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EDITORIAL

Welcome to the fourth issue of HTB South, which contains a wealth of conference reports including from the 16th CROI in Montreal and the 4th Southern African AIDS Conference held in Durban.

Happy reading!

HTB South is supported by a grant from the Monument Trust. Nathan Geffen is remunerated from this grant.

Southern African HIV Clinician's Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinician's Society has grown to a membership of over 15 000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

The Southern African HIV Clinician's Society is the largest special interest group within the South African Medical Association (SAMA). It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

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CONFERENCE REPORTS

16th Conference on Retroviruses and Opportunistic Infections (CROI)

8-11 February 2009, Montreal

Introduction

This is one of the most important HIV conferences and this years meeting was no exception.

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

http://www.retroconference.org

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.

C O M M E N T

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 importance of a simple NCI assessment tool, perhaps using motor function, to identify those patients 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.http://www.retroconference.org/2009/data/files/webcast.htm

1. Michael Malim. Host restriction factors and viral escape mechanisms. Program Committee Workshop for New Investigators and Trainees (Part 1). Web cast Feb 8, 2009 8:30 AM
http://www.retroconference.org/2009/Abstracts/36777.htm
2. Ancuta P, Kamat A, Kunstman KJ, Kim E-Y, Gabuda D, et al. 2008 Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS ONE 3(6): e2516. doi:10.1371/journal.pone.0002516
http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0002516
3. Emerging patterns of neuropathogenesis on current ART'. Web cast session Feb 11, 2009 10:00 AM
http://www.retroconference.org/2009/data/files/webcast.htm
4. Igor Grant. HIV-associated neurocognitive impairment remains prevalent in the era of combination ART: the CHARTER study. Oral abstract 15
http://www.retroconference.org/2009/Abstracts/35664.htm
5. Bonnet F et al. High Prevalence of mild neurocognitive disorders in HIV-infected patients, ANRS CO3 Aquitaine Cohort. Abstract 474.
http://www.retroconference.org/2009/Abstracts/34643.htm
6. Vassallo M et al. Neuradapt: a prospective study concerning HIV-related neurocognitve impairment. Abstract 464.
http://www.retroconference.org/2009/Abstracts/34781.htm
7. Best B et al. Efavirenz and emtricitabine concentrations consistently exceed wild-type IC50 in cerebrospinal fluid: CHARTER findings. Abstract 702.
http://www.retroconference.org/2009/Abstracts/34400.htm
8. Letendre S et al. Better antiretroviral penetration into the central nervous system is associated with lower CSF viral load. 13th CROI, 8 February 2006, Denver. Abstract 74.
http://www.retroconference.org/2006/Abstracts/26276.htm
9. Ellis R et al. Persisting high prevalence of HIV distal sensory peripheral neuropathy in the era of combination ART: correlates in the CHARTER study. Abstract 461.
http://www.retroconference.org/2009/Abstracts/34362.htm
10. Byrd D et al. Substance use and HIV infection: neurocognitive effect, the CHARTER cohort. Abstract 478.
http://www.retroconference.org/2009/Abstracts/34478.htm
11. Everall I et al. The neuro-epidemiology of HIV in the US in the era of ART, from the National NeuroAIDS Tissue Consortium . Oral abstract 155.
http://www.retroconference.org/2009/Abstracts/33846.htm
12. Bradford Navia. Persistence of HIV-related brain injury in the HAART era: a multicenter proton magnetic resonance spectroscopy study. Oral abstract 156.
http://www.retroconference.org/2009/Abstracts/36115.htm
13. Beau Ances. Additive effects of aging and HIV serostatus on cerebral blood flow. Oral abstract 157.
http://www.retroconference.org/2009/Abstracts/35577.htm
14. Dulioust A et al. High frequency of neurocognitive disorders in older HIV-infected patients despite a sustained virological and immunological response on cART: the Sigma study. Abstract 459.
http://www.retroconference.org/2009/Abstracts/34961.htm
15. INSIGHT Trial Network
http:www.insight-trials.org
16. Network on European AIDS Treatment (NEAT)
http://ec.europa.eu/research/health/poverty-diseases/projects/131_en.htm
17. Greely H et al. Towardsresponsibleuseofcognitive-enhancingdrugsbythehealthy.Editorialcommentary.Nature456,702-705(11DecemberTowards responsible use of cognitive-enhancing drugs by the healthy. Editorial commentary. Nature 456, 702-705 (11 December 2008) I doi:10.1038/456702a; Published online 10 December 2008
http://www.nature.com/doifinder/10.1038/456702a

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 just begun, 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/mm^3

Mari Kitahata presented a study on behalf of the North American AIDS Cohort Collaboration on Research and Design. [1] The study has since been published in the NEJM. [2] 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. 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.

Analyses were conducted on two groups of patients who received medical care between January 1996 and December 2005 who had not had a previous AIDS-defining illness and had not been on antiretroviral treatment. The patients were identified from a cohort of 67,527 people who were screened.

The first analysis examined over 8,000 patients with CD4 counts of 350 to 500. Median baseline CD4 and viral load were around 430 and 4.2 log in both the immediate and deferred groups. Just over

2,000 began treatment immediately and about 6,200 deferred. The relative risk of death in the deferred group was 1.69 (1.26-2.26; p<0.001).

In the second analysis, about 2,200 of 9,100 patients with CD4 counts above 500 initiated treatment and 6,935 deferred. Median baseline CD4 and viral load were around 660 and 3.6 log in both the immediate and deferred groups. The relative risk of death in the deferred group was 1.94 (1.37-2.79; p<0.001).

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

In an accompanying editorial in the NEJM, Paul Sax and Lindsey Baden state that the "study adds to a growing body of data supporting earlier treatment for HIV infection." They also explain, "Potential additional benefits of earlier therapy for HIV may include a lower rate of drug-specific toxic effects, a greater likelihood of achieving a normal CD4+ count, a reduction in immune activation and inflammation, and a decreased risk of HIV transmission."[3]

They continue, "Analyses of cost-effectiveness have shown that antiretroviral therapy also compares favourably with other widely adopted medical interventions. Increasing the CD4+ threshold to start therapy at a range of 350 to 500 cells/mm3 would add only a few years of additional therapy onto projected decades of treatment and hence generate a relatively small added lifetime cost."

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

The 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. [4]

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/mm3 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 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. [5]

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. [6]

The evidence showing that patients with CD4 counts above 350 would benefit from initiating treatment is subject to confounding and inconsistent. The START trial has begun and will go a long way to answering the critical question of when the best time to begin treatment is.

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. Oral abstracts are available as a webcast.

1. Kitahata M et al. Initiating rather than deferring HAART at a CD4+ count >500 cells/mm3 Is associated with improved survival. 16th CROI, Oral abstract 71.
   http://www.retroconference.org/2009/Abstracts/35084.htm
2. Sterne J et al. When should HIV-1-infected persons initiate ART? Collaborative analysis of HIV cohort studies. 16th CROI, Oral abstract 72LB.
   http://www.retroconference.org/2009/Abstracts/36714.htm
3. INSIGHT research group.
   http://www.insight-trials.org
4. Walensky R et al. When to Start ART—A Policy Evaluation While Awaiting Trial Results: South Africa. 16th CROI, Abstract 596b
   http://www.retroconference.org/2009/Abstracts/36522.htm
5. Granich RM et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009 Jan 3;373(9657):48-57.
   http://www.ncbi.nlm.nih.gov/pubmed/19038438
6. Hammer S et al. Recommendations for the Use of Antiretroviral Therapy. JAMA 2008.
   http://jama.ama-assn.org/cgi/content/full/300/5/555

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

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

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

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

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

On the contrary, we think that the findings from NA ACCORD provide further interesting epidemiological analyses that support the need to perform a randomised trial to assess whether ART should be initiated at higher levels than is currently the case. Specific comments on the NA ACCORD analyses are given below.

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

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

Specific comments on the NA ACCORD analyses

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

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

   In addition, since the study was not specifically designed to address the question, factors known to predict death from non-AIDS conditions, such as smoking, diabetes, hypertension, and HBV status were not measured and adjusted for, while

most deaths of those with cause known were from non-AIDS conditions. Such confounders could jointly well be strong enough to remove the association observed; i.e. with a joint effect which is stronger than the effect of the single unmeasured confounder considered in the NA ACCORD analysis.

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

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

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

4. The analysis in the lower strata is not relevant to START. In the analysis of people with baseline CD4 count 350-500/mm3, the CD4 count at start of ART in the deferred group is below 228/mm^3 in 25% of patients starting ART in this arm. This means that this analysis is not relevant to whether ART initiation should be at CD4 counts above 350/mm^3, compared with 350/mm3 itself.

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

References

1. Kitahata et al. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. Early release at www.nejm.org April 1, 2009 (10.1056/NEJMoa0807252).
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at
http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 6 April 2009.
3. Canner PL. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. N Engl J Med 1980; 1038.
4. Irvine J, Baker B, Smith J, et al. Poor adherence to placebo or amiodarone therapy predicts mortality: Results from the CAMIAT study. Psychometric Med 1999; 61:566-575.
5. Simpson, SH; Eurich, DT; Majumdar, SR, et al.A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006; 333:15-18.
6. Granger, BB; Swedberg, K; Ekman, I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet 2005; 366:2005-2011.

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.

Ref: Silverberg M. Infection-related Non-AIDS defining cancer risk in HIV-infected and -uninfected persons. 16th CROI, Montreal, 2009. Oral abstract 30.

http://www.retroconference.org/2009/Abstracts/36176.htm

16th CROI: SIDE EFFECTS

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

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

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

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

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

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

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

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

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

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

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

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

for MI; 95%CI 1.4-2.9; p<0.001. RR of 1.9 per 10 years of age for severe CV; 95%CI 1.5-2.4; p<0.001).

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

Reiss recommended the following to deal with these complex results:

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

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

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

Potential abacavir mechanisms

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

The summary of these studies at CROI is similarly complex:

• GSK data from the HEAT study found no differences at 96 weeks in endothelial function markers (vascular cell adhesion molecule-1; sVCAM-1) or inflammation markers (IL-6 and hs CRP) between almost 500 patients randomised to either abacavir/3TC or tenofovir/FTC, each with lopinavir/r in a prospective, randomised study in treatment naive patients. [8]

• Frank Palella and the MACS cohort reported similar findings in over 300 matched pairs (194 women, 96 men). Abacavir use was not independently associated with elevated plasma levels of hsCRP, IL-6, and D-dimer. While changes in the levels of these markers were seen between the baseline and index visits (D-dimer and IL-6 decreases, hsCRP increases), they were comparable among persons who initiated ABC versus non-ABC containing HAART. Women had higher D-dimer and lower CRP levels than men. [9]

• However, Claudette Satchell and colleagues from University College Dublin conducted a prospective study to assess platelet function in 58 patient, 30 of whom were on abacavir-containing regimens (ABC group) and 28 who were on non-abacavir-containing ART (no ABC group). [10] They reported consistently higher platelet reactivity in the abacavir group when exposed to increasing levels of platelet agonists and that these differences remained significant when controlled for gender, age, ethnicity, mode of HIV acquisition, smoking history, diabetes, family history of CVD, systolic blood pressure, use of other classes of ART, use of aspirin and methadone and CD3+, CD4+, and CD8+ T cell count.

Impact of HIV

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

• Carl Grunfeld reported that in the Fat Redistribution and Metabolic Change in HIV infection (FRAM) study, even after adjustment for traditional CVD risk factors, HIV infection was independently associated with as severe an impact on atherosclerosis (measured by increased carotid intima media thickness (IMT)) as traditional CVD risk factors, such as smoking. [11] The presentation also suggested that the previous contradictory results looking at IMT in HIV infection may be explained by the two studies finding a link to HIV having measured both thickness in the common carotid and the internal and carotid bulb (a region associated with more vascular turbulence and impact of HDL and total cholesterol) the five studies finding no association having only measure the common carotid.

• A second analysis from FRAM following over 900 HIV-positive patients and almost 300 HIV-negative controls reported a mortality risk that was 3 times higher among the HIV-positive group even after adjustment for demographic and traditional CVD risk factors. [12]

• Priscilla Hsue and colleagues from San Francisco General Hospital, whose group has also reported significantly increase carotid IMT associated with HIV and treatment, reported a new study showing higher levels of coronary artery calcium (CAC) in almost 250 HIV-positive patients compared to 45 HIV-negative matched controls. After adjusting for age, gender, race, smoking, hypertension, and diabetes mellitus, the HIV-infected subjects had a significantly higher prevalence of detectable CAC (OR = 2.7, 95%CI 1.06 to 6.7, p = 0.037). In the adjusted analysis, only age, gender, and race were significant with no impact seen for duration of HAART, PI-use and time with undetectable viral load. [13]

C O M M E N T

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

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

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

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. Oral abstracts are available as a web cast.

