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EDITORIAL

Welcome to the May/June 2009 issue of HTB which contains a wealth of conference reports including the recent BHIVA meeting in Liverpool, the PK workshop in Amsterdam and additional report from Retrovirus/CROI earlier in the year.

Several issues recur and remaining unresolved. They are likely to be informed by additional research throughout the year.

Cardiovascular disease in the aging HIV population which has higher levels of risk factors than the general population (smoking, lipids, recreational drug use etc) is clearly important. Although the SMART study showed that suppressed viral load from ARV treatment is a protective factor, individual drugs evidently have different CVD profiles, notably abacavir and now lopinavir/r (Kaletra). We include CROI reports, a disturbing case study presented at GSKs satellite meeting at the BHIVA conference, and the EMEA statement on this complex area.

The recommendations for when to start treatment will also continue to be informed by data likely to show a protective impact at higher CD4 counts. As the investigators from the START trial (which has now enrolled the first patients in the US) point out in their response to published results from a US cohort dataset, the risks as well as benefits will only become clear in a randomised clinical trial and it needs to be large enough to be powered to address risk of low incidence events.

Other reports from CROI focus on women's health and paediatric care, especially the difficulties of dosing, formulations and drug interactions.

Drug interactions are again highlighted in reports from the PK Workshop and from the Liverpool drug interaction site including a potential interaction between raltegravir and etravirine, and new interaction charts on ARVs and drugs to treat flu and swine flu.

Finally, we include two reviews by Richard Jefferys on studies looking at the role of the gut and microbial translocation.

Happy reading...

Supplements with this issue

We include two supplements with this issue.

The first is the 2009 update to Introduction to Combination Therapy. This is probably the most widely used resource for newly diagnosed patients in the UK and by patients prior to starting treatment.

The second is a reprint of the 'treatment passport' that, despite its unassuming cover, is a resource developed with the HIV pharmacists group and the Royal Free to help people track their treatment history.

As with all publications, additional copies of both booklets are available free, including in bulk for use in UK clinics – please order in the usual way.

CONFERENCE REPORTS

15th Annual Conference of the British HIV Association (BHIVA)

1-3 April 2009, Liverpool

<http://www.bhiva.org>

Introduction

The annual BHIVA conferences consistently provide an opportunity to understand important aspects of HIV care, including the first presentations of results from national audits, lectures from international experts on emerging concerns and a wealth of studies from junior researchers.

The spring meetings are attended by up to 700 delegates from all health care fields including strong community attendance supported by a scholarship programme.

This year's highlights are detailed in summary reports below. The low-points unfortunately included several company satellite sessions, trumped by a session from GSK suggesting that a patient with a previous history of heart attack – clearly the highest risk for a subsequent heart attack – should continue abacavir because some studies, generally those not designed to look at cardiovascular risk do not support the findings from D:A:D. However, D:A:D is the largest international prospective study powered to look at the cardiovascular impact of antiretroviral therapy.

This session, incidentally, was prior to the most recent statement from the EMEA recognising the complexity of data, (for details and comment see below in this issue of HTB). It is difficult to understand why any doctor would want to be faced with the ethical dilemma of explaining to any patient with a high CVD profile who was maintained on abacavir, when alternative

treatment options were available, and who has a subsequent heart attack, or to their family should it prove fatal, why a clear caution from both the D:A:D and SMART studies, had not filtered down to that individual patient.

We rarely report from satellite meetings – even when the content is balanced and informative – and several of the sessions at BHIVA this year were of a very high standard– simply because they are usually skewed by some degree of marketing bias.

However, this year we will make one exception, because the GSK satellite included a case study of a patient with a history of previous heart attack who was recommended to continue taking abacavir. It is difficult to see why, when alternative options are available, abacavir would not be considered as a modifiable risk, at least until the D:A:D results can be explained by other factors.

BHIVA recommends all patients have their cardiovascular risk measured on an annual basis, and certainly prior to starting treatment. Given that many patients report never having been told their cardiovascular risk, this might be a very appropriate area for educational events.

GSK could also have included the information that a prior cardiovascular event is the highest predictive risk factor for a subsequent event, and that patient history in addition to Framingham risk assessment (which doesn't factor in previous CVD) is critical.

On a more positive note, the abstract book and a selection of slide sets of the oral presentations are available to download from the BHIVA website.

<http://www.bhiva.org>

Reports in this issue include:

- Superinfection identified in 2 out of 8 patients with unexpected viral load increases
- Peripheral DEXA scans to identify rates of reduced bone mineral density
- Vitamin D deficiency, supplementation and tenofovir
- High rate of lost and untested TB biopsy samples and low screening for latent TB

Superinfection identified in 2 out of 8 patients with unexpected viral load increases

Simon Collins, HIV i-Base

The rate and risk of reinfection with a second strain of HIV after primary infection are unclear with most instances reported as case studies. While reinfection clearly occurs, with viral load of the transmitting partner likely to be a significant risk factor, the clinical importance of a second infection, based on current limited data, appears largely related to acquisition of a resistant strain and its impact on reducing treatment options.

A pilot study by Doyle and colleagues at UCL looked for treatment-naive patients who were at risk of reinfection from sexual exposure, who experienced a significant viral load increase (>0.5 log) during routine viral load clinic monitoring. Eight patients were identified (all sub-type B) and phylogenetic analyses were performed on the stored and most recent samples.

In two patients, early sequences formed separate clusters to late sequences, with no evidence of viral recombination, indicating a second infection.

One patient was reinfected 5 months after his initial diagnosis during acute infection, and experienced similar seroconversion symptoms at the time of viral load increase. He also acquired syphilis and herpes in the subsequent 6 months.

A second patient had been diagnosed HIV-positive 3 years earlier and experienced no symptoms and no other STIs at the time of superinfection. He controlled both the first infection and the superinfection without HAART, with a set-point viral load of 3.5 log₁₀ copies/mL and a stable CD4 count >1000 cells/mm³.

These two cases indicate that reinfection is unlikely to be a rare event and can occur both in the early and established disease, even in the presence of effective immune responses.

C O M M E N T

While the study conclusion is that targeted screening based upon sexual history and viral load can achieve a high detection rate and is important in the context of transmitted resistance, it is not appropriate to conclude that early HAART should be used as a public health measure between consenting HIV-positive adults who choose to use neither condoms nor treatment.

Ref: Doyle T et al. High-risk sexual behaviour and HIV-1 superinfection: an indication for early initiation of antiretroviral therapy? Poster abstract P150.

Peripheral DEXA scans to identify rates of reduced bone mineral density

Simon Collins, HIV i-Base

Short and colleagues presented results from using a portable DEXA scanner to identify high rates of reduced bone mineral density and relationship to ARV use in 168 HIV-positive men (median age 45) treated in Brighton.

Both osteopenia and osteoporosis have been reported at alarming rates compared to age- and gender-matched HIV-negative populations, routine bone density assessments, however, are not routinely yet included in patient management. With time, cost and scanner access reported as limiting factors to change this, researchers at Brighton used a donated portable DEXA scanner (cost new ~ £15-20K) and peripheral scans (taking two minutes) as part of a routine outpatient clinic.

Patients were recruited consecutively from May to August 2008 and underwent a forearm portable DEXA and standard DEXA imaging (lumbar spine and femoral neck) within 12 weeks.

Osteopenia at any site by DEXA was found in 100/168 (60%) overall (70% in ARV-naive, 53% in those with <3 years treatment and 58% in the group with > 3 years ARV use. Osteoporosis at any site was found in 22/168 (13%) overall; and at 5%, 11%, 17% by ARV use in the same groups respectively.

ARV exposure/weeks ($p=0.03$), HIV infection >13 years [OR 2.81 (1.6–5.1) $P = 0.00$] and fracture post infection [OR 3.23 (1.6–6.6) $P = 0.02$] were independently associated with osteoporosis at any site and no alcohol use was protective [OR 0.35]. Peripheral DXA had a 95% sensitivity and 35% specificity to identify osteoporosis at any site, with a negative predictive value of 98%.

Ref: Short CS et al. Evaluation of peripheral dual energy X-ray absorptiometry to detect osteoporosis in an HIV-seropositive male population. Oral abstract O2.

Vitamin D deficiency, supplementation and tenofovir

Simon Collins, HIV i-Base

T Welz and colleague from Kings College Hospital presented results from a cross-sectional study of serum 25(OH)D levels in over 1000 HIV-positive adults. Median age was 40 years (IQR 35, 46), 60% men, 35% white, 58% black, CD4 452 cells/mm³ (IQR 324, 613). [1]

Just over 90% patients were defined as sub-optimal (<30 lg/L), 73% as deficient (<20 lg/L), 34% as severely deficient (<10 lg/L) and 6% with undetectable levels. Although median serum 25(OH)D was slightly higher in the summer than winter (14.2 versus 11.2 lg/L; $p<0.001$), this did not significantly improve the proportion of patients with less deficiency.

Factors associated with lower serum 25(OH)D were black race ($p<0.001$), low CD4 nadir ($P<0.002$) and efavirenz use ($p<0.004$). Tenofovir use was associated with a higher level ($p=0.001$). However, patients with low 25(OH)D on tenofovir were twice as likely to have an elevated ALP than those on abacavir (OR=2.4 [CI 1.5, 3.9]; and four times as likely compared to other NRTIs (OR=4.6 [CI 1.6, 13.3]).

The presentation concluded that their results supported routine testing as calcium and ALP did not detect low 25(OH)D levels. Testing is inexpensive (~£20) and vitamin D supplementation is inexpensive, even when higher doses are needed.

The benefits of vitamin D and calcium supplements were reported by Childs and colleagues from Kings College London, in 32 HIV-positive men with suboptimal levels of 25(OH)D (<30 ng/mL). Daily supplement vitamin D3 (VD3) were prescribed dosed by baseline levels: 2800 IU [25(OH)D < 10]; 1800 IU [25(OH)D = 10–20]; 800 IU [25(OH)D = 20–30], all with additional 1g calcium citrate daily.

Follow-up tests were performed on 20 subjects: 16 on tenofovir-containing HAART; 4 on non-tenofovir-containing HAART.

There was a strong association between suboptimal 25(OH)D levels and parathyroid abnormalities. Among the 32 subjects with suboptimal 25(OH)D, mean PTH was 80 ± 32 pg/mL in those on tenofovir and 56 ± 19 pg/mL in those on non-tenofovir HAART ($p=0.02$). Among subjects with suboptimal 25(OH)D, 37% (10/27) on tenofovir had PTH >ULN, indicating secondary hyperparathyroidism (SHPT), while none of the 10 subjects with low vitamin D on non-tenofovir HAART had SHPT ($p=0.03$).

VD3 supplementation increased 25(OH)D by 9.8 ± 5.6 ng/mL ($P < 0.001$) and PTH fell 18.9 ± 31.7 pg/mL ($p=0.002$). Parathyroid hormone (PTH) rose 4.4 pg/mL among subjects in the bottom third of baseline PTH values. In contrast, it fell 5.3 pg/mL among subjects in the middle third, and fell 44.7 pg/mL among subjects in the top third ($p=0.001$, ANOVA). All subjects in the upper third were on tenofovir and all experienced a PTH decrease.

The researchers concluded that VD3/calcium supplements increased serum 25(OH)D and decreased PTH and are a safe and effective treatment for HAART-associated hyperparathyroidism.

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1. Welz T et al. Risk factors for vitamin D deficiency in an ethnically diverse urban HIV cohort: Which antiretrovirals are implicated? Oral abstract O6.

- Childs K et al. Vitamin D and calcium supplements reverse the secondary hyperparathyroidism that commonly occurs in HIV patients on TDF-containing HAART. Poster abstract P89.

High rate of lost and untested TB biopsy samples and low screening for latent TB

Simon Collins, HIV i-Base

E Elliot from the Lawson Unit in Brighton presented one of several interesting papers looking at practical aspects of efficiency and care, in this instance, the appropriate testing of biopsy samples. [1]

The group identified all tissue sampling undertaken on HIV-positive patients by reviewing hospital coding records from 2003 to 2008 and weekly ward lists from 2006 to 2008 and cross referenced this with records on the pathology database. Four consultants independently identified samples that should have been sent to microbiology.

Of the identified 62 samples that would be expected to go to microbiology, all were sent to histopathology but only 20 were also sent to microbiology. Out of 42 samples that were not sent to microbiology, request forms in 28 clearly stated TB or other infection as a potential diagnosis. Of these 42 samples, 13 samples from 12 patients subsequently had mycobacterial (n = 9) or other infection identified on blood cultures, re-sampling or histology.

The researchers concluded that more than a third of tissue samples in HIV patients were sent to microbiology, and this resulted in many missed or delayed diagnoses and that the hospital is now developing clearer clinical pathways for tissue biopsy.

The importance of latent TB diagnosis, through a more comprehensive screening of newly HIV-diagnosed African patients, was reported by Okpaluba and colleagues from Leeds Teaching Hospitals. [2]

Of 101 new HIV-diagnoses, 70% were in African patients, but only 24/70 patients were tested for TB either at HIV diagnosis or through other screening programmes. In these patients, 4/24 samples were found to be abnormal and 3 people were treated for latent TB.

This study highlighted both the sub-optimal screening in a high-risk patient group, together with the cost effectiveness of treating latent TB and using the immune-based interferon-gamma (TB Quantiferon Gold) testing for diagnosis.

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- Elliot E et al. Tissue biopsy in HIV-infected patients: how often do samples get sent for microbiological analysis? Poster abstract 124.
- Okpaluba U et al. Introducing a protocol for diagnosing and treating latent TB in newly diagnosed HIV patients: feasibility and cost effectiveness. Poster abstract P72.

CONFERENCE REPORTS

16th Conference on Retroviruses and Opportunistic Infections (CROI)

8-11 February 2009, Montreal

Introduction

Abstracts and webcasts can be accessed via the conference website at the following link:

<http://www.retroconference.org>

The following reports from the conference are included in this issue of HTB:

- Assessing the cardiovascular impact of HIV, abacavir, and new signals for lopinavir/r
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- HDL particle concentration predicts cardiovascular disease in SMART
- No effect of hormonal contraception on HIV disease progression in large multi-country cohort
- Pregnancy, family planning, and HIV acquisition in HPTN 039
- Progression and regression of pre-malignant cervical lesions in HIV-positive women from Soweto
- CD4 count >250 was not predictive of rash-associated hepatotoxicity among women initiating nevirapine-based ART in Zambia, Thailand, and Kenya
- HIV testing of infants at immunisation clinics in Kwazulu-Natal

- Rapid HIV disease progression in South African infants co-infected with cytomegalovirus
- Pharmacokinetic studies in very young infants
- Double-dose lopinavir/ritonavir provides insufficient lopinavir exposure in children receiving rifampicin
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- Etravirine dose selection in children aged 6 to 17
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16th CROI: SIDE EFFECTS

Assessing the cardiovascular impact of HIV, abacavir, and new signals for lopinavir/r

Nathan Geffen, TAC and Simon Collins, HIV i-Base

Peter Reiss summarised the growing number of studies on the relationship between abacavir and cardiovascular disease (CVD). [1] Four of six studies show an increased risk, while two, based on clinical trial data, do not.

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study found an increased relative risk of 1.68 (95%CI 1.33-2.13) for myocardial infarction (MI) in subjects recently taking abacavir. The relative accumulated risk was much smaller (1.07 per year; 95%CI 1.01-1.44). Importantly, this years analysis from D:A:D looked at individual PI effects for the first time and reported that after adjusting for lipids, cumulative (but not recent) exposure to indinavir or lopinavir/ritonavir was associated with an annual increased relative rate of MI (RR, 95%CI 1.08 [1.02-1.14] and 1.09 [1.01-1.18], respectively). [2]

Sensitivity analysis of boosted and unboosted use of indinavir and saquinavir in a limited numbers of patients in D:A:D did not identify ritonavir-boosting as a risk factor. There were no statistically significant associations between recent or cumulative use of tenofovir, ddC, AZT, d4T, or 3TC and MI risk or with cumulative exposure to nevirapine, efavirenz, nelfinavir or saquinavir.

