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CONTENTS

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EDITORIAL

Welcome to the March/April 2009 issue of HTB.

For London readers we include an update on our attempts to obtain commissioner funding. While this is not the most important news in HTB, we include it to show our continued attempt to get a better response from commissioners on our important services, and also to show the many people who wrote letters of support last year, that this made a difference for us in continuing to argue our case.

The fax-back i-Base appeal support form on page 45 includes only a couple of tick boxes. It important for us to hear when clinics have no budgets for our resources as this may help us access national funding. Please consider this two-minute support if your clinic hasn't already answered this point.

For the main news in this issue, please forward straight to the first reports from our conference coverage from this year Retrovirus Conference, still one of the most important annual meetings.

Supplements with this issue

We also include two supplements with this issue.

This first is a revised and updated 2009 edition of our Guide to HIV and Hepatitis C Coinfection.

As part of this resource we made a short youtube video with Dr Sanjay Bhagani about an alternative to liver biopsy called FibroScan. Check out the link here:

http://www.youtube.com/watch?v=l_E4ZGmKooA

The second supplement is a new format developed from a resource that has been online for several years: the i-Base Training Manual for Advocates. While this introduction to clinical trials has been written mainly for advocates we thought this might be of interest for other healthcare professional and patients interested in research.

This booklet will shortly be available online in Spanish, Russian, Portuguese and Italian, supported by NEAT, the new Network for European AIDS Trials.

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.

i-BASE FUDING UPDATE

London Commissioners disregard costs in 2008 tender

Last year, i-Base funding was withdrawn by the London HIV Commissioners as part of their re-structuring of services for HIV-positive people. They have since refused to review the process or the final outcome, despite extensive letters of support from patients, doctors and other healthcare professionals, detailing the importance of the services we provide.

We have since learned, using the Freedom of Information Act, that the tender process failed to evaluate costs in the bidding process, despite many of the i-Base bids being significantly lower, and other evaluable aspects of the bids being comparable.

Given the importance of getting value for money from public funds, and the widespread discussions relating to the low level of funding available, this demands a review of the process and the current level of support for expert-patient produced and generated material and for smaller organization to receive appropriate levels of support for the services they produce.

We are still awaiting a formal response from our correspondence to Diane Middleditch, interim chair of Chelsea and Westminster PCT, printed below.

To: Diana Middleditch, Interim Chief Executive, Kensington and Chelsea Primary Care Trust

23 February 2009

Re: PAN-LONDON HIV PROGRAMME – TIPI CONTRACTS

Dear Diana

Thank you for your letter dated 9 May 2008 (attached) in which you briefly stated that you were satisfied with the evaluation of the TIPI tenders which took place earlier in the year.

As you are aware, we are an expert patient involvement organisation in NHS healthcare focussed on HIV information services and training. The guide to HIV treatment we have produced since 2000, updated at least annually (2008 edition enclosed) was highly commended in the BMA Patient Awards this year and is used by hospitals across London when patients are

newly diagnosed or starting treatment. In the tender process earlier this year, our bid priced provision of this guide across London at £5,000 (£0.90p a copy) but this bid was rejected. We fought for eight years to establish and maintain excellent resources that are a model recognised by WHO and many international and national experts, yet for some reason the largest purchaser of HIV patient services in the UK - who nonetheless continues to use all our products - refuses to provide any funding for them.

I am therefore now writing to ask you to clarify a number of points:

1. We have recently learned that the difference in financial considerations (including budgets, unit costs and value for money) between the two bids for the Treatment Information contract was not in fact evaluated at all. I would understand this if the two bids concerned were very similar, but this was not the case. I-Base bid for 80% of the total Treatment Information contract at a cost of around £70,000. The bid which won the contract bid for 100% of the contract but for a cost of £200,000. As you will appreciate, this is a considerable difference, which, given the cost pressure for this work, requires some explanation. The question therefore arises whether you and the other Commissioners were aware either that the financial aspect of the two bids was not evaluated in any meaningful way, or were aware of this fact but did not consider it be important. Were you aware that the bids with higher rather than lower costs won on nearly every stream? The results of the qualitative evaluation of the two bids for the treatment information workstream produced results that were very close indeed, so one would therefore expect financial considerations to take on a even greater determinative importance. This clearly was not the case.
2. The second concern relates the creation and distribution of the 15 'more in depth booklets'. Our tender was £15,000 for the development, design, printing and distribution of five booklets, that would cover all the subjects that would have been covered in 15 booklets. This is contrasted to the cometitor tender of £52,195 for 15 booklets. We are concerned that the competitor bid was for the development and design of resources that already exist; prior to the award of the contract the organisation concerned already produced precisely 15 booklets which were funded from previous annual TIPI funding over the last 7 years. We do not understand the basis on which the Commissioners determined that the alternative tender constituted value for money, given that the development and design of their booklets has already been funded. Can you explain why this resource is effectively being funded twice? Was this cost consideration drawn to your attention by the Commissioners?
3. We also note that our costing for the 10 factsheets were significantly less than the competitor bid with our tender priced at £3,150, as contrasted to £14,035. Given this difference, what reasons did the Commissioners give you to prefer a tender for one particular resource which was nearly five times the price of the other? Given such a significant difference, their decision cannot have been based upon value for money.
4. A similar concern arises over the treatment workshops resource. I-Base has already run similar workshops, which have been a proven success. I-base tendered to provide this service at a cost of approximately £24 per person. The competitor bid tendered for this resource at a cost of £40 per person. Were you aware of this difference in cost? If so, what justified the decision to disregard such a considerable cost saving? If you were not aware of this difference in cost, why were you not aware of it?
5. The final point concerns the continued level of demand from London hospitals and patients for i-Base services. This demand has in fact increased since i-Base was defunded by you in April 2008, and the demand is coming directly from the end users in the London health care system that the TIPI contracts were intended to support. If these essential information services were being adequately provided by the organisation which won public funding to provide them then demand for i-Base's services in London should have fallen. It clearly has not. This means that we now have a situation where essential HIV information resources in London have lost their funding but continue to be used in preference to the resources to which the public funding has been transferred. I should point out that we have not been funded nationally for our work either - though we did apply, as suggested by the commissioners.

It becomes a matter of public interest when decisions about the award of public funding for what in health charity terms are considerable sums of money appear to have been taken with so little – if any - regard to cost. I should be grateful if you could therefore explain what you knew about the costing issues I raise above at the time that you and others ratified the contract award decision made by the Commissioners.

I've enclosed a selection of letters of support for our services. I am obliged to point out that the likelihood of us being able to continue providing these services without any government support for the next three years is extremely poor. Given this, I wonder what suggestions you have for how we can ensure that this does not happen and that essential HIV information services in London are not lost.

I look forward to hearing your thoughts on the issues raised in this letter.

Yours sincerely

Simon Collins, HIV i-Base

cc by email: London HIV Commissioners

C O M M E N T

We received acknowledgement of our letter on 18 March with a promise for a detailed response within two weeks.

When this issue of HTB went to press on 9 April we had not received any formal response to these points.

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:

- HIV infection in the brain: a long-term limitation of HAART?
- When to start HAART – a key research question with the least available data
- Major studies rule out any benefit of Interleukin-2 (IL-2): results from ESPRIT and SILCAAT
- Higher rates of non-AIDS cancers in HIV-positive people
- High rates of HIV acquisition in pregnancy and post partum in Francistown, Botswana
- Effect of single dose nevirapine on subsequent nevirapine-containing HAART: long term outcomes
- Covering the nevirapine 'tail'
- Lopinavir/r containing regimen superior to nevirapine containing regimen in women previously exposed to single dose nevirapine
- Higher risk of transmission with delayed control of maternal viral Load despite viral loads of <500 copies/mL at delivery
- Risk factors for adverse pregnancy outcomes in Botswana
- Premature delivery and mother-to-child HIV transmission: a risk/benefit analysis among women receiving HAART
- PEPI-Malawi
- Effect of breast feeding vs formula feeding on maternal health
- Children on HAART do extremely well at South African clinic
- PK and drug interaction studies at CROI

16th CROI: NEUROLOGICAL IMPACT OF HIV

HIV infection in the brain: a long-term limitation of HAART?

Simon Collins, HIV i-Base

The recent focus on the impact of unsuppressed viral replication in the SMART and other studies, has lead to emerging concerns that overlap the issues of aging, cardiovascular health, bone disease and higher rates of some cancers. For the last three years at CROI, neurological function has expanded from the previous single lectures to full plenary sessions. This year provided perhaps the most compelling and concerning results yet from many different research approaches.

While many discussions on HIV in the brain focus on viral replication, cell activation was highlighted in pre-meeting lectures as more important than viral replication in terms of disease. Current understanding of the pathogenesis of HIV infection in the brain starts with infected monocytes (CD16+/CD14+ indicating a degree of activation) that cross the blood-brain barrier and are more prone to infecting endogenous tissues in the brain such as microglia etc. It is the process of activation of either infected cells or bystander cells that leads to the production of viral proteins, excitatory amino acids, cytokines and free radicals which lead to the death of neurons. The degree of inflammation appears out of proportion to the amount of virus in the brain. [1]

However, cerebrospinal fluid (CSF) viral load and drug penetration are also clearly an important factor in most studies looking at neurological function and HIV disease.

High plasma levels of LPS (another key area of recent research arising from early and rapid depletion of CD4 cells in the gut mucosa, see further HTB CROI reports) and soluble CD14 have also been associated with higher rates of HIV-associated dementia, linking ongoing immune activation to neurological complications. [2]

An oral session on Monday, available as a webcast, included an important and diverse collection of studies on HIV and cognitive function. [3]

Igor Grant presented an update from the Charter study, aspects of which have been presented at earlier CROI meetings. This is a cohort study of 1555 patients at six sites initiated in 2002 by the US NIH to look at neurological complications and biomarkers relating to neuropathy and neurocognitive impairment (NCI) that are still prevalent despite HAART. [4]

The group broadly represents the US HIV demographics. About one-fifth of the group are women, half are African-American and 40% non-Hispanic White. A quarter of the patients were infected through drug use and 60% are gay men. Mean age at enrolment was 43 (+/-8) and median CD4 count and nadir were 420 (IQR 256-603 cells/mm3) and 174 (49-300 cells/mm3) respectively. Most patients had other health issues that could contribute to impairment, but these were minimal for around half the patients and severe in only 15%. Prior AIDS was diagnosed in around 60% and 26% were coinfected with HCV.

Approximately 70% of patients were on HAART, with 15% treatment-naïve, another 15% having interrupted treatment.

Viral load was suppressed to <50 copies/mL, in 60% plasma samples and 34% of CSF. Although 5% of the patients had greater CSF levels than plasma, less than 1% of patients with undetectable virus in blood had detectable viral load in CSF (mean 235 copies/mL). Notably, approximately 40% of 300 patients with an undetectable viral load using the <50 test, had detectable CSF viral load using a more sensitive (<2 copy/mL) test.

Detectable CSF viral load was associated with both assumed CNS penetration of the HAART regimen used and a greater likelihood of cognitive impairment in terms of lower CPE scores ($d=0.25$; $p<0.03$).

Based on a panel of tests, NCI was found in just under half the group and the rates were higher when other factors were present. For example, the highest rate of NCI (80%) was in the 15% patients with severe cofactors. Rates were higher in patients with more severe HIV-infection and whose CD4 counts had dropped the lowest before treatment.

Compared to pre-HAART cohort data, HAART has not reduced patterns of impairment. These cross-sectional baseline results are important, but interpretation is limited because viral load results were not categorised by treatment use, because of the high rate of co-morbidity, and the lack of a matched HIV-negative control group. When looking at the 843 patients in the group not confounded by co-morbidity factors, CD4 nadir <200 cells/mm3 and unsuppressed viraemia were associated with significantly higher rates of NCI. Imaging on a sub group of these patients found a 30% incidence of abnormal changes (either reductions in white matter or cortical grey matter or an increase presence of abnormal white matter), and that these had at least a modest relationship with cognitive function.

Even though exact prevalence of NCI may be debated, there seems consensus that rates are higher than they should be and this was supported by other groups.

Fabrice Bonnet presented results from the ANRS Aquitaine cohort, suggesting that 25% adults with well-controlled HIV-infection had a mild cognitive disorder, and that this compared to a rate of 6% in an elder French general population (age 65 years or older). [5]

Matteo Vassallo, presenting data from the prospective French Nueradapt study, found only 30% of patients to have normal function scores, again, only explained by co-morbidity factors in a perhaps half of these patients (mainly relating the HCV coinfection and use of antidepressants). [6]

The Charter study has taken five years to enrol and the results presented this year were from a single time-point when patients joined the study. The group will now follow patients to track brain function and changes over time.

Three other presentations from Charter were also present at CROI.

In abstract 702, Best and colleagues reported that both efavirenz and FTC concentrations consistently exceed wild-type IC50 in CSF. [7] This has implications for earlier studies looking at CSF penetration scores, including from the Charter group who

previously evaluated both drugs as having only intermediate penetration based on IC50 concentrations. [8] More importantly, it has implications for how CSF penetration is interpreted for the current first-line regimens.

Roland Ellis and colleagues reported that despite HAART, and reduced use of d-drugs, HIV Distal Sensory Peripheral Neuropathy (DSPN) was present in almost 60% of the Charter cohort. [9]

Finally, also controversially, Desiree Byrd and colleagues reported in abstract 478 that current or historical substance use (IDU, cocaine, methamphetamine) was not associated with compromised neuropsychological function at baseline when important co-factors were considered, suggesting that "historic substance use and acute stimulant use do not require special consideration in cross-sectional analyses of neuropsychological function in neuro-AIDS research". [10]

The oral symposium, included several other studies looking at brain function, contributing to a compelling focus on overlapping issues of aging.

A study from Ian Everall, from the US National NeuroAIDS tissue Consortium, looked at autopsy results from almost 600 people who had died since 1999, many of whom were known to have neurological problems. [11]

Although only around 100 patients (~18%) had evidence of brain disease that would directly affect brain function (5% with cerebral lymphoma), only 25% of the remaining 500 patients were described as having 'normal' brains. Lowest-ever CD4, not being on treatment, and detectable viral load at death were all associated with higher of this evidence of brain impairment.

Brad Navia and colleagues, from Tufts University and the HIV Neuroimaging Consortium, used Proton Magnetic Resonance Spectroscopy (MRS) to prospectively track changes brain function in 300 asymptomatic patients whose CD4 nadir was less than 200 cells/mm3 and who had been on treatment for at least a year. Importantly, this study excluded patients with neurological, psychiatric or medical health issues or active drug use. [12]

Most patients had been HIV-positive for over 12 years with a CD4 nadir of <50 cells/mm3. Median age 47 (30% aged 50-50), 25% non-white, and 50% with an education level <12 years.

When looking at three brain regions, the group found patterns of inflammation (Cho/Cr and MI/Cr metabolite ratios) that were independent of cognitive function suggesting brain injury at all stages of HIV infection and linking decreases in neuronal biomarkers (NAA/Cr metabolite ratio) to patients with reduced cognitive function that are associated with evidence of neuronal damage. Age, lowest ever CD4 count, and detectable CSF viral load suggested a strong effect on the risk for brain injury in the HAART era.

Beau Ances and colleagues from Washington University School of Medicine looked at the relationship between HIV and aging with findings that were particularly sobering for the long-term implications of this area of research. [13]

HIV infection (for four year or less) in a range of studies has been linked to premature aging by ten years. This group looked at changes in blood flow in the brain (in 26 HIV-positive patients aged 20-62, 58% of who were on HAART and 25 HIV-negative controls) and the response to a panel of tasks that showed an equivalent CNS aging linked to HIV of an additional 15-20 years.

Patients not on HAART had larger functional changes in blood flow and lower baseline blood flow, but no significant differences were found by age (when comparing patients <50 to > 50 years old.

In a graphic used to illustrate these data (as sensitive as the ubiquitous HIV progression train travelling to the site of an impending ravine), both age and HIV were shown to strain a bridge which broke completely when HIV, aging and co-morbidity were combined.

Ances summarised the importance of a multi-disciplinary approach to future research on HIV, aging and brain function, including neuropsychological performance testing, CSF biomarkers (of astrocyte and endothelial dysfunction), and both structural and functional MRI imaging.