1. Reiss P. Abacavir and cardiovascular risk. 16th CROI. Oral abstract 152.

http://www.retroconference.org/2009/Abstracts/36788.htm

2. Lundgren J. et al. Risk of myocardial infarction with exposure to specific ARV from the PI, NNRTI, and NRTI drug classes: the D:A:D study. 16th CROI, 2009. Oral abstract 44LB.

http://www.retroconference.org/2009/Abstracts/36644.htm

3. See http://www.i-base.info/htb/v9/htb9-9-10/Abacavir.html
4. Cooper DA et al. Simplification with fixed-dose tenofovir/emtricitabine or abacavir/lamivudine in adults with suppressed HIV replication: the STEAL study, a randomised, open-label, 96-week, non-inferiority trial. 16th CROI, 2009. Abstract 576.

http://www.retroconference.org/2009/Abstracts/33890.htm

5. Lang S et al. Impact of specific NRTI and PI exposure on the risk of myocardial infarction: a case-control study nested within FHDH ANRS CO4. 16th CROI 2009. Abstract 43LB.

http://www.retroconference.org/2009/Abstracts/36525.htm

6. Cutrell A et al. Abacavir and the potential risk of myocardial infarction. The Lancet. 2008 Apr 26;371:1413.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)60492-4/fulltext

7. Benson C et al. No association of abacavir use with risk of myocardial infarction or severe cardiovascular disease events: results from ACTG A5001. 16th CROI 2009. Abstract 721.

http://www.retroconference.org/2009/Abstracts/34820.htm

8. McComsey G et al. Similar reductions in markers of inflammation and endothelial activation after initiation of abacavir/lamivudine or tenofovir/emtricitabine: the HEAT study. 16th CROI 2009. Poster abstract 732.

http://www.retroconference.org/2009/Abstracts/36331.htm

9. Palella F et al. Inflammatory markers among abacavir and non-abacavir recipients in the Womens' Interagency HIV Study and the Multicenter AIDS Cohort Study. 16th CROI 2009. Oral late-breaker abstract 150LB.

http://www.retroconference.org/2009/Abstracts/36746.htm

10. Satchell C et al. Platelet hyper-reactivity in HIV-1-infected patients on abacavir-containing ART. 16th CROI 2009. Oral late-breaker abstract 151LB.

http://www.retroconference.org/2009/Abstracts/36730.htm

11. Grunfeld C et al. HIV infection Is an independent risk factor for atherosclerosis similar in magnitude to traditional cardiovascular disease risk factors. 16th CROI 2009. Oral abstract 146

http://www.retroconference.org/2009/Abstracts/33991.htm

12. Modrich L et al. Factors associated with mortality in the study of fat redistribution and metabolic change in HIV infection. 16th CROI 2009. Poster abstract 706.

http://www.retroconference.org/2009/Abstracts/34462.htm

13. Hsue P et al. HIV infection is independently associated with detectable coronary artery calcium. 16th CROI 2009. Poster abstract 724.

http://www.retroconference.org/2009/Abstracts/33705.htm

HDL particle concentration predicts cardiovascular disease in SMART

Nathan Geffen, TAC

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

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

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

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

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

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

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

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

The CVD events were as follows:

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

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

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

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

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

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

C O M M E N T

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

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

References

1. Duprez D et al. High-density lipoprotein particles but not low-density lipoprotein particles predict cardiovascular disease events in HIV patients: Strategies for Management of ART study. Oral abstract 149.
   http://www.retroconference.org/2009/Abstracts/34492.htm
2. Phillips AN et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. Antivir Ther. 2008 13(2):177-87.
   http://www.ncbi.nlm.nih.gov/pubmed/18505169

16th CROI: WOMEN'S HEALTH

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

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

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

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

Table 1: Overall rate of death or ART eligibility

	Events	Rate*	95% CI
Death	66	1.1	0.9-1.4
ART eligible	881	17.0	15.9-18.2
Death or eligible	902	17.4	16.3-18.6

*Rate per 100 person years

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

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

Table 2. Impact of contraception category on progression

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

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

Dr Stringer concluded that there was no evidence of hormonal contraception accelerating HIV disease progression in this dataset. However she noted that differences between progesterone-based methods of contraception could not be

elucidated. She suggested that further research in this field is needed.

C O M M E N T

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

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

Pregnancy, family planning, and HIV acquisition in HPTN 039

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

Table 1. Risk factors for pregnancy

Risk factor	HR	95% CI	p
Age >34 vs<21 years	0.22	0.13-0.38	p=≤0.0001
Unmarried status	1.97	1.12-3.49	p=0.02
Oral contraception vs none	0.68	0.47-0.98	p=0.05
Injectable contraception vs none	0.24	0.14-0.4	p<0.001

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

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

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

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

C O M M E N T

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

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

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

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

Polly Clayden, HIV i-Base

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

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

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

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

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

• Regression to normal in women with baseline LSIL smears.

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

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

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

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

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

The investigators reported 83/682 (12.2%) of women with normal, ASCUS or LSIL smears at baseline progressed to incident HSIL. Additionally, 157/544 had incident LSIL or worse after normal at baseline.

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

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

C O M M E N T

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

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

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

Polly Clayden, HIV i-Base

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

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

The trials included in this analysis were conducted in Western Europe and North America. There are few data available from women initiating NVP-containing HAART in Africa and Asia.

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

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

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

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

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

Grade 3 - severe (>5.0 x ULN), >200.

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

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

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

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

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

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

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

C O M M E N T

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

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

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

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

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

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

16th CROI: MATERNAL HEALTH AND PMTCT

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 coworkers 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 coworkers 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 vs 178 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 single dose nevirapine exposure.

References

1. Jourdain G et al. 4-Year Clinical and therapeutic consequences of intra-partum single-dose nevirapine for the prevention of perinatal HIV in Women Who Subsequently Initiated a Nevirapine-based ART. 16th CROI, Montreal, 2009. Abstract 954.

http://www.retroconference.org/2009/Abstracts/35185.htm

2. Lockman S et al. Long-term maternal and paediatric virologic outcomes on nevirapine-based HAART following receipt of peripartum single-dose nevirapine or placebo, Botswana. 16th CROI, Montreal, 2009. Abstract 955.

http://www.retroconference.org/2009/Abstracts/36058.htm

3. Jourdain G et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. N Engl J Med Volume 351, 15 July 2004.
4. Lockman S et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. N Eng J Med Volume 356, January 11, 2007.

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 nevirapine (NVP) resistance following receipt of single dose 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.

References

1. van Dyke R et al. A phase II study of the incidence of nevirapine resistance mutations in HIV-infected Thai women receiving a single intrapartum dose of NVP followed by a postpartum tail of ZDV/ddI or ZDV/ddI/LPV/r: IMPAACT P1032. 16th CROI, Montreal, 2009. Abstract 95aLB.
http://www.retroconference.org/2009/Abstracts/36716.htm
2. Jourdain G et al. Efficacy and Safety of 1-Month Post-partum zidovudine and didanosine to prevent HIV-1 nevirapine resistance mutations following intrapartum single-dose nevirapine. 16th CROI, Montreal, 2009. Abstract 95bLB.
http://www.retroconference.org/2009/Abstracts/36724.htm
3. McIntyre JA et al. Addition of short course Combivir to single dose Viramune for the prevention of mother to child transmission of HIV-1 can significantly decrease the subsequent development of maternal and paediatric NNRTI-resistant virus. 3rd IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, 2005. Abstract TuFoO2O4.
4. Chi B et al. Single dose tenofovir and FTC for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. Lancet. Vol 370:1698-705.
5. Arrive E et al. The TEmAA ANRS 12109 phase II trial, step 1: Tolerance and viral resistance after single-dose nevirapine and short-course of tenofovir disoproxil fumarate and emtricitabine to prevent mother-to-child transmission of HIV-1. 15th CROI, Boston, 2009. Abstract 45b.
http://www.who.int/hiv/pub/mtct/guidelines/en
6. Farr S et al. Addition of 7 Days of zidovudine + lamivudine to peripartum single-dose nevirapine effectively reduces nevirapine resistance at 2 and 6 eeks post-partum in HIV-infected mothers: Lilongwe, Malawi. 16th CROI, Montreal, 2009. Abstract 958b.
http://www.retroconference.org/2009/Abstracts/36679.htm

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 November 2008. [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 un-infected 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

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

Polly Clayden, HIV i-Base

Claire Townsend and coworkers from the Institute of Child Health in London, England 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 British HIV Association (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 years	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 42LB3.
3. http://www.i-base.info/htb/v9/htb9-3-4/Infant.html
4. http://www.retroconference.org/2009/data/files/webcast.htm

16th CROI: PAEDIATRICS

HIV testing of infants at immunisation clinics in KwaZulu-Natal

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

C O M M E N T

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

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

Since estimations suggest that as many as 89% of HIV-infected children will have died before they are 5 years old in sub-Saharan African, currently the overwhelming majority of children who could

benefit from WHO recommendations are neither being tested nor treated.

Ref: Rollins et al. Universal HIV testing of infants at immunization clinics in high HIV prevalence settings: Acceptable, feasible, and potential for high returns. 16th CROI, February 2008, Montreal, Canada. Poster abstract 899b.

http://www.retroconference.org/2009/Abstracts/36509.htm

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

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

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

C O M M E N T

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

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

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

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

References

Oral abstract presentations are also online as web casts.

1. Prendergast A et al. Accelerated HIV disease progression in African infants co-infected with cytomegalovirus. 16th CROI. February 2009. Montreal, Canada Oral abstract 93LB. http://www.retroconference.org/2009/Abstracts/36757.htm
2. Prendergast A et al. Randomised, controlled trial of 3 approaches to management of HIV-infected infants. 15th CROI, February 2008, Boston, USA. Oral abstract 77LB. http://www.retroconference.org/2008/Abstracts/33523.htm
3. Guibert et al. decreased risk of congenital cytomeglavirus infection in children born to HIV-infected mothers in an era of highly active antiretroviral therapy. CID 48:11 p1516-1526. (1 June 2009).

Pharmacokinetic studies in very young infants

Polly Clayden, HIV i-Base

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

Nevirapine (NVP)-based HAART is recommended for infants with no perinatal NVP exposure from mother-to-child transmission prophylaxis or NNRTI-based maternal HAART. Protease

inhibitor-based HAART, usually lopinavir/ritonavir (LPV/r), is recommended for NNRTI-exposed infants.

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

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

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

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

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

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

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

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

Table 1. PK parameters children 3-6kg

	AUC0-12h (h.mg/L)	Cmax (mg/L)	Cmin (mg/L)
NVP	78.74 (54.67-106.75) [30.22]	8.10 (6.08-9.74) [2.41]	4.93 (2.36-7.06) [2.63]
d4T	0.94 (0.74-1.11) [0.32]	0.27(0.21-0.36) [0.11]	<0.015 (<0.015-<0.015) [-]
3TC	7.00 (3.86-9.27) [3.71]	1.46 (0.52-2.13) [0.85]	0.13 (0.08-0.17) [0.05]

Mean (IQR), [standard deviation]

The investigators found large interpatient variability in Cmin concentrations of NVP.

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

The investigators noted that 4/15 (27%) children had sub-therapeutic levels of NVP Cmin(<3.0mg/L compared to 3/63 >6kg(p=0.02). This occurred most frequently in children <5 months (3/6, 50%) vs >5 months (1/9, 11%) but the number of children was too small for this to reach statistical significance. The dose range in the younger children was 324-406 mg/m2 daily.

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

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

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

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

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

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

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

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

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

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

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

C O M M E N T

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

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

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

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

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

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

Urgently required now is an easier to use, store and transport paediatric formulation of LPV/r. Cipla (who also produce Baby and Junior Triomune) have developed a "sprinkle" formulation using melt extrusion technology (similar to the newer LPV/r tablets). The formulation is in the same 4:1 drug ratio in 100/25 mg sachets. This is appropriate for even the youngest children, as it allows the drug to be easily mixed in with food. PK studies are currently planned or underway.

References

1. WHO Antiretroviral Therapy for Infants and Children 2008. Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group Meeting WHO Headquarters, Geneva, Switzerland, 10-11 April 2008.
http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf
2. Mulenga et al. Pharmacokinetics of nevirapine in 3- to 6-kg, HIV-infected infants taking pediatric fixed-dose combination tablets. 16th CROI, 2009. Poster abstract 881.
http://www.retroconference.org/2009/Abstracts/34683.htm
3. L'homme et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on fixed dose combination tablets. AIDS 2008: 22(5), 557-559.
4. WHO Summary of Paediatric Dosing.
http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf
5. Nikanjam et al. Lopinavir population pharmacokinetic model and dose simulation predicts rapid increase in exposure for HIV-infected infants initiating therapy at <6 months of age. 16th CROI, February 2009, Montreal, Canada. Abstract 880.
http://www.retroconference.org/2009/Abstracts/34368.htm
6. Carrarelli et al. Lopinavir pharmacokinetic maturational changes and variability in HIV-infected infants beginning Kaletra therapy at <6 weeks of age. 15th CROI, February 2008, Boston, MA, USA. Abstract 573.
http://www.retroconference.org/2008/Abstracts/31505.htm

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

Polly Clayden HIV i-Base

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

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

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

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

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

Baseline characteristics and PK parameters are median (IQR).

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

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

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

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

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

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

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

C O M M E N T

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

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

PI-based HAART in HIV-infected and HIV/TB coinfected children in South Africa

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

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

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

C O M M E N T

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

Ref: Reitz et al. Virologic Response to protease inhibitor-based ART among children younger than 2 Years of age co-treated for TB in South Africa. 16th CROI, February 2009, Montreal, Canada. Abstract 910.

http://www.retroconference.org/2009/Abstracts/34444.htm

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.