The SMART study supported the D:A:D results on abacavir, with patients using abacavir having a significantly higher risk of heart disease in four measured categories, including MI (RR 4.3; 95%CI 1.4-13). [3]

In the STEAL study, a randomised trial comparing abacavir + 3TC versus tenofovir + FTC in 360 treatment experienced patients in Australia, David Cooper and colleagues reported eight CVD events in the abacavir group versus one in the tenofovir arm (HR: 7.7; 95%CI 0.02-0.98); p=0.046). However, the abacavir arm had significantly more current smokers at baseline (40% v. 29%). This is a small trial, but randomisation means any differences are unlikely to be due to confounding/channeling bias. [4]

Furthermore, a case-control study in the ANRS CO4 study, looking at the effect of specific antiretroviral drugs on MI risk among more than 11,500 patients in the French Hospital Database, showed recent abacavir (less than one year) to double the risk of a heart attack (OR=2.19, 95%CI: 1.19-4.02). This study also reported a significantly increased risk for lopinavir (OR = 1.38/year, 95%CI 1.10 to 1.74), and amprenavir/fos-amprenavir (OR = 1.55/year, 95%CI 1.20 to 1.99). [5]

Yet, GlaxoSmithKline's abacavir database which included nearly 15,000 patients, show no increased risk of MI (RR 0.86; 95%CI 0.4-1.86; p=0.71) or coronary artery disorders (RR 0.59; 95%CI 0.35-1.01; p=0.06). If anything their data shows a trend in favour of ABC for the latter. However, many commentators have pointed out that registrational trial databases are short duration in younger and generally healthier patient groups, and are not designed or powered to look for cardiovascular events. Additionally, many members of the 'control' group may have received treatment with other drugs (e.g protease inhibitors) that may themselves increase the risk of MI. [6]

Constance Benson presented data of 3,200 patients randomised to their first ART regimen in one of five ACTG studies. Follow-up data was available for over 2,100 patients through the ALLRT long-term protocol. [7]

Follow-up was censored at the first of off-study, death, initiation of non-randomised abacavir or 6 months after the last visit or discontinuation of randomised [HAART]. Risk was estimated for multiple factors including abacavir exposure, gender, race, age, viral load, CD4 count, ddl use, smoking, hypertension, high cholesterol, hyperglycaemia and family history of CVD. An event was classified as MI if confirmed by two independent reviewers.

Severe CVD events were identified in 63 patients, of which 27 were MI. Significant increases in the risk of events were detected for hypertension (RR of 2.3 for severe CVD; 95%CI 1.3-4.1; p=0.007) and older age (RR of 2.0 per 10 years of age for MI; 95%CI 1.4-2.9; p<0.001. RR of 1.9 per 10 years of age for severe CV; 95%CI 1.5-2.4; p<0.001).

They found no association between either MI or severe CVD and recent abacavir use (RR of 1.2 for MI; 95%CI 0.5, 3.1; p=0.82. RR of 0.8 for severe CVD; 95%CI 0.4-1.5; p=0.5). Of note, however, male sex (a well known risk factor for MI) was not identified as a risk factor for MI in the study, emphasizing the lack of power.

Reiss recommended the following to deal with these complex results:

“Although differences in study design, statistical power, endpoint definitions, and procedures to capture and validate endpoints may each contribute to these discrepant findings, additional possible explanations also need to be considered. Reviewing the characteristics of the various patient populations which were studied, one could for instance speculate whether the likelihood of identifying the CVD risk associated with abacavir may be greater in those who are first exposed after their HIV infection is already suppressed.

Data suggest a pathogenic mechanism (possibly of a proinflammatory nature) involving acute processes, such as plaque rupture or subsequent thrombosis, rather than a chronic one affecting atheroma formation.

For now, it seems prudent to withhold abacavir from patients with high underlying CVD risk if suitable alternative regimens are available. If not, patients’ absolute CVD risk in the presence of abacavir should be minimised by aggressive management of traditional CVD risk factors”.

Potential abacavir mechanisms

Explaining the D:A:D and other findings are complicated by not having a clear mechanism of action for any effect. While this is common by definition for any unexpected reaction, especially in HIV care - most notably for fat accumulation - it is an area that many research groups are looking at.

The summary of these studies at CROI is similarly complex:

- GSK data from the HEAT study found no differences at 96 weeks in endothelial function markers (vascular cell adhesion molecule-1; sVCAM-1) or inflammation markers (IL-6 and hsCRP) between almost 500 patients randomised to either abacavir/3TC or tenofovir/FTC, each with lopinavir/r in a prospective, randomised study in treatment naive patients. [8]
- Frank Palella and the MACS cohort reported similar findings in over 300 matched pairs (194 women, 96 men). Abacavir use was not independently associated with elevated plasma levels of hsCRP, IL-6, and D-dimer. While changes in the levels of these markers were seen between the baseline and index visits (D-dimer and IL-6 decreases, hsCRP increases), they were comparable among persons who initiated ABC versus non-ABC containing HAART. Women had higher D-dimer and lower CRP levels than men. [9]
- However, Claudette Satchell and colleagues from University College Dublin conducted a prospective study to assess platelet function in 58 patients, 30 of whom were on abacavir-containing regimens (ABC group) and 28 who were on non-abacavir-containing ART (no ABC group). [10] They reported consistently higher platelet reactivity in the abacavir group when exposed to increasing levels of platelet agonists and that these differences remained significant when controlled for gender, age, ethnicity, mode of HIV acquisition, smoking history, diabetes, family history of CVD, systolic blood pressure, use of other classes of ART, use of aspirin and methadone and CD3+, CD4+, and CD8+ T cell count.

Impact of HIV

Several studies also provided evidence for the role of HIV in cardiovascular disease:

- Carl Grunfeld reported that in the Fat Redistribution and Metabolic Change in HIV infection (FRAM) study, even after adjustment for traditional CVD risk factors, HIV infection was independently associated with as severe an impact on atherosclerosis (measured by increased carotid intima media thickness (IMT)) as traditional CVD risk factors, such as smoking. [11] The presentation also suggested that the previous contradictory results looking at IMT in HIV infection may be explained by the two studies finding a link to HIV having measured both thickness in the common carotid and the internal and carotid bulb (a region associated with more vascular turbulence and impact of HDL and total cholesterol) the five studies finding no association having only measure the common carotid.
- A second analysis from FRAM following over 900 HIV-positive patients and almost 300 HIV-negative controls reported a mortality risk that was 3 times higher among the HIV-positive group even after adjustment for demographic and traditional CVD risk factors. [12]
- Priscilla Hsue and colleagues from San Francisco General Hospital, whose group has also reported significantly increase carotid IMT associated with HIV and treatment, reported a new study showing higher levels of coronary artery calcium (CAC) in almost 250 HIV-positive patients compared to 45 HIV-negative matched controls. After adjusting for age, gender, race, smoking, hypertension, and diabetes mellitus, the HIV-infected subjects had a significantly higher prevalence of detectable CAC (OR = 2.7, 95%CI 1.06 to 6.7, p = 0.037). In the adjusted analysis, only age, gender, and race were significant with no impact seen for duration of HAART, PI-use and time with undetectable viral load. [13]

C O M M E N T

While consensus on the use of abacavir in patients at high cardiovascular risk appears to be following Peter Reiss’s summary statement, the new data on individual PI effect are new, linked to lopinavir and not apparently related to the boosting effect of ritonavir. Lower use of both indinavir and ddI should make those data largely of historical interest.

The focus on the potential mechanisms is likely to continue, but drug-related side effects are often observed and yet poorly understood. Indeed the exact mechanisms for the activity and toxicities of many drugs is frequently poorly understood.

Reducing modifiable cardiovascular risks is clearly an important goal on an individual patient level given the accumulating evidence linking untreated HIV infection to heart disease, but this can be a challenge in practice.

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Unless stated otherwise, all references are to the Programme and Abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. 8-11 February 2009, Montreal. Oral abstracts are available as a web cast.

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Intensive smoking cessation programme reports limited success at 6 months

Simon Collins, HIV i-Base

The scale of the problem of smoking often highlighted in discussions of the abacavir data with a comment such as 'patients would reduce their risk more from stopping smoking rather than discontinuing abacavir not only is unhelpful for non- and ex-smokers but also of limited benefit for current smokers who have unsuccessfully tried to quit.

Karen Tashima presented results showing a limited 6 month success rate (~10%) in around 450 HIV-positive US smokers (average 18/day), randomised to more intense motivational interventions (ME; 4 long (30 minute) counselling sessions) compared to standard of care (SC; 2 brief 3 minute sessions), both with nicotine patches. While the study as a whole found no additional benefit to the ME programme, it had significant differences by race.

Only around 50% and 60% of patients attended the 2- and 4-month follow-up visits with an increase to 72% at 6-month possibly related to greater financial compensation at that time point. Overall, 6-month quit rates by intent-to-treat analysis were 9% (9% ME, 10% SC, $p = 0.76$).

Higher quit rates were seen among Hispanic patients (19% overall, 14% ME, 24% SC) and lowest among African Americans (5% overall, 9% ME, 0% SC), with significant differences in the standard care arm ($p = 0.01$). Failure to use nicotine replacement predicted smoking at 6 months ($p < 0.05$).

Multivariate predictors of 6-month smoking abstinence among patch users included black race vs white ($p = 0.003$), baseline self-ability or change in self-ability to refuse cigarettes ($p < 0.001$), change in belief to quit ($p = 0.003$).

C O M M E N T

Most commentators found these results depressing, including the presenter, although it was also pointed out that many people need to attend several programmes before they are successful.

Indeed, 68% of participants had previously used nicotine patches and 20% had previously managed to quit for over one year: highlighting the fragility of even these modest success rates.

Patients did not have to express an interest in trying to quit and the financial reimbursement may have encouraged participants with a low motivation. This intervention may have looked more impressive if patients had been selected more appropriately.

Ref: Tashima K et al. Positive paths: a motivational intervention for smoking cessation among HIV+ smokers. Oral abstract 148.
<http://www.retroconference.org/2009/Abstracts/35613.htm>

HDL particle concentration predicts cardiovascular disease in SMART

Nathan Geffen, TAC

Daniel Duprez presented a nested case-control study from the SMART study showing that intermittent HAART was associated with a decrease in high-density lipoprotein (HDL) particle concentration in comparison with continuous HAART and that lower total HDL particles and especially the concentration of small HDL particles predicted cardiovascular (CVD) events. [1]

SMART found that CD4-guided treatment interruptions caused an excess risk of CVD compared to continuous treatment (HR:1.57; 95%CI 1.00-2.46; p=0.05). Stopping treatment was associated with a decline in both HDL and low-density lipoprotein (LDL) cholesterol. However, the net change in terms of the total cholesterol TC:HDL ratio was unfavourable. The positive effect of a reduction in LDL cholesterol was not sufficient to make up for the decline in HDL on the interruption arm. [2]

HDL is one of five major lipoprotein groups and HDL particles transport cholesterol and triglycerides in the blood. While HDL particles generally removes cholesterol from artery walls and are considered "good" cholesterol, LDL particles directly contribute to plaque formation and are considered "bad" cholesterol. However, HDL can be further grouped into large, medium and small particles.

Duprez explained that subjects with the same HDL-cholesterol might have different concentrations of HDL-particles. To illustrate this he described two 52-year old men who both had HDL-cholesterol of 36mg/dL. However, concentrations of large and small HDL particles respectively were 8 and 23 μ mol/L in one compared to 3 and 28 μ mol/L in the other.

The aim of the case-control study was to describe the relationship between lipoprotein particle size and concentration with CVD. About 240 subjects with CVD events prior to the closure of SMART were compared with two controls, matched on country, age, gender and date of randomisation.

There were statistical differences in baseline characteristics for prior AIDS (37% v. 25%, p=0.0005), current smoker (52% v. 40%, p=0.001), diabetes (17% v. 8%, p=0.0007), on blood pressure lowering drugs (45% v. 31%, p<0.0001) and prior CVD (13.3% v. 5.2%, p=0.0004) between the CVD and control cases respectively. There were, however, no statistically significant differences in age, gender, race, CD4 count viral load count and on anti-cholesterol drugs.

At baseline, there were no differences in total cholesterol, LDL particles, very low density lipoprotein (VLDL) particles, LDL cholesterol and triglycerides. but HDL cholesterol (38 v. 42, p=0.03), TC: HDL ratio (5.2 v. 4.7, p=0.05) and HDL (28.4 v. 30.2, p=0.0001) were significantly different.

Odds ratios (with subjects in lowest quartile used as reference) were adjusted for age, race, viral load, CD4 count, BMI, smoking, diabetes, HBV or HCV, use of anti-cholesterol medications, prior CVD and major baseline ECG abnormalities.

The CVD events were as follows:

- 124 cases of non-fatal coronary heart disease (CHD),
- 62 cases of non-fatal atherosclerotic non-CHD (strokes, peripheral arterial disease),
- 26 cases of non-fatal congestive heart failure (CHF) and
- 36 fatal cardiovascular cases.

Concentrations of VLDL particles, LDL particles and HDL particles were all significantly associated with non-fatal CHD, but only HDL particle concentration was associated with non-fatal atherosclerotic CHD.

HDL particle concentration approached statistical significance for predicting fatal CVD (unadjusted OR:0.3 95%CI 0.1-1.1, p=0.08).

Total HDL particle concentration was statistically associated with CVD (adjusted OR: 0.41, p=0.001).

When grouped by size, small - but not large or medium - HDL-particles were significantly associated with CVD (Adjusted OR: 0.55, $p=0.03$). LDL particles did not predict CVD events overall.

In the intermittent HAART arm, there was a significant decline in total (2.2, $p<0.0001$), medium (1.1, $p=0.002$) and small ($p=0.03$) HDL particles concentrations at one month relative to the continuous HAART arm.

C O M M E N T

This study improves our understanding of the role of various lipid particles in CVD events in HIV-positive people, and further research on the relationships between lipoproteins, HIV, ARVs and CVD is warranted.

Factors at baseline other than HIV, such as smoking, diabetes and hypertension, were all statistically correlated with CVD events in SMART.

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16th CROI: WOMEN'S HEALTH

No effect of hormonal contraception on HIV disease progression in large multi-country cohort

Polly Clayden, HIV i-Base

Some studies have suggested that hormonal contraceptive use is associated with accelerated HIV disease progression in untreated women.

In an oral presentation, Elizabeth Stringer showed data from the MTCT Plus Initiative, a family based HIV care and treatment programme with pregnancy as an entry point to care and includes 14 sites in Africa and Thailand.

Between 2003-2008, MTCT Plus enrolled and followed 7846 women. Women received 6 monthly CD4 measurements and contraceptive use was self reported and varied by site.

This analysis included women with available contraception and CD4 data, who were not yet eligible for treatment, and not pregnant (or within 90 days of delivery).

Contraception exposure was defined in three categories: progesterone only, which included implants and injectables; combined oestrogen-progesterone; and no exposure to hormonal contraception, which included no contraception and all non-hormonal forms of contraception.

The primary endpoint in this analysis was disease progression defined as eligibility for ART (according to WHO criteria) or death.

The investigators used Kaplan Meier method and Cox proportional hazard regression to estimate time to disease progression. Contraception exposure was categorised according to the method reported on entry to the cohort. The investigators also performed a separate time-varying analysis in which women who switched methods contributed person-time to each exposure category.

Dr Stringer reported that 4530/7846 women in the cohort were eligible for this analysis. Of these, 830 women were exposed to progesterone only contraception; 226 to combined oestrogen-progesterone and 3099 had no hormonal exposure. The remaining 375 women received contraception but the method was unknown.

Baseline characteristics were similar across the exposure groups and all groups had a median CD4 count of >400 cells/mm³. There was considerable variability of initial contraception method prescribed across sites.

Dr Stringer reported that during the period of analysis, 902 women overall reached a primary endpoint (see Table 1).

Table 1: Overall rate of death or ART eligibility

	Events	Rate*	95% CI
Death	66	1.1	0.9-1.4
ART eligible	881	17.0	15.9-18.2

Death or eligible	902	17.4	16.3-18.6
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*Rate per 100 person years

When the investigators looked at time to primary endpoint according to exposure, they found no difference between the three exposure categories, $p=0.42$.

Furthermore, multivariate analysis controlling for age, parity, baseline WHO stage, CD4 count, BMI, Hb, condom use and site, with no exposure as the reference, revealed no difference in disease progression between the three exposure categories (see Table 2).

Table 2. Impact of contraception category on progression

	Crude HR (95% CI)	Adjusted HR (95%CI)	Time varying AHR (95% CI)
No exposure	1.0	1.0	1.0
Progesterone only	1.0 (0.8-1.2)	1.0 (0.8-1.2)	0.9 (0.8-1.2)
Combined progesterone-oestrogen	1.0 (0.7-1.3)	0.9 (0.6-1.2)	0.8 (0.6-1.1)

Finally, when they looked at the hazard of disease progression by site, neither progesterone only nor combined progesterone-oestrogen contraception use appeared to have an impact.

Dr Stringer concluded that there was no evidence of hormonal contraception accelerating HIV disease progression in this dataset. However she noted that differences between progesterone-based methods of contraception could not be elucidated. She suggested that further research in this field is needed.

C O M M E N T

These findings are reassuring, but as the study investigators suggest, more data is needed.

Ref: Stringer et al. Effect of hormonal contraception on HIV disease progression: a multi-country cohort analysis. 16th CROI, February 2009, Montreal, Canada. Oral abstract 175.
<http://www.retroconference.org/2009/Abstracts/35287.htm>

Pregnancy, family planning, and HIV acquisition in HPTN 039

Polly Clayden, HIV i-Base

Pregnancy has been reported to be a period during which women may be at an increased risk of HIV acquisition.