Finally, Dulioust and colleagues, confirmed significant NCI in a cross-sectional study group of 37 patients older than 60 in the Neurosigma substudy. [14]

In this study, people with active neurologic or psychiatric diseases and low educational level were excluded. Patients underwent a brief neuropsychological exam (assessing psychomotor speed, attention, cognitive sequencing, and shifting cognitive sets) in addition to the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS), and the Instrumental Activity of Daily Living (IADL).

All patients (except one) were on HAART, suppressed to <50 copies/mL: 73% were men; median age was 67 (range 60 to 84 years). Median duration of HIV infection and of ART were respectively 11 (IQR 5 to 17) and 10 (IQR 3 to 14) years. Median nadir and current CD4 count was 113 cells/mm3 (IQR 80 to 239) and 522 cells/mm3 (IQR 443 to 675) respectively.

One or more CVR factors was present in 27 patients (diabetes 27%, hypertension 49%, dyslipidaemia 43%). Neurocognitive

impairment was detected in 19 patients (51%). Severe impairment was observed in 11 patients (30%), including 4 with abnormal daily activity. Geriatric depression score was abnormal in 7 patients (19%).

The study again highlighted that these rates were significantly more frequent than in the general aging population, and are also under-diagnosed.

COMMENT

The optimism that durable viral suppression could normalise life expectancy may need to be tempered by emerging data from several fields suggesting increased age-related complications.

In 2009, we are at the time where a potential 20-year impact on advanced aging would expect to show clinical symptoms, as this impact on biological age will have greater significance as people reach their 50's and 60's. Cognitive differences between a 20 and 40 year old, or even a 40 and 60 year old may have little impact on daily activity but is likely to present greater difficulties if a 60 year old patient has brain function of an 80 year old.

The focus on possible earlier physical and mental aging may be something to highlight in prevention messages.

This importance of additional well-funded research is clearly important in both adults and children. Neurological sub-studies are planned in the START and NEAT trials that are both due to start shortly. [15. 16]

This also raises the imprtance of a simple NCI assement tool, perhap susing motor function, to identify those patinets most in need of more detailed follow-up.

'Nature' also carried an interesting editorial commentary on the use of cognitive-enhancing drugs by the 'healthy' population. [17]

References

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. All oral abstracts are available as webcasts.
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Other links:
https://www.charterresource.ucsd.edu/

16th CROI: TREATMENT STRATEGIES

When to start HAART – a key research question with the least available data

Nathan Geffen, TAC

With the international START study about to open this month, several studies at CROI contributed results confirming the importance of the 'when-to-start' discussions.

US and Canadian cohort analysis starting HAART at CD4 >500 cells/mm3

Mari Kitahata presented a study at CROI on behalf of the North American AIDS Cohort Collaboration on Research and Design. [1]

This collaboration includes 60 geographical regions in the US and Canada and records demographic and other data from multiple observational cohorts in the IDEA database. The study compared all-cause mortality in patients who initiated HAART with CD4 counts > 500 cells/mm3 with those who deferred treatment until their CD4 counts were below 500. This group has previously reported that initiating HAART at 350-500 has improved survival over starting when CD4 counts are below 350.

Kitahata explained that the study attempted to mimic clinical trial conditions as closely as possible. State-of-the-art statistical techniques were used. The methods account for time varying confounders that are measured but, as with other observational studies, do not deal with unmeasured confounders.

The study included all patients with CD4 counts > 500 actively followed up between 1996 and 2006, but excluded patients already on HAART and with prior AIDS-defining illnesses. Any statistically significant differences in baseline demographics, were not considered clinically relevant. Median baseline CD4 and viral load was around 660 and 3.6 log in both the immediate and deferred groups.

The analysis included over 9,000 patients and over 28,000 patient-years of follow-up. Just over 2,600 patients (8,900 PYFU started immediate treatment (or within 1.5 years of their first CD4 count since 1996) and the remainder deferred HAART. Approximately 2,600 patients in the deferred group still had CD4 counts above 500 when the study ended.

Mortality was consistently worse in the deferred group from 1997 with a relative hazard of 1.6 [95%CI 1.3-1.9; p<0.001] in the deferred group. Older age was a significant independent predictor of mortality, (RH 1.6 for every 10 years of age [95%CI 1.5-1.7; p<0.001]. Surprisingly, controlling for HCV co-infection of history of IDU made little difference (RH 1.5 95%CI 1.2-1.9; p<0.01, and RH 1.6, 95%CI 1.1-2.2; p<0.01, respectively. Sex, race, baseline CD4 and viral load were not predictors of mortality.

The finding that deferring HAART was associated with higher mortality was robust when controlling for sex, race, cohort, CD4, viral load, HCV, history of IDU and calendar year. A sensitivity analysis showed that the cumulative effect of confounding factors would have to have a combined relative hazard of 4.0 as well as four times greater odds of deferring treatment to only accomplish reducing the relative hazard of mortality in the deferred arm from 1.6 to 1.3.

The MACS, SWISS and CASCADE cohorts analysis

Jonathan Sterne presented the results of a study conducted by the When to Start Consortium of HIV Cohort Studies. [2]

They combined data from seven cohorts (including MACS, the Swiss HIV cohort and CASCADE) and compared patients starting HAART across several CD4 ranges to determine when to start. Their results are not entirely consistent with Kitahata et al. They too used state-of-the-art statistical techniques, but with different methodology, to analyse an even larger number of person-years.

Their data included over 21,000 patients comprising over 68,000 person-years of follow-up. There were 5,356 AIDS events and 3,630 deaths. Patients presumed to be infected by IDU were excluded.

They compared hazard ratios for AIDS or death in patients who started HAART in adjacent CD4 ranges from when they started treatment. However, a naïve comparison of hazard ratios between two sets of patients in adjacent CD4 ranges would be incorrect because this would not take into account the time taken to move from a higher CD4 range to a lower one.

For example, a naïve comparison of the time to AIDS or death in a patient who starts treatment at 350 cells/mm^3 versus one who starts at 250 would be wrong, because it does not account for the time the patient starting with a CD4 count of 250 took to move from 350 to 250. A correct calculation must take this "lead time" (to use Sterne's phrasing) into account. Furthermore, unseen events, such as a patient with a CD4 count of between 251 and 350 who dies without using treatment also need to be taken into account. Sterne accounted for unseen events and lead times by imputing from data in the pre-HAART era to the deferred CD4 ranges.

Table 1: Hazard ratios by CD4 count

Lower CD4 range	Higher adjacent CD4 range	Hazard ratio of higher vs lower range, adjusted for lead time and unseen events
351-450	451-550	0.99 (95%CI 0.76-1.29)
276-375	376-475	1.19 (95%CI 0.96-1.47)
251-350	**351-450**	**1.28 (95%CI 1.04-1.57) ****
0-100	**101-200**	**3.35 (95%CI 2.99-3.75) ****

****** indicates a statistically significant hazard ratio.

Adjusting for age at initiation, sex and risk group did not materially alter the naïve hazard ratios.

Deferring HAART until a CD4 count below 250 was clearly associated with increased risk AIDS or death (see Table1). They also showed, albeit less profoundly, that delaying treatment until CD4 was below 350 was associated with an increased risk of AIDS or death. In contrast to Kitahata et al, they did not conclude that HAART should be started in patients with CD4 counts higher than 450 cells/mm3.

Sterne explained that their study did not account for serious non-AIDS events. He emphasised that a clinical trial was needed to eliminate the effects of confounding such as, he suggested, people who defer HAART possibly having poorer adherence.

START Trial

Details of the soon-to–enrol Strategic Timing of Antiretroviral Treatment (START) trial were presented at an INSIGHT meeting shortly before CROI. This study will randomise ART-naive patients with a CD4 count > 500 cells/mm3 to either immediate HAART or to defer treatment until CD4 drops to below 350 or an AIDS event.

The pilot phase will include 900 patients (450 to each arm) and roll out to 4,000 patients, 2,000 in each arm. Enrolment for this international study is due to start in March 2009 with about 70 sites in 23 countries.

The trial will compare the event rate in the deferred arm versus the immediate arm and also estimate the fraction of non-AIDS events. There will be four sub-studies. These will be in genomics, neurology, informed consent and arterial stiffness.

The primary funder is the Division of AIDS of NIAID. Several other NIH institutions are funding the trial as well as ANRS (France), BMBF (Germany), NEAT (European Network AIDS Trials) and the NHMRC (Australia). Drug supply for the study is provided by pharmaceutical company support.

C O M M E N T

The evidence that patients with access to non-d4T-based regimens benefit from starting at CD4 counts closer to 350 than 200 cells/mm3 is now widely integrated into national and even WHO guidelines.

A mass of observational data and a sub-study of the SMART trial also support the potential benefits of starting even earlier, both for patient health and reduced transmission. [4, 5]

The START trial is going to be essential to provide well-powered evidence from a large randomised study on both risks and benefits that can never be tracked in cohort studies. There is also broad scientific and community equipoise on the starting at levels above 350 cells/mm3.

It is premature to recommend broad HAART use at CD4 counts over 500 cells/mm3 given the lack of supporting data, but the 2008 IAS (US) guidelines provide a useful summary on evidence for not having an upper CD4 cut-off. [6]

They emphasise that real world complications make this a complicated and individualised decision. Results from randomised studies are needed now more than ever.

The SMART study, run by the same research collaboration, overturned many previous assumptions about treatment interruptions, continuous treatment (being protective of cardiovascular, renal and hepatic health) and HIV pathogenesis (over the inflammatory impact of unsuppressed viraemia).

START, if sufficiently resourced, is likely to provide similar insight from a wealth of sub-studies that are also only possible from such a design. Whatever its findings, this is likely to be the most important research trial to enrol for at least the next five years.

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16th CROI: IMMUNE-BASED STUDIES

Major studies rule out any benefit of Interleukin-2 (IL-2): results from ESPRIT and SILCAAT

Nathan Geffen, TAC

The results of two Interleukin-2 (IL-2) trials, ESPRIT and SILCAAT, were presented at CROI. Based on previous evidence that IL-2 raises CD4 counts, the objective of the trials was to determine whether this translated to greater clinical benefits than HAART alone. Patients were randomised to either HAART or HAART plus IL-2.

Both studies reported similar results, primarily that IL-2 provided no additional clinical benefit, even though it raised CD4 counts. Despite this disappointing finding, with over 5,800 patients followed for seven years this is a rich data set that will hopefully explain these unexpected results.

Marcelo Losso presented the ESPRIT study which included over 4,000 patients from over 250 sites in 25 countries with CD4 counts of 300 cells/mm^3 or higher. [1]

The IL-2 regimen consisted of at least three 5-day cycles (7.5 MIU twice daily) at eight week intervals in the first year. Optional additional cycles were encouraged to meet predefined goals of a CD4 counts >1,000 cells/mm3 or double baseline levels. The primary endpoint was an opportunistic disease or death. Secondary endpoints included serious non-AIDS illnesses and grade 4 clinical events.

The study needed 320 primary events to detect a 27% difference between the two groups with 80% power. By November 2008, 323 primary events were observed with a median follow up of 7 years and the study was closed.

Baseline demographics included: mean age 41 years, 19% women, 76% Caucasian. Median and nadir CD4 counts were approximately 450 (IQR 372-584) and 200 (IQR 91-306) cells/mm3 respectively. Viral load was <500 copies/mL in 80% of patients. 26% had prior clinical AIDS. Average time on HAART was just over 4 years. Both groups were well balanced in all these characteristics.

Over all follow-up, the IL-2 group had an average CD4 count that was 160 cells/mm3 higher than the control group (95% CI 145-174, p<0.001). The difference in CD4 cells was maintained throughout the study, but decreased from year one (approximately + 207 cells/mm3 vs +21 cells/mm3) over the seven-year period, as use of IL-2 cycles diminished. The IL-2 group spent 6% of their time at CD4 counts less than 300 and 57% of their time at CD4 counts greater than 600 versus 9% and 36% respectively for the control group. There were no significant differences in viral load between the two groups throughout the study period.

The rate of opportunistic disease or death in the IL-2 and control groups was 1.13 versus 1.21 per 100 patients-years respectively and this was not statistically significant. There were 107 versus 116 deaths respectively. The hazard ratio (HR) was 0.93 (95%CI: 0.75, 1.16). Yet, based on the difference in CD4 count, the predicted HR was 0.74 showing that it would be extremely unlikely not to find a difference, if one existed.

There was not a statistically significant difference in the rate of non-AIDS events, but the IL-2 group had 466 grade 4 events versus 383 in the control and this was significant (HR: 1.23; p=0.003). Of these, vascular events were the biggest contributor (HR: 2.81; p<0.001). The most common vascular event was deep vein thrombosis (>100 days after a cycle) with 13 in the IL-2 group versus 2 in the control. There was also a trend to more common psychiatric events relating to depression in the IL-2 arm (n=44 vs 29, HR 1.4, p=0.1).

Yves Levy presented results from the SILCAAT study, which had a similar study design to ESPRIT, but enrolled patients with lower CD4 counts (50 to 299 cells/mm3) and a lower IL-2 dose with more cycles (six 5-day cycles using 4.5 MIU twice-daily at eight-week intervals. [2] Additional cycles were used to maintain the CD4 count 150 cells/mm3 above baseline. Non-AIDS events were not categorised separately as in ESPRIT.

The trial included about 1,700 subjects in 139 sites in 11 countries. Median follow-up was just under 8 years. It was similarly powered to ESPRIT, but when it was closed on the same date only 227 endpoints had been seen.

Baseline characteristics were similar to ESPRIT, except that median and nadir CD4 counts were approximately 200 (IQR 155 – 255) and 60 (IQR 25-108) cells/mm3 respectively.

Median number of cycles was 7 with 72% patients using at least 6 cycles. The average difference in CD4 cells between the IL-2 and control groups was 59 cells/mm3 over the period of the study (p<0.001). The difference was greater for patients with higher CD4 counts. As with ESPRIT, the differences were greatest at the end of year 1 (99 cells/mm3) dropping to a median difference of 38 cells/mm3 at the end of year 6. The IL-2 group spent 23% of their time with a CD4 count below 200 and 38% of their time with a CD4 count above 300 versus 29% and 28% respectively in the control group. Interestingly, the percentage of patients who started a new class of drugs was lower in the IL-2 group (31% versus 37%, p=0.02).

The rate of opportunistic disease or death in the IL-2 and control groups was 1.92 versus 2.12 per 100 patient-years, with 81 versus 77 deaths (1.38/100py vs 1.31/100py, respectively). As with ESPRIT, these results were not statistically significant. The biggest causes of death were non-AIDS related illnesses. Of these, cancers were the largest contributor.

There were 38 grade 4 events in the IL-2 arm in the first year versus 19 in the control (HR: 2.02; p=0.01). However, in contrast to ESPRIT, after the first year there were no differences. Grade 4 events for gastrointestinal tract disorders (HR 1.83, p=0.01) and psychiatric events (HR 2.52, p=0.03) were both significantly higher in the IL-2 arm.

Both studies demonstrated that CD4 cell count is not a reliable surrogate marker for clinical outcomes in the evaluation of IL-2. The pooled HR for the two studies was 0.93 (95%CI: 0.78, 1.09; p=0.33; events: 267 v. 283; deaths: 188 v. 193).

C O M M E N T

The consistency of the findings from both studies confidently rules out the possibility of even a modest clinical benefit from IL-2.

Both presenters suggested that the lack of clinical benefit from IL-2 can perhaps be explained either by the expanded CD4 cells lacking functional equivalence, and a planned analysis of events by CD4 count may confirm this, or that the higher rate of serious IL-2 related complications cancelled out any benefit.

Tehy also concluded that absolute CD4 count may not be the an appropriate surrogate marker for immune-based therapy.Although future IL-2 studies are unlikely, some of the same researchers have been looking at IL-7.

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Higher rates of non-AIDS cancers in HIV-positive people

Nathan Geffen, TAC

Michael Silverberg presented a case-control retrospective analysis from the Kaiser Permanante cohort of HIV-positive and HIV-negative patients, to determine differences in non-AIDS cancer rates post HAART (1996-2007). [1]

They found significantly higher non-AIDS infection-related cancers (anal, Hodgkin's, liver, oral cavity/pharynx) in the HIV-positive group, as reported in many previous studies.

The analysis compared over 20,300 HIV-positive patients, matched for age and sex, with ten HIV-negative cases each (i.e. over 203,000 controls), giving well over a million years of follow-up. The mean follow-up period was 4.2 and 5 years in the HIV-positive and HIV-negative groups respectively. Mean age was 40 years. This was a predominantly white MSM male (90%) cohort. Patients were followed until cancer, death, the end date of the study or they left the health provider. Time analyses looked at three four-year periods: 1996-99, 2000-3 and 2004-7.