References

1. Moultrie H et al. Mortality and virological outcomes of 2105 HIV-infected children receiving ART in Soweto, South Africa. 16th CROI, Montreal, 2009.
2. Little K et al. Disease progression in children with vertically-acquired HIV infection in sub-Saharan Africa: reviewing the need for HIV treatment. Curr HIV Res 2007, Mar;5(2):139-53.
http://www.ncbi.nlm.nih.gov/pubmed/17346131
3. Cross Continents Collaboration for Kids Analysis and Writing Committee. Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis. AIDS. 2008 Jan 2;22(1):97-105.
http://www.ncbi.nlm.nih.gov/pubmed/18090397
4. Violari A et al. Early antiretroviral therapy and mortality among HIV-infected infants [Internet]. N Engl J Med. 2008 Nov 20;359(21):2233-44.
http://www.ncbi.nlm.nih.gov/pubmed/19020325
5. Severe P et al. Antiretroviral therapy in 1000 patients with AIDS in Haiti. N Engl J Med. 2005 Dec 1;353(22):2325-2334.
http://content.nejm.org/cgi/content/abstract/353/22/2325

Etravirine dose selection in children aged 6 to 17

Polly Clayden, HIV i-Base

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

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

The investigators reported the mean (SD) Cmax in stage I and II, respectively, was 495 (453) and 757 (680) ng/mL; Cmin was 184 (151) and 294 (278) ng/mL; and AUC12h was 4050 (3602) and 6141 (5586) ng•h/mL.

When they compared PK parameters to those reported in adult trials (n = 575), population derived Cmin was 393 [391] ng/mL and AUC12h was 5506 [4710] ng•h/mL, they found the levels achieved in children participating in stage II with the higher dose to be more appropriate.

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

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

Further studies in children are ongoing or planned.

C O M M E N T

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

Ref: Konigs et al. Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years inclusive. 16th CROI, February 2009, Montreal, Canada. Poster abstract 879.
http://www.retroconference.org/2009/Abstracts/35446.htm

Preliminary results from first paediatric raltegravir study

Polly Clayden, HIV i-Base

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

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

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

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

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

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

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

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

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

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

C O M M E N T

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

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

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

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

16th CROI: PHARMACOKINETICS

New boosting alternatives to ritonavir: GS-99350 and SPI-452

hiv-druginteractions.org

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

Nevirapine: fluconazole and TB treatment

hiv-druginteractions.org

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

Effect of substance use on HAART pharmacokinetics

hiv-druginteractions.org

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 use 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

16th CROI: TUBERCULOSIS

HIV and TB from CROI

Nathan Geffen, TAC

There were many studies on TB and HIV at the 16th CROI. While the reports on TB diagnostics were bleak, there have been advances in TB treatment, particularly the use of prednisone in patients with Immune Reconstitution Inflammatory Syndrome related TB. There were also important scientific findings presented on how TB can be managed more effectively using existing technologies. Data on drug-resistant TB continues to be very concerning, with some studies reporting extremely high mortality rates.

Integration of TB and HIV care

Further evidence of the need to integrate TB and HIV treatment was presented. This makes the case for integration incontrovertible.

Salim Abdool Karim and his team at CAPRISA based at the University of Kwazulu-Natal conducted a randomised controlled trial that showed that initiating HAART in HIV/TB-co-infected patients, with CD4 counts <500 during TB treatment significantly improves survival. Over a three-year period, 645 HIV-positive patients diagnosed with TB were given standard TB treatment and cotrimoxazole. Patients were randomised to either receive HAART (lamivudine, didanosine and efavirenz) while on TB treatment (integrated arm) or to defer HAART until the end of their TB treatment course (sequential arm). Participants commenced HAART, on average, 67 days after starting TB treatment on the integrated arm and 261 days on the sequential arm.

The Drug Safety Monitoring Board (DSMB) recommended stopping the sequential arm because mortality was 55% lower in the integrated arm (95%CI 0.26 to 0.79; p=0.0049. 5.1/100 person-years [24 deaths; n=431] versus 11.6/100 person-years [26 deaths; n=214].

Two integration strategies are being tested and this part of the trial is ongoing. The integrated strategy would be simpler to implement if clinics integrate TB and HIV care. [1]

C O M M E N T

In the sequential arm TB patients (including those with CD4 < 200) had HAART delayed until the end of the TB treatment. The result was substantially increased mortality compared to those who started HAART while on TB treatment. It is important to note that treatment protocols throughout sub-Saharan Africa have for several years advised that TB patients with low CD4 counts (CD4 < 200 in South Africa) start HAART during their TB treatment.

A poster by Geoffrey Fatti and researchers with Absolute Return for Kids (ARK) showed an analysis of 109 facilities treating over 35,000 patients with TB, of which 98 facilities did not provide HAART. In the remaining 11 facilities, ARK introduced HAART. In facilities where ARK operated, TB cure rates averaged 79%, while at the non-HAART facilities, it was 71%. This is a relative increase of 11.3% (95% CI: 9.1-13.6; p< 0.0001)

Default rates at the former were 6% as opposed to 11% at the latter (p<0.0001). The authors speculated that the reasons for

this might be that "TB patients are screened for HIV and visa versa, resulting in earlier diagnosis, referral and management." They also explained that TB patients receiving HAART at ARK-supported sites "receive group education, individual counseling, adherence support tools and community adherence psychosocial support."

ARK's high quality of care is obviously a confounding factor in this study. [2]

Andrea Howard and her colleagues analysed 238 PEPFAR funded HIV sites that collectively treat 93,935 patients. They found three key factors associated with a greater number of patients being screened for TB. These were the availability of TB services, the site being located in a rural setting, a greater provider to patient ratio and a greater age of the TB screening programme. Certainly the first of these factors supports integration of TB and HIV treatment. In multivariate analysis, the mean proportion of patients screened for TB if screening took place on site was 76% versus 56% if screening took place off-site (p=0.03). [3]

As a corollary of the above studies, a poster by Stephen Lawn and researchers from the Desmond Tutu HIV Centre at the University of Cape Town showed the need for HAART programmes to screen more pro-actively for TB and to place people on HAART at higher CD4 counts to reduce the risk of TB. They examined their cohort of HAART patients and found, unsurprisingly, that TB rates were much higher at lower CD4 counts and in the first few months of HAART.

They diagnosed 203 cases of TB in during 2,785 person-years of follow-up (7.3/100py). The TB incidence rate per 100 patient-years for CD4 count strata were as follows:

0-100: 16.8;
101-200: 9.3;
201-300: 5.5;
301-400: 4.6;
401-500: 4.2;
>500: 1.5.

The TB rates within the 0-200 cells/mm3 strata was 1.7 times higher than the rates in corresponding CD4-strata during the first four months of HAART (p=0.026). But this higher risk did not remain significant after four months of HAART.

The authors concluded that the excess adjusted risk of TB during early HAART among those with baseline CD4 counts less than 200 cells/mm3 was consistent with "unmasking" of disease missed at baseline screening. They further explained that TB prevention would be improved by HAART policies that minimised the time patients spend with CD4 cell counts below 500 cells/mm3. In patients whose immune systems had recovered to CD4 counts above 500 cells/mm3, TB rates were much lower, albeit still approximately twice the background population rate. [4]

Diagnostics

There was disappointing news on the diagnostics front. Several research groups showed that symptoms, such as coughing, differentiate poorly between patients with and without active TB. Smear tests, x-rays and PCR tests are also poor predictors of who has TB. The definitive TB culture test takes weeks to return a result (an average of 23 days according to a study conducted in Cape Town [5], but often much longer, ranging from 6 to 50 days), which is far too slow for determining if a patient should be treated.

At a pre-conference meeting on TB, Peter Godfrey-Fausett and Helen Ayles of the London School of Hygiene and Tropical Medicine presented the results of TB diagnostics used in the ZAMSTAR community based prevalence studies. ZAMSTAR consists of four sites: one peri-urban and one rural in Zambia, and one medium density and one high density urban site in South Africa. This is a massive sample of 14,330 patients, both HIV-positive and HIV-negative.

They showed that coughing and other symptoms are a poor predictor of culture positive TB. The tables below show sensitivity and specificity percentages for various symptoms.

Table 1: Sensitivity of different TB symptoms (sensitivities are percentages)

	Total	SA	Zambia	HIV-ve	HIV+ve
Number	14,330	6,297	8,033	5,666	2,297
Any symptom	83	79	90	83	95
Any cough	62	59	67	67	67
Prolonged cough	34	28	43		
TB suspect	35	30	43	36	49
TB suspect or any other 2 symptoms	68	64	75	69	79

Table 2: Specificity of different TB symptoms (specificities are percentages)

	Total	SA	Zambia	HIV-ve	HIV+ve
Number	14,330	6,297	8,033	5,666	2,297
Any symptom	38	43	34	36	29
Any cough	76	76	77	78	73
Prolonged Cough	93	92	94		
TB suspect	92	91	93	94	91
TB suspect or any other 2 symptoms	63	68	59	61	53

Tables from Godfrey-Faussett et al.

While using the presence of any symptom to diagnose TB is reasonably sensitive, it is very unspecific, resulting in many false positive diagnoses. However, using only a prolonged cough to screen TB is reasonably specific but highly insensitive, resulting in many cases of TB going undiagnosed.

Godfrey-Fausett considered the implications of this for Isoniozid Prophylaxis Therapy (IPT). Despite the preference to avoid providing IPT to people with active TB, there is no accurate mechanism for diagnosing active TB other than the tardy culture test. It is difficult to determine which patients should receive IPT. Godfrey-Fausett discussed various algorithms for minimising the risk of placing someone with active TB onto IPT. He also suggested that it is not necessarily a serious problem to put someone with active TB on IPT. [6]

Ingrid Bassett and her colleagues at McCord Hospital in Durban compared the cost of intensive TB screening for HIV-positive patients starting HAART against the World Health Organisation (WHO) standard of only doing a smear-test on patients who have had a cough for two to three weeks. The intensive TB screening

procedure consisted of screening all patients regardless of cough and other symptoms of TB. This involved taking a chest x-ray, collecting a sputum sample, doing an AFB smear test and doing a culture test (liquid (MGIT) and 7H11 solid medium).

They calculated the additional costs incurred by this intervention versus what their costs would have been had they just done smear tests on patients with two to three week coughs. They found that just over 19% (159 cases) of their 824 patients tested positive for TB using a culture test. Using just a cough and smear test (i.e. the WHO recommendation) yielded very poor sensitivity and specificity (52% [95%CI: 44-60] and 63% [95%CI: 55-96] respectively).

The most accurate predictor of culture-positive TB was to consider cough, other symptoms of TB and the chest X-ray combined, but even though this was 93% [95%CI: 88-97] sensitive, its specificity was poor: 15% [95%CI: 13-18] (smear test added no additional sensitivity or specificity). The cost per case identified using the WHO screening criteria was $240. The cost per case identified with intensive TB screening was $300. To identify all 159 cases of active TB cost an additional $360 per case.

They concluded that neither cough nor sputum smear alone were sensitive enough to serve as the trigger for screening HIV-infected patients for TB. They explained that compared to screening based on cough, intensive screening doubles the TB cases identified with only a modest increase in the cost per case identified and that sputum cultures should be performed routinely in all patients prior to HAART initiation in areas of high HIV/TB prevalence. [7]

Shaheen Hassim and her colleagues examined the sensitivity and specificity of PCR testing for determining resistance to isoniazid and rifampicin. Unfortunately, sensitivity and specificity, as with smear testing, was poor. A positive culture test matched a positive PCR result only 55.8% of the time. Specificity was better, 88.3%. [8] See Table 3.

Table 3: Sensitivity and specificity of PCR for determining resistance to isoniazid and rifampicin

Smear-positive n (percentage)			Smear-negative n (percentage)		
	Culture+	Culture-		Culture+	Culture-
PCR+	30 (96.8)	0	PCR+	18 (32.7)	47 (11.7)
PCR-	1 (3.2)	1	PCR-	37 (67.3)	355 (88.3)

Similarly distressing results were found by David Edwards and his group from their cohort in a Cape Town township. They screened 236 patients for TB using a combination of symptoms of cough, weight loss, fever and night sweats. 62 (26.3%) patients were culture-positive. Their screening procedure had a sensitivity of 78%, but specificity was very low (35%). They also found that Chest x-rays were normal in a third of cases. They also found that a Lipoarabinomannan ELISA test had a specificity of 99% but a sensitivity of only 31%.

The sensitivity increased to 51% in patients with a CD4 count ≤100 cells/mm3. More than a quarter of patients had culture-positive TB. Symptom screening, sputum smears and x-rays were poorly predictors of TB. On the other hand, sputum culture was slow. The authors poignantly concluded that new more rapid diagnostic tests are urgently needed. [5]

C O M M E N T

The state of TB diagnostics is poor. Until it improves, it is worth considering offering, on a regular basis, a TB culture test to every patient with HIV and offering IPT to those whose culture test is negative. Smear-positive patients as well as smear-negative patients with symptoms of TB should be treated presumptively until their culture tests come back. It appears at least 3 in 10 patients with TB can be correctly diagnosed quickly if the Lipoarabinomannan ELISA test is more widely introduced HTB would be interested in hearing from clinicians what they think of this, how regularly screening should take place and what the cost implications would be.

Treatment: matters look a little more promising for TB treatment.

Graeme Meintjes presented the results of a double-blind placebo controlled trial of prednisone for the treatment of patients who develop clinical deterioration of active TB as a consequence of Immune Reconstitution Inflammatory Syndrome (IRIS) after starting HAART. This steroid is used by many clinicians to treat paradoxical TB IRIS but this is the first clinical trial to determine its safety and efficacy.

55 patients were randomly assigned to prednisone and 54 to placebo. The median CD4 count was 53 prior to HAART and 116 at the time they were enrolled on the trial. Average time in hospital spent by prednisone patients was shorter than those on placebo (1 [IQR: 0-3] versus 3 [IQR: 0-11], p=0.05). The cumulative number of hospital days of the prednisone group was 282 versus 463 days for the placebo group. There were also fewer hospital procedures in the prednisone arm (29 versus 38). Further evidence of prednisone's benefits are that during the four weeks of the study, five patients switched to open-label prednisone in the prednisone arm versus 19 in the placebo arm due to clinical deterioration (p=0.001).