It is usual in HIV prevention trials to remove women from study drug during pregnancy.

A poster from the HPTN 039 study group showed findings from an analysis of the effect of pregnancy on time off study drug and risk of HIV acquisition. This was a randomised double-blind placebo-controlled trial that studied the efficacy of herpes simplex virus-2 (HSV-2) suppression with acyclovir, to prevent HIV acquisition.

There were 1358 HIV-negative, HSV-2-positive women from Zimbabwe, Zambia, and South Africa enrolled in HPTN 039. Women who were pregnant at either screening or enrollment were ineligible, and study drug was discontinued if women became pregnant while in the trial. Contraception services were provided at trial sites.

The investigators used a Cox proportional hazard model stratified by trial site, and adjusted for baseline predictors and time-varying sexual behavior covariates to estimate risk of acquiring HIV.

They reported 226 pregnancies during 18 months of follow up. These occurred at a median time of 7.9 months from enrollment. The incidence of pregnancy was 13.2/100 person years, which accounted for 4% of missed time on study drug among women in the trial (of note only 47.8% of pregnancies were full term).

In multivariate analyses, younger age, contraceptive use and unmarried status were associated with pregnancy. (See Table 1).

Table 1. Risk factors for pregnancy

Risk factor	HR	95% CI	p
Age >34 vs <21 years	0.22	0.13-0.38	$p \leq 0.0001$
Unmarried status	1.97	1.12-3.49	$p=0.02$
Oral contraception vs none	0.68	0.47-0.98	$p=0.05$

Injectable contraception vs none	0.24	0.14-0.4	p<0.001
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Condom use was not effective as contraception in this study, condom use vs none [HR 1.1; 2 95% CI 0.71-1.75, p=0.63].

There was no evidence that women were of increased risk of HIV acquisition during pregnancy through to 6 weeks post partum [HR 0.64, 95%CI 0.23-1.78, p=0.4].

Risk factors for HIV acquisition were: younger age (>34 vs <21 years HR 0.28 (0.13-0.61), p<0.001); new partners in last 6 months (yes vs no HR 3.98 (95% CI 1.6-9.8), p=0.003); lack of condom use (condom use vs none, HR 0.27(95%CI 0.08-0.96), p=0.04) and bacterial vaginosis (HR 2.05 (1.2-3.6), p=0.01).

The investigators wrote: "For biomedical HIV prevention trials, on-site provision of contraceptive methods and family planning education can reduce pregnancies and time off study drug".

C O M M E N T

Previous studies have suggested that pregnancy may increase the risk of HIV transmission and that this is due to the biological state of pregnancy rather than any behavioral factors. This study shows no increased risk with pregnancy. These conflicting findings need to be explored.

It is worth noting that, while not effective as contraception, condom use was associated with a significant reduction in HIV transmission risk. However, it may be very difficult to separate out the effects of pregnancy and sexual behaviour (as I guess that women will reduce their sexual activity when they are pregnant).

Ref: Reid et al. Pregnancy, family planning, and HIV acquisition in HIV Prevention Trials Network 039: relevance for HIV prevention trials among Sub-Saharan African women. 16th CROI, February 2009, Montreal, Canada. Poster abstract 985.

Progression and regression of pre-malignant cervical lesions in HIV-positive women from Soweto

Polly Clayden, HIV i-Base

A poster authored by Tanvier Omar and coworkers reported progression and regression of pre-malignant lesions in a prospective cohort of HIV-positive women in Soweto, South Africa.

HIV-positive women >18 years, receiving ART or in pre-ART care, were offered cervical smears as part of a comprehensive package of primary care. Smears were assessed using the Bethesda system. Women with high-grade squamous intraepithelial lesions (ASC-H or HSIL), or worse were referred for colposcopy, treatment, and possible loop excision of the transformation zone.

In this study, women who had a least one smear were included in the prevalence analysis. Women with at least two smears were included in the assessment of incidence, progression and regression. The progression analysis included smears at least 5.5 months apart and regression at least 11 months apart.

Using Cox proportional hazard regression the investigators estimated predictors of incident events of either:

- HSIL in women with baseline normal, atypical squamous cells of undetermined significance (ASCUS); or low-grade squamous intraepithelial lesions (LSIL) smears; or
- Regression to normal in women with baseline LSIL smears.

1951/2533 (76.8%) of women had at least one cervical smear and 763 (30%) women had more than one smear 5.5 months apart.

At the time of their baseline smear their median age was 32.6 years and median CD4 count was 328 cells/mm³.

Baseline prevalence rates were: 59.2% (95% CI 57.0-61.3); 18.8% (95% CI 17.1-20.5), 17.1% (95% CI 14.4-18.8), for normal, LSIL and HSIL smears respectively. Based on 161 cases of progression among those with normal, ASCUS or LSIL smears, the investigators reported overall progression rates of 11.4/100 person years (95% CI 9.7- 13.3, n=927).

In multivariate analysis CD4 <200 cells/mm³ (with >500 CD4 cells/mm³ as reference), HR 2.27 (95% CI 1.38-3.72) and younger age (for every increase of 5 years), HR 0.83 (95% CI 0.74-0.94) were predictors of progression. ART did not appear to offer protection but there was insufficient time on ART to predict progression.

The investigators found rates of regression to be low in this analysis; 106/191 (55.5%) women with baseline LSIL remained LSIL and 38 (19.9%) women progressed at their second visit >1 year later.

The investigators reported 83/682 (12.2%) of women with normal, ASCUS or LSIL smears at baseline progressed to incident

HSIL. Additionally, 157/544 had incident LSIL or worse after normal at baseline.

They wrote: "Earlier initiation of screening, shorter screening intervals in women with CD4 counts <200, and more proactive management of LSIL should be tested."

"Our results add urgency to improving access to an affordable, effective HPV vaccine." They added.

C O M M E N T

It is hard to develop recommendations for a package of services that are evidence based for use in this setting.

Ref. Omar et al. Progression and regression of pre-malignant cervical lesions in HIV-infected women from Soweto: A prospective cohort. 16th CROI, February 2009, Montreal, Canada. Poster abstract 974.
<http://www.retroconference.org/2009/Abstracts/34593.htm>

CD4 count >250 not predictive of rash-associated hepatotoxicity among women initiating nevirapine-based ART in Zambia, Thailand, and Kenya

Polly Clayden, HIV i-Base

Nevirapine (NVP)-containing HAART is the most frequently used regimen in resource-limited countries.

In 2004 Boehringer-Ingelheim, manufacturers of nevirapine (Viramune) performed a retrospective analysis of hepatotoxicity events among 633 women receiving NVP within the company's trials. This analysis revealed 11% women having hepatotoxicity with pre-treatment CD4 count >250 cells/mm³ vs 0.9% with CD4 ≤250 cells/mm³. Following these results the company changed the Summary of Product Characteristics to include a caution that women with higher CD4 counts are at increased risk of hepatic toxicity.

The trials included in this analysis were conducted in Western Europe and North America. There are few data available from women initiating NVP-containing HAART in Africa and Asia. A poster from Anouk Kesselring which looked at this issue using data from several cohorts.

A poster from Philip Peters and coworkers from the CDC and centres in Zambia, Thailand and Kenya, showed findings from an evaluation of risk factors for rash-associated toxicity among women receiving NVP-containing ART between May 2005 and January 2007 in this multi-country cohort. This was a prospective observational study.

The investigators included 820 (497 Zambian, 192 Thai, and 131 Kenyan) treatment-naïve women initiating NVP-containing ART in this analysis. Women received ART in accordance with national guidelines. NVP was initiated at half dose for the first two weeks of treatment.

Liver function tests (LFTs) were performed at 2, 4, 8, 16, and 24 weeks. Women also received a clinical evaluation for rash. Hepatotoxicity was graded:

Grade 1 - mild (transaminase [AST or ALT] elevation 1.25 to 2.49 times the upper limit of normal [x ULN]), 50-99;

Grade 2 - moderate (2.5 to 4.99 x ULN), 100-199; and

Grade 3 - severe (≥5.0 x ULN), ≥200.

Rash associated hepatotoxicity (RAH) was defined as an ALT or AST elevation ≥ grade 2 with concomitant rash. The investigators used multivariate analysis to identify variables associated with hepatotoxicity and RAH.

At baseline women were a median age of 32 years (IQR 28-36) with a median CD4 count 149 cells/mm³ (IQR 83-215) and 86% had normal LFTs. The investigators reported that hepatotoxicity (≥ grade 2) occurred in 109 (13%) women and for 41 (5%) it was severe. In multivariate analysis abnormal baseline LFT was associated with severe hepatotoxicity AOR 3.0 (95%CI 1.4-6.2).

RAH occurred in 27 (3%) women (Zambia 2%, Thailand 7%, Kenya 2%). Of these 8/123 (6.5%) women had a baseline CD4 <50 cells/mm³; 13/576 (2%) had a CD4 of 50 to 250 cells/mm³; and 6/121 (5%) women with a CD4 ≥250 cells/mm³.

RAH was also significantly associated with abnormal LFT at baseline, AOR 3.1 (95% CI 1.2- 8.2). Thai ethnicity AOR 4.5 (95%CI 1.8-11.4) was also associated with RAH.

Baseline CD4 ≥250 cells/mm³ was not associated with either severe hepatotoxicity [AOR 1.1; 95%CI 0.4-2.7] or RAH [AOR 1.6; 95%CI 0.6-4.4]. When the investigators looked at the frequency of RAH and severe hepatotoxicity stratified by CD4 count, women <50 cells/mm³ had the highest rates; 7% and 6.5% of RAH and severe hepatotoxicity respectively. They also noted that there was an increased risk for RAH at CD4 ≥200 cells/mm³ vs 50-199 cells/mm³, p=0.004.

Three women (0.4%) died with symptoms suggestive of fatal hepatotoxicity, All 3 deaths had a baseline CD4 <100 cells/mm³ in women being treated for tuberculosis.

The investigators wrote: "Public health officials should be aware that limiting nevirapine use to women with a CD4 cell count <250 cells/mm³ may not limit hepatotoxicity."

C O M M E N T

While restricting nevirapine use to men with CD4 count <400 cells/mm³ and women with CD4 count <250 cells/mm³ will improve the safe use of this highly effective therapy, the introduction of nevirapine should always be with caution and careful monitoring.

As noted in this study, patients eligible for treatment with nevirapine, especially women, will have low CD4 counts and are therefore often at risk of opportunistic infections.

The case for using nevirapine in conjunction with other hepatotoxic therapies (eg common antituberculosis therapies) or in patients with abnormal LFTs, should always be carefully considered.

Gender and ethnic differences in drug handling are emerging as important factors and conclusions from studies based on selected populations cannot necessarily be generalised.

Ref: Peters et al. CD4 cell count >250 Cells/mm³ does not predict rash-associated hepatotoxicity among women initiating nevirapine-based ART in Zambia, Thailand, and Kenya. 16th CROI, February 2009, Montreal, Canada. Poster abstract 986.

<http://www.retroconference.org/2009/Abstracts/33861.htm>

16TH CROI: PAEDIATRICS

HIV testing of infants at immunisation clinics in Kwazulu-Natal

Polly Clayden, HIV i-Base

A poster from Nigel Rollins and coworkers in Kwazulu-Natal (KZN), South Africa presented results from an acceptability and feasibility study of routine HIV testing of infants attending immunisation clinics in a setting with high HIV prevalence.

Although universal treatment of infants <12 months is now recommended in WHO guidelines, routine postnatal testing of infants is uncommon and many HIV-infected children are not identified early enough to benefit from this recommendation.

In this study, all mothers bringing their infants for immunisation at 6, 10 or 14 weeks of age to three primary healthcare sites in KZN were offered HIV testing. Heel pricks were performed and blood collected on filter paper. If HIV antibodies were detected the dried blood spots (DBS) were tested for HIV by DNA PCR.

If the infant was infected, mothers were referred to routine HIV services after counselling that they would also be expected to be HIV-positive.

The investigators reported that between November 2007 and February 2008, 646 mothers were offered HIV testing for their infants. Of this group, 584 (90.4%, 95% CI 87.8%-92.5%) consented and 332 (56.8%, 95% CI 52%-60.9%) returned to collect the results.

They found that women who self reported their own HIV-positive status were more likely to return for results than those who reported themselves to be HIV-negative, $p=0.001$.

HIV antibodies were present in 247/584 (42.3%) of infant DBS and 54/247 (21.9%) had positive DNA PCR results (54/584, 9.2% of all infants tested). Among the women reporting themselves to be HIV-negative, 7.2% of infants had HIV antibodies detected. The mother-to-child-transmission rate for these infants was 38%.

The investigators found that, in this study, HIV testing at immunisation clinics was acceptable and feasible. Over half of the infected infants were identified which, they noted, "contrasts sharply with the experience of PMTCT programmes in which routine testing of infants is achieved in only 8% of HIV-exposed infants."

C O M M E N T

Routine testing at immunisation clinics, in settings with high HIV prevalence, offers a feasible entry point into care for infants before 12 months of age.

As the investigators mention, although WHO guidelines recommend early diagnosis and treatment, only 8% of infants born to pregnant women with HIV are tested before they are two months old. Most studies report that children start ART when they are about 5 years old when they already have severe immunodeficiency and when they are identified through health facilities due to clinical symptoms. In these circumstances, mortality in the first few months of treatment is high.

Since estimations suggest that as many as 89% of HIV-infected children will have died before they are 5 years old in sub-Saharan African, currently the overwhelming majority of children who could benefit from WHO recommendations are neither being tested nor treated.

Ref: Rollins et al. Universal HIV testing of infants at immunization clinics in high HIV prevalence settings: Acceptable, feasible, and potential for high returns. 16th CROI, February 2008, Montreal, Canada. Poster abstract 899b.
<http://www.retroconference.org/2009/Abstracts/36509.htm>

Rapid HIV disease progression in South African infants co-infected with cytomegalovirus (CMV)

Polly Clayden, HIV i-Base

In an oral presentation, Andrew Prendergast from Oxford University showed data from a study looking at the impact of cytomegalovirus (CMV) on HIV disease progression in a small group of South African infants. [1]

This was a sub-study of the Paediatric Early HAART STI Study (PEHSS), conducted in Durban. PEHSS was a feasibility trial of three management approaches in HIV-infected infants who were diagnosed by HIV PCR at either one or 28 days old. They were then randomised 2:1 to immediate or deferred antiretroviral therapy (ART). [2]

In this sub-study, the investigators performed real time CMV PCR on cryopreserved plasma samples taken at 3 to 4 months of age. Pre-ART CD4% decline was compared between CMV-positive and CMV-negative infants.

Samples were available for 54/63 (86%) of infants enrolled in PEHSS taken at a median of 98 (IQR 88-103) days; 32/54 (59%) were CMV-positive at time of evaluation. Baseline characteristics, including maternal disease status, were similar between the CMV-positive and negative infants but CMV-positive infants were more likely to be breastfed, $p=0.01$.

The investigators found no significant clinical differences in the two groups of infants but they noted a trend towards failure to thrive in CMV-positive infants (43% vs 17%, $p=0.07$).

CD4 percentage at birth was similar between CMV-positive and CMV-negative infants (median 45%, $p=0.56$). However the decline in CD4 percentage from birth was twice as fast in CMV-positive compared to CMV-negative infants (median 10.5%/month vs 5.0%/month; $p=0.007$) and pre-ART CD4 percentage nadir was significantly lower (median 21% vs 37%; $p<0.0001$). CD4% tends to be used as the preferred marker of immune decline in early childhood because it naturally varies less with age than the absolute CD4 count.

They also found after 12 months post-ART initiation that the difference in CD4 percentage persisted in CMV-positive compared to CMV-negative infants (median 29% vs 36%; $p=0.004$).

Interestingly, however, absolute CD4 count nadir was no different between CMV-positive and CMV-negative infants. Dr Prendergast demonstrated that the CMV-positive infants had a huge CD8 cell expansion associated with CMV infection and this rise in CD8 proportion causes much of the impact on CD4 percentage. These data question the validity of using CD4 percentage as the preferred marker of immunological status in infancy, since the CD8 count has such an impact on the CD4 levels.

As over half of HIV-infected infants in this study acquired CMV in the first 4 months of life, and these in turn showed more rapid CD4 percentage decline, Dr Prendergast asked whether CMV prophylaxis or treatment could slow disease progression in infants? Most importantly he emphasised that infants must access early HIV diagnosis and antiretroviral treatment given the speed of CD4 decline, especially in settings of high CMV prevalence.

C O M M E N T

Although this study is very small it raises questions and adds to the argument for early HIV diagnosis and initiation of treatment in infants.