Non-AIDS defining cancers were diagnosed in 3% of the HIV-positive and 2% of the HIV-negative groups. Rates for infection-related non-AIDS-defining cancers (per 10,000 person-years) were 29.7 for HIV-positive and 4.4 for HIV-negative patients. Infection-related cancers accounted for 46% and 13% of the cancers in HIV-positive and HIV-negative subjects respectively. This difference was significant for any infection-related cancer [RR: 7.4; 95%CI 6.4 – 8.5], or each taken individually. It was particularly high for anal cancer [RR: 80; 95%CI 50.2 – 126.4], Hodgkin's lymphoma (RR 17.4; p <0.001), head and neck (RR 2.1; p <0.001), and gynecologic (RR 2.9; p = 0.001).

Interestingly, the incidence rates for any infection-related cancer came down 4% per year in HIV-positive subjects and went up by 4% per year in HIV-negative patients (p<0.001, adjusted for age and sex). This difference between the two groups was also significant for each infection-related cancer analysed separately, again with anal cancer having the largest per annum decrease (6% decline versus 13% increase, p<0.001). The 4% per year decline in any infection-related cancer over time in HIV-positive subjects was significant (p=0.003), but this was not significant when each cancer was considered separately.

The risk of any non-infection related cancer (lung, melanoma, kidney, hematologic, colorectal, prostate) was also higher in the HIV-positive group [RR: 1.2; 95%CI 1.1–1.4], but the differences were less pronounced. Analysed separately, this was only significant for lung, melanoma and kidney cancers. Except for lung cancer, there were no statistically significant time-related differences.

Silverberg pointed out the study's strengths: its large size, that the two comparative groups were drawn from the same population and that the cancer data was obtained from comprehensive registries. But he also noted the considerable limitations: no consideration of smoking, CD4 count or cancer screening practices. Also the study has limited data on women, lower-income (uninsured) patients and non-white patients.

C O M M E N T

While the increased relative risk was high, the absolute risk of cancer was small during the follow-up period for both groups. Of course, with a longer follow-up period that would undoubtedly rise given that cancer is a common cause of mortality, irrespective of HIV status.

Despite the study's limitations, the high correlation between being HIV-positive and increased risk of cancer in this cohort indicates that regular cancer screening is particularly important for HIV-positive patients.

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16th CROI: MATERNAL HEALTH AND PMTCT

High rates of HIV acquisition in pregnancy and post partum in Francistown, Botswana

Polly Clayden, HIV i-Base

In an oral presentation Lydia Lu from the CDC showed worrying findings from a study of HIV incidence during pregnancy and the first post-partum year (in which the majority of women breastfed) among women in Francistown, Botswana. [1]

Dr Lu explained that women are routinely tested for HIV in Botswana at a median of 22 weeks gestation. However, this strategy may fail to identify women with acute infection in the window period or infection acquired after testing. Maternal seroconversion during pregnancy or breastfeeding greatly increases the risk of mother to child transmission.

The study included women with a documented negative HIV test during pregnancy: 400 on maternity wards, and 400 attending immunisation clinics with infants age 9-15 months.

To calculate the number of women infected post testing and in turn paediatric infections, the study investigators assumed a total of 43,000 annual births in Botswana and a 32.4% HIV prevalence, giving 29,068 women whose first ante natal clinic (ANC) test is negative. The transmission rate for mothers receiving prevention of mother to child transmission (PMTCT) interventions in Botswana is currently 4.7%. Using data previously reported describing very high rates among women seroconverting during pregnancy and breastfeeding, receiving no intervention, they assumed rates of 73% and 36% respectively among post partum transmissions. [2]

Rapid testing and counselling were conducted in accordance with local guidelines, and HIV-positive women were referred for HIV care, PMTCT, and infant testing. Women tested on maternity wards (n=400) had a median interval of 17 weeks from their negative test and those attending immunisation clinics with available data (n=244) a median of 62 weeks (with infants of a median age of 11 months).

Dr Lu reported HIV incidence of 5/400, 1.3% (95% CI, 0.5-3.1%) among women tested on maternity wards and 7/244, 2.9% (95% CI 1.3-5.6) at immunisation clinics.

The investigators calculated an overall HIV incidence of 1.8% at one year (see table 1).

Table 1. Calculation to estimate incidence at 1-year post partum

Incidence	(2.9-1.3)	1.6%	1.8%
Weeks	(62-17)	45 weeks	52 weeks

They then estimated, of 43000 pregnant women in Botswana in 2007, 13932 (34.7%) were diagnosed during ANC and the remainder, 29068 (65.3%), assumed to be HIV negative. Of this group 378 (1.3%) would be infected during pregnancy and 450 (1.8%) while breastfeeding.

A transmission of 4.7% among 13932 women would result in 620 HIV-positive infants. A transmission rate of 73% among 378 women infected in pregnancy would result in 276 HIV-positive infants; and of 36% among 450 women infected 1-year post partum would result in 186. Therefore they estimated incident cases of maternal HIV to account for 462/1082 (43%) of infant infections.

The investigators concluded: “In this mature and successful PMTCT programme, new and undetected maternal infections may be causing nearly half of infant infections.” They offered a number of recommendations including: better prevention strategies; routine re-testing; identification of the most appropriate intervention in pregnancy (start HAART?) and the safest infant feeding for women with new infections while breastfeeding.

C O M M E N T

These data, while sobering, provide one of the most important messages from this conference and the investigators must be congratulated for such a clear analysis.

Previous reports from other settings have revealed transmissions that are most likely attributed to maternal serconversion. In a survey of mothers and infants at 6-month immunisation in KwaZulu-Natal, Rollins at al reported a group of women (7.6%), having tested HIV-negative during the antenatal period but with HIV antibodies identified in the dried blood spots of their infants and 31.2% of these infants were infected. [3]

The investigators suggested that these women may have been in the window period at the time of their HIV tests or they may have been infected during pregnancy. And among the 54 infants born to undiagnosed women reported in the Perinatal Transmission Survey of HIV in England, at least 20% were born following maternal seroconversion during pregnancy. [4]

The significant question is, of course, what to do about it? To which, as yet, there is simply no straightforward answer. The investigators suggest better prevention strategies, but coy discussions about “husbands” that we heard following the presentation are unlikely to be very effective. Some have suggested that this would be a potential useful role for PrEP.

Re-testing is an obvious answer, but when? Too early and the risk of seroconversion remains, too late and the efficacy of PMTCT interventions decrease and earlier in utero infection will be missed.

It is unclear what was meant by, “better infant feeding”. Avoiding breastfeeding completely for all women? But the same group last year

showed scary mortality findings from a group of formula fed infants in the PMTCT programme in Francistown, when the water became contaminated. [5]

This issue provides a big obstacle to prevention of paediatric HIV.

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Effect of single dose nevirapine on subsequent nevirapine-containing HAART: long term outcomes

Polly Clayden, HIV i-Base

Two posters showed results of long term outcomes for women receiving nevirapine (NVP) containing HAART who had previously received single dose NVP for prevention of mother to child transmission (PMTCT). [1, 2]

Gonzague Jourdain and co-workers reported 4-year results for women in PHPT-2. In 2004 this group had reported an association with impaired treatment response at 6 months in women receiving single dose NVP vs placebo in addition to AZT from 28 weeks gestation. [3]

Women initiated NVP containing HAART postpartum at CD4 </= 250 cells/mm3. Viral load and CD4 tests were performed 6 monthly. After 6 months, women with confirmed virologic failure or CD4 decrease were able to switch to a PI. Treatment failure was defined as: viral load >400 copies/mL after 4.5 months, or CD4 <50 cells/mm3 after 6 months, or switch to PI, or death.

The 221 NVP-exposed and the 48 -unexposed women (the same group that were included in the earlier analysis) were well matched, with median age 28.7 years (IQR 25.1 to 32.7), weight 50 kg (46 to 56), CD4 168 cells/mm3 (79 to 219), viral load 4.63 log10 copies/mL (4.00 to 5.09).

The investigators found, four years after initiation of treatment, 65% of the NVP-exposed and 73% of the -unexposed were still being followed, p=0.32. In the exposed and unexposed groups, 69 vs 6 women experienced virologic failure, 2 vs 0 immunological failure, 11 vs 5 switched to a PI, 6 vs 0 died, respectively.

Overall 41% of NVP-exposed women failed vs 23% of unexposed women, p=0.02). The majority failed within two years of treatment initiation. In multivariate analysis, single dose NVP (adjusted hazard ratio 2.0, p=0.04), pregnancy CD4 cell count (AHR 1.17 per 50-cell decrease, p=0.02), and viral load (AHR 1.47 per log10 copies/mL increase, p=0.01) were associated with failure.

When the investigators looked failure defined as viral load as >50 copies/mL, they found treatment initiation within 6 months of delivery to be associated after adjustment for age, CD4 and viral load during pregnancy and at initiation of treatment (AHR 2.23, p<0.001).

They also found that the risk of failure in NVP-exposed women decreased as the length of interval from delivery to treatment initiation increased (AOR 0.93 per month increase, p=0.001). However it remained independent in unexposed women. They noted that predicted risks of failure in both groups were similar only at 18 months.

They concluded that the consequences of single dose NVP exposure were, “still significant after 4 years of therapy, justifying the development of strategies to prevent resistance mutations”.

Shahin Lockman and co-workers showed similar results among women in long term follow up in the Botswana Mashi trial, in which all women (n=1200) received AZT from 34 weeks gestation and either single dose NVP or placebo. [4] Women initiated NVP containing HAART post partum when they met WHO criteria (CD4 <200 cells/mm3 or AIDS illness).

The follow up for women on HAART in this study was up to five years; the median duration was 42 months. The primary endpoint for the study was virologic failure (defined as viral load >400 copies/mL at 6 months or > 1 log drop at 3-months).

The investigators reported that 360/1200 women in Mashi initiated NVP-containing HAART post partum (182 had received

single dose NVP vs178 placebo). Of these 61 (17%) initiated treatment within 6 months of delivery and 299 >/= 6 months of delivery. Excluding death, 16% of women were lost to follow up at 42 months and 19% by 60 months. Women initiated HAART at a median of19 months after delivery. Viral load results were available for 96% of women.

They found a difference in viral failure between NVP-exposed and placebo- women by timing of HAART initiation after an interval since delivery 6 months vs > 6 months (p=0.003 for interaction); at <12 months, p=0.0001. But they found no difference in viral failure in those starting HAART >=12 months postpartum, p=0.7822 and late virologic failure was uncommon across all subgroups (see Table 1).

Table 1: Virologic failure rates in women initiating HAART after prior sdNVP vs placebo exposure by interval since delivery

Months after HAART initiation	# (%) failing, placebo arm	# (%) failing, sdNVP arm	p-value
HAART started <6 month`s after placebo/sdNVP (n = 61)	n = 37	n = 24	
6	0 (0%)	9 (37.5%)	0.0001
12	1 (2.9%)	11 (45.8%)	< 0.0001
24, 36	2 (5.4%)	11 (45.8%)	0.0002
48, 60	2 (5.4%)	12 (50.3%)	< 0.0001
HAART started >6 months after placebo/sdNVP (n=299)	n = 141	n = 158	
6	7 (5.1%)	12 (7.7%)	0.36
12	13 (10.0%)	19 (12.9%)	0.46
24	18 (14.6%)	23 (16.1%)	0.74
36	19 (15.9%)	27 (20.2%)	0.39
48, 60	20 (17.7%)	27 (20.2%)	0.64

They concluded: "Women starting NVP-based HAART >/= 6 months after sdNVP exposure had similar long term rates of virologic failure as non-sd-exposed women**."**

C O M M E N T

The findings from these studies were unsurprising. They add to the growing evidence that prior use of single dose nevirapine contributes to virologic failure when HAART is initiated within six months (and maybe within 12 months) after sdNVP exposure.

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Covering the nevirapine 'tail'

Polly Clayden, HIV i-Base

Two oral late breakers presented by researchers working in Thailand showed strategies to reduce risk of NVP resistance following receipt of single dose nevirapine (NVP). [1, 2]

Previous studies have demonstrated reduction in resistance using short courses of antiretrovirals as "tail' coverage. Currently 7 days of AZT and 3TC are recommended in the WHO pregnancy guidelines. [3, 4, 5, 6]

First presenting author, Russel Van Dyke, was from IMPAACT P1032. This group hypothesised that longer duration or a more potent regimen may further reduce incidence of resistance.

P1032 was a 3 arm randomised, open label, phase 2 study conducted in Thailand between June 2006 and June 2008 (and used historic controls). Pregnant women with CD4 >250 cells/mm3 were enrolled at 28-38 weeks gestation. All women received intrapartum single dose NVP (and were stratified according to whether or not they received an additional short course of antepartum AZT). Women were randomised to: Arm A, 7 days AZT+ddI+LPV/r; Arm B, 30 days AZT+ddI or Arm C, 30 days AZT+ddI+LPV/r. This trial was conducted in non-breastfeeding women.

Resistance testing was performed at 2, 3, 4, 5, 6 and 8 weeks post partum. Consensus sequencing was used and if negative by sequencing, oligonucleoside ligation assay (OLA), an ultra sensitive single point assay that can detect K103N, Y181C and G190A >2-5% of viral population.

The controls were women with CD4 >250 cells/mm3 from the PHPT-2 trial, in which women received single dose NVP or short course AZT and single dose NVP, and for whom matched samples were available at 2 and 6 weeks. The primary end point was a new NVP resistance mutation within 8 weeks post partum.

P1032 included 169 women in the analysis and 119 women from PHPT-2 were selected for the control group. Women in P1032 were slightly older than those in PHPT-2, median 28 vs 26 years, p=0.03 and a greater proportion received AZT during pregnancy, 78% vs 19%, p<0.001. Additionally they had higher median CD4, 456 vs 414 cells/mm3; lower median viral load 3.5 vs 4.0 log10 copies/mL, p<0.001; and a greater proportion were </=500 copies/mL, 25% vs 8%, p<0.001.

Intent to treat analyses found significantly lower incidence of NVP-resistance mutations in P1032 vs PHPT-2 at 2 or 6 weeks post partum (see table 1). In Arm A, one woman lost to follow up was missing 6 and week samples and assumed to have resistance.

Table 1: Incidence of NVP-resistance mutations at 2 or 6 weeks post partum

	Arm A **AZT + ddI + LPVr; 7days**	**Arm B** **AZT + ddI; 30 days**	**Arm C** **AZT + ddI + LPV/r; 30 days**	**PHPT-2**
N	56	57	57	119
Week 2 or 6 post partum	2 (3.6%)	4 (7.1%)	3 (5.3%)	37 (31.1%)
95% CI	0.5-12%	2-17%	1.1-15%	23-40%
95% CI for difference P1032 vs PHPT-2	13-43%	8.6-40%	11-42%	NA
Sequencing only	1 (1.8%)	0	0	15/112 (13.4%)

Combined incidence at weeks 2, 3, 4, 5, 6 or 8 weeks post partum in P1032 were: Arm A, 4 (7.1% [95% CI, 2-17%]); Arm B, 7 (12.5% [95% CI, 5.2-24%]) and Arm C, 3 (5.3% [1.1-15%]).

Maternal and infant adverse events were uncommon and similar in the three arms.

In summary, the investigators found P1032 Arms A and C had <10% incidence of NVP resistance mutations, with confidence intervals excluding >17%. All three arms were significantly lower than the control group but the study was not powered to show equivalence between the arms.

“Seven days of HAART following single-dose nevirapine prevents the selection of most nevirapine resistance mutations”, they concluded.

Second presenting author, Gonzague Jourdain, reported findings from PHPT-4. This study evaluated a “tail” of one month AZT+ddI. Dr Jourdain noted that these antiretrovirals were selected for their potency and low risk for selection of NRTI mutations. This study avoided 3TC, FTC and tenofovir as Hepatitis B is common among Thai women.

The primary endpoint was selection of new NVP mutations at any timepoint post partum. This study also used consensus sequencing and OLA performed at baseline, 7-10, 37-45 and 120 days.

Pregnant women with CD4 cell count >250 cells /mm3 and haemoglobin >8.0 mg/dl were enrolled and matched to case controls from PHPT-2. The women were well matched between the two groups but women in PHPT-4 were slightly older, 27.8 vs 25.9 years, p=0.009. 229 women were exposed to single dose NVP, of these 222 had 7 days visit (14 samples missing); 219 had 37 days visit (5 samples missing) and 194 had 120 days visit (2 samples missing).