Also, all six patients lost to follow-up were in the placebo arm (p=0.01) Nine patients had potential drug-related side effects in the prednisone arm versus three in the placebo but this was not significant (p=0.07). A 5-point score demonstrated significant symptom improvement in the prednisone arm compared to placebo at 2 weeks (p = 0.003). [9]

C O M M E N T

This study showed that prednisone reduces hospitalisation and procedures. It also improved symptoms. There was no statistically significant difference in mortality (3 on prednisone versus 2 on placebo), but as Meintjes pointed out this was likely due to the exclusion of patients who had severe IRIS (eg neurological involvement) from the study (they were given prednisone) and the switching of patients to open-label prednisone when their health deteriorated.

Elizbeth Corbett gave a summary of the state of TB research. She showed a slide of the TB drug development pipeline, which looks more promising than a few years ago. There are six drugs in pre-clinical trial stages, two in phase one and three in phase two trials. Three existing drugs are being tested, either for new use or in higher dose, in phase III trials.[9]

The most promising new drug is TMC207. The interim results of a phase II trial comparing MDR TB treatment plus TMC207 versus MDR TB treatment plus placebo were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy in October 2008. The study showed that the drug was safe and well-tolerated over eight weeks in patients with drug-resistant TB. 47.5% of patients in the TMC207 arm were culture-negative at the end of the eight weeks as opposed to 8.7% in the placebo arm. [10]

C O M M E N T

In a pre-CROI presentation Charles Flexner of the Division of Pharmacology at John Hopkins University explained the pharmacology of TMC207. He concluded his talk by provocatively suggesting that it should be tested to see if it could eradicate latent TB with a single dose. Flexner's idea, albeit speculative, is exciting: a large percentage of people in Southern Africa are infected with latent TB with the potential to become active TB if their immune systems are weakened. If TMC207 worked against latent TB, this would be a major breakthrough against the disease. However, Flexner also pointed out the problem that the lack of profitability of TB drugs was a hindrance to pharmaceutical company development.

Also see our article on TMC207 on page 38.

Prevention

The standard IPT regimen is 300mg of isoniazid daily for six months. A Cochrane Review has concluded that this reduces the risk of developing active TB in people with HIV, but the review also said that more research was needed to find the best regimen. [12]

Neil Martinson and his colleagues conducted a randomised trial on 1,150 patients to determine if alternative regimens had advantages over standard IPT.

His team compared four regimens:

Regimen 1: 900mg of rifapentine plus 900 mg of isoniazid once weekly for 12 weeks (n=329)

Regimen 2: 600mg of rifampicin plus 900 mg of isoniazid twice weekly for 12 weeks (n=329)

Regimen 3: 300mg of isoniazid daily for the entire trial (an average of nearly 4 years for most of the 164 patients on this arm)

Regimen 4: Standard IPT regimen (n=328)

There were no statistically significant differences in TB incidence or death between the arms. There was a statistically significant greater number of grade 3 and 4 toxicities in the continuous isoniazid arm (regimen 3). 54 patients were tested for resistance. One had rifampicin resistance (regimen 1), one had streptomycin resistance and three had MDR-TB (one in regimen 3 and and two in regimen 1).(13)

Since none of these regimens proved superior to the standard regimen, it should continue to be the TB prevention regimen of choice. However, the effectiveness of the other regimens was not inferior either and in some settings or with some patients it might make sense to use them.

Drug-resistant TB: news on drug-resistant TB in South Africa continues to be concerning.

A poster by Max 'O Donnell presented data on XDR TB patients at King George V Hospital in Durban. In 2006-2007, 1,771 cases of MDR TB and 242 cases of XDR TB were referred to the hospital. O'Donnell and his team specified a six-month study period, in which they attempted to enrol 72 XDR TB patients. Four refused enrolment, six died prior to starting treatment and two had insufficient data, leaving a cohort of 60. The patients were transferred to the hospital from 26 different health facilities representing seven of the province's 11 districts. This implies that XDR TB is quite diffuse in Kwazulu-Natal. 25% of patients came from Tugela Ferry, 11% from Durban and 8% from Pietermaritzburg. 43 were HIV-positive, 12 negative and the remainder unkown. 21 were on HAART. At least 11 had never been treated previously for TB and at least 28 had never been treated for MDR TB. Three were health workers.

25 died and 6 defaulted, meaning that less than half were alive and accounted for by the end of the six month study period. Only 12 patients had converted to a negative culture. 17 were still in treatment. Interestingly, HIV disease increased the risk of death but this increase was not statistically significant, quite likely because the sample was too small to detect it. [14]

So while some treatment success was achieved, the outcomes for XDR TB remain very poor.

This was confirmed by a study from Tugela Ferry by Neel Gandhi and colleagues, which found extremely high mortality rates in patients with MDR and XDR TB. They used the local TB register to identify drug resistant cases diagnosed from 2005 to 2007. They found 272 MDR TB cases and 382 XDR TB cases. One-year mortality was 82% and 69% for XDR and MDR cases respectively.

They noted that "40% of MDR and 54% of XDR TB cases died within the first 30 days." On a promising note, one-year mortality in MDR cases dropped from 87% in 2005 to 45% in 2007 (p=.009). 30-day mortality also improved for MDR TB, from 57% to 32%. Unfortunately no statistically significant improvements in XDR TB occurred.

One-year and 30-day mortality were proportional to the number of resistant drugs (p<0.001) see table 4. [15]

Table 4: 30 day mortality proportional to number of resistant drugs

Number of resistant drugs	30 day mortality	One-year mortality
6	56%	90%
4 to 5	47%	75%
3	40%	65%
2	34%	61%

Another study from Tugela Ferry by Palav Babaria and colleagues at Church of Scoland Hospital found alarmingly high rates of TB, including drug-resistant strains, among HIV-positive patients. They screened 263 HIV-positive patients. 52 (20%) were culture-positive for TB. Only 24 tested smear-positive, once more underlining the lack of reliability of this test in HIV-positive patients. Symptoms of TB were not a good predictor of disease, because most patients presented with coughs, night

sweats, chest pains, weight loss and fever irrespective of their TB status. 13 patients had at least MDR TB (resistant to both isoniazid and rifampin), of whom 7 met the criteria for XDR TB as well. [16]

C O M M E N T

The study by Gandhi et al made excellent recommendations on what is needed: a test that can diagnose MDR and XDR TB within one to two weeks, intensified case finding to identify patients at an earlier stage of disease, expansion and decentralisation of second-line TB treatment programmes, creation of integrated HAART and 2nd-line TB treatment programmes and infection control programmes in areas where TB patients congregate.

The first of these, a better quicker diagnostic, is beyond the immediate control of the South African Department of Health, but the remaining recommendations are all achievable with current technologies. If we are to mitigate the effects of drug-resistant TB, the money and resources needed to implement these recommendations must be made available.

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. Oral abstracts are available as a web cast.

1. Abdool Karim S et al. Initiating ART during TB Treatment Significantly Increases Survival: Results of a Randomized Controlled Clinical Trial in TB/HIV-co-infected Patients in South Africa. 16th CROI 2009. Oral abstract 36a.
http://www.retroconference.org/2009/Abstracts/34255.htm

2. Fatti G et al. Improved TB Treatment Outcomes at Facilities Enhanced by a Non-governmental Organization-assisted ART Program: Western Cape, South Africa. 16th CROI 2009. Poster abstract 591.
http://www.retroconference.org/2009/Abstracts/33694.htm

3. Howard A, Saito S, Nash D, Flam R, Elul B, Scardigli A, Oyeledun B, Cunningham A, Hoos D, El-Sadr W. On-site Location of TB Services Is Associated with TB Screening of HIV-infected Patients at Enrollment in HIV Care Programs: 6 Sub-Saharan African Countries. 16th CROI 2009. Poster abstract 590.
http://www.retroconference.org/2009/Abstracts/36106.htm

4. Lawn S, Myer L, Edwards D, Wood R. Short- and Long-term Risks of TB Associated with CD4 Cell Response to ART in South Africa. 16th CROI 2009. Poster abstract 788.
http://www.retroconference.org/2009/Abstracts/34727.htm

5. Edwards D et al. Baseline Screening for TB among Patients Enrolling in an ART Service in South Africa. 16th CROI 2009. Poster abstract 780.
http://www.retroconference.org/2009/Abstracts/36271.htm

6. Godfrey-Faussett P. et al. Sensitivity, specificity and predictive values of symptoms to detect tuberculosis in the ZAMSTAR community based prevalence studies. Presentation at pre-CROI obtained through personal communication.

7. Bassett I et al. Intensive TB Screening for HIV-infected Patients Ready to Start ART in Durban, South Africa: Limitations of WHO Guidelines. 16th CROI 2009. Poster abstract 779.
http://www.retroconference.org/2009/Abstracts/34392.htm

8. Hassim S. Active Sputum Acquisition Permits Detection of Substantial Rate of Multidrug-resistant TB in a High-risk Population in South Africa. 16th CROI 2009. Poster abstract 781.
http://www.retroconference.org/2009/Abstracts/34089.htm

9. Meintjes G et al. Randomized Placebo-controlled Trial of Prednisone for the TB Immune Reconstitution Inflammatory Syndrome. 16th CROI 2009. Oral abstract 34.
http://www.retroconference.org/2009/Abstracts/34429.htm

10. Corbett E. Prospects for Better Control of HIV/TB: From the Clinic to the Community. 16th CROI 2009. Plenary abstract 19.
http://www.retroconference.org/2009/Abstracts/36637.htm

11. Levin J. Conference Reports for NATAP: Interim analysis of a double- blind, placebo-controlled study with TMC207 in patients with Multi-Drug Resistant (MDR) Tuberculosis: effective and safe. 2008.
http://www.natap.org/2008/ICAAC/ICAAC_95.htm

12. Volmink J et al. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Review. 2003.
http://www.cochrane.org/reviews/en/ab000171.html

13. Martinson N et al. Novel Regimens for Treating Latent TB in HIV-infected Adults in South Africa: A Randomized Clinical Trial. 16th CROI 2009. Oral abstract 36bLB.
http://www.retroconference.org/2009/Abstracts/36768.htm

14. O'Donnell M. et al. Improved Survival for Patients with Extensively Drug-resistant TB and HIV in South Africa. 16th CROI 2009. Poster abstract 785.
http://www.retroconference.org/2009/Abstracts/34552.htm

15. Gandhi N et al. High Early Mortality among HIV-infected Patients with Extensively Drug-resistant or Multidrug-resistant TB in Rural South Africa. Poster abstract 784.
http://www.retroconference.org/2009/Abstracts/36299.htm

16. Babaria P et al. High Rate of Unrecognized TB and Drug-resistant TB among ART Clinic Patients in Rural South Africa. Poster abstract 782.
http://www.retroconference.org/2009/Abstracts/36257.htm

CONFERENCE REPORTS

4th South African AIDS Conference

31 March – 3 April 2009, Durban, South Africa

Abstracts and some of the presentations from this conference can be found on the conference website:

http://www.saaids.com/

HAART coverage and unmet need in South Africa

Nathan Geffen, TAC

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

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

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

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

• The number of adults with untreated clinical AIDS as at mid-2008 was 430,000. Using this criterion, HAART coverage is 54%.

• The number of adults with untreated clinical AIDS or CD4 counts < 200, i.e. the Department of Health criteria, was 760,000, in which case coverage is only 40%.

• If the CD4 count criterion was changed to less than 350, i.e. according to the Southern African HIV Clinicians Society guidelines, then 1.8 million people were untreated. In this case coverage is a mere 22%.

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

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

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

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

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

C O M M E N T

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

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

References

1. Johnson L. How big is the need for antiretroviral treatment? 4th South African AIDS Conference, Durban, 31 March - 3 April 2009.
2. See: http://www.tac.org.za/community/keystatistics
3. Department of Health. National Strategic Plan for HIV and AIDS Statistics. October 2008.

HIV-related medical interventions needed in Southern Africa

Nathan Geffen, TAC and Polly Clayden, HIV i-Base

At the 2007 South African AIDS Conference, we presented on medical interventions urgently needed in the South African public health system. [1]

Nearly two years later, Francois Venter, President of the Southern African HIV Clinicians Society, gave a plenary presentation in which he described drug priorities over the next five years in Southern Africa. [2] These as well as the interventions in the 2007 paper are briefly described here. Many of the interventions highlighted by Venter remain the same as those highlighted in 2007. There has been little progress introducing these into the South African public health system.

Tenofovir

Stavudine remains part of the first line regimen in many African countries. Stavudine also drives most switches due to toxicity. It is associated with severe cases of lipoatrophy that reduce public confidence in HAART, and it is also more implicated in lactic acidosis than any other antiretroviral (ARV). Venter proposed that stavudine be replaced with tenofovir in first-line regimens. Tenofovir has a better side-effect profile, treats hepatitis B, has a lower pill burden and possibly has resistance advantages. Venter pointed out that the key barrier to the introduction of tenofovir is that it costs about ten times as much as stavudine.

Protease inhibitors and new generation ARVs

While lopinavir/ritonavir is used in the 2nd-line regimen in the South African public health system, as well as in first-line for children <3 years of age, Venter pointed out that new drugs will be needed as more patients fail second-line regimens or do not tolerate lopinavir/ritonavir.

Darunavir and atazanavir are registered and available in the private sector, but not the public sector. Atazanavir/ritonavir are similarly priced to lopinavir/ritonavir (R452 v. R407), but in the case of atazanavir, ritonavir has to be bought separately and is not yet available in a heat stable version. Abbott has submitted heat-stable ritonavir to the FDA and registration is likely before the end of the year but based on past experience it is likely to be several more years before it is registered in South Africa.

Darunavir is expensive at R1,034 per month. There is no prospect of it being used in the public sector unless its price comes down substantially. Raltegravir is also registered but extremely expensive at R2,396 per month.[2] Etravirine and maraviroc remain generally unavailable in Southern Africa. Maraviroc is unlikely to ever be available in public or NGO facilities in Southern Africa because of the complexity and cost of screening for CXCR4-tropic HIV.

Paediatric formulations

The complexities of using liquid formulations of paediatric ARVs (such as transportation, storage, cost, taste and dosing) are a barrier to the roll out of HIV treatment in children.

A number of solid 1st and 2nd line paediatric formulations, including fixed dose combinations (FDCs), are already manufactured. Several of these are prequalified by WHO, or other stringent national regulatory authorities (including FDA tentative approval). So far no paediatric FDCs are available in SA. Procurement of solid paediatric formulations for the SA public health system would contribute both to ease and cost-saving in treatment of children with HIV.

Paediatric treatment initiation

Based on the results of the CHER study, conducted in South Africa, which have been known for over 18 months, US and WHO paediatric guidelines recommend immediate initiation of HAART for infants upon diagnosis. Yet this is still not policy in the South African public health system, in part because the Department of Health's ARV revised guidelines are under departmental review. New guidelines have not been published since 2004.

Adult combination treatments

Merck's Atripla remains unregistered in South Africa despite being approved by the FDA in July 2006. Cipla's Triomune (stavudine, lamivudine, nevirapine) is probably the most used regimen in sub-Saharan Africa but is not on the South African public health system tender and consequently it is unavailable in most public health facilities (with some exceptions). Consequently pill counts remain unnecessarily high for most patients. There appears to be reluctance by the Department of Health to include combination medicines in the tender. The reasons for this are unclear.

TB

Venter acknowledged the call for greater access to rifabutin for TB and MAC because of interactions between rifampicin with boosted protease inhibitors as well as efavirenz and nevirapine. However he pointed out that TB results were largely good with rifampicin based regimens and that the public health consequences of moving to a new rifabutin-based regimen, which would not be co-formulated, needed to be carefully considered. Price is also a barrier: Four days of rifabutin treatment is equivalent to a full course of rifampicin. Venter also highlighted the need for improved TB diagnostics to be introduced.

Other HIV-related conditions

Venter highlighted the lack of access to several OI interventions and other HIV-related conditions:

Even though the price of amphotericin B has come down, it is still unavailable to many patients with cryptococcal meningitis because hospitals do not stock it due to hidden costs associated with hospitalisation, diagnosis, drug administration and manometry.

Hepatitis B vaccinations are not widely administered in the public sector.

Ganciclovir remains unaffordable for the treatment of CMV retinitis.

Clindamycin, primaquine and possibly pentamadine/atovaquone need to be introduced as substitutes for cotrimoxazole in patients with with sulphur allergies (and who therefore cannot tolerate cotrimoxazole). Primaquine and pentamadine are not available in South Africa, while atovaquone is only available in combination with proguanil for the treatment of malaria.

Chemotherapy, including doxorubicin, etoposide, cyclophosphamide and vincristine, should be more widely available.

Venter showed data from a report in press of the percentage of subjects on a HAART programme with raised cholesterol and triglycerides above the US National Cholesterol Education Program III recommendations. This indicates the need for drugs for the management of hypertension, diabetes and cholesterol including ACE-inhibitors, antihypertensives, insulin, oral hypoglycaemics, pravastatin and atorvastatin need to be more accessible, as well as lab tests to measure lipids and glucose.

In the 2007 paper, insufficient access to fluconazole, for the treatment of candidiasis and cryptococcal meningitis, and acyclovir, for the treatment of HSV and shingles, were described. This remains the case in 2009.

Circumcision

Despite four years since the effectiveness at reducing female-to-male transmission was shown in Orange Farm, the first of three clinical trials (RR of HIV acquisition [circumcised/uncircumcised] 0.40; 95% CI: 0.24-0.68; p<0.001) as well as the ongoing success of the Orange Farm project, no concrete steps have been taken to scale up this intervention in the public health system.[4]

While the Department of Health is not solely responsible for the delayed or sub-optimal introduction of many of the above interventions, it has not been pro-active at reducing the barriers to accessing them.

References

1. Geffen N et al. Accessing life-saving medical technologies for HIV. 3rd South African AIDS Conference. Durban, 2007. http://www.tac.org.za/documents/AccessingEssentialMedicalTechnologiesFINAL-20070625.pdf
2 Venter F. South Africa Presentation: Key Drugs for the Next Five Years. 4th South African AIDS Conference, Durban, 31 March - 3 April 2009. Plenary presentation.
3. Medprax data supplied to TAC. Private Sector Single Exit Medicine Prices. Prices as of 12 May 2009. http://www.tac.org.za/community/node/2021
4. Auvert B et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005 Nov; 2(11). http://www.ncbi.nlm.nih.gov/pubmed/16231970

Table 1. Interventions needed in the South African public health system

Intervention	Current status and barriers
Tenofovir to replace stavudine, at least in some cases, in first-line regimen	Tenofovir is widely used in the private sector but not in public facilities. The Western Cape and Gauteng provinces are using tenofovir to a limited extent. The Department of Health's ARV guidelines are from 2004 and therefore only include stavudine. Price of tenofovir is substantially higher than stavudine.
Early infant treatment based on CHER study	Paediatric guidelines for the public health system need to be updated to include this. Nevertheless in some facilities clinicians are treating infants early.
Combination ARVs: e.g. Triomune, Atripla need to be introduced.	Atripla is not yet registered. Triomune is not on the public sector tender.
Voluntary male medical circumcision	Despite ongoing success of ANRS project in Orange Farm, no progress has been made implementing circumision in the public health system.
Introduction of more protease inhibitors, including darunavir and atazanavir	There do not appear to be plans to introduce these. Registration of heat-stable ritonavir in the US and South Africa would facilitate wider use. Darunavir is expensive.
Raltegravir as a salvage treatment	Raltegravir is available in the private sector but not public. No salvage treatment is envisaged in the 2004 guidelines. Cost of raltegravir remains prohibitive.
Solid 1st and 2nd line paediatric HIV medicines needed in public health system particularly FDCs	Progress is unclear. Paediatric guidelines need to be adopted that include these.
Increased access to rifabutin instead of rifampicin for TB and MAC treatment.	Rifabutin is not generally available in the public sector. It is much more expensive than rifampicin. It is not co-formulated as part of a full TB regimen (in contrast to rifampicin).
Amphotericin B for cryptococcal meningitis	This is available in the public health system, but often not used because of hidden costs.
Fluconazole for cryptococcal meningitis and candidiasis	While available in the public health system, many facilities still do not stock fluconazole. No data is available to HTB of fluconazole distribution in the public health system in recent years.
Gancyclovir for CMV	This is not generally available in the public health system because of its high price.
Cotrimoxazole substitutes for patients with sulphur allergies	Primaquine and pentamadine are not available in South Africa, while atovaquone is only available in combination with proguanil for the treatment of malaria and is not generally available in the public health system.
Chemotherapy for treatment of cancer including doxorubicin, etoposide, cyclophosphamide and vincristine	Not widely available in public health system. Some of these drugs remain highly priced.

CONVERENCE REPORTS

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

1-3 April 2009, Liverpool, England

http;//www.bhiva.org

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

Simon Collins, HIV i-Base

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

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

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

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

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

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

C O M M E N T

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

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

Vitamin D deficiency, supplementation and tenofovir

Simon Collins, HIV i-Base

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

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

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

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

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

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

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

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

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

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

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

Simon Collins, HIV i-Base

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

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

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

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

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

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

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

References

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

CONFERENCE REPORTS

10th Intl Workshop on Clinical Pharmacology of HIV Therapy

15-17 April 2009, Amsterdam

Introduction

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

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

http://www.HIVpresentation.com

Genetic markers linked to early discontinuation of three antiretrovirals

Mark Mascolini, natap.org

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

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

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

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

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

- Atazanavir: 121 patients, 62.5% at risk stopped versus 18.9% not at risk

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

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

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

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

References

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

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

Mark Mascolini, natap.org

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

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

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

Four amprenavir or fosamprenavir trials with ritonavir doses ranging from 50 mg twice daily to 200 mg twice daily

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

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

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

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

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

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

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

C O M M E N T

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

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

Ref: Hill A, van der Lugt J, M. Boffito M. How much ritonavir is needed to boost protease inhibitors? Systematic review of 16 dose-ranging PK trials. 10th International Workshop on Clinical Pharmacology of HIV Therapy, April 15-17, 2009, Amsterdam. Abstract O_07.

TB COINFECTION

TMC207 reduces time to sputum conversion in phase II trial in patients with drug-resistant TB

Nathan Geffen, TAC

The results of the first of two stages of a double-blinded phase II Tibotec trial on the new TB drug TMC207 have been published in the NEJM.[1] Its purpose was to evaluate the safety, tolerability, pharmacokinetics, and antibacterial activity of TMC207. 47 hospitalised patients in South Africa aged 18 to 57 with sputum-positive TB and resistant to isoniazid and rifampin – ie they had multi-drug-resistant TB (MDR-TB) - were randomised to receive either TMC207 or placebo as an addition to their MDR treatment. The study was run from 5 June 2007 to 23 January 2008.

Besides standard exclusion criteria, patients resistant to aminoglycosides, other than streptomycin, and fluoroquinolones were excluded. So were patients who had previously been treated for MDR TB, had neurologic or severe extrapulmonary TB, had HIV with a CD4 count lower than 300 cells/mm3, had received ART or antifungal medication or both in the previous 90 days or had significant cardiac arrhythmia.

The dosing regimen was 400 mg once daily for weeks 1 and 2, followed by 200 mg three times a week for weeks three through eight, the length of time patients were enrolled in this stage of the study. The study drugs were provided as TMC207 100-mg tablets (or placebo) and were taken with water immediately after breakfast. The preferred background regimen for all patients was kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone. The primary efficacy end point was the time to the conversion of sputum cultures from positive to negative, defined as two consecutive negative cultures. Cultures were performed weekly.

23 patients were in the study drug arm and 24 in the placebo one. 74% of the patients were male, 55% black and 87% HIV-negative. Median age was 33.Three patients were excluded from the final analysis, two because they met study exclusion criteria and one because his or her culture test (MGIT) gave a negative result throughout the study despite originally being smear-positive. 41 patients (20 and 21 in the TMC207 and placebo groups respectively) completed the study.

There were no significant differences in adverse events except for nausea (six cases in the TMC207 arm versus one in the placebo arm; 26% vs 4%; p=0.04). There were two grade four events, one in each arm. These were considered unrelated to TMC207.

The majority of patients achieved average steady-state plasma TMC207 concentrations above the target of 600 ng per milliliter throughout the dosing period. Sputum culture conversion did not predict average steady-state plasma concentrations of TMC207.

TMC207 resulted in 11.8 times quicker conversion to sputum-negative culture (95%CI: 2.3-61.3; p=0.0003). The proportion converting to negative culture during the 8 weeks was 48% for TMC207 (10 of 21 patients) versus 9% in the placebo group (2 of 23 patients). Treatment responses were similar irrespective of

trial centre and lung cavitation.) At week four 57% in the placebo group and 77% in the TMC207 group had negative sputum smears (acid-fast bacilli). At week eight these proportions were 68% for the placebo group and 84% for the TMC207 group. The change from baseline in the log10 count of colony-forming units (CFUs) in the sputum TB culture were also measured in a sub-group of 22 patients (9 TMC207 vs 13 placebo). The median log10 CFU decreased to zero by week four in the TMC207 arm and week eight in the placebo arm.

Background on TMC207

In July 2003, Janssen Pharmaceutica, a subsidiary of Johnson & Johnson (J&J) filed a patent application for quinoline derivative drugs for the treatment of mycobacterial diseases including TB. The patent was published in February 2004.[2] One of these drugs, TMC207 was first described in Science in December 2004 by Andries et al.[3] It was originally called R207910 but it was renamed to reflect that Tibotec, another J&J subsidiary, is developing it. Andries et al. examined a class of drugs called diarylquinolines which were chemically optimised from a lead compound. They announced that they had found 20 molecules with an in vitro minimum inhibitory concentration (MIC) below 0.5 μg/ml against a strain of TB, H37RV. This strain was derived from a human-lung TB isolate in 1934 and is used extensively in biomedical research as a standard [4] TMC207 was the most effective of three of these drugs which were effective against TB in vivo.

The chemical name for TMC207 is 1-(6-bromo-2-methoxy-quinolin-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol. The molecular formula is C32H31BrN2O2 and the molecular weight is 555.51 daltons.

Andries et al. ran experiments to select TB bacteria resistant to TMC207. They then genetically sequenced these resistant strains and found that only one gene was affected on three independent strains. This gene codes a part, F0, of ATP synthase. This is a protein that uses protons to convert ADP to ATP. F0 is a membrane proton channel. Researchers have therefore determined that TMC207 works by inhibiting the proton pump of ATP synthase. This is a different mechanism to current anti-TB drugs. This together with Andries et al.'s laboratory experiments indicates that if TMC207 is effective it will not be cross-resistant with other TB drugs.

In the Andries et al. study TMC207 appeared to be selectively active against TB; much higher MICs were required for laboratory efficacy against other bacteria (a subsequent study indicated activity against Buruli ulcer and leprosy in mice [5] [6]). At appropriate concentration (10 times MIC) the drug reduced bacterial load by 3 log units after 12 days. The effect was not improved with higher concentrations, suggesting, the authors say, that the effect is time-dependent rather than concentration dependent.

Another Tibotec study showed that TMC207 has in vitro activity against latent (or dormant) TB.[7] This is because, according to the authors, dormant TB bacteria have residual ATP synthase activity.

In another phase II study 75 treatment-naïve patients with newly diagnosed smear-positive pulmonary tuberculosis were randomized to once-daily oral TMC207 (25 mg, 100 mg, or 400 mg), 600 mg rifampin (RIF), or 300 mg isoniazid (INH) for 7 days. Significant bactericidal activity of 400 mg TMC207 was observed from day 4 onward and was similar in effect to INH and RIF over the same period. The authors concluded that TMC207 demonstrated bactericidal activity with a delayed onset and was well tolerated, and no study drug-related serious adverse events occurred.[8]

Ongoing TMC207 trials

There are five TMC207 trials registered with clinicaltrials.gov of which one is complete [9-12]. The four incomplete ones are:

- TMC207-TiDP13-C208: This is a phase II, placebo-controlled, double-blind, randomized trial to evaluate the anti-bacterial activity, safety, and tolerability of TMC207 in subjects with newly diagnosed sputum smear-positive pulmonary infection with MDR-TB. This is the second stage of the study discussed in this summary and is currently recruiting patients including in six South African hospitals. The second stage consists of a 24 week treatment period for 150 patients. All patients will be followed for 96 weeks after the last dose of TMC207 or placebo. It is planned to complete in May 2011.
- TMC207-TiDP13-C110: This will be a phase I study to examine, in 16 healthy volunteers, the interactions between TMC207 and lopinavir/ritonavir. Recruitment has not begun.
- TMC207-TiDP13-C117: This will be a phase I study in 16 HIV-positive people to examine the interactions between TMC and nevirapine. Recruitment has not begun.
- TMC207-TiDP13-C209: This will be a phase II, open-Label trial with TMC207 as part of an MDR-TB treatment regimen in 225 patients with sputum smear-positive pulmonary infection with MDR-TB. The estimated study completion date is June 2012. Recruitment has not begun.

C O M M E N T

There is a pressing need for new TB drugs globally for several reasons: to improve treatment outcomes for patients with drug resistant TB, to shorten the course of standard TB treatment, to improve and shorten the treatment of latent TB and to allow options for patients who develop toxicities that make them intolerant of the currently used drugs.

Several new TB drugs are in development. It is too early to say with certainty if any of these are safe and effective for the treatment of TB in humans. TMC207 is the most promising of these, especially since it has in vitro activity against dormant TB.

Pharmaceutical companies do not consider TB drugs particularly profitable. Consequently there are relatively few in development in relation to the pressing global need. Those that are will take a long time to get through the drug development cycle. TMC207's history goes back to at least 2004, possibly even 2003, and yet, if it proves safe and effective, it is unlikely to be registered anywhere before 2011, perhaps even 2012. This is a much longer development period than for many ARVs, even though the need for new TB drugs is at least as great.

In the meantime compassionate access for TMC207 should be considered for patients with DR-TB and no other options.

References

1. Diacon AH et al. The diarylquinoline TMC207 for multidrug-resistant Tuberculosis. N Engl J Med. 2009 June 4. 360, 2397-2405. http://content.nejm.org/cgi/content/abstract/360/23/2397

2. Guillemont J Patent (International publication number: WO 2004/011436.
http://www.wipo.int/pctdb/en/wo.jsp?IA=EP2003050322&wo=2004011436&DISPLAY=STATUS
3. Andries K et al. A diarylquinoline drug active on the ATP synthase of mycobacterium tuberculosis. Science. 2005 January 14. 307, 223-227.
http://www.sciencemag.org/cgi/content/abstract/307/5707/223
4. Sanger Institute mycobacterium tuberculosis H37Rv project.
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=genomeprj&cmd=ShowDetailView&TermToSearch=224
5. Ji B et al. Bactericidal activities of R207910 and other newer antimicrobial agents against mycobacterium leprae in mice. Antimicrob. Agents Chemother. 2006 April 1. 50, 1558-1560.
http://aac.asm.org/cgi/content/abstract/50/4/1558
6. Ji B et al. In vitro and in vivo activities of rifampin, streptomycin, amikacin, moxifloxacin, R207910, linezolid, and PA-824 against mycobacterium ulcerans. Antimicrob. Agents Chemother. 2006 June 1. 50, 1921-1926
http://aac.asm.org/cgi/content/abstract/50/6/1921
7. Koul A et al. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed ATP homeostasis. J. Biol. Chem. 2008 September 12. 283, 25273-25280.
http://www.jbc.org/cgi/content/abstract/283/37/25273
8. Rustomjee R et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob. Agents Chemother. 2008 August 1. 52, 2831-2835.
http://aac.asm.org/cgi/content/abstract/52/8/2831
9. NIH TMC207-TiDP13-C208: Anti-bacterial activity, safety, and tolerability of TMC207 in patients With multi-drug resistant mycobacterium tuberculosis (MDR-TB).
http://clinicaltrials.gov/ct2/show/NCT00449644
10. NIH TMC207-TiDP13-C110: Interaction study in healthy volunteers with lopinavir/ritonavir.
http://clinicaltrials.gov/ct2/show/NCT00828529
11. NIH TMC207-TiDP13-C117: Interaction study in Human Immunodeficiency Virus-Type 1 (HIV-1) infected patients with nevirapine (NVP).
http://clinicaltrials.gov/ct2/show/NCT00910806
12. NIH TMC207-TiDP13-C209: Trial to evaluate the safety, tolerability, and efficacy of TMC207 as part of an individualized multi-drug resistant tuberculosis (MDR-TB) treatment regimen in patients with sputum smear-positive pulmonary MDR-TB.
http://clinicaltrials.gov/ct2/show/NCT00910871

Relationship between TB IRIS and drug-resistant TB

Nathan Geffen, TAC

Graeme Meintjes et al. have published a detailed analysis of 100 prospectively evaluated patients with suspected TB IRIS from February 2005 to July 2006 at GF Jooste Hospital in Cape Town. The authors' analysis elucidates the relationship between TB IRIS and drug-resistant TB. [1]

The TB incidence rate in the Western Cape province is 1,031 per 100,000 population and more than 10,000 people have initiated HAART in the catchment area for GF Jooste Hospital. Many patients initiate late and TB and HIV co-infection is high. Consequently, as the authors explain, hundreds of TB IRIS cases have been seen.

Paradoxical TB-IRIS occurs in patients who are diagnosed with TB prior to ART initiation. These patients are typically improving on TB treatment, but then 1-4 weeks after starting ART develop new or recurrent TB symptoms and clinical manifestations, such as enlarging TB lymph nodes or worsening radiographic pulmonary infiltrates. There are many other reasons for clinical deterioration in such patients and because there is no diagnostic test for TB IRIS, the diagnosis of the condition can be difficult. Diagnosis requires exclusion of TB treatment failure due to resistance or suboptimal drug concentrations, as well as alternative opportunistic infections (OIs).

During the diagnostic work-up of patients with suspected TB-IRIS in the study the authors found a high prevalence of unsuspected drug-resistant TB in their cohort, with implications for the diagnosis and management of TB IRIS. In particular, prednisone, which is an effective adjunctive treatment for TB IRIS, and other corticosteroid therapies may worsen outcomes if used in patients on incompletely efficacious TB treatment or with other untreated OIs. The 100 patients in this report were being assessed for the clinical trial that ultimately determined the efficacy of prednisone against placebo in patients with mild and moderate TB IRIS (reported on in this issue). 38 of these 100 patients were enrolled in that study and 25 received corticosteroids outside the study, usually for severe TB IRIS.

Baseline data and subsequent diagnoses

66 patients were female and 34 male. The median age was 31 [IQR: 26-35]. Patients were initially diagnosed with TB using culture tests (41 people), smear microscopy (31) and clinical and radiological data (24). Subsequent tests showed that the remaining four patients were incorrectly diagnosed with TB despite receiving TB treatment (3 had NTM infections and 1 had lymphoma). Of the patients clinically and radiologically diagnosed with TB at baseline, seven were later confirmed with smear or sputum tests..

After presentation with suspected TB-IRIS the following diagnoses were made after work-up and sending samples for TB culture and drug susceptibility testing;

- 80 patients were diagnosed with TB IRIS and no resistance.
- Nine patients were diagnosed with TB IRIS and then discovered to have rifampicin resistance, seven of whom were also found to have INH resistance (ie. MDR TB).
- Four patients were known with rifampicin resistance at presentation, of whom three were known to have MDR TB.
- Seven patients with suspected TB IRIS were diagnosed not to have TB-IRIS but received a diagnosis of an alternative OI.

The first two groups initially fulfilled the case definition of TB IRIS. There were no statistically significant differences in baseline data except a shorter duration from initiation of TB treatment to HAART in the first two groups compared to the third.

The median baseline CD4 count was 50 cells/mm3 (IQR: 26-94). Follow-up CD4 counts were available for 77 patients. CD4 counts increased by a median of 139 (IQR: 64-241) from their pre-HAART values in 73 patients. They declined in the remaining four. In 65 of 74 patients with viral load performed on HAART it was below 400 copies/mL. In four patients with viral loads > 1000, CD4 cell counts nevertheless increased during HAART.

The paper describes a wide variety of methods, procedures and mechanisms used to diagnose TB, diagnose TB IRIS and determine drug susceptibility results, including use of cultures performed on sputum (55%), lymph node or abscess aspirate (18%), pleural fluids (8%), CSF (8%) and other specimens (11%); radiographs and FASTplaque assays (rapid rifampicin susceptibility test), to name a few. It also gives case histories for the nine patients subsequently diagnosed with rifampicin resistance and clinical data for the 80 patients without resistance. The most frequent TB-IRIS symptoms in this latter group were constitutional (68 people), including night sweats, anorexia, malaise, and weight loss; respiratory (48 people) and abdominal (47 people) including abdominal pain, nausea, vomiting and diarrhea. The symptoms for the nine rifampicin-resistant patients were similar Blood tests were also similar between the two groups although the median C-reactive protein level was higher in the resistant group (179mg/L [IQR: 100-212] vs 96mg/L [IQR:70-152]; p=0.05). There was evidence of immune activation using ELISpot in both groups, albeit less so in the resistant group.

Drug resistance and IRIS not mutually exclusive

The nine patients with subsequently detected rifampin-resistance improved while receiving standard TB treatment prior to HAART and then deteriorated during the weeks after HAART initiation (3-48 days which is characteristic of TB IRIS). The same occurred in the additional four patients with known rifampicin resistance although they were on MDR treatment prior to HAART. The authors ask whether the condition of these 13 patients deteriorated because of sub-optimally treated TB, TB IRIS or both. They propose that based on their clinical observations that TB IRIS and TB drug resistance may overlap and are not mutually exclusive. They suggest that patients with rifampicin resistance might be at greater risk of TB IRIS because of higher mycobacterial loads. This has implications for the case definition of TB IRIS.

C O M M E N T

This study's detailed clinical histories and descriptions of diagnosis may be useful for clinicians who need to diagnose TB, drug-resistant TB and TB IRIS. However, the complexity of this work is not replicable in the public health system outside research and referral hospital settings especially when the intensity of investigation and wide variety of diagnoses that were made are taken into account. Yet these findings are important because the proportion of drug-resistant cases and initial misdiagnoses was substantial. Two conclusions follow from this: (1) TB diagnostics need to be improved and simplified. This is not a new observation, but this paper exemplifies this need. (2) It is urgent that Meintjes et al.'s findings, both in this paper and their work on prednisone, be used to update the TB treatment guidelines in the South African public health system, taking into account constraints on health worker time and the need for simple protocols.

Ref: Meintjes G. et al. Novel Relationship between Tuberculosis Immune Reconstitution Inflammatory Syndrome and Antitubercular Drug Resistance. Clinical Infectious Diseases 2009;48:667–676
http://www.journals.uchicago.edu.ezproxy.uct.ac.za/doi/full/10.1086/596764

High risk of stavudine substitution associated with TB treatment

Nathan Geffen, TAC

Daniel Westreich and colleagues have examined the risk of stavudine substitution for patients on TB treatment in the Themba Lethu clinical cohort. [1] This cohort comprises adults at one of the largest public clinics providing HAART in South Africa. Stavudine is part of the first-line regimen used in the South African public health system and most of sub-Saharan Africa. It has a poor side-effect profile compared to other currently used ARVs and is associated with lactic acidosis, lipid disorders, lipodystrophy and peripheral neuropathy, but it is also the cheapest ARV which is why it is so widely used. Westreich et al. report that more than 20% of patients in this cohort required substitution of stavudine because of toxicity --primarily lipodystrophy or peripheral neuropathy-- by 36 months after treatment initiation.[2]

Westreich et al. examined four groups among over 7,000 patients on HAART from April 2004 to March 2007:

- patients not on TB treatment (n=5,226);
- patients on ongoing treatment, i.e. those who started TB treatment at least 15 days before initiating HAART (n=1,272);
- patients on concurrent treatment, i.e. those who started TB treatment and HAART within 14 days of each other (n=224); and
- patients who needed TB treatment at least 15 days after commencing HAART (incident treatment group, n=344).

All TB regimens contained isoniazid, which is also associated with peripheral neuropathy. The outcome was all-cause stavudine substitution, defined as the substitution of stavudine with another ARV, usually AZT, while the remainder of the regimen was unchanged. Patients were followed up until they substituted stavudine, contracted a second episode of TB while receiving HAART, died, were lost to follow up, had multi-drug substitution or until the end of the follow-up period. Results were adjusted for sex, ethnicity, employment, age, history of HAART, history of TB treatment, pregnancy, peripheral neuropathy at HAART initiation, hemoglobin level (adjusted for sex, altitude and pregnancy), BMI, CD4 count, WHO stage, calendar date, whether treatment was initiated after consultation fees were abolished in October 2006 and stavudine dosage.

260 (3.7%) patients died, 1,252 (17.7%) were lost to follow-up and 1,219 were changed off stavudine, of whom 203 had multi-drug substitutions, 172 were switches to second-line HAART and 842 had single stavudine substitutions. The crude rate of single stavudine substitutions was 12.4 per 100py [95%CI: 11.6-13.3] with a median time to single-drug stavudine substitution of 347 days [IQR: 175-535].

The absolute rate of stavudine substitution increased with time from HAART initiation:

- months 0-6: 7.9/100py (95%CI: 6.9-9.1),
- months 6-12: 12.3/100py (95% CI, 10.8-14.0),
- rest of follow-up: 18.1/100py (95%CI: 16.4-20.0).

Peripheral neuropathy was the main cause of substitution (362 out of 842, 43%). Lipodystrophy was responsible for 205 (24%)

switches. Lactic acidosis or symptomatic hyperlactatemia was responsible for 168 (20%). 21 (2%) were due to a combination of toxicities and 86 (10%) had no reason recorded.

The ongoing and concurrent TB treatment groups were significantly associated with stavudine substitution in the first two months of TB treatment, but not the incident group, when compared to those not on TB treatment. The hazard ratio for the ongoing group remained significant in months 3 to 6 of TB treatment. The adjusted hazard ratio for the three TB-treatment groups compared to the no-TB treatment group is given in Table 1, broken down by number of months on HAART.

Table 1. Adjusted HR for stavudine substitution by months on HAART and 95% CI

TB treatment group	0 to 2 months	3 to 6 months	7 or more months
Ongoing	3.18 (1.82-5.56)	2.51 (1.77-3.54)	1.19 (0.94-1.52)
Concurrent	6.60 (3.03-14.37)	1.88 (0.87-4.09)	1.07 (0.6-1.76)
Incident	0.99 (0.46-2.12)	1.18 (0.6-2.25)	0.87 (0.28-2.73)

The study found that patients who switched because of peripheral neuropathy were 1.53 times more likely to have TB at HAART initiation or during follow-up (95%CI: 1.33-1.75). This suggests that the risks of stavudine and isoniazid for neuropathy compound each other. Interestingly, those who switched because of lactic acidosis or lipodystrophy were less likely to have TB (RR: 0.58; 95% CI: 0.48-0.71).

The results were not sensitive to stavudine dose, multi-drug substitutions, or TB treatment lasting nine months rather than six months. However if only patients without a history of TB were considered, the hazard ratios in the ongoing and concurrent groups in the first two months of treatment rose to 3.56 and 7.57 respectively. The authors suspect that lingering peripheral neuropathy from previous drug exposures in those with a history of TB treatment included in the no TB treatment group might therefore have resulted in the true impact of current TB treatment on stavudine substitution being underestimated.

The authors also suggest that they underestimate peripheral neuropathy because most TB patients in SA receive vitamin B6 for the prevention of this INH-related neuropathy. Also amitriptyline is prescribed to patients who develop peripheral neuropathy. Take these two two treatments away and the number of substitutions would likely increase. The authors did not analyse low-level peripheral neuropathy not requiring substitiution. They explain therefore that the impact of TB treatment on the risk of stavudine toxicities may be higher than the impact of TB treatment on the risk of stavudine substitution. They further explain that the surprising lack of stavudine substitution in the incident group might be because of a decrease in susceptible patients or because the risk of stavudine toxicity is reduced with low viral load they hypothesize.

Overall, one in 18 of all patients with TB at baseline (the ongoing and concurrent groups) need a stavudine substitution versus one in 42 for patients who do not receive TB treatment. The authors state that because more than 20% of patients who commence HAART are on or need TB treatment, this has considerable public health implications.

Several confounding factors might have biased the analysis. Patients with TB might be more exposed to other drugs that increase the risk of peripheral neuropathy. Further, health workers might be more likely to look for peripheral neuropathy in patients taking isoniazid and stavudine.

C O M M E N T

This is yet another study which demonstrates the need to replace stavudine with tenofovir in sub-Saharan African first-line regimens, at least for patients at risk of TB. The large difference in price between the two drugs, the fact that the only readily available three-in-one combination pill (Triomune) contains stavudine (a factor important outside of South Africa, because Triomune is not used in the public sector in SA) as well as the long delays in updating and publishing the South African Department of Health guidelines remain barriers to this happening.

As the authors recommend, regular monitoring for peripheral neuropathy in patients taking stavudine, especially if they are on isoniazid, is essential. In particular, patients should be asked about sensations of pain, numbness or tingling in the toes and feet.

References

1. Westreich DJ et al. Tuberculosis treatment and risk of stavudine substitution in first-line antiretroviral therapy. Clinical Infectious Diseases. 2009; 48:1617-23 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)60492-4/fulltext
2. Boulle A et al. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. Antivir Ther 2007; 12:75360 http://www.ncbi.nlm.nih.gov/pubmed/17713158

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

TREATMENT ACCESS

FDA approval of generic ARVs

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

Approval date	Drug	Company
5 January 2009	d4T capsules 30/40 mg	Matrix, India
18 February 2009	tenofovir DF 300mg tablets	Aurobindo, India
27 February 2009	fixed dose combination d4T/3TC/nevirapine 30mg/150mg/200mg & 40mg/150mg/200mg	Aspen Pharmacare, South Africa
10 March 2009	lopinavir/ritonaviropinavir/ ritonavir tablets, 200/50mg	Matrix, India
16 March 2009	3TC,150 mg tablets	Alkem Labs, India
18 March 2009	d4T/3TC FDC tablets, 30/150mg & 40/150mg	Aspen Pharmacare, South Africa
30 March 2009	tenofovir/FTC (emtricitabine) tablets, 300/200mg	Matrix, India
30 March 2009	abacavir/3TC tablets, 600/300 mg	Matrix, India
31 March 2009	nevirapine tablets, 200 mg	MacLeods, India
29 April 2009	tenofovir DF 300mg tablets	Cipla, India
7 May 2009	fixed dose 3TC/AZT 150mg/300mg, co-packaged with nevirapine 200mg	Hetero, India
29 May 2009	3TC/AZT 150mg/300mg	Macleods, India

"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 also known as the Orange Book.

An updated list of generic tentative approvals is available on the FDA website:

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

There are currently 92 tentatively approved formulations including five paediatric products.

HIV medicine prices in the South African private sector

The Treatment Action Campaign (TAC) updates its website weekly with the latest private sector prices in South Africa, supplied by Medprax, of a range of AIDS drugs. The URL is:

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

The lowest prices for certain drugs and drug combinations as of 22 May 2009 are shown in Table 1 below.

These medicines are extremely expensive and need to be reduced:

- A 500mg vial of gancivlovir costs R2558.25 (manufacturer Roche)
- 60 raltegravir 400MG tablets costs R2396.44 (manufacturer MSD)
- 120 darunavir 300MG tablets cost R1034.21 (manufacturer/ distributor Tibotec and Aspen)

If there are any errors or concerns about the above list (e.g. stockouts of certain brands), please let TAC know.

Table 1: Medicines (based on one month for average adult unless otherwise stated)

	Lowest Price Brands	Price (incl. VAT but excl. dispensing fee)
1st line DOH guidelines with nevirapine		
Stavudine (30mg)		
Lamivudine (150mg)	VARI-STAVUDINE	R31.27
Nevirapine (200mg)	SONKE-LAMIVUDINE	R44.40
TOTAL	SONKE-NEVIRAPINE	R171
		R246.67
1st line DOH guidelines with efavirenz		
Stavudine (30mg)	VARI-STAVUDINE	R31.27
Lamivudine (150mg)	SONKE-LAMIVUDINE	R44.40
Efavirenz (600mg)	AURO-EFAVIRENZ	R135.66
TOTAL		**R211.33**
1st line DOH guidelines combination		
Lamivudine/stavudine/nevirapine	SONKE LAMINEVSTAV	R231.18
Lamivudine/stavudine/nevirapine	TRIOMUNE 30	R284.49
1st line US recommendation		
Tenofovir (245mg)/FTC (200mg)	TRUVADA	R397.71
Efavirenz (600mg)	AURO-EFAVIRENZ	R135.66
TOTAL		**R533.37**
2nd Line DOH guidelines		
AZT (300mg)	AURO-ZIDOVUDINE	R223.44
Didanosine (100mg)	SONKE-DIDANOSINE	R110.31
Lopinavir (133mg)/ritonavir (33mg)	KALETRA	R406.80
TOTAL		**R740.55**
Fluconazole (200mg/30 capsules)	APEX FLUCONAZOLE	R256.94
Atorvastatin (40mg)	ASPAVOR	R169.08
Pravastatin (40mg)	PRANALIP	R168.58

OTHER NEWS

Review of the HSRC's prevalence, incidence, behaviour and communication survey

Nathan Geffen, TAC

The Human Sciences Research Council (HSRC) published its much awaited 2008 HIV prevalence, incidence, behaviour and communication Survey in June 2009. [1] This is the third such survey. The previous ones were conducted in 2002 and 2005. Previously the survey only included people over two years old, but this one included all ages.

This year's report is much shorter than the other two and contains less detail. The HSRC explains that more detail will be made available in journal articles that will be submitted for publication. The report contains a plethora of interesting data.

Sample

The sample consisted of 15,000 households, 15 from each of 1,000 enumeration areas. Of these 13,440 (90%) were valid occupied households. The occupants of 10,856 (81%) agreed to be interviewed.

23,369 individuals were identified as eligible to be interviewed (a parent or guardian was interviewed for children aged 11 and under). 20,826 (89%) completed a behavioural interview. 15,031 (64%) agreed to provide a blood sample to be tested for HIV. The HIV tests were anonymously linked to the interview. The acceptance rates for HIV tests by sex were 62% for males and 69% for females, and by race were 69% for Africans, 53% for whites, 75% for coloureds and 48% for Indians.

The researchers extensively analysed factors associated with refusal to have an HIV test that could have biased the results. They concluded, "Although some associations were statistically significant due to the large sample sizes, the differences between those tested and not tested were all less than 10% and most were less than 5%. Based on this more detailed analysis of HIV risk-associated characteristics in survey respondents who were interviewed and tested and those who were interviewed but refused HIV testing we conclude that the HIV survey results were not biased due to HIV testing refusal."

At most four people from any household were interviewed, one from each of these age groups: under 2, 2-14, 15-24, 25 and above. Calculations were weighted to compensate for under-representation of enumeration areas, households and individuals.

The survey does not include people in institutions, e.g. prisons, army barracks, university residences and boarding schools.

Prevalence

The weighted HIV prevalence rate was 10.6%. No confidence interval was provided for this estimate. For people over the age of two there was no significant difference in prevalence at a national level from 2002 to 2008:

2002: 11.4% (95%CI 10.0-12.7)

2005: 10.8% (95%CI 9.9-11.8)

2008: 10.9% (95%CI 10.0-11.9)

The consistency across all three surveys implies that we can say with confidence that prevalence among people in South Africa over the age of two who are not living in institutions is approximately 11% and that it has not changed significantly in recent years.

At a provincial level, there is only one significant change in prevalence. In 2002, the Western Cape prevalence was 10.7% (95%CI 6.4-15.0). This changed to 1.9% (95%CI 1.2-3.0) and 3.8% (95%CI 2.7-5.3) in 2005 and 2008 respectively. As can be seen, the change from 2002 to 2005 is significant but not from 2005 to 2008. There is no reason why the prevalence in the Western Cape should have dropped so much from 2002 to 2005, even taking into account the province's successful prevention of mother-to-child transmission programme (PMTCT) programme, whose effect on prevalence in any case would be partially or wholly offset by the corresponding success of the HAART programme. [2] Furthermore the Western Cape antenatal HIV prevalence increased from 12.4% to 15.7% from 2002 to 2005. Most likely, this is a sampling problem or statistical anomaly in one or more of the three HSRC surveys.

When broken down by the three older age groups, there is a significant drop in prevalence in the 2-14 age group from 2002 to 2008. This possibly reflects some effectiveness of the PMTCT programme. There was no significant change in the 15-24 and 25+ age groups across the three surveys. See Table1.

Table 1: HIV prevalence by province for people aged above two years old in the three HSRC household surveys. Percentages are weighted. Taken from page 32 of the 2008 report.

Province	2002 (n)	2002 (%)	2002 (95%CI)	2005 (n)	2005 (%)	2005 (95%CI)	2008 (n)	2008 (%)	2008 (95%CI)
Western Cape	1,267	10.7	6.4-15	2,204	1.9	1.2-3.0	2,098	3.8	2.7-5.3
Eastern Cape	1,221	6.6	4.5-8.7	2,428	8.9	7-11.4	1,984	9.0	7.2-11.2
Northern Cape	694	8.4	5.0-11.7	1,144	5.4	4.0-7.2	1,227	5.9	4.5-7.8
Free State	540	14.9	9.5-20.3	1,066	12.6	9.5-16.7	960	12.6	10.5-15.1
Kwazulu-Natal	1,579	11.7	8.2-15.2	2,729	16.5	14.0-19.3	2,464	15.8	13.4-18.6
North West	626	10.3	6.8-13.8	1,056	10.9	8.4-14.0	1,156	11.3	9.1-14.0
Gauteng	1,272	14.7	11.3-18.1	2,430	10.8	8.9-12.9	2,093	10.3	8.3-12.7
Mpumalanga	550	14.1	9.7-18.5	1,224	15.2	12.3-18.5	988	15.4	11.9-19.7
Limpopo	679	9.8	5.9-13.7	1,570	8.0	6.0-10.6	1,252	8.8	6.5-11.9
National	**8,428**	**11.4**	**10.0-12.7**	**15,847**	**10.8**	**9.9-11.8**	**14,222**	**10.9**	**10.0-11.9**

The 2008 survey also introduced prevalence measures for people in groups at high risk of HIV infection, an important development, which will hopefully provide a rich source of data. See Table 2.

Table 2: HIV prevalence in groups at risk

At-risk population	n	HIV+ %	95% CI
African females 20-34	1,395	32.7	29.7-36.0
African males 25-49	944	23.7	20.1-27.7
Males 50+	946	6.0	4.4-8.1
Men who have sex with men	86	9.9	4.6-20.2
High-risk drinkers	965	13.9	10.4-18.2
Recreational drug users	490	10.8	7.2-15.8
People with disabilities	458	14.1	9.9-19.6

It is worth noting that 4,238 males over 15 agreed to have an HIV test. Of these 86 affirmed that they have sex with other men, ie 2%. Taken from page 36 of the 2008 report.

Incidence

The HIV/AIDS National Strategic Plan was published in April 2007. It set a target to reduce HIV incidence by 50% by 2011. Consequently the HSRC report has a detailed discussion on incidence.

The 2005 survey used the BED-assay to estimate incidence. In December 2005 a UNAIDS reference group released a statement on the reliability of this method. The group explained, "Based on the ... evidence, the Reference Group recommends that at present the BED-assay not be used for routine surveillance applications, neither for absolute incidence estimates, nor for monitoring trends." [3] The BED-assay methodology for estimating incidence has subsequently been improved, though it is complex and should ideally be corroborated with additional studies. [4]

The BED-assay calculation of incidence was not ready at the time the 2008 survey went to print. Instead the survey determined incidence for each year of age for 15 to 20 year-olds by deriving it from single year age prevalences. It concluded that, "there was a substantial decrease in incidence in 2008 in comparison to 2002 and 2005, especially for the single age groups 15, 16, 17, 18, and 19." This is an unusual incidence calculation method that works as follows (using an example in the report):

- Proportion of 14-year olds infected is 0.0311 (ie prevalence is 3.11%).
- Proportion of 15-year olds infected is 0.0389 (ie prevalence is 3.89%).
- The difference in prevalence between 14 and 15-year-olds is 0.0389 – 0.0311 = 0.0078.
- The proportion of the population of 14-year-olds that is uninfected is 1 - 0.0311 = 0.9689.
- Incidence is calculated as the change in prevalence divided by the proportion of the population at risk, ie 0.0078/0.9689 = 0.008 (ie incidence for 15-year olds is 0.8%).

The calculation assumes that incidence remains the same from one calendar year to the next and that prevalence in the 15-20 year age group is unaffected by AIDS (hence the calculation cannot be done for older ages). The validity of these assumptions is uncertain. More critically, the method does not calculate confidence intervals or p values. The report also does not provide confidence intervals for prevalence for each year of age 15 to 20. However, given that the national 95% confidence intervals for prevalence in 15-24 year olds are wide and overlapping across the three surveys (7.5%-11.4% in 2002, 8.7%-12.0% in 2005 and 7.2%-10.4% in 2008), it is unlikely that any incidence calculation for 15-20 year-olds based solely on prevalence estimates would show a statistically significant decline.

It is plausible that incidence has declined from 2002 to 2005 to 2008. However, there is insufficient evidence to conclude this from the HSRC report.

Unless more compelling data is published by the HSRC it will be difficult to assess whether the incidence target of the NSP has been achieved. Hopefully the BED-assay results will provide a robust estimate of incidence. If not then researchers should consider doing large longitudinal surveys in some of the country's high-risk areas, so that we can better understand incidence. One recent such study found an incidence of 3.4 per 100py (95%CI 3.1-3.7) in Umkhanyakude district, Kwazulu-Natal and no sign of decline over a five year period. [5]

Behavioural measures

The report examined these behavioural determinants of HIV incidence: sexual debut, intergenerational sex, multiple sexual partners and condom use. In contrast to the prevalence measure, this part of the survey depends on the manner in which questions are phrased, how well they are understood and the willingness of interviewees to tell the truth.

Nationally, 5% (95%CI 3.8-6.5) in 2002, 8.4% (95%CI 7.2-9.9) in 2005 and 8.5% (7.1-10.1) in 2008 of 15 to 24 year-olds said they had sex before reaching 15 years old. While there is a significant difference between 2002 and the 2005 to 2008 period, it is difficult to interpret this. At provincial level, the increase between 2002 and the 2005-2008 period was only significant in North West and Free State.

In 2005 2% of males (95%CI 1.0-4.2) and 18.5% (95%CI 13.7-24.4) of females in the 15-19 age group said they had a sexual partner at least five years older than them. In 2008 0.7% (95%CI 0.2-2.7) of males and 27.6% (95%CI 21.7-34.5) of females said they had a sexual partner at least five years older than them. This was not measured in 2002. The differences between 2005 and 2008 are not statistically significant.

Among males aged 15 to 49, 9.4% (95%CI 8.1-10.9) in 2002, 17.9% (95%CI 15.5-20.6) in 2005 and 19.3% (95%CI 17.3-21.6) in 2008 said they had more than one partner in the past 12 months. Amongst females aged 14 to 49, 1.6% (95%CI 1.1-2.3), 2.9% (95%CI 2.3-3.7) and 3.7% (95%CI 2.9-4.8) made the same claim. It is not clear why there was a large and significant rise from 2002 to 2005. (Tables 3.15 and 3.16 of the HSRC report appear to give contradictory data for 15 to 49 years olds nationally in 2002. I have assumed Table 3.16 has an error.)

It is plausible that both these factors, ie high rates of intergenerational sex of female youth and high rates of multiple partners of males are drivers of the HIV epidemic.

The survey reports significantly increased reported condom use overall, by sex and by age group between the 2005 and 2008 reports. Reported condom use at last sex was 35.4% (95%CI 33.4-37.3) in 2005 and 62.4% (95%CI 60.2-64.6) for people 15

years and older. Reported condom use was similar between males and females. It is unclear how condom use could have increased so massively over a three year period. Perhaps the increase reflects reality, but it could also be that it has become more socially desirable to report use of condoms.

Amongst people who reported multiple sexual partners, reported condom usage was 75.2% (95%CI 69.2-80.4), with no significant change since 2002 and 2005. There was also no significant difference between males and females.

Awareness of HIV status

The survey found that the percentage of people who reported having had an HIV test in the last 12 months and knowing the results doubled between from 11.9% in 2005 to 24.7% in 2008. More women said they know their status than men (28.7% v. 19.9%). These results are significant, though worryingly low and probably explain why so many people present so late for HAART. Among groups defined as being at high risk, 35.7% (95%CI 32.5-39) of African women aged 20-34 years said they had been tested in the last 12 months and learnt their status. Next were MSM, but the confidence interval was very wide (95%CI 17.2-40.3). For African men aged 25-49 it was 25% (95%CI 21.6-28.7).

Knowledge of HIV

The survey measured knowledge of HIV prevention. If interviewees agreed with these two statements they were scored as knowledgeable about HIV prevention:

- To prevent HIV infection, a condom must be used for every round of sex
- One can reduce the risk of HIV by having fewer sexual partners

The survey reports large and significant declines in this measure since 2005 in people aged 15 to 49 years. Participants who answered yes to both questions declined from 64.4% (95%CI 62.5-66.3) in 2005 to 44.8% (95% CI 42.9-46.7) in 2008.

This is implausible. Knowledge is unlikely to deteriorate in what is essentially the same population over a three year period and certainly not by such a large amount. On the contrary it is only likely to increase. Much more plausible explanations are: this is a statistical anomaly; there is something different about the samples between the 2005 and 2008 surveys; the HIV knowledge questions were asked differently; or there was a something different about the way the interviewers carried out their functions.

Furthermore, the wording of the two test statements could have been better; they are not a convincing measure of HIV prevention knowledge. For example, with regard to the first statement, interviewees might consider having an undetectable viral load sufficient to prevent HIV infection. With regard to the second statement interviewees might believe that using condoms consistently negates the risk of having multiple partners. Even if these views are incorrect (and it is not clear that they are), they imply a sophisticated knowledge of HIV prevention.

Participants had to correctly indicate whether these statements were true or false to be marked as knowledgeable about AIDS myths:

- There is a cure for AIDS
- AIDS is caused by witchcraft
- HIV causes AIDS
- AIDS is cured by having sex with a virgin

63.8% (95%CI 62.5–65.1) of people got all four correct. This was not significantly different from 2005.

(Note: The survey also included measures of the exposure of four HIV communication programmes, but I have omitted these in this report.)

References

1. Shisana et al. South African national HIV prevalence, incidence, behaviour and communication survey 2008: A turning tide among teenagers? 2009. Cape Town: HSRC Press. http://www.hsrc.ac.za/Document-3238.phtml
2. Azevedo V. City Health: Khayelitsha. July 2007. http://www.tac.org.za/community/files/KhayelitshaCapeTownCityCouncil-July2007.pdf
3. UNAIDS. UNAIDS Reference Group on Estimates, Modelling and Projections statement on the use of the BED-assay for the estimation of HIV-1 incidence for surveillance or epidemic monitoring. December 2005. http://www.epidem.org/publications/bed%20statement.pdf
4. CDC. Using the BED HIV-1 Capture EIA Assay to Estimate Incidence Using STARHS in the Context of Surveillance in the U.S. http://www.cdc.gov/hiv/topics/surveillance/resources/factsheets/bed.htm
5. Bärnighausen T. Lack of a decline in HIV incidence in a rural community with high HIV prevalence in South Africa, 2003-2007. AIDS Res Hum Retroviruses. 2009 Apr. 25(4) 405-9. http://www.ncbi.nlm.nih.gov/pubmed/19320571

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 release 'New 10-Year Pllan Omits Critical I Protections on HIV and Human Rights'. (11 March 2099)

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 I Support for Harm Reduction":

http://www.hrw.org/en/news/2009/01/19/international-support-harm-reduction

Human Rights Watch's work on drug pollicy:

http://www.hrw.org/en/news/2009/03/09/un-drug-summit-undo-decade-neglect

Job vacancy: Editor post for the Southern African HIV Nursing Magazine

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

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

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

Qualifications

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

Experience

- 10 years practical work experience
- Experience and/or knowledgeable of the HIV/AIDS sector

Experience with an NGO, implementation-focused donor or development organisation

Experience and/or knowledge in the academic publishing field

Proven track record as a published author in academic publications

Remuneration

Remuneration is dependent on skills, experience and qualifications.

To apply

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

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

Closing date 28 August 2009 Only short-listed candidates will be contacted For more information about the Society visit

http://www.sahivsoc.org

ON THE WEB

Online videos from Community Media Trust

A selection of some of the most important and impressive educational resources, developed by the Community Media Trust (CMT) 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 Nobbanda (2005)

http://www.beatit.co.za/siyayinqoba-beat-it-2005/episode-2

PMTCT - Bongiwe M Mkhutyukellwa (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

In addition, an entire treatment literacy series produced by CMT is available in English, Xhosa, Zulu and Portuguese at:

http://www.beatit.co.za/treatment-information-treatment-literacy-series/index

The topics are:

Chapter 1 - What is HIV?
Chapter 2 - The origin of HIV
Chapter 3 - The history of the HIV pandemic
Chapter 4 - Number of People Living with HIV/AIDS (PLWHA)
Chapter 5 - Varieties of HIV
Chapter 6 - How people get HIV
Chapter 7 - Different kinds of germs
Chapter 8 - The HIV lifecycle

This series is an excellent resource for nurses and HIV counsellors.

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 recognise 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 Organisations 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.

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 by email:

rsaucier@sorosny.org

FUTURE MEETINGS

2009 conference listing

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

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

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

http://www.virology-education.com

16-18 July 2009: 4th International 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

30 July -2 August 2009: 3rd Ditan International Conference on Infectious Disease (DICID), Beijing China

http://www.bjditan.org/zymosis/en/index.html

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

http://www.asm.org

5 -8 October 2009: IVth Meeting Latin American Society for Mycobacteria and Tuberculosis, Rosario Argentina

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

http://www.idsociety.org

3-7 December 2009: 40th Union World Conference on Lung Health, Cancun Mexico

http://www.worldlunghealth.org/Conf2009/website/

HIV i-BASE

HIV i-Base is an HIV-positive led treatment information service. We produce information both for clinicians and other health workers and for people with HIV.

Our publications are used and have been adapted in many countries and settings.

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

All i-Base publications are available online.

http://www.i-base.info

i-Base produce five non-technical treatment guides, which are available online as web pages and PDF files.

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

- Introduction to combination therapy
- A guide to changing treatment
- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV

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

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

Recent questions include:

- Will that be considered an overdose?
- Could this be SJS?
- Do my medicines still work?
- I am positive; can I have a tetanus jab?
- What is the deal with reinfection (of HIV)?
- Was in contact with blood in a hotel room, am I at risk?
- How important is it to take etravirine with food?
- What if I don't get a response to the HepB vaccine?
- Shall we change our combinations and if yes-to what?
- Are there any restrictions on the type of work I can do?
- Can we adopt a child?
- Do HIV meds have any dermatological (skin) effects?
- Will loosing weight protect my CD4 count?
- Are there HIV-positive restrictions on travel to Dubai, Malaysia or Hong Kong?

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

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

HIV i-Base
www.i-Base.info

Southern African HIV Clinician's Society
www.sahivsoc.org

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