It would be interesting to look at responses to treatment by CMV status in CHER to see if the CMV effect is supported in larger patient numbers. It would also be interesting to look at whether CMV was acquired during pregnancy or at birth, and the risk of transmission through breastfeeding.

Similar findings were recently reported in a western cohort, which supports both early maternal ART in pregnancy and early ART in infected infants. [3]

A number of studies (including one from Jane Deayton at the Royal Free published in the Lancet) have previously reported that CMV viraemia is a risk factor for disease progression, even in the HAART era. Whilst CMV prophylaxis is not routinely used in adults, pre-emptive therapy is certainly used in transplant recipients, and some groups do believe that CMV prophylaxis should be considered in high-risk groups. So, this is an issue of debate at the moment. Several trials are underway (including one at the RF) of potential CMV vaccines. This may be particularly helpful for pregnant women as CMV during pregnancy is associated with a large proportion of birth abnormalities.

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Pharmacokinetic studies in very young infants

Polly Clayden, HIV i-Base

The World Health Organization (WHO) recommends ARV treatment for all HIV-infected infants <12 months old, and that this should be started as early as possible. [1]

Nevirapine (NVP)-based ART is recommended for infants with no perinatal NVP exposure from mother-to-child transmission prophylaxis or NNRTI-based maternal ART. Protease inhibitor-based ART, usually lopinavir/ritonavir (LPV/r), is recommended for NNRTI-exposed infants.

There is however a scarcity of pharmacokinetic (PK) data on which to base dosing to support these recommendations. Two posters at CROI provided useful data for NVP and LPV/r in this age group.

Nevirapine exposure infants weighing 3-6kg receiving paediatric fixed dose combinations

A study conducted by Veronica Mulenga and coworkers from the CHAPAS trial in Zambia, looked at PK in infants weighing 3-6kg receiving fixed dose combination tablets. [2]

This group had previously reported data from a 12-hour PK study of nevirapine (NVP), stavudine (d4T) and lamivudine (3TC) receiving Triomune Baby (50mg NVP, 6mg d4T and 30mg 3TC) and Triomune Junior (double Baby dose). These tablets were developed with higher ratios of NVP to NRTI doses, according to paediatric dosing recommendations, to prevent under dosing of NVP. [3]

This earlier evaluation only included two children weighing 3-6kg, therefore the investigators performed a further PK sub-study of 14 children weighing 3-6kg.

The sub-study enrolled 16 children >1month of age and eligible for treatment in accordance with WHO guidelines. Children were initiated on full-dose NVP with a target dose of 300mg/m². Target doses for d4T and 3TC were 2 mg/kg and 8 mg/kg respectively. With these targets, children in the WHO 3-6kg weightband receive one tablet twice daily. [4]

Samples were taken at t=0, 2, 6 and 12 hours after an observed dose, within four weeks of starting Triomune Baby.

One child was excluded because of non-adherence. Among the remaining 15 children there were 8 girls and 7 boys with a median (IQR) age of 5.3 months (4.1-8.4) and weight of 5.3kg (4.2-5.5). The children's daily doses were 348 mg/m² (324-386), 2.3 mg/kg (2.2-2.9) and 11.3 mg/kg (10.9-14.2) for NVP, d4T and 3TC respectively. See table 1 for PK parameters

Table 1. PK parameters children 3-6kg

	AUC _{0-12h} (h.mg/L)	C _{max} (mg/L)	C _{min} (mg/L)
NVP	78.74 (54.67-106.75) [30.22]	8.10 (6.08-9.74) [2.41]	4.93 (2.36-7.06) [2.63]
d4T	0.94 (0.74-1.11) [0.32]	0.27 (0.21-0.36) [0.11]	<0.015 (<0.015-<0.015) [-]
3TC	7.00 (3.86-9.27) [3.71]	1.46 (0.52-2.13) [0.85]	0.13 (0.08-0.17) [0.05]

Mean (IQR), [standard deviation]

The investigators found large interpatient variability in C_{min} concentrations of NVP.

When these data were compared with PK parameters from the previous study of children >6kg there was a difference of 15-20% lower NVP exposure in the 3-6kg weight band. d4T and 3TC parameters were comparable to the higher weight bands.

The investigators noted that 4/15 (27%) children had sub-therapeutic levels of NVP C_{min}(<3.0mg/L compared to 3/63 >6kg

($p=0.02$). This occurred most frequently in children <5 months (3/6, 50%) vs >5 months (1/9, 11%) but the number of children was too small for this to reach statistical significance. The dose range in the younger children was 324-406 mg/m² daily.

They suggest that the clinical consequences of NVP exposure may be minor as infants will be <5 months for a short time after treatment initiation, but that this requires further evaluation.

Model predicts rapid increase in lopinavir exposure in infants <6 months

Mina Nikanjam and coworkers performed a population PK analysis to characterise changes in lopinavir/ritonavir (LPV/r) PK in maturing young infants, and to assess dosing in this population. [5]

This group had previously shown that LPV/r exposure in infants <6 weeks of age receiving 300mg/75mg/m² 12 hourly, is lower than in older children receiving recommended doses. [6] However, the exact age at which LPV PK becomes similar to that in older populations is poorly understood.

This analysis used PK data from 31 infants <6 weeks of age from a prospective study, IMPAACT/PACTG P1030 to evaluate a 300mg/75mg/m² 12 hourly dose. 12 hour PK profiles (pre, 2, 4, 8 and 12 hr) were performed at week 2 of treatment and at 1 year of age.

Infants who did not achieve target LPV exposure at week 2 ($C_{pre} >1\text{mcg/mL}$) received a modified dose and a repeat analysis after 2 weeks. Trough LPV concentrations were taken regularly for up to 4 years and determined using LC/MS/MS method.

The investigators developed a population PK model using 549 LPV concentrations using NONMEM non-linear regression software and allometric weight scaling. Empiric post-hoc LPV PK parameter estimates were generated from visits with multiple samples. The final model used Monte Carlo simulations to estimate appropriate LPV dosing in this infant population.

The investigators reported that age was a powerful predictor of apparent clearance (CL/F), and was best described as a non-linear co-variate for bioavailability (F). They found half-life to be less affected by age. Ritonavir (RTV) levels correlated with LPV levels.

The interpatient variability for CL and volume of distribution (V) were 31.6% and 42.9% respectively. The median CL/F decreased with increasing age: 0.34 (<3 months, $n=17$), 0.22 (3-6 months, $n=19$), 0.13 (approx 1 year, $n=26$) L/h/kg. As did the median V/F : 3.2 (<3 months), 2.4 (3-6 months) and 1.4 (approx 1 year) L/h/kg. The median AUC increased with increasing age: 49.8 (<3 months), 67.1 (3-6 months) and 11.10 (approx 1 year) mcg*hr/mL. Based on this model LPV AUC in a typical infant would reach the adult value of 80mcg*hr/mL by 9 months of age.

Monte Carlo simulations predicted very low troughs of LPV (<1 ug/mL) occurring with the study dose with 20% frequency in infants <3 months but <1% in older infants. Using new WHO weightband dosing recommendations, the model predicted a lower frequency (13%) of troughs <1 ug/mL in the very young infants.

The investigators suggested that LPV concentration increases during the infants' first year are likely to be due to increased bioavailability. Also the rapid increase in LPV exposure was likely to account for overall good virological suppression observed (most infants achieved viral load <400 copies/mL at 48 weeks) despite low concentrations at the start of therapy.

C O M M E N T

Both studies suggest large interpatient variability in exposure in young infants, but that this may be of little clinical consequence (and clearly things get easier as the children get older).

The introduction of food with LPV/r may play a significant role in increasing the absorption as the infants mature. However, there are probably some developmental issues relating to pancreatic exocrine function that also contribute to this.

The WHO dosing guidelines were constructed with the doses "rounded-up" and represent on average larger doses than the FDA labelled dose, which will counter the reduced absorption to some degree.

Although the investigators recommend frequent monitoring in young infants, the clinical response in the earlier LPV/r study provides the rationale for LPV/r use in resource-limited settings where this is not available.

Healthcare workers should be cautious of mal-absorption in infants with diarrhoea as well as in those that do not experience a clinical improvement.

Suitable solid paediatric formulations also make treating children more feasible. The fixed dose combination tablets used in CHAPAS are dispersible and can therefore be used in even the youngest infants in place of oral formulations. The investigators have not reported problems, according to Zambian health workers, and they are popular with families, as they are easy to carry. Of note, this study initiated the children with full dose NVP, which meant there was no change of dosing at two weeks after starting treatment.

Urgently required now is an easier to use, store and transport paediatric formulation of LPV/r. Cipla (who also produce Baby and Junior

Triomune) have developed a “sprinkle” formulation using melt extrusion technology (similar to the newer LPV/r tablets). The formulation is in the same 4:1 drug ratio in 100/25 mg sachets. This is appropriate for even the youngest children, as it allows the drug to be easily mixed in with food. PK studies are currently planned or underway.

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<http://www.retroconference.org/2008/Abstracts/31505.htm>

Double-dose lopinavir/ritonavir provides insufficient lopinavir exposure in children receiving rifampicin

Polly Clayden HIV i-Base

Rifampicin-based TB treatment is recommended for children (there is no formulation of rifabutin for young children nor is it widely available). In South Africa children with HIV who are <3 years old receive lopinavir/ritonavir-based antiretroviral 1st line regimens. Rifampicin reduces trough concentrations of lopinavir by more than 90%. Additional boosting with ritonavir to a 1:1 ratio during TB treatment provides adequate concentrations in adults and children but this strategy is complex with oral solutions and not always feasible.

Helen McIleron from the University of Cape Town presented findings from a pharmacokinetic (PK) study using double dose lopinavir/r (LPV/r) (ratio 4:1) with rifampicin in young children who were >6 months of age. This strategy has achieved adequate concentrations in healthy adult volunteers.

In this study, children with TB/HIV (n=17), received 460/115mg/m² LPV/r +2NRTIs, once established on rifampicin-based TB treatment. Children without TB (n=24) were used as a control group and received the standard dose LPV/r 230/57.5mg/m² +2 NRTIs.

Table 1. Baseline characteristics and PK of children receiving LPV/r

	TB/HIV n=17	Controls n=24	p-value
Male/female	4/13	16/8	0.007
Age (months)	15.0 (12.4-24.9)	19.1 (13.8-26.8)	0.615
Weight (kg)	8.64 (7.02-9.96)	10.55 (8.38 -12.55)	0.007
Cpre (mg/L)	0.76 (0.17-1.62)	4.25 (3.42-8.10)	0.0001
Cmax (mg/L)	4.45 (2.51-8.22)	7.94 (6.86-13.40)	0.008
AUC0-8h (mg.h/L)	22.29 (13.03-47.30)	45.15 (37.25-81.38)	0.010

Baseline characteristics and PK parameters are median (IQR).

Pre-dose sampling was performed at 2, 4, and 8 hours after dose and determined using LC-MSMS method.

Following an interim analysis and DSMB review of plasma levels in 15 children with TB/HIV the study was stopped.

The investigators reported a median (IQR) LPV dose of 486 mg/m² (478-497) in cases and 234 mg/m² (228-241) in controls.

Characteristics and PK of the children are shown in Table 1. There were more girls than boys with TB/HIV and children with TB weighed less than controls.

They noted that among a subgroup of 5 cases sampled 12 hours after the observed dose 12-hour LPV concentrations were 0.65 mg/L lower than Cpre showing that adherence to the previous dose is unlikely to be the reason for the low concentrations.

The investigators found high interpatient variability within both groups of children. The median LPV Cpre, Cmax and AUC0-8h were reduced by 82%, 44% and 51% respectively among children receiving double dose LPV/r with rifampicin-based TB treatment; 10(59%) had subtherapeutic LPV/r Cpre (<1 mg/L) vs 2 (8%) controls.

They do not recommend this approach in young children and Dr McIlleron concluded: "There is an urgent need to establish safe, effective and feasible co-treatment for young children with HIV associated tuberculosis".

C O M M E N T

These data are important to offer guidance for "what not to do" in this population. They also argue for easier to use solid paediatric formulations of LPV/r and RTV.

Ref: McIlleron et al. Double-dose lopinavir/ritonavir provides insufficient lopinavir exposure in children receiving rifampicin-based anti-TB treatment. 16th CROI. February 2009, Montreal. Oral abstract 98.
<http://www.retroconference.org/2009/Abstracts/34615.htm>

PI-based ART in HIV-infected and HIV/TB coinfecting children in South Africa **Polly Clayden, HIV i-Base**

South African HIV guidelines recommend PI-based regimens for children <3 years old. Young children mostly receive lopinavir/ritonavir (LPV/r) but in some cases full-dose ritonavir (RTV) is used if a child is also being treated for TB.

Cordula Reitz and co-workers evaluated factors associated with virologic suppression among children receiving protease inhibitors in Johannesburg in the NEVEREST study.

NEVEREST enrolled HIV-infected children who had been perinatally exposed to nevirapine (NVP). Children age >6 months to 24 months received LPV/r based ART and children less than 6 months old or receiving TB treatment (rifampicin/isoniazid for 6 months + pyrazinamide for 2 months) received RTV-based ART. All children received d4T+3TC.

Viral suppression was defined as reducing viral load to <400 copies/mL. Kaplan Meier methods were used to calculate the probability of achieving viral suppression at 9 months or death.

This analysis included 254 children with a median age of 8.75 months (IQR 5.18-13.8), median CD4 percentage 18.95% (IQR 12.8-24.5) and 80.2% were WHO stage III or IV.

Of these, 138 (54.3%) children started ART with a LPV/r-based regimen and 116 (45.7%) a RTV-based regimen. 54 (46.6%) were <6 months old and 62 (54.3%) were receiving TB treatment (by 9 months an additional 37 [14.6%] children began TB treatment).

The investigators reported an overall mortality rate of 14%. Higher mortality was significantly associated with younger age ≤12 months vs >12 months [AHR 2.9, 95%CI 1.1-7.8], pre-treatment weight for age z-score (WAZ) ≤-4 vs >-2 [AHR 3.3; 95%CI 1.4-8.2] and higher pre treatment viral load ≥750,000 copies/mL vs ≤100,000 copies/mL [AHR 3.1; 95%CI 0.4-23.5].

The probability of viral suppression (<400 copies/mL) was 83.7% at 9 months after starting ART. Children receiving TB treatment were less likely to achieve viral suppression than children never treated for TB, 78.3% vs 94.1% respectively.

The overall probability of viral rebound at 4 months was 17.6%. Only TB treatment was associated with viral rebound; 8/15 (53.3%) children who started TB treatment after ART and achieved viral suppression had viral rebound compared to 12% without TB and 2.8% probability among those who started TB treatment before ART, p<0.0001 [AHR 5.2; 95% CI 2.1-12.9].

Although the researchers reported high rates of viral suppression among children <2 years they wrote; "How best to treat HIV-infected children who require TB treatment remains an unsolved problem. There is an urgent need to further evaluate the pharmacokinetics and clinical outcomes in children co-treated for these two diseases so that evidence-based recommendations can be made."

C O M M E N T

Once again, we need more PK data in younger children and better PI formulations.

Ref: Reitz et al. Virologic Response to protease inhibitor-based ART among children younger than 2 Years of age co-treated for TB in South Africa. 16th CROI, February 2009, Montreal, Canada. Abstract 910.
<http://www.retroconference.org/2009/Abstracts/34444.htm>

Etravirine dose selection in children aged 6 to 17

Polly Clayden, HIV i-Base

Christoph Konigs and coworkers from paediatric centres in Europe performed a dose finding study of etravirine (ETR) in treatment experienced children ≥ 6 years and weighing ≥ 20 kg.

This was a phase 1, open label trial in two sequential stages. 21 HIV-positive children on stable lopinavir/r-based ART with viral load < 50 copies/mL were enrolled in each stage. Children in stage I received 4mg/kg ETR bid following a meal (included in HTB reports from CROI last year). Children in Stage II received 5.2mg/kg ETR bid following a meal. ETR was added to background regimen for 7 days. After the morning dose on day 8 the investigators performed a 12 hour PK evaluation. 100mg and proportional 25mg tablets were used in this study. PK for 19 and 20 children were available in stages I and II, respectively.

The investigators reported the mean (SD) C_{max} in stage I and II, respectively, was 495 (453) and 757 (680) ng/mL; C_{min} was 184 (151) and 294 (278) ng/mL; and AUC_{12h} was 4050 (3602) and 6141 (5586) ng·h/mL.

When they compared PK parameters to those reported in adult trials ($n = 575$), population derived C_{min} was 393 [391] ng/mL and AUC_{12h} was 5506 [4710] ng·h/mL, they found the levels achieved in children participating in stage II with the higher dose to be more appropriate.