Dr Jourdain reported that at one month post partum there were no NVP mutations detected in PHPT-4 vs10.4 in PHPT-2 using consensus sequencing; 1.8 vs 19.2 using OLA and 1.8 vs 20.7 overall, p<10 to 10.

He noted that 5 (2.3%) of cases and 2 (0.9%) of controls had NRTI mutations, p=0.45. And at one month median haematocrit was 35.3% in cases vs 37.6% in controls. Serious adverse events were uncommon and similar across both groups.

He concluded: “One month of ZDV/ddI postpartum prevented the selection of virtually all NNRTI resistance mutations detectable using consensus sequencing”. He added that the resistance mutations detected in 2% of patients by OLA were no longer observed at four months. He suggested that AZT+ddI tail coverage for one month post partum may be a reasonable option for women receiving single dose NVP.

C O M M E N T

These two studies add to the existing data demonstrating that covering the nevirapine works. Additionally a poster at this conference showed findings from the BAN study, Malawi in which women with CD4 ≥250 cells/mm3 receiving single dose nevirapine plus 7 days AZT/3TC tail coverage post partum were compared to women receiving single dose nevirapine alone. [6]

This study also showed a significant reduction (62%- 9%) in nevirapine resistance among the women receiving tail cover.

Although the PHPT-4 presentation showed this, head to head comparisons between regimens are difficult, as the original tail cover study (TOPS) took all comers and the subsequent studies exclude women who meet eligibility criteria for treatment. Choice of regimen should depend on local situation and access.

It is unequivocal that women needing treatment for their own health should receive it, but until the question of universal HAART for all pregnant women vs AZT plus single dose nevirapine prophylaxis for healthier women is answered, women receiving prophylaxis need to be protected from acquisition of resistance, and in turn from the increased risk of virologic failure with subsequent NNRTI containing HAART.

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Lopinavir/r containing regimen superior to nevirapine containing regimen in women previously exposed to single dose nevirapine

Polly Clayden, HIV i-Base

Shahin Lockman presented findings from the A5208 (OCTANE) study on behalf of the study team. [1]

OCTANE is a comparison of treatment regimens in women previously exposed to single dose nevirapine (NVP). We reported early results from this study previously in the November/December 2008 issue of HTB, following the DSMB recommendation that OCTANE Trial 1 be unblinded and interim findings made public, due to superior results in the lopinavir/r (LPV/r) vs the nevirapine (NVP) containing arm of the study. [2]

Dr Lockman showed further data from Trial 1, in which 241 women were randomised to receive either NVP+tenofovir (TDF)+ emtricitabine (FTC) (n=121)or LPV/r+TDF+FTC (n=120).

Results were from an intent-to-treat analysis. 41 women reached a primary endpoint of virologic failure (defined as <1 log10 below baseline, 12 weeks after starting treatment or as viral load >/=400 copies/mL at or after 24 weeks of treatment*)* or death. Of these 31 (26%) were in the NVP and 10 (8%) in the LPV/r arm, HR 3.55(95% CI 1.71,7.34), p=0.0007.

Virologic failure occurred in 22% of women in the NVP arm and 8% in the LPV/r arm, p=0.002. And 3% vs 1% died in the NVP and LPV/r arms respectively, p=0.21. These deaths were not associated with antiretroviral treatment.

44 women discontinued NVP or LPV/r in their first regimen, of these 38(31%) were in the NVP and 6 (5%) in the LPV/r arms respectively, HR, 7.43 (95% CI 3.14, 17.59), p=0.0001.

Dr Lockman also reported findings from preplanned sub-studies.

Of 239/241 women for whom baseline resistance test results were available 33 (14%) had NVP associated mutations (28, K103N and 5, Y181C). The median time since single dose NVP exposure was 11 months in this group of women vs 17 months in 206 women without NVP resistance, p=0.024.

An analysis of proportions of women with virologic failure or death by presence of baseline NVP resistance, revealed an overall rate of 25% in the NVP arm (n=120) vs 8% in the LPV/r arm (n=119), p=0.001. 73% in the NVP arm vs 6% in the LPV/r arm had resistance, p=006. 18% in the NVP arm and 9% in the LPV/r arm had no NVP resistance, p=0.057. (Interaction of difference between treatment arms and presence or absence of resistance, p=0.04).

And proportions of women with virologic failure or death by time since last single dose NVP exposure were: 37% in the NVP arm vs 3% in the LPV/r arm in women receiving treatment after a 6 to <12 month interval since single dose NVP exposure, p=0.008 (n=78); 26% vs 12% in women with a 12 to <24 month interval, p=0.56 (n=98); and 12% vs 10% in women with >/= 24 month interval, p=0.72 (n=65). (Interaction of difference between treatment arms and continuous time since last single dose NVP exposure, p=0.2).

She noted that these findings might not apply to women receiving other PMTCT interventions with single dose NVP such as short course AZT or with AZT/3TC "tail". Also that treatment success in the LPV/r was very high. The OCTANE investigators are waiting on results from Trial 2 (LPV/r vs NVP containing HAART in NVP unexposed women) in order to fully interpret Trial 1 results.

C O M M E N T

We commented extensively on this study in the November/December 2008 issue of HTB. [2]

References

1. Lockman S et al. Lopinavir/ritonavir+tenofovir/emtricitabine is superior to nevirapine+tenofovir/emtricitabine for women with prior exposure to single-dose nevirapine: A5208 ("OCTANE"). 16th CROI, Montreal, 2009. Abstract 94LB. http://www.retroconference.org/2009/Abstracts/36738.htm
2. http://www.i-base.info/htb/v9/htb9-11-12/OCTANE.html

Higher risk of transmission with delayed control of maternal viral Load despite viral loads of <500 copies/mL at delivery

Polly Clayden, HIV i-Base

A poster from the French Perinatal Cohort showed results from a case control study looking at transmission among women receiving ART with viral load <500 copies/mL at delivery.

Between 1997 and 2006 the reported MTCT rate in this cohort was 1.6% and 0.6% for those with viral load <500 copies/mL at delivery.

In this case note review, the investigators matched 3 to 4 uninfected infants with each infected child from a total of 3972 infants. They included 19 cases and 60 controls and the women were well matched for origin, first appointment, timing of

HIV diagnosis, timing of last viral load test, type of ART and mode of delivery.

Of the infected infants (n=16) 39% had positive PCR at birth, indicating infection in utero. There was a higher proportion of women with viral load >1000 copies/mL in cases than controls at 28 weeks, 92.3% vs 31%, p=0.03 and 32 weeks, 78.6% vs 26.3%, p=0.04. And when the investigators restricted the analysis to intrapartum transmission the results remained statistically significant, 100% vs 25%, p<0.01 at 28 weeks and 85.7% vs 23.5%, p<0.01 at 32 weeks.

Women in the control group were more likely to have initiated ART before they became pregnant than the cases, 45% vs

16%, p=0.02. Among the 49 mothers initiating ART in pregnancy, viral load decrease was slower among cases vs controls despite similar timing of initiation, 29.5 weeks (IQR 23 to 31.5) in cases vs 30 weeks (IQR 24-32) in controls.

The investigators wrote: "Insufficient control of viral load (>1000 copies/mL) at 28 to 32 gestational weeks is a risk factor of residual HIV-1 MTCT even in mothers under ART with a controlled viral load near delivery. This concerns intra-partum as well as in utero transmission."

C O M M E N T

This study underscores the importance of controlling viral load in the third trimester and not only at delivery.

Ref: Tubiana R et al. Delayed control of maternal viral load during pregnancy is associated with higher risk of MTCT despite viral loads of <500

Copies/mL at delivery: A case/control study in the ANRS French Perinatal Cohort CO1/10/11. 16th CROI, Montreal, 2009. Abstract 929.

http://www.retroconference.org/2009/Abstracts/35500.htm

Risk factors for adverse pregnancy outcomes in Botswana

Polly Clayden, HIV i-Base

It is unclear whether the use of highly active antiretroviral treatment (HAART) in pregnancy is associated with adverse outcomes and data from resource-limited settings are particularly lacking.

A poster authored by Jennifer Chen, Roger Shapiro**,** and co-workers from Botswana and the USA showed results from a prospective review of obstetrical records of women who delivered at 20 weeks or greater in four facilities in Botswana between October 19, 2007 and June 30, 2008.

This study particularly evaluated stillbirths, preterm delivery (<37 weeks gestation) (PTD), low birth weight (<2500g) (LBW), small for gestational age (SGA) and neonatal death.

The investigators found 5676 recorded birth outcomes, of which 5327 (94%) women had a documented HIV test**.** Among those with an HIV test, 1629 (30.6%) had a positive result.

The investigators observed high overall rates of: still birth, 2.7% and 3.6%; PTD, 20.6% and 27.3%; LBW, 13.5% and 20.4%; SGA, 19.4% and 23.8% and neonatal death, 1.9% and 2.7% in HIV negative and positive women respectively.

Of the HIV positive group, 146 women received no antiretrovirals (ARV); 471 received AZT; 112 initiated HAART and 127 continued HAART from prior to the current pregnancy. Median CD4 counts were 283 cells/mm3 for those receiving no ARV and 417 cells/mm3, 266 cells/mm3 and 378 cells/mm3 for women who initiated AZT, initiated HAART, and continued HAART from prior to the current pregnancy respectively.

The majority of women initiated on HAART or AZT did so at 28 weeks gestation, so the investigators noted that they were unable to capture early pregnancy outcomes comparing these groups.

CD4 cell count was lower among women who received HAART (p<0.0001).

The investigators found in multivariate analysis, HAART was associated with SGA and possibly with stillbirths, and this association remained after adjustment for CD4 cell count (See table 1).

Table 1. Multivariate analyses of HIV positive women

Risk factor	**Stillbirth** AOR (95% CI)	**PTD** AOR (95% CI)	**SGA** AOR (95% CI)
HAART continued vs all others*	2.0 (0.9, 4.4)	1.2 (0.8, 1.9)	**1.8 (1.2, 2.8)**
HAART initiated vs AZT initiated by 30 weeks	3.7 (0.9, 15.6)	1.2 (0.6, 2.7)	**2.8 (1.4, 5.7)**
HAART continued vs HAART initiated**	--	--	0.7 (0.4, 1.2)

*All others includes HIV-positive women on no ARV intervention and those who later initiated ARVs.

**Multivariate analyses that compared women who continued HAART with those who initiated HAART were not performed for the outcomes stillbirth and preterm delivery, since women who continued HAART had more opportunities for events in pregnancy.

The investigators also found anaemia to be associated with PTD (p=0.0001) in HIV positive women, but anaemia was not associated with HAART use. However, they reported hypertensive complication at delivery was more common among women receiving HAART from prior to the current pregnancy (p=0.02) and was a risk factor for stillbirth, OR 7.2 (95% CI 3.8, 13.7), PTD, OR 1.7 (95%CI 1.3,2.4) and SGA, OR 2.1 (95% CI 1.4, 3.0). They suggest that this may be a potential explanation for some associations between HAART and adverse outcomes.

They wrote, “High risk obstetrical and neonatal care need to be prioritised in Botswana to address the large number of HIV-infected pregnant women with increasing access to HAART for treatment and PMTCT.”

C O M M E N T

These data add to the accumulating evidence that HAART in pregnancy may be associated with adverse outcomes and re-emphasise the importance of Phase 4 studies. Importantly they come from the region of the world where ARVs will be most widely prescribed in pregnancy. Understanding the mechanisms and determining whether these events are substance-specific or part of the spectrum of immune reconstitution will help policy makers and healthcare workers to make decisions about therapy.

Botswana is planning a pilot of universal HAART for 50,000 HIV-positive pregnant women, which is expected to generate important large-scale outcome data.

Ref: Chen J et al. A et al. Risk Factors for Adverse Pregnancy Outcomes among HIV-infected Women in Gaborone, Botswana. 16th CROI, Montreal, 2009. Abstract 949.
http://www.retroconference.org/2009/Abstracts/34104.htm

Premature delivery and mother-to-child HIV transmission: a risk/benefit analysis among women receiving HAART

Polly Clayden HIV i-Base

Claire Townsend and co-workers from the Institute of Child Health performed a risk benefit analysis looking at transmission and prematurity among HIV-positive pregnant women receiving HAART, using Monte Carlo modelling. The analysis was based on singleton births, from 1990 to 2007, women reported to the National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland.

The investigators used logistic regression models to estimate the association between HAART and both prematurity and mother-to-child transmission (MTCT), adjusting for relevant covariates. They used Monte Carlo simulation methods to estimate the incremental risks (prematurity <37 and <32 weeks) and benefits (reduction in MTCT) compared to AZT monotherapy. They obtained confidence intervals by taking the 2.5% and 97.5% quantiles of the simulated results.

They found that HAART was associated with a 1.5- and 2-fold increase in premature delivery at <37 weeks, (adjusted odds ratio AOR 1.47, 95% CI 1.07-2.02) and <32 weeks (AOR 2.06, 95% CI 0.9 to 3.88), respectively, after adjusting for injecting drug use, HIV symptoms, and CD4 count.

HAART was associated with a 7-fold (87%) decrease in MTCT (AOR 0.13, 95% CI 0.06 to 0.27, n = 5267), compared with early monotherapy (i.e. before 1998, when it was widely used), adjusting for mode of delivery, sex, and gestational age.

In the model the investigators used a scenario of exclusive monotherapy as baseline, with a prematurity rate of 10.3% (107/1037) (1.4%, 15/1037, <32 weeks) and an MTCT rate of 7.0% (12/172). Using Monte Carlo simulation, the investigators estimated an incremental risk-benefit ratio associated with exclusive HAART of 0.68 (95%CI 0.01 to 2.22) premature infants (0.23 at <32 weeks, 95%CI -0.01 to 0.94) for each infection prevented. In other words, preventing HIV in 10 infants by treating women with HAART would result in approximately 7 additional premature births, including 2 at <32 weeks.

The investigators concluded that although prematurity is associated with significant morbidity, long-term complications generally only occur in very premature infants, although there are serious consequences for all HIV-positive children. Therefore they considered HAART superior to monotherapy in these two scenarios.

They noted however that given the risks, in a selected group of healthier women, AZT monotherapy (and elective caesarean) - as in the BHIVA guidelines - remains a reasonable option. They added that the acceptable risk/benefit ratio is likely to vary between populations, depending on available resources and baseline prematurity rates.

C O M M E N T

This risk benefit analysis of HAART use in pregnancy is very useful

Although based on data from the UK and Ireland, it would be very interesting to see a similar risk benefit analysis applied to settings where interventions for premature babies are uncommon.

Ref: Townsend C et al. Premature Delivery and Mother-to-Child HIV Transmission: Risk: Benefit Analysis of HAART in Pregnancy. 16th CROI, Montreal, 2009. Abstract 927.
http://www.retroconference.org/2009/Abstracts/34802.htm

PEPI-Malawi

Polly Clayden, HIV i-Base

Taha Taha presented data from the PEPI (Post Exposure Prophlaxis of Infants) trial, conducted in Malawi, evaluating the effect of maternal HAART on postnatal transmission following cessation of extended infant antiretroviral prophylaxis. [1]

In the PEPI trial, all mothers received single dose nevirapine (NVP) in labour and uninfected infants were randomised to receive either: one week AZT (control arm); control plus daily NVP to infants for 14 weeks, or control plus daily NVP and

AZT to infants for 14 weeks. (These findings were presented at CROI last year and reported in HTB). [2, 3]

The trial demonstrated that extended infant prophylaxis from birth to 14 weeks reduced breast-feeding transmission by >65% during the time of prophylaxis. However, this effect diminished over time.

The investigators then examined the association between maternal HAART use and postnatal transmission after cessation of infant prophylaxis. Dr Taha noted that when PEPI began in 2004, HAART was not available in Malawi but while the trial was being conducted it became available in 2006 through the government programme.

Eligible women (with clinical indication and/or CD4 >250 cells/mm3) were referred to the antiretroviral treatment clinic. Dr Taha reported that this was not without logistical problems and some women did not receive HAART due to clinic waiting time; missed visits; delays with drug availability; partner consent and refusals. Overall coverage was limited, with only 13% women receiving HAART during follow up and >80% of those initiated it >14 weeks post partum.

