010, Vienna

http://www.aids2010.org

50th ICAAC

12–15 September 2010, Boston

http://www.icaac.org

3rd Intl Workshop on Clinical PK of TB Drugs

11 September 2010, Boston

http://www.virology-education.com

BHIVA Autumn Conference

7–8 October 2010, London

http://www.bhiva.org

12th Lipodystophy Workshop 2010

4–6 November 2010, London

http://www.intmedpress.com/lipodystrophy

10th International Congress on Drug Therapy in HIV Infection

7-11 November 2010, Glasgow

http://www.hiv10.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website has been completely redesigned with new portals for healthcare professionals, HIV-positive people and community advocates.

It is even faster and easier to access, use and 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/qa

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.

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://i-base.info/category/publications/clinic-forms

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://i-base.info/home/africans-and-treatment-infomation/

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 meeting, held in Cape Town earlier 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 from 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.

i-Base Treatment Guides

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

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

- Introduction to combination therapy (June 2009)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment: what to do when your treatment fails (September 2008)
- Guide to HIV, pregnancy & women's health (January 2009)
- Guide to avoiding & managing side effects (May 2008)

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://i-base.info/category/translations/

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.

ARV4IDUs

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

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/qa

Recent questions include:

- What can I do about my abdominal fat?
- Concerned about HIV positive friend?
- Is it okay to start having sex again?
- What two measures are there that may enhance the quality of life of infected individuals?
- What resources are available for someone affected by HIV or Hepatitis B/C? 7 - Estou recebendo o melhor tratamento? (Am I getting the best treatment?)

- La glaucoma puede estar relacionada con los medicamentos que estoy tomando? (Is my glaucoma related to my medication?)
- Have I been infected?
- What support is there for me?
- Which drugs should I take if I go back to Chile?
- Why do we use CD4% as well as CD4 counts?
- Why is my viral load fluctuating so much?
- How do I know when to take treatment with a fluctuating CD4 count?
- Does late testing work?
- Where can I get a genetic test for delta 32 gene?

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://i-base.info/order

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

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HIV i-Base is a registered charity no 1081905 and company reg in england no 3962064. HTB is also known as DrFax

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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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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HIV 'Treatment Passports' - Booklets for patients to record their own medical history

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

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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** ☐ _____ _____

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