All children had a viral load < 50 copies/mL on day 8. The majority of side effects were grade 1 or 2, most commonly rhinitis or headache. Two children in stage 1 had a mild to moderate rash on day 8. No child discontinued treatment due to toxicity.

The target dose of ETR in children 6-17 years was selected as 5.2mg/kg bid, which provides comparable exposure to the adult dose of 200mg bid.

Further studies in children are ongoing or planned.

C O M M E N T

Tibotec intend to market the 25-mg tablet for children (and adults who have difficulty swallowing the 100-mg tablets) once they have the initial paediatric indication.

Ref: Konigs et al. Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years inclusive. 16th CROI, February 2009, Montreal, Canada. Poster abstract 879.

<http://www.retroconference.org/2009/Abstracts/35446.htm>

Preliminary results from first paediatric raltegravir study

Polly Clayden, HIV i-Base

Adrew Wiznia and coworkers from IMPAACT P1066 showed preliminary results from the first paediatric study of raltegravir (RAL).

This is an ongoing prospective, non-randomised, open label, dose-finding trial of RAL plus optimised background regimen (OBR) in treatment-experienced children.

Children aged ≥ 12 to < 19 years (cohort 1) and > 6 to < 12 years (cohort IIA). The children are enrolled sequentially older to younger.

Children in stage I received RAL poloxamer film tablets that were added to a stable, failing ART regimen. Pharmacokinetics (PK) was done on day 7 to 12 and then OBR started.

The study had enrolled 36 patients (22 in cohort I and 14 in cohort IIA). They initially received a 6 or 8mg/kg dose bid with a maximum dose of 600mg bid.

The study demographics included: 47% male, 67% black, and 25% white. Median baseline viral load was 4.4 log (range 3.1 to 5.9) copies/mL and were similar between the cohorts. Median CD4 percentage was 22 (range 0 to 42%).

Six children had grade 3/4 adverse events: 5 had neutropenia, 1 increased lipids, and 1 increased creatinine associated with aminoglycoside use. One grade 4 neutropenia and one elevated GGT was possibly associated with RAL.

There were no deaths. Four children were withdrawn from the study, 3 because of poor adherence (cohort 1) and one at the request of the doctor (cohort IIA).

In an intent-to-treat analysis of those treated at 8 mg/kg 23/30 (77%) and 24 of 14/30 (86%) were < 400 copies/mL (50% and 63% < 50 copies/mL) at weeks 8 and 12 respectively. Median CD4 percentage was 24% at both timepoints.

The investigators wrote: "Preliminary, short-term and partial data from IMPAACT P1066 suggests that RAL + OBR in children ages 6 to 18 was generally safe, well tolerated and effective. Enrollment into these cohorts, as well as use of a chewable formulation for children <12 years of age, is continuing".

C O M M E N T

For cohort IIA, repeat PK and safety evaluations at a uniform dose of 400 mg bid regardless of weight is ongoing.

Merck will continue this paediatric programme with sequential age strata down to 4 weeks of age.

In addition to the chewable formulation, oral granules for suspension are planned for children less than two years old.

Ref: Wiznia A et al. Safety and efficacy of raltegravir in pediatric HIV infection. Preliminary analysis from the International Maternal Pediatric Adolescent AIDS Clinical Trials group, P1066. 16th CROI, February 2009, Montreal, Canada. Poster abstract 874.
<http://www.retroconference.org/2009/Abstracts/36282.htm>

CONFERENCE REPORTS

10th Intl Workshop on Clinical Pharmacology of HIV Therapy

15-17 April 2009, Amsterdam

Introduction

The following early reports are included thanks to natap.org. Further coverage will be included in the next issue of HTB.

Although it is disappointing that abstracts from the virology-education meetings are not published online, selected presentations from the meeting can be found at:

<http://www.HIVpresentation.com>

Reports in this issue are:

- Genetic markers linked to early discontinuation of three antiretrovirals
- Efavirenz lowers levels of darunavir given as 900/100 mg once daily with ritonavir
- How much (or how little) ritonavir do you need to boost another PI?

Genetic markers linked to early discontinuation of three antiretrovirals

Mark Mascolini, natap.org

Pharmacogenetic markers that purportedly signal antiretroviral side effects predicted discontinuation of atazanavir, efavirenz, and tenofovir (but paradoxically not abacavir) within the first year of treatment in the Swiss HIV Cohort Study (SHCS). [1]

Sara Colombo and colleagues cautioned that gender and ethnicity also correlated with stopping antiretrovirals and complicate interpretation of their results. But they plan a randomised study to see if monitoring patients for toxicity-related genetic shifts can improve antiretroviral care.

SHCS investigators used Veracode technology to search for 13 pharmacogenetic markers thought to signal antiretroviral toxicity on 9 genes. They targeted markers linked to (1) central nervous system toxicity with efavirenz, (2) Gilbert syndrome with atazanavir, (3) cardiovascular disease with lopinavir, (4) renal proximal tubulopathy with tenofovir, and (5) hypersensitivity to abacavir. The abacavir hypersensitivity marker they focused on was not HLA-B*5701 [2], but the HCP5 gene shift designated rs2395029.

The study involved 577 treatment-naive people starting their first antiretroviral regimen from 2004 through 2008. This group was three quarters male (73%) and white (79%), though 13% were black Africans. Within the first year of treatment, 190 people (33%) stopped one or more antiretrovirals because of toxicity. For tenofovir, efavirenz, lopinavir, and atazanavir, people with risky genes stopped each of these drugs substantially more often than people without the genetic risk markers:

- Tenofovir: 500 patients, 28.6% at risk stopped versus 13.6% not at risk
- Efavirenz: 272 patients, 67.6% at risk stopped versus 27.4% not at risk
- Lopinavir: 184 patients, 51.4% at risk stopped versus 32.6% not at risk
- Atazanavir: 121 patients, 62.5% at risk stopped versus 18.9% not at risk

The HCP5 genetic marker was not a good predictor of quitting abacavir, perhaps because the study considered stopping abacavir for any reason, not just the hypersensitivity reaction, and because people in Switzerland started getting HLA-B*5701 screening before beginning abacavir during this period.

For the other four drugs, hazard ratios adjusted for other risk factors found that genetic markers independently predicted stopping efavirenz (adjusted hazard ratio [aHR] 3.10, 95% confidence interval [CI] 1.48 to 6.46, $p=0.0259$ and atazanavir (aHR 7.31, 95% CI 2.86 to 18.72, $p<0.0001$). There was a strong trend toward an independent effect of genetic markers on quitting tenofovir (aHR 2.30, 95% CI 0.99 to 5.31, $p=0.052$) but not lopinavir (aHR 1.42, 95% CI 0.62 to 3.25, $p=0.41$).

Gender had a big impact on genetic risk for efavirenz-related central nervous system toxicity. Among women, 80% of those with a risk marker versus 42.5% of those without a risk marker stopped efavirenz. Respective rates for men were 50% and 24.3%. The SHCS investigators noted that certain genetic markers they analysed are more common in nonwhites and that most of the nonwhites in this group were women.

Colombo and colleagues believe their study “highlights the interest of conducting a prospective clinical trial of pharmacogenetics-driven choice of first-line antiretroviral therapy.” They plan such a trial in which clinicians planning a first-line regimen are randomised to receive or not receive antiretroviral advice based on analysis of each first-line patient’s toxicity risk markers. At this point, though, it is not clear which markers have a negative predictive value high enough to reliably warn physicians away from using a certain drug. HLA-B*5701 has a 100% negative predictive value for hypersensitivity to abacavir. [2]

References

1. Colombo S et al. Association of pharmacogenetic markers with premature discontinuation of first-line ART. 10th International Workshop on Clinical Pharmacology of HIV Therapy, April 15-17, 2009, Amsterdam. Abstract O03.
2. Mallal S et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358:568-579.

Efavirenz lowers levels of darunavir given as 900/100 mg once daily with ritonavir

Mark Mascolini, natap.org

A standard dose of efavirenz significantly lowered darunavir concentrations when healthy volunteers added the NNRTI to 900/100 mg of darunavir/ritonavir once daily. [1]

In a study reported separately by NATAP, this same once-daily dose of darunavir/ritonavir controlled HIV well in 25 people with moderate protease inhibitor (PI) experience and no mutations that make HIV resistant to darunavir. [2] But these researchers did not specify whether anyone took efavirenz with darunavir/ritonavir.

Efavirenz induces the CYP3A4 enzyme involved in metabolism of darunavir and ritonavir. As a result, efavirenz lowered darunavir trough concentrations by 31% when darunavir/ritonavir was taken at a dose of 300/100 mg twice daily in an earlier study. To test the impact of efavirenz on a 900/100mg once-daily dose of darunavir/ritonavir, these researchers recruited 12 healthy volunteers in Singapore with weights ranging from 50 to 83 kg and ages from 24 to 49 years. Seven volunteers were men. Everyone took 900/100 mg of darunavir/ritonavir once daily for 10 days, then added 600 mg of efavirenz daily through day 24. Then they stopped the PIs and took only efavirenz from day 25 through 38.

After people added efavirenz to darunavir/ritonavir, darunavir’s minimum concentration (C_{min}), area under the curve (AUC), and terminal half-life (T_{1/2}), all fell significantly, while oral clearance (CL/F) rose significantly:

- Average C_{min} (ng/mL): Before EFV 2137, with EFV 1180, ratio 0.43, $p=0.0003$
- Average AUC (hr/ng/mL): Before EFV 103,261, with EFV 89,498, ratio 0.86, $p=0.049$
- Average T_{1/2} (hr): Before EFV 15.3, with EFV 8.5, ratio 0.56, $p=0.00001$
- Average CL/F (hr): Before EFV 9657, with EFV 11,392, ratio 1.17, $p=0.047$

Ritonavir C_{min}, AUC, and T_{1/2} also dropped significantly when volunteers added efavirenz, and those changes probably affected darunavir values. Efavirenz T_{1/2} was 66% longer with the PIs than without them ($p=0.01$), but efavirenz concentrations did not change after people stopped darunavir/ritonavir.

Grade 3 hepatitis developed in 1 woman and resolved spontaneously after 150 days. One woman had a grade 2 rash and 3 had a grade 1 rash. Triglycerides rose 20% with darunavir and 52% during the PI/efavirenz phase. In an AIDS Clinical Trials Group study of previously untreated people, efavirenz plus lopinavir/ritonavir (and no nucleosides) resulted in significantly more grade 3 or 4 lab toxicity (usually high triglycerides) than either of those drugs plus nucleosides [3].

Because darunavir minimum concentrations remained above the EC₅₀ for nonresistant virus with efavirenz in the Singapore study, the researchers suggested this regimen may be effective for previously untreated people with no PI or nonnucleoside resistance mutations. But they cautioned that the clinical significance of the interaction they discovered must be explored in people with HIV.

References

1. Lee LS et al. Pharmacokinetics of darunavir 900mg and ritonavir 100 mg (DRV/r) once daily when co-administered with efavirenz 600mg once daily in healthy adult volunteers. 10th International Workshop on Clinical Pharmacology of HIV Therapy, April 15-17, 2009, Amsterdam. Abstract P29.
2. Curran A et al. Pharmacokinetics, efficacy and safety of darunavir/ritonavir 900/100 mg once-daily. 10th International Workshop on Clinical Pharmacology of HIV Therapy, April 15-17, 2009, Amsterdam. Abstract P14.
3. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med. 2008;358:2095-2106.

How much (or how little) ritonavir do you need to boost another PI?

Mark Mascolini, natap.org

Protease inhibitors (PIs) fall into two groups - those whose concentration correlates closely with the boosting dose of ritonavir, and those that do not - according to a 16-study systematic analysis by Andrew Hill (University of Liverpool) and colleagues at other centers. [1]

Finding the lowest effective boosting dose could cut costs and lower the risk of side effects. Hill suggested 50 mg of ritonavir once daily - or less - may be enough to boost some PIs.

Hill analysed results of 16 PI/ritonavir dose-ranging studies:

- Four amprenavir or fosamprenavir trials with ritonavir doses ranging from 50 mg twice daily to 200 mg twice daily
- One atazanavir cohort study with ritonavir doses ranging from 100 to 200 mg once daily
- One darunavir trial with ritonavir doses ranging from 100 mg once daily to 200 mg twice daily
- One indinavir trial with ritonavir doses ranging from 100 to 400 mg twice daily
- Three saquinavir trials with ritonavir doses ranging from 50 mg once daily to 400 mg twice daily
- One tipranavir trial with ritonavir doses ranging from 100 to 200 mg twice daily
- Five lopinavir trials with ritonavir doses ranging from 50 mg twice daily to 266 mg twice daily

For each PI, Hill calculated the geometric mean ratio for the boosted PI with higher versus lower doses of ritonavir. For the five lopinavir/ritonavir trials, he performed a meta-analysis of geometric mean ratio data to estimate the effect of the lopinavir dose versus the ritonavir dose on area under the curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}).

The overall analysis showed that boosted PIs fell into two groups: PIs whose concentration depended on the size of the ritonavir boost (the dose-dependent group), and PIs whose concentration did not depend on the size of the ritonavir boost (the dose-independent group). Hill clarified that "dose independence" does not mean levels of that PI would be the same with or without ritonavir. Indinavir, lopinavir, and tipranavir are dose-dependent PIs, while (fos)amprenavir, darunavir, and saquinavir are dose-independent PIs.

Limited data from a cohort study suggest that atazanavir is a dose-independent PI, but Hill could not confidently classify it based on results presented to date. For all the PIs analysed, dose dependence was not affected by the oral bioavailability of the PI or by the effect of each PI on ritonavir concentrations.

These studies showed that 50 mg of ritonavir is enough to boost saquinavir once daily or fosamprenavir twice daily. Hill cautioned that the saquinavir finding comes from a single study. Similarly, the darunavir, tipranavir, and indinavir findings rest on one study each. The minimum ritonavir boosting dose for darunavir and atazanavir remains to be defined, Hill proposed, but it may also be under 100 mg.

The lopinavir/ritonavir meta-analysis showed that lopinavir AUC, C_{max}, and C_{min} rose proportionally as the ritonavir dose increased. But lopinavir AUC, C_{max}, and C_{min} did not rise in a proportional manner as the lopinavir dose rose. Hill figured that a 200/150-mg twice-daily dose of lopinavir/ritonavir (one Meltrex 200/50-mg tablet plus one 100-mg dose of ritonavir twice daily) would yield a lopinavir AUC, C_{max}, and C_{min} within 10% to 20% of those values with the 400/100-mg twice-daily dose (two Meltrex 200/50-mg tablets twice daily). He suggested these findings may mean that a higher ritonavir dose could be used with a lower dose of other dose-dependent PIs to achieve the same drug levels.

Hill concluded that a lower-dose ritonavir tablet -50 mg *or less* - "could lower costs and improve tolerability, while boosting several commonly used PIs to a similar level compared with the current 100mg dose. Right now, when not coformulated with lopinavir, ritonavir comes as a 100mg soft-gel capsule. He also suggested these findings may be helpful in designing new PI boosters, because the ritonavir results show that different doses of a booster may be required to boost different PIs or other boostable drugs.

C O M M E N T

Whether lower ritonavir-boosting doses might be equally effective has been a long-standing question raised by community advocates since the first days of PI-boosting. Studies have been limited by the only formulation being the 100mg capsule. However, the availability of the new non-refrigerated meltrex tablet formulation of ritonavir, hopefully in 100mg and 50mg tablets will broaden these options.

While this study is interesting from a theoretical perspective, the interpatient variability of drug levels associated with protease inhibitors means that clinical studies and individual therapeutic level monitoring (TDM) will be essential before considering modification of the currently recommended doses.

Reference

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CONFERENCE REPORTS

4th South African AIDS Conference

31 March – 3 April 2009, Durban, South Africa

HAART coverage and unmet need in South Africa

Nathan Geffen, TAC

In an oral presentation, Leigh Johnson of the Centre for Actuarial Research at the University of Cape Town presented an analysis of South Africa's HAART requirements. [1] Johnson is one of the developers of the Actuarial Society of South Africa's AIDS models, including ASSA2003. [2]

Albeit that HAART has been available at a few public sector research and pilot sites for about a decade, the implementation of treatment in the public sector began in 2004. The number of people on treatment in both the private and public sector has risen from about 50,000 at the start of the programme in mid-2004 to about 550,000 in mid-2008. [3]

This is based on Department of Health statistics as well as Johnson's research of private sector and NGO treatment numbers. The Department of Health data is subject to limitations. The most glaring is that five of the country's nine provinces (Eastern Cape, Gauteng, Kwazulu-Natal, Limpopo and North West) only track the number of people who initiated treatment, not the number currently on treatment. Patients lost to follow up and deaths are therefore included in its count. To correct this, Johnson calculated a rate of retention in these provinces based on data from the Western Cape. He also checked the quality of his adjusted estimates against sales data from the pharmaceutical company supplying the bulk of the state tender.