The investigators defined three groups of women for evaluation: eligible women receiving HAART; eligible women untreated and ineligible women. Infant infection rates were calculated using Kaplan-Meir estimates and person time contributed by infants stratified by maternal HAART category. Hazard ratios were calculated adjusting for infant prophylaxis arm.

A total of 2318 infants uninfected at 14 weeks were included (representing 2750 person years of follow up). The majority of infants, 73% (1694), had mothers with high CD4 count for the duration of follow up; the remainder had mothers with low CD4 count. Of this group, 5.6% (133) had high CD4 count early, which declined to <250 cells/mm3 during follow up and 21% (491) had low CD4 throughout follow up. 310 women received HAART at sometime post partum: 45% (279/624) with low CD4 and 2% (31/1694) with clinical indication.

130 (5.6%) infants became infected during follow up. Of these, 5 infants had mothers receiving HAART (279 person years of follow up); 53 had eligible but untreated mothers (502 person years of follow up) and 72 infants had ineligible mothers (1969 person years of follow up).

The cumulative HIV infections among infants, uninfected at 14 weeks, at 6 months were 1.3% (95% CI, 0.7-2.5%), 0.9% (95% CI, 0.4-1.9%) and 1.8% (95% CI,1.1-3.1%) in the control (n=722), extended NVP (n=804) and extended NVP plus AZT (n=792) arms respectively. This increased by approximately 1-2% every 3 months, rising to 6.9% (95% CI, 5.0-9.4%), 8.2% (95% CI, 6.1-11.1%) and 7.9% (95% CI, 5.9-10.4%) cumulative infections at 24 weeks in the in the control, extended NVP and extended NVP plus AZT arms respectively. At no time point during follow up did the difference in study arms reach statistical significance.

When the investigators looked at the association between HIV transmission and maternal HAART use they found that HAART use in eligible women was associated with a significant transmission reduction of 82% compared to untreated women. Additionally being ineligible for HAART (73% of mothers) was associated with a 65% reduction in transmission. (See Table 1).

Table 1. Post natal HIV transmission (between 14 weeks and 24 months) and association with maternal HAART use

	Rate /100 person yrs	Rate ratio	Adjusted rate ratio*	95% CI
HAART eligible untreated	10.6 (7.9-13.8)	1.0	1.0	-
HAART eligible treated	1.8 (0.6-4.2)	0.18	0.18	0.07-0.44
HAART ineligible	3.7 (2.9-4.6)	0.35	0.35	0.25-0.5

*Adjusted for infant prophylaxis study arm

The investigators concluded that an effective strategy for late presenting mothers in order to prolong safer breastfeeding would be:

- Starting extended infant prophylaxis at birth
- Rapid identification of women with low CD4 counts and fast initiation of HAART
- Continuing infant prophylaxis for women ineligible for HAART.

C O M M E N T

The limited coverage among women referred for HAART in this study is notable. Jeff Stringer provided an excellent overview of prevention of breast-feeding transmission in the Wednesday plenary at this conference. [4]

References

1. Taha T et al. Effect of maternal HAART on postnatal HIV-1 transmission after cessation of extended Infant Antiretroviral Prophylaxis. 16th CROI, Montreal, 2009. Abstract 92.
2. Taha T et al. Extended infant post-exposure prophylaxis with antiretroviral drugs significantly reduces postnatal HIV transmission: The PEPI-Malawi Study. 16th CROI, Montreal, 2009. Oral abstract 42LB

3. http://www.i-base.info/htb/v9/htb9-3-4/Infant.html
4. http://www.retroconference.org/2009/data/files/webcast.htm

Effect of breast feeding vs formula feeding on maternal health

Polly Clayden, HIV i-Base

Shahin Lockman presented findings from a prospective substudy from the Mashi PMTCT study. In this analysis, the investigators looked at maternal health outcomes by randomised infant feeding strategy.

Mothers were followed for up to five years post partum and received: clinical evaluation, CD4 at enrolment, delivery and then every 3-6 months; viral load at enrolment, delivery and the 6,12 and 24 months post partum and serum was taken 6 moths post partum from a random sample of 131 women (65 breast feeding/66 formula feeding) and tested for B12, vitamins A and E, selenium, albumin and hsCRP.

The primary endpoint was time to maternal death, AIDS or CD4 decline to <200cells/mm3. This was an intent-to-treat analysis using data from March 2001 to September 2007.

The investigators followed 1200 women for a median of 54 months. Baseline characteristics were similar in both arms: median CD4 was 366 and median viral load was 4.4 log10. In the formula feeding arm (n=602), 93% women exclusively formula fed. In the breastfeeding arm 95% initiated breastfeeding, only 18% exclusively breastfed for the full 5 months.

Overall, 372 (31.0%) of women reached an endpoint: 204/598 (34.1%) women in the breastfeeding arm and 168/602 (27.9%) in the formula feeding arm, p=0.08. Of the women experiencing an endpoint 26% vs 21% experienced CD4 decline; 6% vs 2% AIDS and 3% vs 3% death in the breastfeeding and formula feeding arms respectively.

The investigators found that, in multivariate analysis, formula feeding was not a predictor for the composite endpoint (adjusted hazard ratio, AHR 0.82, 95% CI, 0.67-1.01, p=0.07).

Factors associated with reaching an endpoint included baseline CD4 </=350 (AHR 0.54, 95% CI 0.43-0.68, p<0.01), viral load >/= median (AHR 1.42, 95% CI 1.14-1.77, p<0.01) and any education (AHR 0.59, 95% CI, 0.36-0.98, p=0.04).

They reported a trend towards faster progression to an endpoint among women in the breastfeeding vs formula feeding arm, which appeared to emerge more than 2 years after the end of the feeding strategy.

In the subgroup tested for micronutrients there was no difference in micronutrients or albumin between the two arms. Median hsCRP levels were higher in the women in the breastfeeding than the formula feeding arm, 2.28 vs 1.05 mg/L, p<0.01.

Reference: Lockman S et al. The Effect of Breast Feeding vs Formula Feeding on Maternal HIV Disease Progression, Mortality, and Micronutrient Levels in a 1200-Person Randomised Trial, Botswana. 16th CROI, Montreal, 2009. Abstract 176.
http://www.retroconference.org/2009/Abstracts/34385.htm

CROI: PAEDIATRICS

Children on HAART do extremely well at South African clinic

Nathan Geffen, TAC

Dr Tammy Meyers presented data from a large cohort of children on HAART at Harriet Shezi Children's Clinic in Chris Hani Baragwanath Hospital, Soweto, South Africa. [1]

Of the 2,102 children who started treatment between April 2004 and March 2008), 1,734 (82%) are still alive and in the programme. Most of these children started with severely compromised immune systems. Based on earlier studies of untreated children at this stage of HIV disease [2, 3], nearly all would have died had they not been placed on HAART. By the end of the study, half the children had been on HAART for at least 17 months.

Kaplan Meier analysis showed that more than 90% of the cohort suppressed viral load to <400 copies/mL after 18 months on the programme. On average, CD4 percentage rose from 11% to over 25%. The children showed remarkable improvements in both weight and height improvement.

Most of the 132 deaths (6% of the cohort) occurred within the first 90 days of treatment, relating to late treatment. Meyers stressed that infants should now be treated on diagnosis, based on the findings of the CHER study, published last year, which showed that treating infants treated immediately upon diagnosis (as opposed to deferring treatment until their CD4 percentage met the current SA guidelines for initiating treatment) had much lower mortality. [4]

The factors at baseline that predicted death included being severely underweight, having a high viral load, being on TB

treatment and younger age. But even among some of these categories, children did well. For example, 28% of children were on TB treatment, a much greater percentage than the number of deaths.

Both clinical trials and cohorts of children have previously been published showing excellent results on HAART. For example, a widely publicised successful cohort on 94 Haitian children was reported in 2005. [5]

The contribution of the Harriet Shezi study is that this is a large African cohort in a resource-limited setting.

From over 3,550 children in the clinic database, 369 were excluded because they were in the clinic before the start of the cohort period. Another 389 were excluded because they had no follow-up. This left 2,795, of whom 2,216 were initiated on HAART. 91 were excluded from the study because they had no further visits after initiation. 23 were excluded because they were over 15. Of the remaining 2,102 included in the analysis, 1,734 were alive and active at study end. 132 died. 104 transferred and 132 were lost to follow up.

Interestingly, of the 579 children who did not start HAART (presumably because they were ineligible according to SA guidelines), 264 are alive and active in the programme. 78 died (double the proportion in the treatment cohort). 189 were lost to follow up (more absolutely than the treatment cohort) and 67 transferred.

The cohort was roughly half boys and half girls. Median viral load was over 100,000 [IQR log viral load: 4.6-5.8 copies/mL]. Median CD4% was 11.5% [IQR: 6.9-16.2%]. Weight and height for age z-score median was 2.12 [IQR: -3.3 to 1.14] and -2.6 [IQR: -3.6 to -1.7]. Median age was 4.3 years.

The median follow-up time on HAART was 17 months [IQR 6-29]. The mortality rate was nearly 15 per 100 child years follow-up (CY) within the first 90 days and then about 2/100 CY. The mortality rate was markedly higher in children under 18 months old: over 30/100C within the first 90 days and 5/100CY after that. Based on a graph reading, the median CD4 rose to between 25 and 30%.

An important conclusion by the authors is that a high percentage of children starting HAART are co-treated for TB, warranting investigation of drug interactions.

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CROI: DRUG INTERACTIONS

PK and drug interaction studies at CROI

HIV-druginteractions.org

The following selected summaries have been edited from a full report from CROI from www.HIV-druginteractions.org.

- New pharmacoenhancers: GS-9350 and SPI-452
- Interactions with raltegravir: with twice-daily atazanavir and standard dose lamotrigine
- Effect of tenofovir on abacavir phosphorylation
- Nevirapine: fluconazole and TB treatment
- PI Interactions: reduced lopinavir levels in children using rifampicin; potential 50mg ritonavir boosting; reduced atazanavir levels in pregnancy
- Other interaction studies

New boosting alternatives to ritonavir: GS-9350 and SPI-452

GS-9350 is a potent CYP3A inhibitor currently in development by Gilead Sciences.

This oral presentation described the safety, tolerability and pharmacokinetics of GS-9350 and compared its effect on midazolam with that of ritonavir. [1]

The two key goals in the development programme were i) to maintain the potent mechanism based inhibition that ritonavir has on CYP3A and ii) to remove anti-HIV activity from the booster. In the laboratory screen there was greater specificity for inhibition of CYP3A versus some other CYP enzymes than ritonavir. Also there was less induction potential through activation of nuclear receptors than ritonavir and reduced potential for lipid abnormalities as assessed by in vitro adipocyte function tests.

Importantly the physiochemical properties of the molecule allow formulation as a solid dosage form. In the initial clinical studies GS-9350 was generally well tolerated and there was no evidence of PR or QTc prolongation. GS-9350 demonstrated non-linear pharmacokinetics and doses of 100 or 200 mg exhibited a similar inhibition effect on midazolam apparent clearance as that of ritonavir 100 mg (92%, 95% and 95%, respectively).

Based on these data a "quad" tablet containing tenofovir + emtricitabine + elvitegravir + GS-9350 will go forward to further study.

Sequoia Pharmaceuticals are developing SPI-452, a potent and selective inhibitor of CYP3A that also lacks antiviral activity. [2]

Its tolerability, pharmacokinetics and ability to booster darunavir and atazanavir were evaluated in healthy volunteers. When dosed up to 200 mg once daily for 15 days, SPI-452 was well tolerated and safe, with no serious adverse events. There were no significant changes in triglycerides or LDL cholesterol. Trough concentrations of darunavir were increased by 29-fold and those of atazanavir increased by 13-fold.

References

1. Mathias A, et al. GS-9350: A pharmaco-enhancer without anti-HIV activity. 16th CROI, Montreal, 2009. Oral abstract 40. http://www.retroconference.org/2009/Abstracts/34852.htm
2. Gulnik S, et al. Preclinical and early clinical evaluation of SPI-452, a new pharmacokinetic enhancer. 16th CROI Montreal, 2009. Oral abstract 41.
http://www.retroconference.org/2009/Abstracts/36253.htm

Interactions with raltegravir: with twice-daily atazanavir and standard dose lamotrigine

The pharmacokinetics of atazanavir and raltegravir were investigated in HIV-negative subjects receiving **twice daily unboosted** atazanavir (300 mg twice-daily) and raltegravir (400 mg twice daily). [1]

Coadministration decreased atazanavir AUC (17%), Cmax (11%) and Cmin (29%). Atazanavir Cmin was 817 ng/ml (GM, range 250-1550 ng/ml), which is well the above the 10-fold protein binding adjusted EC90 for atazanavir against wild type HIV, and was moderately lower than historical values obtained with atazanavir/ritonavir. When given with atazanavir, the AUC, Cmax and Cmin of raltegravir increased by 54%, 39% and 48%, respectively. Mean QRS and PR interval increases were observed and require further investigation.

A second study investigated the pharmacokinetics of lamotrigine (100 mg single dose) when given alone or with raltegravir (400 mg twice daily) to 24 HIV-negative subjects. [2]

Coadministration had no significant effect on lamotrigine AUC (1% decrease) or Cmax (6% decrease). The ratio of lamotrigine glucuronide to lamotrigine was similar when taken alone (0.35) or with raltegravir (0.36). These results suggest that raltegravir is not expected to alter the metabolism of drug metabolised by UGT1A4 or UGT2B7 (e.g. valproic acid, diclofenac, carvediol).

C O M M E N T

Combining raltegravir with atazanavir is one of several potential nucleoside-sparing combinations but is complicated by a two-way drug interaction (atazanavir levels are reduced while raltegravir levels increase). This study suggests that twice-daily atazanavir may overcome these problems without using ritonavir and matching the BID dosing required by raltegravir. However, current pricing of this option is likely to limit practical use, even if future clinical studies show good efficacy and tolerability.

References

1. Zhu L, et al. Pharmacokinetics and safety of twice daily atazanavir and raltegravir in healthy subjects. 16th CROI, Montreal, 2009. Abstract 696.
http://www.retroconference.org/2009/Abstracts/33949.htm

2. Van Luin M, et al. Raltegravir has no influence on UGT1A4/2B7 when using lamotrigine as a phenotypic probe. 16th CROI, Montreal, 2009. Abstract 693.
http://www.retroconference.org/2009/Abstracts/34609.htm

Effect of tenofovir on abacavir phosphorylation

Intracellular concentrations of the active phosphorylated metabolites of abavavir (carbovir triphosphate) and tenofovir (tenofovir disphosphate) were determined in HIV-positive, treatment-naïve subjects following administration of abacavir (600 mg once daily) and tenofovir (300 mg once daily) alone and in combination.

The addition of tenofovir had no effect on carbovir triphosphate AUC (1694 vs 1895 fmol.h/10^6 cells, alone vs combination), but there was a trend towards an increase in tenofovir diphosphate AUC on addition of abacavir, though this was not statistically significant (1209 vs 2700 fmol.h/10^6cells, alone vs combination, p=0.08).

Interestingly, viral decay during tenofovir plus abacavir dual therapy was 0.04 $\log_{10}$/day faster than during tenofovir monotherapy.

C O M M E N T

This interesting study still doesn't help shed light on why triple-nuke combinations including abacavir and tenofovir disastrously underperformed clinically.

Ref: Goicoechea M et al. Viral dynamics and pharmacokinetics in vivo of tenofovir disoproxil fumarate and abacavir: evidence of a non-additive antiviral effect. 16th CROI, Montreal, 2009. Abstract 703.
http://www.retroconference.org/2009/Abstracts/33853.htm

Nevirapine: fluconazole and TB treatment

Pharmacokinetics of nevirapine (200 mg twice daily) and fluconazole (200 mg three times weekly) were determined in 27 HIV+ patients and compared to data from 22 HIV+ subjects receiving nevirapine (200 mg twice daily) and placebo. [1]

Fluconazole increased nevirapine AUC by 33 % (from 34297 ng.h/ml to 45685 ng.h/ml); increases were also observed in median Cmax (5028 vs 6354 ng/ml) and Cmin (3709 vs 5116 ng/ml). Despite the increase in nevirapine exposure, there was no evidence of increased hepatotoxicity.

Nevirapine trough concentrations were determined in 20 Ugandan children (age 1.2-11.3 years), seven of whom were receiving concomitant anti-TB therapy which included rifampicin. [2]

Median concentrations in the non-rifampicin group were 4204 ng/ml (range 834 to 15976 ng/ml). Concentrations in the rifampicin group were lower (2920 ng/ml, range 1668 to 9978 ng/ml), with 57% of the children in this group having subtherapeutic concentrations.

References:

1. Wakeham K, et al. Coadministration of fluconazole increases nevirapine concentrations in HIV-infected Ugandans. 16th CROI, Montreal, 2009. Abstract 703. Abstract 700.
http://www.retroconference.org/2009/Abstracts/34543.htm

2. Barlow-Mosha L, et al. Nevirapine concentrations in HIV-infected Ugandan children on adult fixed-dose combination tablet ART, with and without rifampicin-based treatment for active M. tuberculosis infection. 16th CROI, Montreal, 2009. Abstract 909.
http://www.retroconference.org/2009/Abstracts/35604.htm

PI Interactions: reduced lopinavir levels in children using rifampicin; potential 50mg ritonavir boosting; reduced atazanavir levels in pregnancy

Double-dose lopinavir/r insufficient for young children using rifampicin

The effect of doubling the lopinavir/ritonavir dose when given with rifampicin was studied in young children (aged ~0.5-2 years). [1]

Lopinavir/ritonavir was dosed according to body surface area and was administered twice daily at 460/115 mg/m^2 for children receiving rifampicin (n=15) and 230/57.5 mg/m^2 for the control group (n=24). Despite the increase in dose, lopinavir AUC, Cmax and Cmin were significantly lower in the rifampicin group (22.29 vs 48.33 mg.h/L, 4.45 vs 7.94 mg/L, 0.63 vs 4.25 mg/L, respectively). 60% of the rifampicin group had sub-therapeutic trough concentrations (<1 mg/L).

Doubling the dose did not overcome the effect of rifampicin and should not be used in young children.

There is an urgent need to establish safe, effective and feasible co-treatment for young children with HIV associated TB.

Low dose (50mg) ritonavir may be sufficient to boost saquinavir

This study investigated the possibility of using a lower dose of ritonavir (50 mg) to boost saquinavir concentrations. [2]

Pharmacokinetics were determined in 18 Thai HIV-positive subjects who received saquinavir (1500 mg twice daily) with ritonavir (100 mg or 50 mg twice daily). Saquinavir pharmacokinetics showed no significant difference when boosted with 100 or 50 mg ritonavir (AUC 27.6 vs 31.0 mg/L.h; Cmax 3.9 vs 4.6 mg/L; Cmin 0.13 vs 0.16 mg/L; median values).

Ritonavir concentrations were significantly higher with the 100 mg dose than with the 50 mg dose.

The lower dose of ritonavir had to be administered as the solution – once an acceptable formulation is available, the lower 50 mg dose should be investigated in larger studies and with other protease inhibitors.

C O M M E N T

As this study was in Thai patients, weight may be a factor that needs consideration before this is looked at in other patient groups.

Atazanavir levels reduced with tenofovir in pregnancy

Atazanavir pharmacokinetics were determined in 27 pregnant women receiving atazanavir/ritonavir alone (300/100 mg once daily, n=14) or with tenofovir (300 mg once daily, n=13). [3]

Median atazanavir AUC and trough concentrations during the third trimester were found to be lower in the presence of tenofovir (32.7 vs 37.5 μg.h/ml, 0.59 vs 0.72 μg/ml, respectively). Atazanavir exposure increased post partum, but was still lower in the presence of tenofovir (AUC 41.9 vs 57.9 μg.h/ml, Ctrough 0.95 vs 1.20 μg/ml). A dose increase of atazanavir/ritonavir to 400/100 mg once daily may be necessary to ensure adequate atazanavir exposure in pregnant women, especially if treatment-experienced or receiving tenofovir.

References

1. McIlleron H, et al. Double dose lopinavir/ritonavir provided insufficient lopinavir exposure in children receiving rifampicin based anti-TB treatment. 16th CROI, Montreal, 2009. Oral abstract 98.
   http://www.retroconference.org/2009/Abstracts/34615.htm
2. Van Der Lugt J, et al. A 50 mg boosting dose of ritonavir generates adequate saquinavir plasma concentrations in Thai HIV-infected patients.16th CROI, Montreal, 2009. Abstract 697.
   http://www.retroconference.org/2009/Abstracts/34488.htm
3. Mirochnick M, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy.16th CROI, Montreal, 2009. Abstract 941.
   http://www.retroconference.org/2009/Abstracts/34312.htm

Other interaction studies

Effect of substance abuse on ART pharmacokinetics

This study looked at a group of 275 patients, 47% of whom were active users of at least one substance (heroin 2%; cocaine 7%; marijuana 13%; tobacco 43%; alcohol 22%; prescription opioids 14%). It was found that a significantly higher proportion of substance users had antiretroviral trough concentrations below the therapeutic range (23% vs 9%, p=0.048). The proportion of patients with an unfavourable treatment outcome (HIV RNA >75 copies/ml) was significantly higher in the substance user group than in the non-user group (40% vs 28%, p=0.044). However, when adjusted for race, substance abuse was no longer associated with virological response.

Ref: Ma Q, et al. Comparison of ART pharmacokinetics and clinical monitoring parameters in HIV-infected patients with and without substance abuse. 16th CROI, Montreal, 2009. Abstract 698.
http://www.retroconference.org/2009/Abstracts/35802.htm

Identification of drug interactions in clinical practice

The AIDS Drug Assistance Programme (ADAP) has been created to help states specifically provide prescription drug access to HIV-infected people ineligible for Medicaid and Medicare. The objective of this study was to assure the uninterrupted access to safe combinations of antiretroviral medications while attempting to determine the prevalence and prospectively restrict any contraindicated antiretroviral drug combination in New York State ADAP. Potential drug interactions were identified from the programme records dispensed over a 2-year period using Micromedex, www.hiv-druginteractions.org, and treatment guidelines.

Targeted dissemination of antiretroviral drug-drug interaction safety concerns to prescribers curtailed such practice by 87% (from 88 to 20 occurrences) with subsequent contraindicated drug-drug interactions denied at pharmacy. However, despite time and education, claims for contraindicated drug interactions still continue. Hard edits and clinical education are essential.

Ref: Rivera C, et al. The introduction of ART drug-drug interventions into the New York State AIDS Drug Assistance Program: the interaction of clinical pharmacology and standard of care. 16th CROI, Montreal, 2009. Abstract 701.
http://www.retroconference.org/2009/Abstracts/34581.htm

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
d4T capsules 30/40 mg	Matrix Laboratories	5 January 2009
Tenofovir DF 300mg tablets	Aurobindo, India	18 February 2009
Fixed dose combination d4T/3TC/nevirapine 30mg/150mg/200mg & 40mg/150mg/200mg	Aspen Pharmacare, South Africa.	27 February 2009
Lopinavir/ritonavir tablets, 200/50mg	Matrix, India	10 March 2009
3TC,150 mg tablets	Alkem Labs, India	16 March 2009
d4T/3TC FDC tablets, 30/150mg & 40/150mg	Aspen Pharmacare, South Africa.	18 March 2009
Tenofovir/FTC (emtricitabine) tablets, 300/200mg	Matrix, India	30 March 2009
abacavir/3TC tablets, 600/300 mg	Matrix, India	30 March 2009
nevirapine tablets, 200 mg	MacLeods, India	31 March 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_No=3D021360&TABLE1=3DOB_Rx

COMMENT

This brings the total of FDA approved generic drugs and formulations to 91 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

DRUG INTERACTIONS

New interaction reports from hiv-druginteractions.org

A selection of the latest news and reviews from the Liverpool University pharmacology team are included below.

http: http://www.hiv-druginteractions.org

Effects of omeprazole on plasma levels of raltegravir

The safety, tolerability and pharmacokinetics of raltegravir alone and in combination with omeprazole were studied in 14 healthy volunteers. Subjects received a single dose of raltegravir (400 mg) alone or 2 h after omeprazole (20 mg once daily for 4 days).

Coadministration increased raltegravir AUC by 3.12-fold, Cmax by 4.15-fold and Cmin by 1.46-fold. As the increase in Cmin was relatively minor and there was no significant change in half-life, the increase in exposure is likely due to an increase in gastric pH increasing the solubility and, absorption and bioavailability of raltegravir rather than an effect on the metabolism or clearance of raltegravir.

Although omeprazole increased raltegravir exposure by 3-4-fold in healthy subjects, exploratory pharmacokinetic data in HIV+ subjects demonstrated a reduced effect. Evaluation of the safety profile in HIV+ patients receiving acid reducing agents has not identified any areas of concern and therefore the authors indicate that the data support the use of raltegravir in patients receiving acid reducing agents with no dosage adjustment. Further investigation is needed to determine i) the pharmacokinetics of raltegravir with acid reducing agents in HIV+ patients and ii) the PK-PD relationship of raltegravir.

Ref: Iwamoto M et al. Effects of omeprazole on plasma levels of raltegravir. Clin Infect Dis, 2009, 48(4): 489-492.
http://www.ncbi.nlm.nih.gov/pubmed/19143531

Interaction study of ketoconazole and ritonavir-boosted saquinavir

This study investigated the steady state pharmacokinetics of saquinavir, ritonavir and ketoconazole in healthy subjects receiving saquinavir/ritonavir (1000/100 mg twice daily) and ketoconazole (200 mg once daily) alone and in combination.

Coadministration had no clinically significant effect on the AUC or Cmax of saquinavir (7% and 2% increases, respectively) or ritonavir (12% and 8% increases respectively). However, the AUC of ketoconazole increased by 2.68-fold and Cmax increased by1.45-fold. Ketoconazole half life increased from 4.3 h to 10.7 h and CL/F decreased by more than 50% (from 8.22 to 3.07 L/h).

In this study the increase in ketoconazole exposure with saquinavir/ritonavir was not associated with unacceptable safety or tolerability. No dose adjustment of saquinavir or ritonavir is required when administered with doses of ketoconazole of 200 mg/day or lower. Based on the hepatotoxicity liability of ketoconazole, high doses (>200 mg/day) are not recommended.

Ref: Kaeser B et al. Drug-drug interaction study of ketoconazole and ritonavir-boosted saquinavir. Antimicrob Agents Chemother, 2009, 53(2): 609-614.
http://www.ncbi.nlm.nih.gov/pubmed/19015329

Tipranavir/ritonavir interactions with clarithromycin, fluconazole and rifabutin

This paper reports on three interaction studies looking at the effects of tipranavir/ritonavir (500/200 mg twice daily) on clarithromycin (500 mg twice daily), fluconazole (200 mg loading dose, followed by 100 mg once daily) or rifabutin (150 mg single doses). To determine the effects of the coadministered drugs on tipranavir, pharmacokinetic values were compared to historical data. Findings for each of the studies are summarised below.

Clarithromycin Coadministration increased clarithromycin AUC and Cmin by 19% and 68%, respectively; Cmax decreased by 5%. AUC, Cmax and Cmin of 14-OH clarithromycin decreased by >95%. Tipranavir AUC and Cmax increased by 66% and 40% respectively; Cmin increased by 2-fold. Coadministration increases both tipranavir and clarithromycin exposure. For clarithromycin, this will not cause problems in patients with normal renal function, but patients using clarithromycin at doses higher than 500 mg twice daily should be carefully monitored for signs of toxicity. The almost complete inhibition of the formation of 14-OH- clarithromycin should be taken into account when treating pathogens susceptible to this pharmacologically active metabolite.

Fluconazole Coadministration had no significant effect on fluconazole AUC, Cmax and Cmin (decreases of 8%, 6% and 11%, respectively). Tipranavir AUC, Cmax and Cmin increased by 50%, 32% and 69%, respectively. No dosage adjustment of fluconazole is required. Fluconazole appeared to have a significant effect on steady-state tipranavir, but the clinical significance

of this increase in the exposure is not known. It has previously been shown that a 45.6% increase in tipranavir exposure does not result in increased toxicity; however, clinical monitoring of patients receiving this combination is advised.

Rifabutin Coadministration increased rifabutin AUC, Cmax and Cmin by 2.9-fold, 1.7-fold and 2.14-fold, respectively. The AUC, Cmax and Cmin of 25-O-desacetyl rifabutin increased by 20.7-fold, 3.2-fold and 7.83-fold, respectively. There was no change in tipranavir AUC or Cmax and Cmin increased by 16%.The small increase in the trough TPV concentration does not appear to be clinically relevant. As a result of CYP3A inhibition by ritonavir, changes of clinical importance in the pharmacokinetics of rifabutin and its active metabolite, 25-O-desacetyl- rifabutin, occurred. When coadministered rifabutin drug levels should be monitored by TDM and the dose should be adjusted accordingly. Patients should be closely monitored for rifabutin toxicity by clinical judgment and laboratory assessments.

Ref: La Porte CJL et al. Interaction studies of tipranavir-ritonavir with clarithromycin, fluconazole and rifabutin in healthy volunteers. Antimicrob Agents Chemother, 2009, 53(1): 162-173.
http://www.ncbi.nlm.nih.gov/pubmed/19015362

Possible interaction between cat's claw and protease inhibitors

This is a case report of a possible interaction between a boosted atazanavir and saquinavir regimen and Cat's Claw (Uncaria tomentosa). The patient (a 45 year old woman with cirrhosis associated with HCV infection) had atazanavir and saquinavir trough concentrations of 1.22 and 3.4 μg/ml respectively whilst taking Cat's Claw. After stopping Cat's Claw for 15 days, trough concentrations for atazanavir and saquinavir decreased to 0.3 and 0.64 μg/ml, respectively. There could be other reasons for the intra-individual variability, but it is worth considering the possibility of an interaction.

C O M M E N T

While there is no evidence of benefit from using the herbal supplement Cat's Claw, if it is metabolised by the liver, it could theoretically interact wide a wide range of medications including antiretrovirals, antifungals, oral contraceptives etc.

Ref: Lopez-Galera RM et al. Interaction between cat's claw and protease inhibitors atazanavir, ritonavir and saquinavir. Eur J Clin Pharmacol, 2008, 64: 1235-1236.
http://www.ncbi.nlm.nih.gov/pubmed/18712519?

Antiretroviral and statin drug-drug interactions

This is a useful concise review on a critical area for the healthcare professional treating HIV+ patients. Not only does HIV itself induce dyslipidemia, but some of the HAART medications also cause lipid abnormalities. Given the impact of HIV drugs on CYP enzymes and the fact that many statins are extensively metabolised by CYP enzymes, understanding the potential for drug-drug interactions is very important.

This review briefly covers HIV and HAART-related dyslipidemia, statin metabolism by CYP450, HAART effects on CYP450 and HAART and statin drug-drug interactions. It concludes with current recommendations.

Ref: Ray GM. Antiretroviral and statin drug-drug interactions. Cardiology in Review, 2009, 17(1): 44-47.
http://www.ncbi.nlm.nih.gov/pubmed/19092370

GUIDELINES

BHIVA guidelines for TB/HIV coinfection are online for comment

The 2009 draft of the proposed BHIVA guidelines on TB/ HIV co-infection are posted online and available for comment.

http://www.bhiva.org/cms1223707.asp

These guidelines have been drawn up to help doctors manage adults with TB/HIV co-infection. They have been extensively revised since the last edition in 2005; most sections have been amended and areas where there is a need for clinical trials or additional data have been highlighted.

The major changes/amendments include:

- A more detailed discussion of gamma interferon tests;
- An update of the drug interactions section and tables;
- An updated section on choice of NNRTI;
- A new section on isoniazid resistance and XDR;

- Guidance on the diagnosis of IRIS;
- New tables for management of adverse reactions.

The Guidelines Writing Group is grateful for all comments. The deadline for comments is Friday 1 May 2009.

US Guidelines on prevention and treatment of Opportunistic Infections updated

The following US guidelines have been updated and are available online:

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.

http://www.hivatis.org

Unfortunately, unlike the main US treatment guidelines, this updated document does not highlight in the text the changes from earlier documents.

However, the introduction states that major changes include:

- Greater emphasis on the importance of antiretroviral therapy for the prevention and treatment of OIs, especially those OIs for which no specific therapy exists;
- Information regarding the diagnosis and management of immune reconstitution inflammatory syndromes;
- Information regarding the use of interferon-gamma release assays for the diagnosis of latent TB infection;
- Updated information on drug interactions that affect the use of rifamycin drugs for prevention and treatment of TB;
- The addition of a section on hepatitis B virus infection; and
- The addition of malaria to the list of OIs that might be acquired during international travel.

TB COINFECTION

WHO global TB control report highlights that 25% of TB-related deaths occur in HIV-positive people

About one-quarter of tuberculosis-related deaths involve an HIV-positive person, twice as high as previous estimates, according to the Global Tuberculosis Control Report 2009, which the World Health Organization released on 24 March to coincide with World TB Day.

The report found a total of 9.3 million new TB cases in 2007, 1.4 million of which occurred in people living with HIV/AIDS. Kevin De Cock, HIV/AIDS director at WHO said that these new estimates do not reflect an increase HIV/TB coinfections or in TB deaths among HIV patients, but rather "better analyses, better data and better methodology". In addition, increased HIV testing among TB patients has revealed cases of HIV that previously went undetected. In previous reports, WHO used data on HIV/TB coinfection from 15 countries; however, the new report includes data from 64 countries, several of which are in sub-Saharan Africa.

According to the report, 55% of recorded TB cases occurred in Asia in 2007, while 31% occurred in Africa. India had the highest number of recorded cases at two million, followed by China with 1.3 million and Indonesia with 530,000.

There were about 1.3 million TB deaths among HIV-negative people and about 456,000 among HIV-positive people in 2007. TB was the primary cause of death among people living with HIV/AIDS in 2007 and HIV-positive people are about 20 times more likely to develop TB than HIV-negative people in countries with high HIV prevalence and are between 26 and 37 times more likely to develop TB in countries with lower HIV prevalence.

The report found a significant increase in the number of HIV tests that are administered to people with TB, particularly in Africa. About 4% of TB patients in Africa were tested for HIV in 2004, compared with 37% in 2007. In several countries, more than 75% of TB patients received an HIV test, according to the report. Although efforts to address HIV/TB coinfection have improved, such efforts are inadequate in many developing countries. De Cock noted that only one in seven HIV-positive people receive preventive treatment for TB. In addition, more than one-third of TB cases worldwide are undiagnosed, increasing the risk of transmission. The report recommended that HIV-positive people receive TB screenings and medications to reduce their risk of developing the disease.

The report also found an increase in drug-resistant strains of TB in recent years. According to the report, more than 500,000

people worldwide have been diagnosed with multi-drug resistant TB. Fewer than 1% of people with MDR-TB were receiving WHO-recommended treatment in 2007. In addition, at least one case of extensively drug-resistant TB has been reported in 55 countries and territories worldwide. XDR-TB is resistant to two of the most potent first-line treatments and at least two of the classes of second-line drugs. Mario Raviglione, director of WHO's STOP TB department, added that the actual prevalence of XDR-TB likely is higher because many developing countries do not conduct tests to determine the extent of drug-resistance in TB patients.

The report also documented concern over funding in the current economic downturn, noting that 94 countries that account for 93% of all TB cases worldwide have a funding shortfall of $1.5 billion to meet the targets in the Global Plan to Stop TB 2006-2015.

Wafaa El-Sadr, a professor of medicine and epidemiology at Columbia University said the report's findings "demonstrate that one cannot think of tackling or controlling the TB epidemic globally without thinking of how we're going to do it in HIV-infected populations".

Source: Edited from Kaiser Daily News. About 25% of TB deaths occur among HIV-positive people, WHO Global TB Control Report says. (25 March 2009)
http://www.kaisernetwork.org/daily_reports/rep_hiv.cfm#57660
The WHO report, together with supporting documents, is available online:
http://www.who.int/tb/publications/global_report/2009/en/index.html

BASIC SCIENCE

Recent basic science updates from Richard Jefferys excellent web log.

CD4 T-cell responses to commensal bacteria in the gut

Richard Jefferys, TAG

There has been a lot of attention given recently to the role of gut CD4 T cell depletion in HIV pathogenesis. Surprisingly, very little is known about which antigens are targeted by gut CD4 T cells; at least one study has reported evidence of memory CD4 T cell responses to candida albicans (the fungus that causes thrush) but an absence of the typical memory responses against opportunistic pathogens (also called "recall responses") found in the blood. [1]

More recently, gut HIV-specific CD4 T cell responses have been detected some elite controllers [2] and in HIV-infected individuals showing robust CD4 T cell recovery in the gut on antiretroviral therapy (this latter data was presented at CROI by Satya Dandekar. [3] Studies in mice have suggested that there are likely be CD4 T cell responses to commensal bacteria in the gut, but there is little research addressing this question in humans. In a new paper in press at Clinical Immunology, Rawleigh Howe and colleagues from Cara Wilson's group at the University of Colorado describe their initial efforts to fill this knowledge gap. [4]

Using flow cytometric techniques, the researchers were able to detect the presence of CD4 T cells making interferon gamma in response to stimulation with several gut commensal bacteria species (Enterobacter, E. coli, Enterococcus species) as well as to the pathogen, Salmonella typhimurium. CD4 T cells making IL-17 – Th17 cells – were also detected but at a much lower frequency. Bacteria-specific CD4 T cell responses could also be detected in the blood but at significantly lower levels; the difference in magnitude between gut and blood ranged from 8.5 to 19.5 fold. When responses to all four bacterial antigens were summed, the median frequency of interferon gamma-producing CD4 T cells was 0.24% in the gut compared to 0.02% in blood.

The researchers suggest that the CD4 T cell responses revealed in this study play a role in containing bacteria in the gut under normal conditions. Such a role would be consistent with recent studies indicating that T cell depletion can lead to systemic dissemination of gut bacteria (microbial translocation). Another implication of the data is that people with HIV infection may have altered CD4 T cell reactivity to commensal bacteria, and Cara Wilson's group is addressing this possibility in ongoing studies.

Source: TAG Basic Science Weblog. (23 Feb 2009)
http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2009/02/cd4-t-cell-responses-to-commensal-bacteria-in-the-gut.html

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4. Howe R et al. Evidence for dendritic cell-dependent CD4+ T helper-1 type responses to commensal bacteria in normal human intestinal lamina propria. Clinical Immunology. doi:10.1016/j.clim.2008.12.003. Article in press.

Accelerated aging of the immune system in HIV infection

Richard Jefferys, TAG

Over the years since AIDS was first recognised, a number of pathogenesis theories have posited that HIV infection causes an accelerated aging of the immune system. Some of the earliest, most hypothetical ideas along these lines suggested that the effects of HIV would be irreversible; thankfully, the success of antiretroviral therapies in restoring immune competence has since shown that this is not the case. Advances in the understanding of the immunological changes that accompany aging have recently allowed a more sophisticated and informed perspective on the parallels with HIV infection to be developed. At the forefront of this field of study is UCLA researcher Rita Effros, and the latest study from her group has just appeared online in the Journal of AIDS. [1]

Fundamental to understanding this research is the division of the main cellular players of the human adaptive immune system (CD4 and CD8 T cells and B cells) into two large pools: naïve cells and memory cells. Naïve cells are those that have yet to encounter a pathogen or other antigen that they recognise, while memory cells are typically the descendants of naïve cells that have done battle with a pathogen (or a faux or attenuated pathogen in the form of a vaccine) in the past. Crucially, maintenance of naïve T cells depends on the output of newly produced cells from the thymus; production is robust in childhood but dwindles after adolescence and becomes a relative trickle in old age. Every infection and vaccination that recruits naïve T cells into becoming memory T cells over a lifetime drains the naïve pool, and while the thymus can "top up" the pool relatively quickly when young, this cannot be accomplished later in life and the ratio of naïve to memory cells gradually shifts as we age. In HIV infection, this process is accelerated, and naïve T cell (and B cell) numbers decline as disease progresses. In parallel, the proportion of memory cells showing evidence of exhaustion and dysfunction increases. Although the extent of the dysfunction is less dramatic, this accumulation of exhausted memory T cells is also seen in aging.

One key marker of T cell dysfunction in the elderly is the loss of the co-stimulatory molecule CD28. In their new paper, Effos and colleagues use data from the MACS cohort to show that faster disease progression in HIV infection is associated with more rapid accumulation of CD28-negative CD8 T cells, in tandem with more rapid loss of naïve CD8 T cells. Loss of CD28 expression on CD4 cells was also significantly associated with disease progression.

Changes in naïve CD4 T cells were more subtle, as the relative proportion of naïve CD4 T cells to memory CD4 T cells in the peripheral blood did not decrease significantly as the absolute numbers of blood CD4 T cells declined. These findings are notably in line with the well-documented impact of age on the progression of HIV infection, because they suggest that older individuals are starting from a worse position immunologically (studies have consistently found that older individuals progress faster on average when compared to their younger counterparts).

In the discussion section of the paper, the authors state: "It has been suggested that the expansion of a few memory T-cell clones, directed at a restricted number of epitopes, fills up the 'immunological space.' Narrowing of the T-cell repertoire may subsequently impair the generation of new immune responses to infections and may also account for the close correlation between the high proportions of CD28-CD8+ T cells and reduced vaccine responses in the elderly. Therefore, despite a significant number of CD8 T cells observed during HIV-1 infection, the CD8+ T-cell compartment is mostly comprised of functionally defective CD28- T cells."

The extent to which these immunological perturbations can be corrected by antiretroviral therapy is still not fully clear, but thymic output of naïve T cells has emerged as a clear correlate of a good immunological response to treatment. [2]

Conversely, slow naïve T cell repletion is associated with poor CD4 T cell count increases and a persistently elevated risk of clinical illness. One consequence of these findings is that therapies that might have the potential to boost naïve T cell production are being studied as potential immune-based therapies in HIV infection. Effros and colleagues also note that strategies to restore function to senescent T cells are under investigation, and approaches to deplete dysfunctional cells (with the aim of allowing functional cells to expand and take their place) are also being considered.

For further background on this topic, a webcast of a talk given by Rita Effros at last year's CROI is online (under the Tuesday webcasts, it is the second presentation in the Symposium on Aging and AIDS). [3]

Source: TAG Basic Science Weblog. (20 Jan 2009)
http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2009/01/accelerated-aging-of-the-immune-system-in-hiv-infection.html

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Immune recovery on antiretroviral therapy

Richard Jefferys, TAG

A free access paper and accompanying commentary in Clinical Infectious Diseases address the issue of long-term immune recovery on antiretroviral therapy (ART). [1, 2]

The paper describes results from ACTG384, the largest and most detailed evaluation of the effects of ART on CD4 T cell counts and other immune parameters. The commentary by Elvin Geng and Steve Deeks provides an excellent overview of the findings.

ACTG 384 stratified participants using baseline CD4 count, and the most striking consequence of being below 50 cells/mm3 was the depletion of naïve CD4 T cells and the consequent skewing of the naïve-memory ratio. The strata used in the study were <50, 51–200, 201–350, 351–500, and >500 cells/mm3, and the median baseline CD4+ naive-memory cell ratio for individuals starting with a CD4 cell count <50 cells was 0.21 at baseline and increased to only 0.43 at week 144 – this was still lower than the median pre-treatment ratio for the higher CD4 strata.

The lower CD4 strata also had the poorest improvement in CD4/CD8 ratio, and as Geng & Deeks note in their commentary "These two trends—a low naive-memory cell ratio and a low CD4:CD8 ratio—have been seen both in those with untreated HIV infection and in the elderly (>75 years of age)." Conversely, individuals who started ART with CD4 counts >350 attained immune profiles that overlapped with HIV-negative individuals.

The ACTG 384 data complement the findings recently reported by Rita Effros and colleagues regarding the premature aging of the immune system in HIV infection. [3]

Geng & Deeks also offer some intriguing thoughts as to how the results may relate to the elevated risk of clinical disease that has been reported in individuals with a poor CD4 T cell recovery on ART: "We believe that the conclusions reached by Robbins et al. might provide a mechanistic explanation for why some patients who receive HAART remain at risk of disease. Naive T cells are critical in both mounting an effective adaptive immune response against novel antigens and maintaining normal T cell homeostasis. Those naive T cells that survive untreated HIV infection are at least partially dysfunctional and have impaired proliferative capacity. It has recently been shown that chronic inflammation contributes to failure of naive T cell homeostasis, either by causing too much proliferation or by causing failure of naive T cells to proliferate in response to either homeostatic signals (which leads to lack of robust peripheral CD4 gains) or to novel antigens (which leads to disease). Tying this together, it is possible to construct a testable model in which those patients who initiate HAART late in their disease course have residual inflammation, suboptimal CD4+ T cell gains, skewed immunophenotypic profiles, persistent T cell dysfunction, and increased risk of all-cause morbidity and mortality."

Among the studies cited in support of this model is the recent Christine Bourgeois paper suggesting that naïve T cell depletion can lead to microbial translocation, which in turn contributes to ongoing immune activation and naïve T cell depletion. [4]

However, the commentary also cautions that: "determining the causal association among these factors will be a challenge, given the complexity of the human immune system and the lack of therapeutic interventions." One important implication of the data is that the few therapies that might have the potential to increase naïve T cell levels (currently, IL-7 and human growth hormone derivatives) deserve urgent and careful evaluation in people with suboptimal immune recovery on ART, as there may be the potential for these approaches to offer significant clinical benefits.

Source: TAG Basic Science Weblog. (4 Feb 2009)
http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2009/02/immune-recovery-on-antiretroviral-therapy.html

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4. http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/07/naive-cd4-t-cel.html

Regulation gone awry? Elevated levels of regulatory T Cells linked to disease progression

Richard Jefferys, TAG

Over the past decade it has become accepted that some T cells play a role in dampening down immune responses. These cells are dubbed 'regulatory T cells' or 'Treg' for short. In lab studies, Treg have been shown to suppress the activation of other T cells, and there is considerable evidence that this regulatory function is also performed in vivo. One problem, however, is that there are no definitive markers for Tregs. Initially, expression of a molecule called CD25 was used to define Treg, but CD25 can also be upregulated by other activated T cells. More recently, a transcription factor, Foxp3, has emerged as a more specific marker for Treg. Although several studies have explored the role of Treg in HIV infection, results have been inconsistent and hard to interpret because approaches to define the cells have varied. A new study in the journal AIDS Research & Human Retroviruses uses the combination of CD25 and Foxp3 to explore whether Treg levels differ in individuals with varying rates of disease progression.

Weiwei Cao and colleagues from UCLA employed a case-control approach to compare twenty fast progressors from the Multicenter AIDS Cohort Study (MACS) to forty matched slow progressors and nine uninfected individuals. Fast progression was defined as an AIDS diagnosis within 4 years after enrolment into MACS, whereas slow progressors were categorized based on the absence for an AIDS diagnosis for at least 8 years after entry into the cohort. Treg constituted 4.6% of CD4 T cells in uninfected study participants and this proportion was only slightly increased to 5.6% in slow progressors. Among fast progressors, however, the proportion of Treg was significantly higher at 11.3%. Further analysis showed that Treg levels correlated with CD4 T cell activation; the proportion of CD4 T cells expressing the activation marker CD38 was 1.5% in uninfected individuals, 7.2% in slow progressors and 16.3% in fast progressors.

In the discussion section of the paper, Cao and colleagues suggest that these two phenomena may be linked, because other studies have shown that T cell activation can lead to the generation of Foxp3-expressing Treg from resting T cells that previously did not express the marker. Therefore it is possible that the persistently elevated levels of T cell activation in HIV infection leads to the observed accumulation of Tregs. Some researchers have suggested that immune activation in HIV infection is caused by a lack of Treg, but Cao and colleagues note that their data appears incompatible with this possibility. Rather, their data argues that Treg either have a negative effect – perhaps by interfering with HIV-specific immune responses, as some prior studies have posited – or alternatively the relative expansion of Tregs is just a by-product of immune activation which has no specific role in HIV disease progression.

Source: TAG Basic Science Weblog. (10 Mar 2009)
<http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2009/03/regulation-gone-awry-elevated-levels-of-regulatory-t-cells-linked-to-disease-progression.html>
Ref: Cao W et al. Regulatory T Cell Expansion and Immune Activation during Untreated HIV Type 1 Infection Are Associated with Disease Progression AIDS Research and Human Retroviruses. February 2009, 25(2): 183-191. doi:10.1089/aid.2008.0140. Free access to full text PDF.
http://www.liebertonline.com/doi/pdfplus/10.1089/aid.2008.0140

Viral resistance to a vaginal microbicide in macaques

Richard Jefferys, TAG

Several years ago it was shown that very high doses of an entry inhibitor-based microbicide protect macaques from infection with SHIV162-p3. [1] A paper in J Virology now raises some important caveats about this approach, including the first reported example of a microbicide selecting for drug-resistant virus. [2]

The microbicide in question is a CCR5 inhibitor called PSC-RANTES. The challenge virus used in the studies is called SHIV162-p3, a lab-created SIV/HIV hybrid in which an HIV envelope that uses CCR5 to gain entry into CD4 T cells is inserted into an SIV genome instead of the SIV envelope.

The new paper, authored by Dawn Dudley and colleagues from Case Western Reserve University and the Tulane Primate Research Center, is based on an analysis of macaques given lower doses of PSC-RANTES that were not protective against SHIV162-p3 infection. In most cases, viruses in these animals showed mutations that were deemed unrelated to PSC-RANTES because similar mutations were seen in controls that were challenged with the same virus in the absence of the microbicide. But the virus in one macaque contained two mutations, K315R in gp120 and N640D in gp41, which were very rare in the challenge virus stock (after infection, compared to their frequency in the challenge virus, these mutations were increased at least 25-fold and 75-fold). Importantly, PSC-RANTES failed to completely inhibit this mutant SHIV, even at high concentrations that inhibited the parent SHIV162-p3 and all other R5-using HIV isolates tested.

Dudley and colleagues acknowledge that this apparent example of resistance was only seen in 1/25 macaques studied, and there is an outlying possibility that the mutations represent a random adaptation of the virus to better replicate in macaque cells. However, they argue that the weight of evidence supports their conclusion that the mutations arose from drug selection

pressure, and that this possibility is particularly concerning given that SHIV162-p3 is a very homogenous virus stock from which the emergence of resistance would have been considered unlikely.

Discussing the implications for microbicides generally, they note that the positive results reported to date with entry inhibitor-based microbicides (PSC-RANTES, BMS-378806, CMPD167, and C52L) have all involved administering relatively high doses and the SHIV162-p3 challenge virus (which "is exquisitely sensitive to many entry inhibitors"). As a result, they believe that "the barrier for selecting resistance to an anti-HIV microbicide (such as PSC-RANTES) has been set very high and possibly beyond physiological relevance." To address these concerns, the authors recommend the development of macaque models that use multiple R5-SHIVs as a challenge in order to better duplicate the diversity of viruses to which individuals are typically exposed. Because the resistance described in their study was associated with a dose of PSC-RANTES lower than that which conferred full protection, they also caution that waning microbicide levels after application could conceivably provide the conditions necessary for the emergence of drug resistance.

Source: TAG Basic Science Weblog. (11 Mar 2009)
http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2009/03/viral-resistance-to-a-vaginal-microbicide-in-macaques.html

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OTHER NEWS

Nations should reject UN drug policy

On 11 March Human Rights Watch, the International AIDS Society, and the International Harm Reduction Association issued a press release in response to the new UN Political Declaration on Drugs. Designed to guide drug policy for the next 10 years, the declaration lacks critically important measures for treating and stemming the spread of HIV, Human Rights Watch, said today.

The groups said that respect for human rights and HIV prevention should be at the heart of the policy, but that critical elements had been stripped from the final declaration. They called on member governments to refuse to support the declaration, which is being considered at the high-level segment of the Commission on Narcotic Drugs (CND) this week in Vienna.

"Government delegations could have used this process to take stock of what has failed in the last decade in drug-control efforts, and to craft a new international drug policy that reflects current realities and challenges," said Prof. Gerry Stimson, executive director of the International Harm Reduction Association. "Instead, they produced a declaration that is not only weak - it actually undermines fundamental health and human rights obligations."

What is at issue is a series of measures known collectively as "harm reduction services," which have been endorsed by UN health and drug-control agencies, including the UN Office on Drugs and Crime, UNAIDS and the World Health Organization. These measures include needle and syringe exchange and medication-assisted therapy (for example, with methadone), both inside and outside prisons, as essential to address HIV among people who use drugs. The groups noted that a wealth of evidence proves harm reduction is essential to HIV prevention for people who use drugs. The action was taken against the direct advice of UNAIDS, the Global Fund to fight AIDS, Tuberculosis and Malaria, and the UN special rapporteurs on health and on torture.

Up to 30 percent of all HIV infections outside of sub-Saharan Africa occur via unsafe injecting drug use. The groups said there is clear evidence that harm reduction interventions can halt or even reverse HIV epidemics among people who inject drugs.

"This political declaration fails public health," said Craig McClure, executive director of the International AIDS Society. "Coming less than 12 months after UN member states convened a high level meeting in New York to restate the international commitment to fight HIV, the denial of any reference in the declaration to life-saving harm reduction programs is unacceptable and unconscionable."

The political declaration also fails human rights. In country after country around the world, abusive law enforcement practices conducted under the banner of the 'war on drugs' result in extensive, and often horrific, human rights violations. In addition, overly restrictive interpretations of the international drug-control treaties at national level result in the denial of access to essential pain medications to tens of millions of people worldwide.

Both of these issues were raised by the UN special rapporteur on health and the UN special rapporteur on torture, who wrote to the CND to urge explicit support for human rights within the political declaration. All member states of the UN have ratified at least one of the core UN human rights treaties, and the UN General Assembly has consistently stated that drug

enforcement must be carried out in a manner consistent with respect for human rights.

"Given the widespread human rights abuses around the world directly resulting from drug enforcement, human rights must be placed at the heart of UN drug policy," said Joseph Amon, director of Human Rights Watch's health and human rights division. "But the political declaration makes scant reference to the legal obligations of member states under international human rights treaties, nor does it insist on respect for human rights in drug policy."

The groups called on member states not to lend their names to a political declaration that does not sufficiently prioritize the centrality of harm reduction and human rights within the global response to drugs, and join the call from other civil society organizations for further efforts across the UN system to find a more effective, coherent, and relevant response to drugs.

Source: Joint HRW, IAS and IHRA press releas 'New 10-Year Plan Omits Critical Protections on HIV and Human Rights'. (11 March 2009)
The UN Political Declaration on Drugs:
http://www.unodc.org/unodc/en/press/releases/2009-12.03.html

January 2009 overview by IHRA and HRW "International Support for Harm Reduction":
http://www.hrw.org/en/news/2009/01/19/international-support-harm-reduction

Human Rights Watch's work on drug policy:
http://www.hrw.org/en/news/2009/03/09/un-drug-summit-undo-decade-neglect

End of the Dr. Rath affair in South Africa?

The Treatment Action Campaign in South Africa reported two positive developments that bring to a conclusion the Matthias Rath vitamin saga that become a story with international significance.

Matthias Rath is a vitamin salesman and charlatan who claimed that his products reverse the course of AIDS and that ARVs are toxic and unnecessary. He also claims his products treat diabetes, heart disease, cancer and many other ailments. He started his activities in South Africa in 2004 and received extensive support from state officials and the Minister of Health for his unlawful and deadly activities.

South African government takes action against Matthias Rath

On 13 June 2008, the Cape High Court ordered the Minister of Health (then Manto Tshabalala-Msimang) to take steps to prevent Rath and his agents from conducting unauthorised clinical trials and from publishing advertisements about the medicinal effects of Rath's product VitaCell. The state was also ordered to investigate these unlawful actions by Rath.

The court case arose because of the state's failure to investigate or stop Rath's unlawful activities. The court also interdicted Rath and several of his agents from continuing the above activities. The applicants in the case were TAC and the South African Medical Association (SAMA).

Last year, TAC member Sylvia Fynn discovered that the South African National Civics Organisation (SANCO) was continuing to distribute Rath's medicines from a facility in Durban. SANCO was also discouraging patients from taking ARVs. Fynn photographed a bin where patients had thrown away their scientifically proven medicines, apparently with the intention of using Rath's medicines. The Southern African HIV Clinicians Society (HIVSOC) also collected information on Rath's activities in Durban. Both the TAC and HIVSOC sent our information to the Department of Health. We have since communicated extensively with the Department. We have been impressed by the co-operation we have received from Department officials.

We are pleased to announce that the Department is attempting to implement the court order. We have received a letter, signed on 27 February, from Dr J. Gouws of the Department's Law Inspectorate stating: "I thank you for the information shared ... I wish to inform you that following the order of the Cape High Court ... the Department has embarked on investigation against Matthias Rath and Dr Rath Health Foundation Africa to ensure compliance with the said Court Order".

The TAC welcomes and thanks the commitment and co-operation of the Department of Health over the last few months in this investigation. We also thank the Southern African HIV Clinicians Society for collecting evidence of continued infringements of the court order. Bringing charlatanism under control following the era of state-supported AIDS denialism is an immense challenge, but by taking action against Rath the Department of Health is sending the right message to other charlatans. This is an important first step.

We hope that a warrant of arrest will soon be issued for Rath. While it is unlikely it will ever be executed because Rath has left South Africa, it will be important symbolically to close this tragic affair, which has directly cost the lives of several of Rath's patients and indirectly cost the lives of countless others who were confused by the false messages of Rath, supported by former Minister of Health Tshabalala-Msimang.

Rath appeal against Cape High Court judgment lapses

Following the Cape High Court verdict, Rath lodged an appeal. TAC in turn counter-appealed (because we believe some aspects of the judgment could be stronger), and applied for an interim execution order. Rath's leave to appeal was granted, but so was TAC's leave to counter-appeal and our request for an interim execution order. Simply put, this means that the Cape High Court order against Rath would stand until the appeal was heard.

Matthias Rath has however failed to file further court papers and is now out of time. The appeal process is therefore over and this court case is now complete. The Cape High Court order stands unchallenged. Our lawyers have therefore begun the process of redeeming their considerable costs from Rath.

TAC, SAMA and many other organisations have campaigned for Rath's unlawful activities to be stopped. To TAC's knowledge, Rath's enterprises no longer have a significant presence in South Africa and the vast majority of Rath's unlawful activities in the country have ended.

Source: TAC press statement
Further information:
http://www.tac.org.za/community/rath

http://www.tac.org.za/community/RathWrongs

ON THE WEB

Conferences:

BHIVA / CHIVA Consensus Conference 'Don't Forget the Children'

Wednesday 10 December 2008, Royal Society of Medicine, London

We are pleased to announce that presentations from the recent BHIVA/CHIVA Consensus Conference are located for your review on the BHIVA website <http://www.bhiva.org>www.bhiva.org

Please follow the direct link to the presentations home page:

http://www.bhiva.org/cms1223342.asp

Guidelines and resources:

Hepatology: a clinical textbook

An excellent updated hepatology textbook edited by leading hepatologists involved in HIV care is available free online:

http://www.hepatologytextbook.com

http://www.hepatologytextbook.com/hepatology2009.pdf

The book contains both approved and non-approved therapies.

Human rights documentation and advocacy: a guide for organisations of people who use drugs

Karyn Kaplan, IHRD

The International Harm Reduction Development Program of the Open Society Institute has released a new guidebook that we would like to share with you: Human Rights Documentation and Advocacy: A Guide for Organisations of People Who Use Drugs. Written by veteran activist Karyn Kaplan, it is available at:

http://www.soros.org/initiatives/health/focus/ihrd/articles_publications/publications/hrdoc_20090218.

People who use illicit drugs face daily harassment, discrimination, and abuse—incidents that often go unreported, due to fears of reprisal and other harmful physical, mental, social, or legal consequences. Investigations into rights violations against people who use drugs or efforts to bring perpetrators to justice are rare. Often law enforcement and the society-at-large do not recognize the basic rights of people who use drugs, and blame the victim for any human rights abuses endured as a result of their drug use. Moreover, some government laws and policies directly violate the rights of people who use drugs or create the conditions for violations to occur.

Human Rights Documentation and Advocacy: A Guide for Organizations of People Who Use Drugs aims to help activists

recognize human rights abuses that are systematically conducted and condoned by state and non-state actors and silently suffered by people who use drugs. The guidebook provides activists with the tools necessary to develop a human rights advocacy plan, particularly by documenting abuses against people who use drugs.

The guidebook includes the following topics:

- Starting human rights documentation
- Guidelines for documenting human rights violations committed against people who use drugs
- Guidelines for conducting interviews
- Monitoring legal systems

The guidebook is being printed in English and Russian. **If you would like a copy, please email me, specifying quantity and language**.

Although intended primarily for drug user activist organisations, the principles, strategies and international law described in the guide are universal and should be very useful to anyone seeking to support drug user health and rights through documentation efforts. A Russian language edition as well as print copies will be ready soon and can be had from IHRD's Roxanne Saucier (rsaucier@sorosny.org).

Community resources:

Online videos from Treatment Action Campaign, South Africa

A selection of some of the most important and impressive educational resources, developed by the Community Media Trust in South Africa, on Khayelitsha - one of the Treatment Action Campaign, South Africa model care centres.

The topics are as relevant now as when they were first filmed.

Senator Obama meets with TAC (2006)
http://www.beatit.co.za/archive-events/22-august-2006-senator-obama-meets-with-tac

Pallative Care at Lizo Nobanda (2005)
http://www.beatit.co.za/siyayinqoba-beat-it-2005/episode-2

PMTCT - Bongiwe Mkhutyukelwa (2002)
http://www.beatit.co.za/beat-it-2002/episode-2

Learners beat HIV (2004)
http://www.beatit.co.za/siyayinqoba-beat-it-2004/episode-4

Children on ARVs beat HIV (2004)
http://www.beatit.co.za/siyayinqoba-beat-it-2004/episode-7

Unregulated Experimentation (2005)
http://www.beatit.co.za/siyayinqoba-beat-it-2005/episode-15

Special report - PMTCT, Khayelitsha Project (2000)
http://www.beatit.co.za/beat-it-2000/episode-3

Beating Kaposi's Sarcoma with treatment (2005)
http://www.beatit.co.za/siyayinqoba-beat-it-2005/episode-7

Healthcare workers and HIV (2004)
http://www.beatit.co.za/siyayinqoba-beat-it-2004/episode-23

Gender based violence (2006)
http://www.beatit.co.za/siyayinqoba-beatit-2006/episode-11

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.

15-17 April 2009: 10th Intl Workshop on Clinical Pharmacology of HIV therapy, Amsterdam

http://www.virology-education.com

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

- 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

i-Base announcements list

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

To subscribe please fill out the form at this link:

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

Training manual – revised, updated and now fully online

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

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

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

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

Additional support material 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

June 2008 edition

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

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

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

March 2009 edition

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

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

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

September 2008 edition

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

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

Guide to HIV, pregnancy & women's health

January 2009 edition

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

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

Guide to avoiding & managing side effects

May 2008 edition

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

Translations of i-Base guides

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

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

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

Please be aware that some of these translations are form 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:

- Can I have unprotected sex with my partner?
- If I take HIV drugs early is there a risk of overdose?
- Is my virus at the point of eradication?
- Is there something wrong with my CD4 results?
- Will my medicine become less effective as a result of the heat?
- When shall I expect the side effects to start?
- Shall I expect my CD4 count to rise?
- What do the results of my husband mean?
- Can I switch my taking the dose with 2 hours?
- I have infected my partner. What shall I do?
- How can I participate in a clinical trial?
- What does "with food" mean for darunavir/ritonavir?
- Is my doctor right to stop my medications?
- Shall I continue treatment during the first trimester?
- For how long can I keep my ritonavir out of the fridge?
- Thank you - I decided to test….
- Does HIV treatment involve injections in the backside?
- Shall I tell my fiancée about my HIV status?
- What herbal teas can I drink for sleep problems?
- Do you think my antidepressant has affected my results?
- Can a foreigner receive ARVs in the UK?
- Can I use EMS if I am HIV-positive?
- What is the 'window period' for twice-daily drugs?
- Can I receive my treatment in Gran Canaria?
- Do darunavir/ritonavir/Truvada cause lipodystrophy?
- Will my clinic inform me that the trial was unsuccessful?
- Is my result negative, because I have waited for too long?
- Will we be able to access genetic therapy?
- Is it safe for an adult to use a babys dummy?
- Can you comment on these herb and selenium studies?
- Can I take St John's Wort if I am not on medications?
- Will the government start to charge for HIV drugs?
- Will having sex every day mean that I am going to progress to AIDS more quickly?
- Can we have a negative baby?
- Can I have a baby if my partner is HIV-negative?
- What would you say to someone who has the very initial questions?

- Could that be a result of anaemia?
- Is Truvada+Stocrin a good combination?
- What are the chances?
- Shall I have the same dosage if I am pregnant?

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/2008

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

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 phoneline 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 phoneline 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 _____

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

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

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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.

REG IN ENGLAND WALES WITH LIMITED LIABILITY REG NO 3962064 CHARITY REG 1081905

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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