Johnson has calculated that in mid-2004, the public sector treated less than 20% of HAART patients (the remainder were treated by the private sector and NGOs). This had increased to nearly 80% by mid-2008. He also calculated unmet need.

- The number of adults with untreated clinical AIDS as at mid-2008 was 430,000. Using this criterion, HAART coverage is 54%.
- The number of adults with untreated clinical AIDS or CD4 counts < 200, i.e. the Department of Health criteria, was 760,000, in which case coverage is only 40%.
- If the CD4 count criterion was changed to less than 350, i.e. according to the Southern African HIV Clinicians Society guidelines, then 1.8 million people were untreated. In this case coverage is a mere 22%.

Using the Department's criteria, the province with the lowest coverage is the Free State (26%). The Western Cape, at 72% has the best coverage.

To determine future need, Johnson ran various scenarios through the ASSA2003 model. He used the Department of Health's estimates of the number of people on HAART, the District Health Barometer's data on PMTCT and results from the Western Cape's programme to calculate HAART effectiveness.

If the target of placing 80% of newly eligible patients on HAART is met by 2010 (80% is the target of the state's National Strategic Plan) and current HIV incidence trends continue, then by 2011 (the end of the target period for the plan), just under 1.5 million people will be on treatment. More than 2 million people will be on treatment in 2014 and more than 3 million in 2020.

If instead, HIV incidence is halved (also a target of the state's plan), then the consequences of this become more apparent the further into the future the estimates are projected. By 2020, half-a-million fewer people will be on treatment in this scenario.

Johnson demonstrated the substantial benefits of the HAART rollout. It conferred 24% fewer AIDS deaths in 2008, than if the programme had not been rolled out. This benefit is becoming more pronounced with time resulting in approximately 200,000 fewer deaths per year for the next decade. In 2008, there were 8% fewer maternal orphans under the age of 18 due to HAART. This becomes even more beneficial over the next 15 years, with nearly a million fewer orphans by the middle of the next decade.

C O M M E N T

Despite the actions of the Mbeki regime, particularly former Health Minister Tshabalala-Msimang, South Africa has rapidly scaled up its HAART rollout. This has been achieved because of the efforts of health workers, researchers activists and some civil servants. Nevertheless, as Johnson has demonstrated, the unmet need is substantial and growing. It will be challenging to meet the prevention and treatment targets of the National Strategic Plan.

Johnson's painstaking analysis of the number of people on HAART as of mid-2008 across all sectors must be considered the definitive estimate of coverage for South Africa. Yet the excellent work of the Centre for Actuarial Research continues to be limited by the quality of the data from the Department of Health on numbers of patients initiated, lost-to-follow-up, currently active and died on the PMTCT and HAART programmes. The Department must prioritise improving the monitoring and evaluation of the HAART and PMTCT programmes.

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T R E A T M E N T A C C E S S

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 tablets	Cipla, India	29 April 2009
Fixed dose 3TC/AZT 150 mg/300 mg, co-packaged with nevirapine 200 mg	Hetero, India	7 May 2009

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

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

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_ http://www.No=3D021360&TABLE1=3DOB_Rx

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 90 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/oashi/aids/listserve/archive.html>

ANTIRETROVIRALS

EMA positive opinion on using tipranavir and darunavir in younger patients

The EMA press release on its April 2009 meeting included the following two positive opinions on using recently approved protease inhibitors in younger patients.

Tipranavir (Aptivus)

To extend the indication to the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adolescents with virus resistant to multiple protease inhibitors above the age of 12, and also to extend the indication in highly pre-treated children aged 2 to 12. The latter indication comes with a new oral solution formulation. Aptivus is currently indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.

Darunavir (Prezista)

To extend the indication to include the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced children and adolescents above the age of 6. This indication also comes with the new strengths 75mg and 150mg film-coated tablets. Prezista is currently indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in treatment-experienced adult patients.

Source: EMA press release 'Meeting highlights from the Committee for Medicinal Products for Human Use, 20-23 April 2009'. (23 April 2009).

Lopinavir/r (Kaletra) cardiovascular risk requires FDA label changes

On 6 April 2009, the US FDA approved changes to the product label for lopinavir/ritonavir (Kaletra) tablets and oral solution, reflecting new warnings and precautions regarding QT/QTc interval and PR interval prolongation information (electrical activity and rhythm of the heart).

The following information was added to the product label.

5. WARNINGS AND PRECAUTIONS

5.5 PR Interval Prolongation

Lopinavir/ritonavir prolongs the PR interval in some patients. Cases of second or third degree atrioventricular block have been reported. Kaletra should be used with caution in patients with underlying structural heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities.

The impact on the PR interval of co-administration of Kaletra with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digoxin and atazanavir) has not been evaluated. As a result, co-administration of Kaletra with these drugs should be undertaken with caution, particularly with those drugs metabolised by CYP3A. Clinical monitoring is recommended.

5.6 QT Interval Prolongation

Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of Kaletra could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.

12. CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Effects on Electrocardiogram

QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once-daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 5.3 (8.1) and 15.2 (18.0) mseconds (msec) for 400/100 mg twice-daily and supratherapeutic 800/200 mg twice-daily Kaletra, respectively. Kaletra 800/200 mg twice daily resulted in a Day 3 mean C_{max} approximately 2-fold higher than the mean C_{max} observed with the approved once daily and twice daily Kaletra doses at steady state.

PR interval prolongation was also noted in subjects receiving Kaletra in the same study on Day 3. The maximum mean (95% upper confidence bound) difference from placebo in the PR interval after baseline-correction were 24.9 (21.5, 28.3) and 31.9 (28.5, 35.3) msec for 400/100 mg twice-daily and supratherapeutic 800/200 mg twice-daily Kaletra, respectively.

Source: FDA list serve (7 April 2009)

NEJM paper: NA-ACCORD cohort study on when to start treatment

Nathan Geffen, TAC

In the last issue of HTB we reported Mira Kitahata's presentation at CROI of an analysis of the NA-ACCORD database to determine when to start treatment. The study has since been published in the NEJM and sheds considerable light on questions that arose from the CROI presentation. [1]

Kitahata's team conducted two analyses. The first analysed over 8,000 patients with CD4 counts of 350 to 500. Just over 2,000 began treatment immediately and about 6,200 deferred. The relative risk of death in the deferred group was 1.69 (1.26-2.26; $p < 0.001$).

In the second analysis, about 2,200 of 9,100 patients with CD4 counts above 500 initiated treatment and 6,935 deferred. The relative risk of death in the deferred group was 1.94 (1.37-2.79; $p < 0.001$).

The crude death rate in the early-therapy 351-500 CD4 group was 1.6 per 100py. It was 1.3 per 100py in the early therapy group in patients with CD4 counts above 500.

In an accompanying editorial, Paul Sax and Lindsey Baden state that the "study adds to a growing body of data supporting earlier treatment for HIV infection." They also explain, "Potential additional benefits of earlier therapy for HIV may include a lower rate of drug-specific toxic effects, a greater likelihood of achieving a normal CD4+ count, a reduction in immune activation and inflammation, and a decreased risk of HIV transmission." [2]

They continue, "Analyses of cost-effectiveness have shown that antiretroviral therapy also compares favourably with other widely adopted medical interventions. Increasing the CD4+ threshold to start therapy at a range of 350 to 500 cells/mm³ would add only a few years of additional therapy onto projected decades of treatment and hence generate a relatively small added lifetime cost." While this argument is true for wealthy countries, it is not clear that it is applicable to poorer ones.

However Sax and Baden conclude with the following important caution, "The NA-ACCORD data do not provide definitive proof that we should be starting antiretroviral therapy in all patients with HIV infection. Such a conclusion would require data from a randomised, prospective clinical trial, and at least three such studies are either ongoing or planned. However, the supportive evidence for the benefits of earlier therapy continues to increase, making strategies to identify patients with HIV infection before the onset of substantial immunodeficiency all the more compelling."

The START trial, which has begun, serves this purpose.

References

1. Kitahata M. et al. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. NEJM. 2009 Apr 30;360(18)
2. Sax P. et al. When to Start Antiretroviral Therapy — Ready When You Are? NEJM. 2009 Apr 30;360(18).

NA ACCORD results support the importance of the START study: response to researchers

The following article was produced by the lead investigators in the START trial but has wider relevance for clinicians and patients following discussion about when to start treatment and the particular importance for data based on randomised studies.

Note to investigators from Andrew Phillips (START statistician), James Neaton (INSIGHT principal investigator) and Abdel Babiker, Sean Emery, Fred Gordin & Jens Lundgren (START protocol co-chairs)

A recently published analysis of a large multi-cohort dataset (NA ACCORD) has considered the question of earlier initiation of ART. [1] Using two starting strata in separate analyses, CD4 350-500/mm³ and > 500 /mm³, the investigators reported lower death rates in patients initiating therapy early compared with those deferring.

The NA ACCORD findings appear consistent with the evidence from epidemiologic studies that were the motivation for the design of START. We did not consider that those data were sufficiently compelling to recommend any change in guidelines to initiation of ART at CD4 count above 350/mm³ in the absence of a trial. That remains our view with the addition of the NA ACCORD analyses to the body of evidence.

On the contrary, we think that the findings from NAACCORD provide further interesting epidemiological analyses that support

the need to perform a randomised trial to assess whether ART should be initiated at higher levels than is currently the case. Specific comments on the NA ACCORD analyses are given below.

The primary reason why findings from large randomised controlled trials are considered the most reliable form of evidence for the impact of an intervention is that unknown and unmeasured confounders would be balanced between arms. No analyses from observational studies can ensure this balance.

It would be a dangerous precedent for medical research if we were to allow our interpretation of analyses from observational data to undermine our ability to perform randomised studies of critical questions of enduring and world-wide importance.

Specific comments on the NA ACCORD analyses

1. As stated by Sax et al in their commentary on the NA ACCORD article, unmeasured confounding could well be strong. People who start ART early are likely to be different to those who do not, particularly in terms of socio-economic status, adherence and health-seeking behavior in general. Guidelines state that the perceived likelihood that a patient will adhere should be taken into account when deciding whether to start ART. [2]

Many aspects of health seeking behavior cannot readily be measured but are likely to be strongly linked to mortality and thus will confound the association between early therapy and mortality. Adherence to placebo has been found to be strongly associated with reduced mortality in several studies. [3-6]

In addition, since the study was not specifically designed to address the question, factors known to predict death from non-AIDS conditions, such as smoking, diabetes, hypertension, and HBV status were not measured and adjusted for, while most deaths of those with cause known were from non-AIDS conditions. Such confounders could jointly well be strong enough to remove the association observed; i.e. with a joint effect which is stronger than the effect of the single unmeasured confounder considered in the NA ACCORD analysis.

2. There are other potential biases in the analysis. Patients in the early therapy group are more likely to be those with a lower natural rate of CD4 count decline and hence better prognosis. For example, consider the analysis of people with baseline CD4 count > 500, and further consider a patient within this analysis who starts ART on the date of the next CD4 count after baseline. If this next CD4 count is > 500 then they will become a patient in the early-therapy group while if the next CD4 count is < 500 they will become a patient in the deferred-therapy group. Thus patients who have a more rapid decline in CD4 count between baseline and the next count are more likely to get into the deferred group and patients with a stable CD4 count are more likely to get into the immediate group. Once the next CD4 count after baseline has been performed, the only way of a patient being in the early-therapy group is if they have demonstrated relative stability in natural CD4 count decline, a factor associated with better prognosis. The extent of the bias caused, and whether it is accounted for by further inverse probability weighting, is unclear.

Another concern is that baseline is later in calendar time in the early-therapy group than in the deferred group. The calendar dates at baseline are not given but the year of starting ART is similar in those in the early therapy and deferred therapy groups in both analyses, suggesting that baseline is on average at an earlier date in the deferred therapy group compared with the early therapy group. This could lead to a bias, which would be removed by adjustment for calendar date of baseline in the analysis. However, simultaneous adjustment for both dates would not be possible.

3. The analysis is opaque, even to statisticians. The methods used are such that it is not possible to show any descriptive data that intuitively give a feel for the higher risk in the deferred group. Based on the number of deaths and person years given the crude death rates are lower for the deferred-therapy group than in the early therapy group in both analyses. The stratification by cohort or use of inverse probability of censoring weighting leads to the relative rates reversing in direction, for reasons that are not easy to intuitively understand. The weighting is used to adjust for censoring due to people starting ART or follow-up ending while still above the CD4 threshold but beyond 6 months from baseline, and for people having a CD4 count that declines below the lower threshold for deferral. Factors associated with loss to follow-up may be different in each case and it is not clear if the same weighting is used. Likewise, the artificial censoring means that there is 2-3 times longer median follow-up in the immediate therapy group, the implications of which are unclear.

4. The analysis in the lower strata is not relevant to START. In the analysis of people with baseline CD4 count 350-500/mm³, the CD4 count at start of ART in the deferred group is below 228/mm³ in 25% of patients starting ART in this arm. This means that this analysis is not relevant to whether ART initiation should be at CD4 counts above 350/mm³, compared with 350/mm³ itself.

5. Another analysis of large collaborative cohorts of the question of early ART initiation carried out recently, using different methods pioneered within the MACS cohort, has concluded that a CD4 count of 350/mm³ is the minimum threshold at which ART should be started. There was no evidence for a mortality benefit from starting at higher CD4 count levels. The reasons for the difference in findings are unclear.

References

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EMA statement on abacavir and the risk of heart attack

Finalising a review of recent data on the risk of heart attack (myocardial infarction) associated with the use of abacavir in HIV-infected patients, the CHMP has concluded that there is insufficient evidence to recommend changes to the therapeutic management of patients. This follows the Committee's review of findings from the D:A:D study in April 2008, which concluded that further data were needed to determine this risk.

Data from observational studies that have become available since April 2008, including the French Hospital Database on HIV, have continued to show a possible link between myocardial infarction and the use of abacavir. Data from clinical trials showed low numbers of myocardial infarction and could not exclude a small increase in risk.

However, the CHMP has concluded that there were inconsistencies between the different studies' findings, and that a causal relationship between treatment with abacavir and the risk of myocardial infarction can neither be confirmed nor refuted. To date, there is no established biological mechanism that could explain a potential increase in risk.

Nevertheless, when prescribing abacavir-containing medicines, prescribers should take action to minimise modifiable risk factors, such as smoking, high blood pressure and high blood-fat levels. The product information for abacavir-containing medicines will be updated to reflect this information.

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) indicated in antiretroviral combination therapy for the treatment of HIV infection. In the European Union, it is available as Ziagen, in combination with lamivudine as Kivexa, and in combination with lamivudine and zidovudine as Trizivir.

C O M M E N T

The timing of this statement together with its tone and unclear content are not helpful. It appears to add little to earlier statements and doesn't reference any new data, if there are any.

It is perplexing that the regulatory authority that mandated companies to study cardiovascular risk, and approved the design and methods for D:A:D, fails to give weight to the findings from the largest prospective study looking at cardiovascular risks associated with HIV treatment.

As the EMA is advising patients taking abacavir to be 'cautioned to minimise cardiovascular risk factors' it would be more helpful for the guidance to be clear that this is because there is a reasonable concern raised in the D:A:D and other studies.

Source: EMA press release 'Meeting highlights from the Committee for Medicinal Products for Human Use, 20-23 April 2009'. (23 April 2009).

BHIVA NEWS

Access to HIV treatment for UK prisoners

BHIVA has been notified of a number of incidents where individuals sent to prison for relatively short terms have not received their ART.

These incidents have been raised with Dr O'Moore in Offender Health at the Health Protection Agency. The Executive Committee is keen to ascertain whether these cases are part of a wider problem.

If you have any concerns regarding access to ART in prisons I would be grateful if you could contact Dr O'Moore directly:

eamonn.omoore@hpa.org.uk

and also copy your correspondence to the BHIVA Secretariat:

jacqueline@mediscript.ltd.uk

HIV and hepatitis coinfection guidelines online for comment

The draft 2009 BHIVA guidelines for the management of coinfection with HIV-1 and chronic hepatitis B or C are online and available for comment:

<http://www.bhiva.org/cms1223977.asp>

The 2009 guidelines have been updated to incorporate all new relevant information since the previous versions in 2005.

The major changes/amendments include:

- Combining the previously separate HBV and HCV guidelines into one document
- Increased discussion on hepatitis screening and prevention;
- Clarification on the role of liver biopsy and non-invasive liver fibrosis assessment;
- More emphasis on screening for delta virus;
- Increased discussion on end-stage liver disease management and HCC screening;
- Molecular diagnostic tests used for the diagnosis and management of HBV and HCV;
- Revised CD4-based guidance on the management of chronic HBV;
- Management of acute HBV;
- Revised guidance on the management of chronic HCV, including ART interactions;
- Management of acute HCV;
- Management of treatment non-responders and relapsers in both chronic HBV and HCV.

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

BHIVA research awards deadline

The 2009 research programme for 2009 is now open. The deadline for applications is 10 July 2009. Launched in 2006, this is intended to provide funding for research projects that will improve the clinical care and management of people living with HIV in the UK.

In 2009, £30,000 is available to be distributed among the successful applicants with a maximum of £10,000 per applicant.

The award is open to any BHIVA member working on HIV disease in any capacity that does, or may, improve HIV clinical care and management in the UK. Laboratory studies are included, as well as clinical and other related projects. It is open to both medically and non-medically qualified BHIVA members.

If you are not a BHIVA member, please complete the BHIVA membership application form and allow 10 days for your application to be processed. You will need your BHIVA members' website login and password in order to submit a BHIVA Research Award application.

For further information and an application form:

<http://www.bhiva.org/cms1187509.asp>

To join BHIVA:

<http://www.bhiva.org/cms1192645.asp>

DRUG INTERACTIONS

Potential interactions between antiviral treatment for swine flu (H1N1) and anti-HIV therapy

www.hiv-druginteractions.org

It is important to consider the potential impact of emerging influenza A (swine flu, H1N1) virus infection and antiretroviral therapy. The H1N1 virus from Mexico is sensitive to the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza), but **not** to the M2 proton channel inhibitors amantadine and rimantadine.

Drug interactions between antiretroviral agents and oseltamivir or zanamivir have not been described to date. Based on their routes of metabolism and clearance, we have produced a chart of predicted interactions between the influenza antivirals and anti-HIV drugs. Since there may be patients who are given a combination of a neuraminidase inhibitor and a M2 proton channel inhibitor, we include information on both classes of drug.

The interactions have been added to web and PDA version of the online drug interaction charts.

These interactions as well as notes on the pharmacological profiles of the influenza antivirals have been summarised in the PDF format document linked below:

http://www.hiv-druginteractions.org/new/Uploaded_Attachment/76_Flu_Chart_update.pdf

Case reports of significant interactions between etravirine and raltegravir

HIV-druginteractions.org

Four cases in HIV-positive subjects were reported, in a letter in the 27 April 2009 edition of AIDS, where lower than anticipated raltegravir concentrations were observed when given with etravirine. [1]

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

In all these cases, raltegravir concentrations were below the mean trough concentration previously observed in initial clinical trials (63 ng/ml, range 29-118 ng/ml). [2] In two of the cases, concentrations were below the in vitro IC₉₅ for raltegravir of 14.6 ng/ml.

An interaction study in healthy volunteers showed that coadministration of raltegravir and etravirine decreased raltegravir trough concentrations by 34%, with minimal effect on AUC and C_{max} (~10% decrease). [3] In this study, the authors concluded that no dose adjustment for either drug was necessary. However, given the wide inter-individual variability in the pharmacokinetics of raltegravir and these reports from HIV+ subjects, a more cautious approach may be required.

C O M M E N T

The authors cite an ICAAC 2008 presentation to state that a PK-PD relationship has been identified for raltegravir and hence the possible interest in TDM. [4] It should be pointed out that Wenning et al indicate that C_{12h} showed little or no association with efficacy but that C_{min} and to a lesser extent C_{min} were associated with efficacy responses.

A main factor in raltegravir PK is food intake. Although the current recommendations are to take raltegravir without regard to food, there are nevertheless substantial differences in PK depending on the timing of food relative to drug intake.

Source: <http://www.hiv-druginteractions.org>

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<http://tiny.cc/ZOjrx>

GUIDELINES

US pregnancy guidelines updated

Revisions to the July 2008 version of the US guidelines for use of antiretrovirals during pregnancy, are usefully highlighted in yellow in the new PDF document, and include:

- A new brief discussion of recent trials on the use of antiretroviral drugs for prevention of mother-to-child HIV transmission through breastfeeding, with addition of these trials to Table 1. The Panel reaffirms that in the United States, where safe, affordable and feasible alternatives are available and culturally acceptable, breastfeeding is not recommended for HIV-infected women (including those receiving HAART).

- A more detailed discussion of duration of infant ZDV prophylaxis is provided. The Panel reaffirms the recommendation for administration of the standard six week course of infant prophylaxis unless there are concerns about adherence or toxicity; in such cases, consideration may be given to reducing the duration of infant prophylaxis from six to four weeks.
- Information regarding animal carcinogenicity and teratogenicity studies have been added to Table 2, as well as information on the new drug etravirine.
- Table 3 has been revised to reflect new information on antiretroviral drug pharmacokinetics in pregnancy and add information and recommendations regarding the use of etravirine. Additionally, atazanavir is now listed as an “Alternative” drug for use in pregnancy, and tenofovir and efavirenz are now listed in the category of “Use in Special Circumstances”.
- Updated information on preclinical animal studies and the Antiretroviral Pregnancy Registry and new data from recent pharmacokinetic studies in pregnancy are provided.

Ref: Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States - April 29, 2009
<http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=9&ClassID=2>

BASIC SCIENCE

Recent basic science updates from Richard Jefferys excellent web log.

Whole body CD4 T cell census questions role of gut

One of the most bizarre and misleading developments in HIV pathogenesis research over the past few years has been the emergence of the following statement (or variations thereof) in papers and presentations: “The majority of all CD4 T cells reside in the gut.” As explained in a review published several years ago by Vitaly Ganusov and Rob De Boer, there has never been any good data to support this claim. [1]

It seems to have emerged in a sort of scientific game of telephone, in which the observation that the majority of IgA-producing B-lymphocytes reside in the gut somehow got transmogrified into the majority of lymphocytes – including CD4 T cells – residing in the gut. Ganusov & De Boer’s survey of the literature - reported on the blog when the review was published - suggests that approximately 12% of lymphocytes are in the gut at any given time, not the majority. [2]

A new paper just published in the journal *Blood* offers compelling confirmation of this estimate by measuring CD4 T cells in the blood and tissues of rhesus macaques (both uninfected and SHIV-infected animals). [3]

The study was conducted by Michele Di Mascio and colleagues from H. Clifford Lane’s laboratory at NIAID, using a technique that applies a radioactive label to CD4 T cells so that they can be visualised using single photon emission computed tomography (SPECT). Di Mascio combined this imaging approach with analyses of tissue samples from multiple body sites in order to generate estimates of the total numbers of cells and the relative contributions of different body compartments.

Among the papers key findings:

1. There was a significant and close correlation between CD4 T cell numbers in lymphoid tissues and peripheral blood CD4 T cell counts. However the relationship was not linear, meaning that early declines in blood CD4 T cell counts reflected relatively small changes in CD4 T cell numbers in lymphoid tissues, but once blood CD4 T cell counts became low, further declines were paralleled by much greater loss of cells from the lymphoid tissues.

The researchers write: “Based on this relationship one could extrapolate that 1) for a subject starting with 1000 CD4+ T cells/mm³ in the peripheral blood, a drop to 500 cells/mm³ is associated with approximately a 20% decrease in the number of CD4+ cells per unit mass of lymphoid tissue; 2) whereas for a subject starting with 100 CD4+ T cells/mm³, a decline to 50 cells/mm³ is associated with approximately a 45% decrease in the number of CD4+ cells per unit mass of lymphoid tissue. Thus, for subjects with low CD4+ T cell counts, changes in the number of CD4+ T cells in the blood predict larger changes in the number of CD4+ cells per unit mass of lymphoid tissues than the changes in lymphoid tissue predicted for individuals with higher CD4+ T cell counts in the peripheral blood.”

2. The total body lymphocyte count is estimated to be between 1.9 and 3.5 trillion, around 4-8 fold higher than previous estimates. The researchers hypothesise that the use of a technique that requires less manipulation of tissue samples may account for the difference. This range for total body lymphocyte count is also used to estimate the proportion of lymphocytes that are in the blood: “Given the above range of (1.9-3.5 trillion) lymphocytes in the body, the blood would contribute between

0.3% and 0.5% to the total pool of lymphocytes.” Prior studies have generally suggested that the blood contains around 2% of total body lymphocytes.

3. The upper limit for the proportion of lymphocytes in the gut is estimated to be 15%: “We observed that each gram of spleen carried at least 10-fold more CD4 cells than each gram of gut in an uninfected monkey. Given that the weight of the spleen (145 g) is approximately 10 fold lower than the weight of the total gut in adult humans (1,100 to 1,500 g), it can be concluded that at the most the gut contains a number of CD4+ T cells equal to that of the spleen. Since the relative contribution of the spleen to the entire pool of lymphocytes is ~15%, then an upper limit for the relative contribution of the gut to the entire pool of lymphocytes should also be ~15%...Our results are consistent with the previously reported low number of total lymphocytes per gram of gut in adult pigs, rhesus monkeys and humans, as recently reviewed by Ganusov et al.”

The study authors conclude by saying: “Taken together these data suggest a need to re-evaluate current assumptions regarding the relative contribution of different tissues to the overall pool of CD4+ T cells.” They acknowledge that further studies are needed to refine and increase confidence in the numbers generated, and while these are some of the best-supported estimates yet published, they do not represent the last word on the subject.

Source: TAG Basic Science Weblog. (07 May 2009)
<http://tagbasicscienceproject.typepad.com>

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Gut bacteria breach the barrier: further confirmation of microbial translocation in HIV infection

Richard Jefferys, TAG

Last October, Guila Marchetti and colleagues reported that DNA from gut bacteria can be detected in the bloodstream of people with HIV, and that elevated bacterial DNA levels correlate with poor immune reconstitution in people on antiretroviral therapy (ART). [1]

The data were concordant with the hypothesis proposed by Daniel Douek, David Price and Jason Brechley that leaking of gut bacteria into systemic circulation – a phenomenon called microbial translocation - contributes to HIV pathogenesis. [2]

The Marchetti study was small, however, involving just 47 participants. A paper just published online in the Journal of Infectious Diseases confirms and significantly extends these findings using several larger cohorts of HIV-infected individuals. [3]

The researchers - led by Wei Jiang and Michael Lederman from Case Western Reserve University - first compared levels of bacterial DNA in a group of uninfected individuals to those in people with untreated HIV infection, or treated HIV infection. Study participants on ART were further subdivided into two groups based on whether their HIV viral load was above or below the limit of detection (400 copies/mL). None of the 15 HIV-negative individuals showed detectable levels of bacterial DNA (the lowest level the test used in the study can reliably detect is 5 DNA copies). In contrast, bacterial DNA was found in 18 out of 19 untreated individuals with HIV infection, with median levels of 132.5 copies per microliter. Study participants on ART fell between these two extremes: the median number of bacterial DNA copies was 8.6 among individuals with undetectable viral loads and 22.8 for those with viral loads above the detection limit (this difference was not statistically significant). The researchers also found that there was a significant association between viral load and bacterial DNA levels in the untreated individuals, but there was no such association with total CD4 counts in peripheral blood (naïve and memory CD4 T cells were not analyzed separately).

Next, a separate cohort of 114 individuals on long-term ART were studied, in order to gain further insight into the impact of microbial translocation on the response to treatment. Higher levels of bacterial DNA were associated with lower CD4 count gains on ART; for every 100-copy increase in bacterial DNA levels, 11 fewer CD4 T cells were gained (although this could also be looked at the other way around, i.e. larger increases in CD4 T cells were associated with lower levels of bacterial DNA). Bacterial DNA levels also correlated with levels of lipopolysaccharide (LPS), another indicator of microbial translocation, and – more weakly - with CD8 T cell activation.

Finally, the researchers used samples from a longitudinal, 54-person study of ART treatment (ACTG 5014) to evaluate changes in bacterial DNA levels over time. Samples were taken before and at 1, 8, and 48 weeks after starting ART. Levels of bacterial DNA declined progressively, and were significantly lower than baseline at the week 8 and 48 timepoints. These changes were independent of changes in HIV viral load, but correlated inversely with CD4 counts after 48 weeks of treatment (the higher the CD4 count, the lower the bacterial DNA level). The study authors note that median bacterial DNA levels were

still higher at week 48 (75 copies per microliter) than had been seen in the first cohort analyzed (8.6 copies). Participants in the first cohort had been on ART for a median of over 6 years, suggesting that bacterial DNA levels decline slowly over a protracted period after starting treatment.

In discussing their data, the authors suggest that microbial translocation in HIV infection is driven by viral replication, either via direct effects on mucosal cells that would normally maintain the integrity of the gut wall, or by indirect effects on immune responses that help contain commensal bacteria within the GI tract. Unlike Marchetti and colleagues, these researchers do not cite the basic immunology literature indicating that T cell depletion can contribute to microbial translocation, although they do consider the possibility that in some cases poor CD4 T cell reconstitution might be a cause as well as a consequence of microbial translocation. In arguing against a primary causative role of CD4 T cell depletion, they note the lack of a correlation between CD4 T cell counts and bacterial DNA levels in untreated individuals, and also cite the fact that microbial translocation occurs in conditions such as inflammatory bowel disease that aren't associated with loss of CD4 T cells.

While this type of research can seem dauntingly complex, it's worth emphasizing that understanding and addressing the causes of poor CD4 T cell reconstitution on ART is critical for improving the care of individuals with HIV infection. As the authors of this paper point out in their introduction, "persistently low CD4 T cell counts are associated with significant increases in non-AIDS-associated morbidities, including cardiovascular disease, liver disease, cancer, and, perhaps, renal disease." Consequently, there is an urgent need to develop and study therapies that might have the potential to improve CD4 T cell recovery in individuals who remain at risk for clinical illness despite ART-mediated viral suppression. The recent failure of interleukin-2 to provide benefit should not discourage development of approaches with different mechanisms of action, such as enhancement of T cell production by the thymus. Other possible avenues of intervention may include attempting to restore the integrity of the gut wall and/or evaluating anti-inflammatory approaches that aim to reduce the immune activation caused by microbial translocation.

Source: TAG Basic Science Weblog. (06 Mar 2009)
<http://tagbasicscienceproject.typepad.com>

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Update on 'the Berlin patient'

Richard Jefferys. TAG

Eleven years ago, a plethora of media stories described the case of "The Berlin Patient," an individual who received antiretroviral therapy during acute HIV infection and subsequently maintained viral load below 50 copies for many years after stopping treatment. [1]

This individual turned out to possess the HLA B*57 allele which is strongly and consistently associated with long term non-progression of HIV infection, and it remains somewhat uncertain if he might have become an elite controller even in the absence of any treatment. At the recent Keystone HIV pathogenesis meeting in Colorado, Guiseppe Pantaleo described another similar case, but in this instance lacking known favorable HLA alleles.

The individual -- dubbed patient 1010 -- was a participant in one of Pantaleo's studies of acute infection treatment. The protocol compared ART alone to ART together with a short course (8 weeks) of treatment with cyclosporin A (CSA); there were 59 individuals in the trial, ten who received ART and 49 assigned to ART + CSA. Results were published in the *Journal of Clinical Investigation* in 2002, and showed that receipt of CSA was associated with significantly higher CD4 counts, a difference which Pantaleo reported has been maintained out to four years of follow up. [2]

Patient 1010 enrolled in the study in March of 1999, approximately two weeks after becoming HIV-infected, with a baseline viral load of 26 million copies. He was randomised to receive ART + CSA and was adherent until stopping ART on December 31, 2000. Surprisingly, viral load rose to just 63 copies two weeks later, and has remained below 50 copies without further treatment during the subsequent eight years of follow up; his CD4 count has stayed stable at around 2,000. Pantaleo noted that he is wild-type for the delta32 CCR5 mutation and also lacks any of the major HLA alleles that have been associated with elite control (his class I HLA types are A*0301, B*0702 and B*4002).

Pantaleo went on to describe the profiles of HIV-specific T cell responses in patient 1010. Around 3.5% of CD8 T cells are HIV-specific, targeting Gag, Vif, and Env proteins. An unusually large proportion of these cells (~80%) produce both IL-2 and interferon gamma, and they have what Pantaleo describes as a "massive capacity" for proliferation upon stimulation with antigen, the highest his lab has ever seen. The proportion of cells making IL-2 is also far greater than Pantaleo has previously seen in studies of untreated elite controllers. The differentiation profile of the HIV-specific CD8 T cells equates with a quiescent central memory phenotype, with over 80% of the cells expressing CCR7, CD127, CD27 and CD28.

Based on this anecdotal case, Pantaleo provocatively hypothesised that the ideal immune profile associated with virological control may be the “quiescent, non-effector” CD8 T cell response he has documented in patient 1010. It appears that the virus is so robustly controlled in this individual that HIV-specific T cells are hardly ever encountering antigen. Pantaleo mentioned that Tae-Wook Chun from NIAID has looked for HIV in the patient and found only 1.7 copies of HIV DNA per microgram of genomic DNA, and 11 copies of HIV DNA per million peripheral blood mononuclear cells (PBMC). Chun has calculated that there are approximately 0.0027 infective units of virus out of 360 million CD4 T cells sampled, the lowest he has ever documented. HIV DNA levels were extremely low even in the gut.

The case adds to a number of reports suggesting that a very small proportion of individuals who interrupt ART after being treated for acute infection can maintain control of viral load for variable periods of time. It is generally unclear if these individuals might have gone on to become elite controllers without treatment, but the high viral load and lack of protective HLA alleles in Pantaleo’s patient appear to argue against this possibility. The individual is also clearly an outlier in terms of the extremely low levels of HIV DNA that are detectable and the strong proliferative capacity and IL-2 producing potential of his HIV-specific T cell responses. The duration of time off therapy -- over 8 years -- is also unusual. Whether CSA may have somehow contributed to this salutary outcome is unclear and almost certainly unanswerable without additional studies.

Although it’s clearly possible -- some might say likely -- that anecdotes such as this one reflect some rare and unknown trait possessed by the individuals involved, they might also be hinting that prolonged and robust immune control of HIV is an achievable goal.

C O M M E N T

There are many well-documented cases of patients who are untreated who suppress viral load and do not progress for many years. However, these patients may start to progress subsequently. So, there really isn’t much evidence yet that ART+CSA actually had any impact on his outcome.

Source: TAG Basic Science Weblog. (15 Apr 2009).

<http://tagbasicscienceproject.typepad.com>

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OTHER NEWS

Iowa: Gay man gets 25 years for one-time non-disclosure to a single complainant

The following report and references to earlier cases, edited from Edwin J Bernard’s HIV transmission and criminalisation blog highlights the level of discrimination that still exists and the disproportionate severity (and hence vulnerability) faced by HIV-positive people.

Edwin J Bernard, web blog

The 25 year jail sentence for a gay man in Iowa earlier this week for not disclosing his HIV status prior to one-time sex with a man he met online, reaches new lows in the history of criminalisation. [1] This is a potential human rights violation almost on par with Willie Campbell’s 35 year prison sentence for spitting. [2]

The ‘Waterloo and Cedar Falls Courier’ reports that Judge Bradley Harris sentenced 34 year-old Nick Clayton Rhoades to 25 years in prison, the maximum punishment under Iowa’s draconian (and mistitled) “criminal HIV transmission” laws, following a guilty plea. [3, 4]

There was no transmission: the male complainant has not tested HIV-positive, and it is now almost a year since the encounter. This subtlety seems lost on the headline writer, who erroneously states: ‘ Plainfield man gets 25 years for “transmitting” HIV’.

Not only was there no sentence reduction due to Mr Rhoades’ plea (after all, he saved the court a lot of time and money; and let’s face it, it was one person’s word against the other, which could have gone either way with a jury), but Judge Harris additionally placed Mr Rhoades on lifetime parole and ordered him to pay court costs and restitution.

In addition, he ordered that must Mr Rhoades must: not contact the complainant for five years, register as a sex offender and undergo a sex offender treatment programme.

Rhoades, who was diagnosed with HIV in 1998, was arrested in September. Living with the virus is like “carrying a concealed weapon,” he told the court, saying he felt guilty for exposing an unknowing individual to the disease.

"I always wanted to be part of the solution, and not part of the problem," said Rhoades, who had previously participated in AIDS education efforts. "Clearly, I've fallen short in this case."

Mr Rhoades sounds like a genuinely remorseful man. He believes that he should have disclosed his status, and didn't. Even if you agree with HIV disclosure laws in general – notwithstanding arguments supporting the concept of shared responsibility of both parties under these circumstances, or the unreliability of disclosure as a way of protecting yourself from sexually transmitted infections – there really is absolutely no justification for this outrageously long prison sentence.

To put this into perspective. A year ago I reported on a 12 year HIV exposure sentence in Arkansas (where the maximum penalty is 30 years) for a man who did not disclose to his girlfriend. [5] At the time, it was the longest sentence I'd heard of for a single complainant. This is a single act!

Notwithstanding Johnson Aziga's likely life sentence after recently being found guilty of murder, [6] the previous longest-ever sentence in Canada was 18 years, and that was for Carl Leone, with 15 complainants, including five who tested positive. [7]

The longest sentence in Europe has been for Christer Aggett, sentenced to 14 years in prison in Sweden, with a dozen complainants, two of whom tested positive, and half of whom were under 15. [8]

In 2006, the Iowa Supreme Court upheld the law after Adam Musser, 25, appealed his four convictions - and 25-year-prison sentences - for having unprotected sex with four different women in 2002 and not telling them he was HIV-positive. [9]

And yet, in 2007, a woman who also pleaded guilty after not disclosing her status to a single complainant during a three month relationship, had her 25 year prison sentence suspended and received four years probation. [10]

Since Judge Harris has also ruled that he can adjust the sentence any time within the next 12 months (and there is already a precedent to suspend sentencing), I suggest that anyone who feels as outraged as I do, contact either Judge Harris, or Mary Stegmeir (mary.stegmeir@wfcourier.com), the journalist who reported the case.

Source: Edwin J Bernard web blog (3 May 2009)

<http://criminalhivtransmission.blogspot.com/2009/05/iowa-gay-man-gets-25-years-for-one-time.html>

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US denies entry to 60 HIV-positive Canadians

Housing Works, a US NGO, in concert with the National AIDS Housing Coalition (NAHC) and the Ontario HIV Treatment Network (OHTN), expressed its outrage as 60 Canadians living with HIV have been denied entry into the United States, contrary to stated U.S. policy that foreigners living with HIV would no longer be barred from entering the country. The groups are calling on Secretary of State Clinton to resolve the matter and to do away with Department of Health and Human Services (DHHS) regulations that keep the HIV travel ban in place.

In July 2008, President Bush signed a law authorising the Department of Health and Human Services to lift the decades-long ban on foreigners living with HIV entering the United States. The U.S. is one of only 14 countries* in the world that bar entry to persons with HIV, a fact that has drawn broad condemnation from both domestic and international human rights organisations. Yet the ban still has not yet been stricken from DHHS regulations; instead, the Department of Homeland Security put into place a series of measures designed to "streamline" the process for entry into the US for people living with HIV. However, this process is an ill-conceived bureaucratic tangle with such onerous requirements that it is tantamount to a complete ban on people living with HIV coming into the United States.

"This new incident proves that AIDS stigma is alive and well in the United States and actively being promulgated by the United States government," said Housing Works President and CEO Charles King. "President Obama says that he wants to repair America's damaged relationships with foreign countries. Let him prove it by taking immediate action to ensure that the DHHS gets this hateful regulation off its books."

The 60 Canadians had planned to attend the North American Housing and HIV/AIDS Research Summit in Washington, D.C. from June 2 to June 5. The OHTN and NAHC are cosponsors of that event.

In March, DHHS officials indicated that granting a “designated event HIV waiver” for the Housing Summit was underway. Such waivers are designed to allow people living with HIV to attend conferences in the U.S. On Friday, May 22, 11 days before the summit start date, the Ottawa Embassy informed the OHTN that each of the 60 people in its delegation to the Washington, D.C. AIDS Housing Summit would have to comply with the new, severely onerous visa process.

The visa process requires, among other things, a face-to-face interview; a photo; a \$131 money order from a specific Canadian bank; an agreement not to extend the visit for any reason; completion of an intrusive and humiliating health form, and a pledge that the applicant has adequate health coverage - something that many US citizens living with HIV/AIDS are still denied.

To add insult to injury, because the OHTN was informed of the new requirements on Friday, May 22, HIV-positive Canadians could not even attempt to meet those requirements until Monday, May 25, barely one week from the June 2 start date of the conference - and to do so, they would have to travel from all over Canada to a specific Ottawa US consulate.

“Not only are these requirements an affront to people living with HIV in Canada, they were impossible to meet. There was no way to physically get people to the Ottawa Embassy on such short notice,” said Dr. Sean B. Rourke, Scientific and Executive Director of OHTN. “Furthermore, requiring people to give their name, a photo and confidential health information to the U.S. government is a violation of their privacy and inconsistent with our commitment to protect personal health information. It shows a lack of sensitivity to the very real stigma and discrimination that people living with HIV/AIDS face every day of their lives.”

*The other countries that ban visits by people living with the HIV besides the United States of America are Brunei, Egypt, Iraq, Yemen, Malaysia, Oman, Qatar, Singapore, Sudan, South Korea, Tunisia, Turks & Caicos Islands and the United Arab Emirates

Source: Housing Works Press Release. (28 May 2009).
<http://www.housingworks.org/news-press/>

Job vacancy: Editor post for of the Southern African Journal on HIV Medicine for the nursing profession

The Southern African HIV Clinicians Society, a not-for-profit organisation with over 15 000 members, seeks to employ an Editor for the Southern African HIV Nursing Magazine.

The successful applicant must be self motivated and able to work in a very dynamic and challenging environment. The editor will be responsible for establishing and maintaining the Southern African HIV Nursing Magazine. This will include:

- Responsibility for acquiring, reviewing and editing all articles published in this magazine.
- Maintaining the magazines standards and editorial policies in line with international standards.

Qualifications

Degree level education preferably in nursing or another health-care related field, with a post-graduate degree in journalism or other relevant discipline, or equivalent experience with progress towards such a preferred qualification.

Experience

- 10 years practical work experience
- Experience and/or knowledgeable of the HIV/AIDS sector
- Experience with an NGO, implementation-focused donor or development organisation
- Experience and / or knowledge in the academic publishing field
- Proven track record as a published author in academic publications

Remuneration

Remuneration is dependent on skills, experience and qualifications.

To apply

To apply, please submit a detailed CV, including contact details of three referees, a letter of Motivation and a copy of an original (and unedited) writing sample to:

The General Manager, The Southern African HIV Clinicians Society, by email to:
fatimas@sahivsoc.org

Closing date 28 August 2009

Only short-listed candidates will be contacted

For more information about the Society visit

<http://www.sahivsoc.org>

FUTURE MEETINGS

2009 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.

4-6 June 2009: 5th Intl HIV and Hepatitis Co-infection workshop, Lisbon

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

9-13 June 2009: XVIII International HIV Drug Resistance Workshop, Fort Myers, Florida

<http://www.informedhorizons.com/resistance2009>

25 - 26 June 2009: 4th Intl Workshop on Hepatitis C Resistance & New Compounds, Boston

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

26-27 June 2009: 4th Intl Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston

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

16-18 July 2009: 1st Intl Workshop on HIV Paediatrics, Cape Town

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

16-18 July 2009: 4th Intl Workshop on HIV Transmission, Cape Town

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

19-22 July 2009: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2009), Cape Town

<http://www.ias2009.org>

12-15 September 2009: 49th ICAAC, San Francisco

<http://www.asm.org>

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

<http://www.idsociety.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

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

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

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

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

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

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

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

NEW publications

- Introduction to combination therapy (May 2009)
- Guide to hepatitis C for people living with HIV (March 2009 edition)

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

- * Clinical trials: a community guide to HIV research

<http://www.i-base.info/manual/en/8.html>

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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 are included on how to understand aspects of science that might be new to a lay reader.

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

Sections include:

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

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

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

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

Generic clinic forms

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

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

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

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

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

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

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

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

Photography by Wolfgang Tillmans

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

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

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

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting for three years. 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.

<http://www.ukcab.net>

World CAB - reports on international drug pricing

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

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

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

Introduction to combination therapy

May 2009 edition

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

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

Guide to hepatitis C for people living with HIV

March 2009 edition

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

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

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

September 2008 edition

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

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

Guide to HIV, pregnancy & women's health January 2009 edition

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

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

Guide to avoiding & managing side effects May 2008 edition

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

Translations of i-Base guides

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

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

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

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

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

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

Treatment 'Passports'

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

HIV Treatment Bulletin (HTB)

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

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

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 800 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- Will that be considered an overdose?
- Could this be SJS?
- Do my medicines still work?
- I am positive; can I have a tetanus jab?
- What is the deal with reinfection (of HIV)?
- Was in contact with blood in a hotel room, am I at risk?
- How important is it to take etravirine with food?
- What if I don't get a response to the HepB vaccine?
- Shall we change our combinations and if yes-to what?
- Are there any restrictions on the type of work I can do?
- Can we adopt a child?
- Do HIV meds have any dermatological (skin) effects?
- Will losing weight protect my CD4 count?
- Are there HIV-positive restrictions on travel to Dubai, Malaysia or Hong Kong?
- How much does it cost to treat HIV in a private hospital?
- Why has my CD4 count dropped? What about cholesterol?
- Could a pain in my side be related to pro-biotic use?
- What is the impact of swine flu in HIV-positive people?
- Can I get resistance from an ARV overdose?
- Am I more at risk of swine flu because I am HIV-positive?
- I have pain in my arms and I'm not on meds
- Does viral load rebound to 113 copies/mL mean I am getting resistance?
- How are the words 'rare' and 'common' defined for side effects?
- My viral load has increased from undetectable to 87 c/mL...
- Will scans from outside the NHS affect my free HIV care?
- What is the effect of alcohol on Truvada and nevirapine?
- What can I do about darkening of the skin and thinning of the limbs and face?
- Which organisation shall I make a donation to?
- Could I have picked up a different strain of HIV?
- Shall I start treatment?
- My skin became darker, what can I do?
- Will the itching disappear over time?
- How often shall I check my CD4 count?

Find HTB on AEGiS

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

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

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

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

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

<http://www.i-base.info/forms/index.html>

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

Some articles are reproduced from other respected sources and copyright for these articles remains with the original authors and sources, as indicated at the end of each article.

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

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

i-Base appeal

This appeal has been launched because both the London Commissioners and the Department of Health have decided not to fund ANY HIV i-Base project in 2008/9.

We would like to thank everyone who helped with letters of support, which came from doctors, nurses, pharmacists, HIV-positive patients and other service users.

We would now like to collect a fax from every clinic that uses our services.

Since April, there has been no drop in the level of our services. We have answered more phonenumber calls, email information requests and distributed more treatment guides than the same period last year. We are just doing this without statutory support.

Some clinics with a budget for patient or healthcare educational material have already agreed to donate an annual amount (£500 - £1000, or £1-2 per patient) towards unlimited use of all our resources. We need to raise £50,000 to cover the withdrawal of Commissioner support.

If your clinic or Trust is able to help, please fax your details using this form so we can contact you. We understand that this will not always be possible, and we still commit to continue providing all publications and services free. But if you can help, then many clinics contributing to our shortfall will make a huge difference.

Name: _____

Hospital/clinic/organisation: _____

Contact phone number: _____

Contact email: _____

Our hospital/clinic/organisation (delete as appropriate) use the following i-Base services. to improve patient care.

- HIV i-Base treatment guides
- HIV i-Base phonenumber and information service
- HIV Treatment Bulletin

Comment: _____

Please tick one of the following boxes:

We ARE able to contribute financially towards these services. Please contact us to arrange details.

Unfortunately we ARE NOT able to contribute financially towards these these services but we would be worried if they did not continue. We are happy for you to use this confirmation and the above comment for future fundraising and sponsorship.

Please fax to: 020 7407 8489



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.

STANDING ORDER DONATION

THANK YOU FOR YOUR SUPPORT

Title: _____ First Name _____ Surname _____

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Telephone (s) _____

Please pay HIV I-Base £ _____ each month until further notice

Please debit my account number _____

Name of account (holder) _____ Bank sort code ____/____/____

Starting on ____/____/____ (DD/MM/YY)

Signature _____ Date ____/____/____ (DD/MM/YY)

To: Manager: (Bank name, branch and address)

Please complete the above and return to: HIV I-Base, 44-46 Southwark Street, London SE1 1UN

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

ONE-OFF DONATION

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

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

GIVE AS YOU EARN

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

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

REFUNDS FROM THE TAX MAN

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

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

HIV i-Base

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Please use this form to amend subscription details for HIV Treatment Bulletin (DrFax) and to order single or bulk copies of other publications. All publications are available free, but if you would like to make a donation please use the form on the inside back page.

Name: _____ Position: _____

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Address: _____

Tel: _____ Fax _____

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I would like to make a donation to i-Base - **Please see inside back page**

HIV Treatment Bulletin (HTB) monthly by Email (PDF format) by Post

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

1 5 10 25 50 100 Other

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

1 5 10 25 50 100 Other

NEW: Introduction to Combination Therapy (June 2008)

1 5 10 25 50 100 Other

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

1 5 10 25 50 100 Other

Guide To Avoiding and Managing Side Effects (May 2008)

1 5 10 25 50 100 Other

Guide To HIV and hepatitis C coinfection (May 2007)

1 5 10 25 50 100 Other

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

Phoneline support material (pls specify required number of each)

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

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

1 Sheet 1 pad 5 pads 10 pads Other

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

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

Office use: