

HIV treatment bulletin

S O U T H

Volume 1 Number 2

September-December 2008

CONTENTS

EDITORIAL	2	CONFERENCE REPORTS: 3rd International workshop on HIV Transmission, 1 - 2 August 2008, Mexico City	18
OCTANE Trial DSMB finds ritonavir-boosted lopinavir superior to nevirapine in HIV-positive women previously exposed to single dose nevirapine	3	• Intermittent tenofovir/FTC PrEP offers monkeys some protection	
CONFERENCE REPORTS: 48th ICAAC and IDSA joint meeting 25-28 October 2008, Washington DC	5	• Tenofovir/FTC gel protects female monkeys from SHIV	
ICAAC: PREGNANCY & MTCT		• Common estimate of heterosexual HIV transmission risk sometimes far too low	
• Antiretroviral Pregnancy Registry finds no increase in congenital anomalies with exposure to tenofovir		TREATMENT ACCESS	20
• No association between maternal antiretrovirals in pregnancy and congenital anomalies		• FDA approval of generic ARVs	
• Pharmacokinetics of saquinavir/ritonavir in pregnancy		• Atripla to be licensed in Latin America and the Asia-Pacific region	
ICAAC: WOMEN'S HEALTH		ANTIRETROVIRALS	21
• HAART suppresses genital tract HIV shedding in HIV/HSV co-infected women		• ARVs calculated to extend life expectancy by 35 years	
• Efavirenz significantly reduces levels of some oral contraceptives		• FDA approves new paediatric AZT dosing	
ICAAC: PAEDIATRIC CARE		• Baseline renal insufficiency and mortality risk in HIV-positive adults in Lusaka, Zambia	
• Lack of efficacy of isoniazid (INH) prophylaxis and PK evaluation in South African infants		• Inflammatory and coagulation biomarkers linked to mortality in large treatment interruption trial	
• 48-week data for darunavir/ritonavir (DRV/r) in treatment-experienced children and adolescents		OPPORTUNISTIC INFECTIONS	25
ICAAC: ANTIRETROVIRALS		• Single high dose fluconazole for oropharyngeal candidiasis (OPC) comparable to standard 14-day treatment	
• Studies of pipeline drugs: RDEA806, PRO140, beviramat, elvucitabine		PREGNANCY & PMTCT	26
• Other antiretroviral studies at ICAAC		• Tenofovir safe in pregnancy in macaque model	
- Early HAART may improve survival		• Antiretroviral therapy in pregnant women and pregnancy outcomes in Abidjan, Cote D'Ivoire	
- Raltegravir in treatment-naïve patients		PAEDIATRIC CARE	28
- Darunavir is comparable to lopinavir in treatment-naïve patients		• ARV therapy in HIV-positive children in Southern Africa	
- Atazanavir is comparable to lopinavir in treatment-naïve patients		TRANSMISSION	29
ICAAC: SIDE EFFECTS & COMPLICATIONS		• Model-based implications of transmission with undetectable HIV viral load	
• Bone loss in SMART study		• HIV RNA is detectable in semen in 5% patients with undetectable blood plasma viral attending fertility clinic	
• Non alcoholic Fatty Liver Disease (NAFLD) is common among HIV-positive patients		• Tenofovir gel as a rectal microbicide: evidence for protection and priming of T cell responses in the SIV challenge model	
ICAAC: TRANSMISSION		• Genetic protection against malaria may increase susceptibility to HIV infection in people of African descent	
• HIV reinfection reported in 10% of couples in Zambian study		BASIC SCIENCE & VACCINE RESEARCH	32
CONFERENCE REPORTS: 17th International AIDS Conference, 3 - 8 August 2008, Mexico City	13	• US cancel Phase 3 HIV vaccine trial	
MEXICO: ANTIRETROVIRALS		• Microbial translocation in immunological non-responders	
• Abacavir and heart disease: SMART study supports an abacavir-associated increased risk of cardiovascular disease		• Control of a superinfecting virus in an elite controller	
MEXICO: PREGNANCY & PMTCT		• Second-oldest HIV-1 sequence identified	
• HAART use in pregnancy and preterm delivery and low birth weight		• Why do we not yet have an HIV vaccine?	
MEXICO: PAEDIATRIC CARE		ABOUT HIV i-BASE	35
• New paediatric formulations of ARVs			

htb south

HIV Treatment Bulletin

HTB is a quarterly journal published in electronic format by HIV i-Base.

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

To order copies send an email to: subscriptions@i-Base.org.uk

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

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HIV i-Base is a registered charity no 1081905 and company reg no 3962064.

HTB was formally known as DrFax

EDITORIAL

Welcome to the second issue of HTB South.

We lead with the news that preliminary results from the OCTANE trial show lopinavir/ritonavir containing HAART to be significantly more effective than nevirapine containing HAART in women who had previously received a single dose of nevirapine to reduce mother to child transmission.

We include conference coverage from the 48th ICAAC and IDSA joint meeting. We also cover a much smaller workshop on transmission held immediately prior to this, which is appropriate given the highlight given to HIV treatment as a prevention tool. This is also covered in some of our reviews of peer-reviewed publications.

Our next issue will include conference coverage, an update on new guidelines and where we are with maternal health and PMTCT.

Happy New Year!

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.

For more information about the Society or on how to become a member please visit:

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OCTANE Trial DSMB finds ritonavir-boosted lopinavir superior to nevirapine in HIV-positive women previously exposed to single dose nevirapine

Polly Clayden HIV i-Base

On October 28th 2008 the National Institute of Allergy and Infectious Disease (NIAID) in the US released a press release in which they explain that an interim DSMB review of a large clinical trial has found LPV/r containing HAART to be significantly more effective than NVP containing HAART in women who had previously received a single dose of NVP to reduce mother to child transmission.

The A5208/Optimal Combination Therapy After Nevirapine Exposure (OCTANE) study is a phase 3 trial of 745 women at 10 sites in seven African countries.

The trial objectives are to evaluate which of two antiretroviral regimens is more effective for women previously exposed to single dose NVP and whether single dose NVP compromises subsequent NVP containing HAART.

OCTANE is composed of Trial 1 and Trial 2. Women in Trial 1 (n=243) were NVP exposed prior to the study and women in Trial 2 (n=502) were unexposed. Women in each trial were randomised to receive either NVP + FTC/TDF or LPV/r + FTC/TDF. Women were eligible for treatment at CD4 \leq 200 cells/mm³.

The primary endpoint for both trials is time from randomisation to virologic failure or death. Virologic failure is defined as <1 log₁₀ below baseline 12 weeks after starting treatment or as viral load \geq 400 copies/mL at or after 24 weeks of treatment (whether or not randomised treatment is being taken at the time of failure).

On October 6, 2008, the DSMB evaluated interim data from OCTANE (median follow up 66 weeks) and found LPV/r to be significantly more effective than NVP in Trial 1, and also associated with fewer side effects.

At trial entry, the women in Trial 1 were a median of 31 years of age with a median CD4 count of 139 cells/mm³ and viral load of 5.15 log₁₀ copies/mL.

At the time of randomisation the time from receiving single dose NVP was 6 to <12 months for 32% of women, 12 to <24 months for 40% and ≥ 24 months for 28%.

The DSMB found that 39 women discontinued treatment (NVP or LPV/r). This included 34/123 (28%) in the NVP arm and 5/120 (4%) in the LPV/r arm (p $<$ 0.0001).

Significantly more, 29(24%) women in the NVP arm, failed to achieve undetectable viral load (n=25) or died (n=4), compared to 8(7%) women in the LPV/r arm who failed to achieve undetectable viral load (n=7) or died (n=1) (p=0.0005).

None of the 5 deaths were reported to be associated with antiretroviral treatment.

The DSMB also found that of the 25/200 women who began the study with resistance to NVP, those in the NVP arm were more likely to be unsuppressed or die than those in the LPV/r arm. 5/13 women (38%) in the NVP arm who began the study with NVP-resistance either had detectable viral load or died, while all of the 12 women in the LPV/r arm who began with

NVP-resistance are alive with undetectable viral load.

Additionally they found a trend for the negative effects of prior single dose NVP exposure to decrease the greater the interval between receiving single dose NVP and initiating NVP containing HAART (see Table 1).

Table 1. OCTANE Trial 1: Women experiencing negative effects of prior single dose NVP exposure on NVP containing HAART by interval since exposure

Time since s/d NVP	NVP arm	LPV/r arm
6 to <12 months	n=15 (37%)	n=1 (3%)
12 to <24 months	n=11 (24%)	n=4 (8%)
>24 months	n=3 (8%)	n=3 (10%)

n= number of women who reached an endpoint at time of DSMB review.

Following the review the DSMB recommended that these findings about Trial 1 be unblinded.

As there are no safety concerns with Trial 2, the DSMB advised that it continue as planned.

The study investigators are notifying all participants of the findings of the DSMB. Treatment with LPV/r is available to the women in Trial 1 who have been receiving NVP, should the participant and investigator choose to change their therapy. Trial 2 will continue as planned until the end of the study June 2009 to determine how the two treatment options compare for women who have not previously taken NVP.

C O M M E N T

That NVP exposed women receiving NVP-containing HAART did less well than those receiving LPV/r-containing HAART is unsurprising.

One thing that is notable about these findings though is that the women in the LPV/r arm had results that were better than might be expected from other studies: 93% were alive and below detection (<400 copies/mL; <50 copies/mL data was not shown) at a median of 66 weeks. This compares to results from the CASTLE study 76% of patients on LPV/r had <50 copies/mL at 48 weeks; ARTEMIS, 78% on LPV/r had <50 copies at 48 weeks; KLEAN, 71% on LPV/r had <400 copies at 48 weeks and in ACTG 5142, 86% on LPV/r had <200 copies/mL at 96 weeks. Although backbones and endpoints vary, the OCTANE LPV/r arm appears to have performed very well. So the results from Trial 2 of LPV/r vs NVP in unexposed women will also be useful and that part of the trial is still ongoing.

Most importantly, the median CD4 of the women at enrollment in OCTANE was 139 cells/mm³, and the median interval since receiving single dose NVP was about 12-18 months. So many of these women may have met the eligibility criteria to start HAART at 200 cells/mm³ for their own health in pregnancy had it been available (and probably all if the threshold was 350 cells/mm³). These women with low CD4 during pregnancy receiving single dose NVP would be at higher risk of NVP resistance and therefore be more likely to fail NVP containing HAART if they started within a year or so of exposure.

That there was a trend for the negative effects of prior single dose

NVP exposure to decrease as the interval between receiving single dose NVP and initiating NVP containing HAART became greater is consistent with other studies. MASHI-Plus, NEVEREST and the CDC studies have all reported that response to NVP containing HAART in women with sd NVP exposure <12 months or so prior to starting HAART was poor compared to those without exposure, but response in women with sd NVP exposure >12 months or so prior to starting HAART was similar to those without exposure. In OCTANE, for women starting HAART ≥ 2 years after sd NVP exposure there was no significant difference between LPV/r and NVP containing HAART. One explanation being that these women had higher CD4 at the time of exposure and therefore less at risk for acquisition of resistance.

Although programmes are increasingly using short course AZT with sd NVP for PMTCT this strategy appears to have only modest impact on acquisition of resistance.

So what needs to be done?

1. HIV-positive pregnant women should have CD4 counts in pregnancy, and these need to be available at all health service levels.

2. Women who meet the criteria for HAART initiation should receive treatment for their own HIV as a matter of urgency. Ideally the threshold should be <350 cells/mm³, but even following the minimum guideline recommendation of 200 cells/mm³ correctly will exclude women most at risk for acquisition of resistance, of mother to child transmission and (often neglected in PMTCT discussion) AIDS and death. This should continue post partum. This is uncontroversial.

3. More controversial is what is the best intervention for women not in need of treatment for their own health. Current WHO guidelines recommend a two-tiered approach in which healthy women receive short course AZT plus single dose nevirapine with AZT/3TC for 7 days post partum to reduce resistance risk. These data re-emphasise the need to include the AZT/3TC "tail" intervention with this strategy to reduce the risk of NNRTI resistance, which has not been adopted in all PMTCT programmes.

4. Should guidelines change to offer short course HAART to healthy women stopping after delivery or breastfeeding? If so what regimen? NVP is out of the question because of hepatotoxicity risk at higher CD4 counts, PIs are very expensive and triple nucleosides have limited data and may be less effective. Additionally following the SMART results concerns have been raised about the safety of treatment interruptions.

5. So one thing is clear, we need more data. Trials are planned or underway, for example, in Thailand and Botswana, and a large trial is planned with sites in US/Brazil and Africa and Asia to address many of these questions. Additionally the Botswana national programme is planning to roll out a pilot of universal HAART in pregnancy. The next WHO guidelines revision will need to address this issue and WHO is convening an initial consultative meeting on this in November 2008.

We will do a detailed review of the current data, ongoing and planned trials and outstanding research questions in the next issue of HTB South.

Particular thanks to James McIntyre and Lynne Mofenson for discussion of these results.

Source: NIAID press release. "DSMB finds ritonavir-boosted lopinavir superior to nevirapine in HIV-positive women who previously took single-dose nevirapine". (28 October 2008).

<http://www.niaid.nih.gov>

CONFERENCE REPORTS

ICAAC: PREGNANCY AND MTCT

48th ICAAC and IDSA joint meeting**25-28 October 2008, Washington DC**<http://www.icaacidsa2008.org>

We were not able to attend the 48th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) this year, which has gradually reduced its focus on HIV, although this year the meeting was combined annual IDSA meeting.

Unfortunately ICAAC continues to make few presentations available online, and only limited access to abstracts (which usually are removed within a month or so of the meeting finishing).

Nevertheless, some of the interesting studies reported below include:

- Antiretroviral Pregnancy Registry finds no increase in congenital anomalies with exposure to tenofovir
- No association between maternal antiretrovirals in pregnancy and congenital anomalies
- Pharmacokinetics of saquinavir/ritonavir in pregnancy
- HAART suppresses genital tract HIV shedding in HIV/HSV co-infected women
- Efavirenz significantly reduces levels of some oral contraceptives
- Lack of efficacy of isoniazid (INH) prophylaxis and PK evaluation in South African infants
- 48-week data for darunavir/ritonavir (DRV/r) in treatment-experienced children and adolescents
- Studies of pipeline drugs: RDEA806, PRO140, beviramat, Elvucitabine
- Other antiretroviral studies at ICAAC
 - Raltegravir in treatment-naïve patients
 - Early HAART may improve survival
 - Darunavir is comparable to lopinavir in treatment-naïve patients
 - Atazanavir is comparable to lopinavir in treatment-naïve patients
- Bone loss in SMART study
- Non alcoholic Fatty Liver Disease (NAFLD) is common among HIV-positive patients
- HIV reinfection reported in 10% of couples in Zambian study

Unless stated otherwise, all references are to the Programme and Abstract of the 48th Annual ICAAC. Abstracts only remain online (follow the link to the Programme Planner) for a short period after the conference ends.

<http://www.icaacidsa2008.org>**Antiretroviral Pregnancy Registry finds no increase in congenital anomalies with exposure to tenofovir****Polly Clayden, HIV i-Base**

The Antiretroviral Pregnancy Registry (APR) is a prospective registry, based in the US, to detect teratogenic effects in infants exposed to maternal antiretroviral therapy. The APR collects data through voluntary reporting from health care providers.

The registry receives reports on approximately 900 pregnant women receiving antiretrovirals each year (approximately 14% of live infants born to HIV-positive women) and has operated since January 1, 1989. It has received information on sufficient numbers of first trimester exposures to 11 antiretrovirals including AZT and TDF to detect at least a 1.5- and 2-fold increase in overall birth defects respectively.

A poster from Olmsheid and Zhang showed that, as of July 31 2007, among 8483 prospective cases reported to the APR, there has been no overall increase in congenital anomalies in infants following any first or second/third trimester antiretroviral exposure compared to the general population. [1]

The authors report that the prevalence of anomalies with any antiretroviral exposure in the first trimester was 2.8/100 live births (95% CI: 2.2-3.5) [74/2673]; with 2nd/3rd trimester exposure 2.6/100 live births (2.1-3.1) [109/4220].

The prevalence of anomalies with first trimester exposure to TDF was 1.6% (0.6-3.4) [6/380] and with 2nd/3rd trimester exposure the prevalence was 1.5% (0.4-3.9) [4/263]. There was no specific pattern of anomalies reported. The prevalence of anomalies with first trimester exposure to AZT was 2.9% (2.2-3.8) [53/1816] and with 2nd/3rd trimester exposure, 2.7% (2.2-3.2) [121/4491].

The authors note that these rates are comparable to those from the CDC population-based birth defects surveillance system (2.7/100 live births).

They write: "To date no increase in prevalence of or any specific pattern of congenital anomalies has been seen with use of TDF in 643 live births through prospective voluntary reporting to the APR."

C O M M E N T

These data are reassuring and are supported in the animal study that we report later in this issue.

Ref: Olmscheid B. and Zhang S. Use of tenofovir disoproxil fumarate (TDF) in pregnancy: Findings from the Antiretroviral Pregnancy Registry (APR). 48th ICAAC, 25-28 October 2008. Washington. Abstract H-456.

The Antiretroviral Pregnancy Registry
<http://www.apregistry.com/>

No association between maternal antiretrovirals in pregnancy and congenital anomalies

Polly Clayden, HIV i-Base

Data from the NISDI Perinatal Study conducted in Argentina and Brazil suggest no association between in utero antiretroviral (ARV) exposure and congenital anomalies (CAs).

The NISDI Perinatal Study is a prospective cohort study of HIV-positive women and their infants.

In this analysis all singleton pregnancy outcomes ≥ 20 weeks gestation were included. CAs were evaluated according to the Antiretroviral Pregnancy Registry criteria. Maternal ARV regimens were categorised according to the most complex regimen received for ≥ 28 days of pregnancy.

Of the women enrolled in this study 995/1229 pregnancy outcomes met the inclusion criteria. The investigators reported that, of these, 60/974 liveborn infants and 1 stillborn infant had at least one CA. They found the overall incidence of CAs in this study was 6.26 defects/100 live births (95% CI: 4.74 -7.78).

They reported no statistically significant differences in the proportion of pregnancy outcomes with CAs according to: whether maternal ART was initiated before conception ($p=0.86$); the most complex ARV regimen received during pregnancy ($p=0.45$) or during the 1st trimester ($p=0.06$).

They wrote: "In this study population, preliminary results suggest CAs were not associated with exposure to ARVs at conception or most complex regimen received during the first trimester or during pregnancy overall."

Ref: Joao E, Calvert GA, Krauss M et al. Maternal antiretrovirals during pregnancy and infant congenital anomalies: The NISDI Perinatal Study. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-457.

Pharmacokinetics of saquinavir/ritonavir in pregnancy

Polly Clayden, HIV i-Base

A prospective multicentre study conducted in Thailand, Spain, UK, Germany and the Netherlands evaluated the PK of RTV boosted SQV in HIV positive pregnant women.

Women in this study received SQV 500mg tablets + RTV, 1000/100mg BID + 2 NRTIs. They were enrolled either before the 2nd (week 20, +/- 2) or the 3rd trimester (week 33, +/-2). The study looked at safety, efficacy and 12 hour PK curves in the 2nd trimester the 3rd trimester and 4-6 weeks post-partum.

Forty women were enrolled, of these 8 discontinued the study before their first PK visit (2 due to toxicities associated with study drugs). The mean age of the women at baseline was 30.3 years, weight 68 kg, 42% of the women were ARV naïve and 42% had viral load < 50 copies/mL.

Two serious adverse events were reported: one abortion and one diabetes gravidarum. AST/ALT grade 3/4 was reported in 2 women, lipids remained unchanged. At 20, 33 weeks of gestation

and 6 weeks postpartum, 73%, 91% and 87% of women had viral load < 50 copies/mL respectively.

The investigators found the mean (SD) SQV AUC 0-12h, was 23.5 (11.9) mg/L.h, on week 20; 23.7 (9.1) mg/L.h, on week 33, and 25.0 (11.8) mg/L.h, on week 6 post partum. None of the women showed a subtherapeutic Cmin of SQV (< 0.10 mg/L) at any timepoint.

In this study SQV/r was safe and effective and plasma concentrations of SQV were not affected by pregnancy.

Ref: Van der Lugt J, Molto J, Hawkins D et al. Safety, efficacy and pharmacokinetics of saquinavir Boosted by ritonavir (1000/100mg BID) in pregnant HIV infected women. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-455.

ICAAC: WOMEN'S HEALTH

HAART suppresses genital tract HIV shedding in HIV/HSV co-infected women

Polly Clayden, HIV i-Base

There are limited data describing the effect of chronic HSV suppression on genital tract (GT) HIV among women receiving HAART.

Preliminary data was shown from a group of 34 women with HIV-1 / HSV-2 co-infection. The women in this study were receiving HAART with plasma viral load < 75 copies/mL stable for at least 3 months prior to entry, and were randomly assigned to receive acyclovir 800 mg twice daily ($n=22$) or no acyclovir ($n=12$). Paired plasma and GT viral loads and GT HSV DNA values were taken every 4 weeks.

The mean baseline age of the women was 46 years and CD4 count 504 cells/mm³. 39% of women were white, 36% black and 18% Latino. None had positive tests for gonorrhoea, chlamydia, syphilis or HSV shedding and one had a positive trichomonas test at baseline.

Over the first 3 study visits ($n= 97$), 5 women experienced an episode of asymptomatic HSV shedding, 1/22 (4.5%) in the acyclovir arm and 4/12 (33.3%) in the control arm ($p=0.04$, OR=0.10, CI 0.0-1.2). These were not associated with GT HIV shedding. 5 women had episodes of GT HIV shedding during 7 follow-up visits (4250-850,000 copies/mL); 3/22 in the acyclovir arm and 2/12 in the control arm ($p=1.0$, OR=0.8, CI 0.08 to 11.0).

The investigators found predictors of GT HIV were detectable plasma viral load (OR 12.8, CI 2.5 -66.4) and baseline GT shedding (OR 5.98, CI 0.96 -37.1). Risk factors for HSV shedding in the acyclovir arm and GT HIV shedding in both arms were poor adherence to acyclovir and HAART respectively.

They concluded that the results of this small study reinforce the importance of HAART in decreasing HIV sexual transmission.

Ref: Nijhawan A, Delong A, Chapman A et al. Highly Active Antiretroviral Therapy suppresses genital tract HIV shedding with or without chronic HSV suppression among HIV-1/HSV-2 co-infected women. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-2328.

Efavirenz significantly reduces levels of some oral contraceptives

Polly Clayden, HIV i-Base

A PK study evaluated the effect of co-administration of EFV 600 mg on an ethinylestradiol (EE) and norgestimate (NGM)-containing oral contraceptive (OC).

This was an open-label, 3-period, single-sequence study conducted in healthy female volunteers. Women received Ortho Tri-Cyclen® LO once nightly (QHS) on Days 1 - 28 (period 1, n=28), Ortho Cyclen® QHS on Days 29 - 56 (period 2, n=23) and Ortho Cyclen with EFV 600 mg QHS on Days 57 - 70 (period 3, n=21).

The investigators determined noncompartmental PK. Adjusted geometric mean ratios (GMR) and 90% confidence intervals (CI) for the PK of EE and the major active metabolite of NGM, norelgestromin (NGMN), were estimated. They also conducted a similar evaluation of the secondary active metabolite levonorgestrel (LNG) PK in a small group of women (n=6). Serum progesterone (PG) levels were determined on Days 18, 46 and 74.

Comparing, period 3 to period 2, the investigators found that EFV had no effect on EE C_{max} or AUC with GMRs (90% CI) of 1.06 (0.95 - 1.19) and 0.90 (0.80 - 1.01), respectively. EFV significantly decreased NGMN C_{max} and AUC with GMRs (90% CI) of 0.54 (0.48-0.61) and 0.36 (0.33-0.38), respectively; LNG exposures (N=6) were also significantly decreased, with AUC GMR (90% CI) of 0.17 (0.13-0.21). PG levels were similar across periods.

The investigators concluded that these results reinforce the need for additional methods of barrier contraception when taking OC and EFV together.

Ref: Sevinsky H, Eley T, He B et al. Effect of efavirenz on the pharmacokinetics of ethinylestradiol and norgestimate in healthy female subjects. 48th ICAAC, 25-28 October 2008. Washington. Abstract A-958.

ICAAC: PAEDIATRIC CARE

Lack of efficacy of isoniazid (INH) prophylaxis and PK evaluation in South African infants

Polly Clayden, HIV i-Base

A South African study looked at isoniazid (INH) prophylaxis in young infants and found no increase in TB free survival. [1]

PACTG 1041 was a phase II/III double blind, randomised, placebo-controlled study of primary INH prophylaxis for prevention TB disease and latent infection infants with perinatal HIV-exposure.

In this study, HIV-positive, BCG vaccinated infants of 3-4 months of age were randomised to daily INH (10-20mg/kg/day) or placebo for 96 weeks. The infants also received cotrimoxazole, and ART where indicated, in accordance with WHO guidelines.

The primary objective of the study was to investigate whether INH

increases TB disease-free survival in young infants. Endpoints were TB disease and mortality at 96 weeks.

HIV-positive children (n=452, 226 per arm) with median age 96 days were enrolled between December 2004 and March 2008.

The children's baseline median CD4% was 27% (range: 6-58%); 91% were CDC clinical category N/A, their median viral load was 666,500 copies/mL and 28% were receiving ART. At time of this scheduled interim analysis 66% of children were receiving ART.

The investigators found, at a median of 36 weeks follow up, 39 (17.3%) and 32 (14.2%) children in the INH and placebo groups, respectively, had TB or died, p=0.34. There were 24 (10.6%) and 22 (8.4%) (p=0.69) cases of TB and 15 (6.6%) and 10 (4.4%) non-TB related deaths in the INH and placebo groups, respectively. They reported no significant difference in rates of adverse event rates between the two groups.

In this study the overall cumulative incidence of TB by 96 weeks was high (22.2%; 95%CI: 15.7, 31.0).

The investigators wrote: "INH prophylaxis did not improve TB-disease free survival in HIV-positive African children with access to ART, indicating the need for alternative strategies to reduce the high public-health burden of childhood TB."

As the appropriate INH infant dose is unknown, PACTG 1041 also investigated INH PK, and determined N-acetyltransferase-2 (NAT2) genotype to evaluate if PG explains INH PK [2].

The PK study target enrollment is 336 infants. Half of the infants were sampled at weeks 0 and 84 at 2 and 4 hours post dose, and the remaining children at weeks 12 and 84 at 1 and 3 hours post dose. INH was quantified in plasma (HPLC). NAT2 genotype was determined using RFLP and phenotypes assigned as slow (S), intermediate (I), and fast (F) acetylators.

This study used a 1-compartment model with first-order absorption and elimination (NONMEM v.VI). Covariates, including NAT2 phenotype, age, weight, sex, and HIV status, were evaluated using stepwise forward inclusion (p=0.05) and backward elimination (p=0.01).

The investigators modeled 306 INH concentrations from 131 infants. The infants had a median age of 171 days (range 91-717 days) at sampling; 53 were HIV-positive; 65 were girls; NAT2 phenotype, 32 S, 46 I, 30 F. Mean (SD) INH dose, 14 (3) mg/kg/d. Mean (SD) INH concentrations at 1, 2, 3, and 4 hours post dose were 12.0 (4.7), 8.3 (3.8), 6.3 (3.0), and 4.4 (3.0) mg/L, respectively.

They found the infants' weight and NAT2 phenotype but not HIV status explained most of the interpatient variability in INH oral clearance (CL/F). Typical CL/F at weeks 0 and 12 for F phenotype were 3.3 and 3.9 L/hr and were 1.4 and 1.7 L/hr for S.

They wrote: "INH PK at a dose of 10-20 mg/kg/d in these infants are similar to published data in older (median 3.8 years) children receiving 10 mg/kg/d. The comparability of PK supports continued evaluation of this dose, which is at least twice that recommended by WHO."

C O M M E N T

The full results of this trial are not yet out (but unlikely to change). The investigators are studying the data to explain

why no benefit was found for pre-exposure prophylaxis despite a high rate of incident TB.

References

1. Madhi SA, Nachman S, Violari A et al. Lack of efficacy of primary isoniazid (INH) prophylaxis in increasing tuberculosis (TB) free survival in HIV-infected (HIV+) South African children. 48th ICAAC, 25-28 October 2008. Washington. Abstract G2-1346a.
2. Kiser J, Zhu R, Nachman S et al. Pharmacokinetics (PK) and Genetics (PG) of Isoniazid (INH) in South African HIV-Exposed Infants-PACTG 1041. 48th ICAAC, 25-28 October 2008. Washington. Abstract A-1826.

48-week data for darunavir/ritonavir (DRV/r) in treatment-experienced children and adolescents

Polly Clayden, HIV i-Base

48-week data was presented from the DELPHI (TMC114-C212) study. DELPHI is a multi site open-label, two-part Phase II study assessing the safety and efficacy of DRV/r plus OBR in treatment-experienced children and adolescents.

Children were dosed according to body weight for ≥ 48 weeks: 20- <30 kg, 375/50mg bid (20 patients); 30- <40 kg, 450/60mg bid (24 patients); ≥ 40 kg, 600/100mg bid (36 patients). PK, safety and efficacy (viral load, CD4 % and CD4 counts) were evaluated throughout the study.

80 children with a median age of 14 years (range: 6-17 years) of which 71% were male received DRV/r. At baseline their mean viral load was 4.64 log, median CD4 was 330 cells/mm³ and CD4 % was 17%. They had a median of 3 primary PI mutations, 11 PI RAMs (65% had ≥ 10 PI RAMs), 2 NNRTI and 4 NRTI RAMs.

The investigators reported that target DRV PK concentrations for treatment-experienced adults were achieved across all ages and weight bands, which confirmed the dose selection.

The majority of patients (74, 93%) experienced one AE. The most frequently reported were: fever, cough, upper respiratory tract infection and diarrhea. Most were grade 1/2. 21 (26%) patients had grade 3/4 AEs but most were considered to be unrelated to DRV/r. 11 (14%) of patients (14%) experienced serious AEs but there were no deaths. One patient discontinued the study because of grade 3 anxiety but this was not considered to be DRV/r related. 6 pts (8%) had grade 2-4 AEs possibly related to DRV/r.

At week 48, 65% of patients had ≥ 1.0 log₁₀ viral load reduction (TLOVR); 59% and 48% were undetectable to <400 and <50 copies/mL (TLOVR), respectively. Their mean CD4 increase was 147 cells/mm³.

The investigators noted that predictive analyses will be performed to evaluate the contribution of the OBR to response rates in this population.

Ref: Blanche S, Bologna R, Cahn P et al. 48-wk safety and efficacy of Darunavir/ritonavir (DRV/r) in treatment experienced children and adolescents in DELPHI. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-894.

ICAAC: ANTIRETROVIRALS

Studies of pipeline drugs

Simon Collins, HIV i-Base

Several posters provided information on interesting compounds in development.

RDEA806 – an NNRTI

Pharmacokinetic results from a Phase 2a study of a new NNRTI from Ardea previously presented at Mexico, was presented by Graeme Moyle from the Chelsea and Westminster Hospital, London. [1]

Two cohorts of 12 treatment naïve HIV-positive patients were randomised (9 active: 3 placebo) to receive either RDEA806 400 mg twice daily (BID), or 600 mg once daily (QD), for 7 days and a single morning dose on Day 8 for PK determination.

All patients achieved viral load reductions of 1.5 - 2.0 log viral load reduction with a trend seen between reductions and C_{trough} (but not C_{max} or AUC).

Mean C_{trough} at steady state were 407 and 112 nM for the BID and QD groups, respectively, and were well above the anti-HIV EC₅₀ for wild-type (3 nM) and resistant (K103N, 2.3 nM) virus.

Studies with additional cohorts to evaluate higher once daily doses with an enteric coated tablet formulation are underway.

A second poster present by Xu and colleagues from Ardea Bio presented results of in vitro resistance mutations selected in the presence of RDEA806. [2]

RDEA806 concentration was increased to 1500 nM in the virus culture over the course of 13 months. K104E was identified after > 300 days with no loss of susceptibility to RDEA806 or other NNRTIs. RDEA806 showed a minor loss of activity to the next virus selected, K104E-E138K-T240I, while efavirenz retained full activity. Virus with the final combination of 5 mutations in RT (K104E-E138K-T240I-V179D-F227L), which reduced phenotypic susceptibility to RDEA806 but only minor to moderate cross-resistance to other NNRTIs, had very low replication capacity.

Reference:

1. Moyle G et al. RDEA806, a novel HIV NNRTI, shows positive outcome in treatment of naïve HIV patients. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-893.

http://www.ardeabio.com/Docs/icaac_rdea201_presentation_FINAL.pdf

2. Xu W et al. Resistance to RDEA806 requires multiple mutations which have limited cross-resistance to other NNRTIs. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-1222.

http://www.ardeabio.com/Docs/ICAAC_2008_806R_poster_v_102208%20final.pdf

PRO140 – a monoclonal antibody to CCR5

In a single dose (5mg/kg) study PRO 140 reduced viral load by -1.83 log in patients with early-stage disease and R5 virus only. At ICAAC results were presented from a randomised placebo controlled study using 5mg/kg and 10mg/kg IV doses in patients with CD4 >300 who had not used ARV treatment for the previous 12 weeks.

Patients were followed for 58 days post-treatment and results presented from an interim analysis on data from the first 15 subjects.

Results: Interim enrollment was equally distributed across the treatment groups. Baseline HIV RNA and CD4 averaged 35,480 copies/mL and 403 cells/mm³, respectively.

At Day 12, mean log₁₀ changes in HIV RNA were +0.06, -1.88 (p<0.0001), and -2.01 (p<0.0001) for placebo, 5mg/kg and 10mg/kg, respectively.

Mean maximum viral load reductions in HIV RNA were 0.48 (range 0.15-0.73) for placebo, 1.90 (range 1.44-2.17, p<0.0001) for 5mg/kg and 2.17 (range 2.09-2.26, p<0.0001) for 10mg/kg groups.

The authors concluded that these results indicated the potential for infrequent IV dosing and that sub-cutaneous dosing was also being evaluated.

C O M M E N T

The mechanism of action of this drug is different from the other CCR5 inhibitors and could potentially be synergistic with them, or work on viruses that have developed resistance to them.

The current intravenous administration of PRO 140 suggests dosing every 2 to 3 weeks, whereas modelling suggests that an increase in the dose might extend that to a month. The manufacturer is investigating other possible modes of administration, including a transdermal patch that might administer a more steady state of the drug.

There are patients who do not adhere to daily may benefit from once every three weeks or longer gap regimen. Future studies might look at prophylactic use of the monoclonal antibody as a form of pre-exposure prophylaxis, at least in high-risk populations.

Reference

Jacobson JM et al. Antiviral activity and tolerability of 5 mg/kg and 10 mg/kg doses of PRO 140, a humanised monoclonal antibody to CCR5. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-1269a.

Beviramat – maturation inhibitor

Lalezari and colleagues presented results from a Phase 2 double-blind, randomised dose escalation study of beviramat (PA-457), a maturation inhibitor that targets the Gag capsid SP-1 cleavage site. [1]

A poster at the Resistance workshop this year reported the impact of baseline polymorphisms in Gag on viral load response. Changes at positions 369, 370 or 371 lead to reductions -0.16 (n=9), -0.24 (n=22) and -0.32 logs (n=11) respectively, compared to -1.08 logs in patients with no changes at 369-371. [2]

59 treatment-experienced patients received 2 weeks of beviramat or placebo as functional monotherapy on top of a failing (VL >2000 copies/mL) background regimen. Patients initially received a 400mg beviramat tablet dose, or placebo; in the modified study, patients received a 250, 300, 350 or 400mg beviramat liquid dose, or placebo.

Of 44 patients given the assigned beviramat dose, the mean VL change was -0.6 log copies/mL vs +0.05 log for placebo (n=13). 12/13 (92%) patients with beviramat trough levels \geq 20

ug/mL and without the key Gag polymorphisms had reductions of \geq 0.5 log; 10/13 (77%) had a VLR >1.0 log (group mean VLR: -1.26 log). 32/46 (70%) beviramat treated patients and 10/13 (77%) placebo treated patients had \geq 1 adverse event (AE). For beviramat and placebo treated patients respectively, the most common AEs were diarrhea (22%; 39%), nausea (20%; 31%) and headache (20%; 23%); all were Grade 1.

Phase 3 studies are planned to include Gag mutations screening criteria and pharmacokinetics to confirm the utility of beviramat in treatment-experienced patients.

References

1. Lalezari J et al. A Phase 2 safety and efficacy study of beviramat (BVM) in heavily treatment experienced HIV+ patients identifies the target Phase 3 study profile. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-891.
2. McCallister S et al. HIV-1 gag polymorphisms determine treatment response to beviramat (PA-457). XVII IHDRW 2008, Sitges. 48th ICAAC, 25-28 October 2008. Washington. Abstract 8.
<http://www.i-base.info/htb/v9/htb9-7-8/Pipeline.html>

Elvicitabine

Elvicitabine (ELV) is a cytosine nucleoside analogue with a long half-life (90 hours), and has been shown in vitro to have potent activity against HIV-1. DeJesus and colleagues presented interim 48-week results from a Phase II study against 3TC in treatment naive patients.

77 subjects were randomised to either ELV 10 mg versus 3TC 300 mg both administered daily in combination with efavirenz 600 mg and tenofovir DF 300 mg. Fifty-five subjects completed 48 weeks of treatment. The proportion of subjects at week 48 with viral load <50 copies/mL in the ITT patient population was marginally higher in the 3TC arm compared to ELV (78% vs. 65%, p=0.07). Adverse events were similar between treatment groups.

C O M M E N T

Elvicitabine's efficacy in this study, in regard to intention-to-treat analysis, demonstrates that it is nonsignificantly inferior to lamivudine. In percent CD4 of +9.9 (6.3) versus +9.1 (7.2) with 3TC arm. Earlier report from 24 weeks study demonstrated more adverse side effects in the ELV arm which were not the case at 48 weeks. This drug will require further studies, particularly an examination of its long-term antiviral activity and safety, to evaluate its role in HIV therapy in the future.

Reference:

DeJesus E et al. Elvicitabine phase II 48 week interim results show safety and efficacy profiles similar to lamivudine in treatment naive HIV-1 infected patients with a unique pharmacokinetic profile. 48th ICAAC, 25-28 October 2008. Washington. Abstract: H-892.

Other antiretroviral studies at ICAAC

Satyajit Das, HIV i-Base

Brief reviews of the main ARV studies at ICAAC.

Early HAART may improve survival

Starting treatment against deferring highly active antiretroviral therapy (HAART) at a CD4 count between 351 and 500 cells/mm³ was associated with a 70% reduction in mortality rates.

This study incorporated collaboration between 22 HIV research cohorts in North America and a standardisation of data to allow their integration and analysis. Patients were those with a CD4 count between 351 and 500 cells/mm³ who were in active follow-up between 1996 and 2006. Patients with previous antiretroviral treatment and those who already had experienced an AIDS-defining illness were excluded.

Over 2450 patients initiated HAART (8358 person-years), and just over 5900 patients (16,636 person-years) deferred treatment during the period of the study. Those who began treatment were more likely to be male sex, older, have a higher viral load at baseline, but the differences in median values between the two groups were not large.

Those who deferred starting HAART had a mortality relative hazard 1.7 times that of patients who began therapy within that CD4 range ($P < 0.001$).

The presenting author suggested that the data strongly support the use of antiretroviral treatment for patients at a CD4 count of 500 and below, regardless of the presence of symptoms.

C O M M E N T

Previous studies have suggested similar trends, but most of the studies did not have the power to find meaningful differences in strategies. Although this was an observational study, aggregation of the cohorts together created sufficient power to reach definitive conclusions.

However, in most centres, even in industrialised countries, a significant number of patients are diagnosed with HIV for the first time with low CD4 counts or with AIDS defining illnesses.

Ref: Kitahata MM et al. Initiating rather than deferring HAART at a CD4+ count between 351-500 cells/mm³ is associated with improved survival. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-896b.

Raltegravir in treatment-naïve patients

Lennox and colleagues reported results in a late-breaker presentation, from the STARTMRK Phase 3 trial comparing raltegravir, against efavirenz, both in combination with Truvada, in treatment-naïve HIV patients. [1] Raltegravir continues to impress with its safety and efficacy, this time with 48-week data from treatment-naïve patients.

Patients were screened for resistance to tenofovir or emtricitabine, and the 563 patients who showed no resistance were enrolled in the randomized blinded trial to add either raltegravir (400 mg twice daily) or efavirenz (600 mg every day at bedtime) to the regimen. At baseline, a significant portion of patients had advanced HIV disease with 47% having a CD4 T-cell count of 200 or less cells/mm³ and 53% having a viral load of more than 10⁵ HIV RNA copies/mL. The primary end point was suppression to less than 50 HIV RNA copies/mL.

Both arms showed high rates of suppression at one year.

Using an intent-to-treat analysis, 86.1% of the raltegravir and 81.9% of the efavirenz groups achieved the primary end point of <50 copies/mL. The difference did not reach statistical significance, but the study easily achieved its goal of demonstrating that non-inferiority of raltegravir to efavirenz ($p < 0.001$).

There was faster initial suppression of viraemia in the raltegravir group, but the two groups converged over time. The increase in CD4 cells from baseline was 26 cells/mm³ higher in the raltegravir group (189 cells/mm³ vs. 163 cells/mm³), but did not reach statistical significance.

Adverse effects were common in both groups (44% vs 77%), with raltegravir maintaining the more favourable profile for moderate to severe events (16% vs 32%).

One of the greatest drawbacks to efavirenz is that a portion of patients experience central nervous system (CNS) problems, some to the point of discontinuing its use. The accumulated CNS adverse events to week 8 favoured raltegravir (10.3% vs. 17.4%). Depression occurred in around 5% of patients in both groups to week 48.

There was one malignancy in the raltegravir arm and nine in the efavirenz arm, most of which were Kaposi's sarcoma.

Total cholesterol, LDL and triglycerides increases were higher in the efavirenz arm (all $p < 0.001$ compared to raltegravir) but efavirenz patients also experienced higher increases in HDL ($p < 0.001$). The total-to-HDL cholesterol ratio dropped slightly in both treatment arms (NS between arms).

In summary, raltegravir showed comparable virological efficacy as efavirenz at 48 weeks in treatment naïve HIV patients, but was better tolerated.

The researchers presented some data looking at whether raltegravir could be dosed once-daily, and QQ studies are planned.

C O M M E N T

This trial possibly brings integrase inhibitors, specifically raltegravir, into the list of drugs that we could consider for first-line use.

However, unless the current price is dramatically reduced to a comparative level of other first-line combinations, it is unlikely to be broadly available anywhere.

Ref: Lennox J et al. STARTMRK, a phase III study of the safety & efficacy of raltegravir (RAL)-based vs Efavirenz (EFV)-based combination therapy in treatment-naïve HIV-infected patients. 48th ICAAC, 25-28 October 2008. Washington. Abstract: H-896a.

Darunavir is comparable to lopinavir in treatment-naïve patients

In the ARTEMIS study, darunavir/ritonavir (DRV/r) appears to be statistically superior to lopinavir/ritonavir (LPV/r) in treatment-naïve patients after 96 weeks of treatment. The study showed non-inferiority at 48 weeks, but at the 96-week endpoint there was statistical significance as far as superiority.

Over 680 patients were randomised to receive either DRV/r 800/100 mg once daily or a total daily dose of LPV/r 800/200 mg with backbone of Truvada (tenofovir/FTC).

At week 96, a greater percentage of patients in the DRV/r group had <50 copies/mL (79% vs. 71%, $p = 0.38$), and the median change in absolute CD4 count was greater (+188 vs +171 cells/mm³). This continues a trend observed in week-48 data.

The authors suggest that tolerability explains much of the difference in dropouts and virologic failure between the two groups.

It is important that the LPV/R arm started with tablets and soft gel capsules as well (Table 1).

Table 1: Lopinavir dosing

LPV dosing		LPV formulation	
QD	15%	Capsule only	12%
BID	75%	Tablet only	2%
BID/QD	11%	Capsule/tablet switch	86%

Ref: Mills A et al. ARTEMIS: Efficacy and Safety of Darunavir/ritonavir (DRV/r) 800/100 mg Once-daily vs Lopinavir/ritonavir (LPV/r) in Treatment-naïve, HIV-1-infected Patients at 96 Wks. 48th ICAAC, 25-28 October 2008. Washington. Abstract H 1250

Atazanavir is comparable to lopinavir/r in treatment-naïve patients

A poster on the CASTLE study extended the comparison of once-daily atazanavir/ritonavir (ATV/r) and twice-daily LPV/r in treatment-naïve patients. [1]

Earlier 48-week data demonstrated the comparability of the two therapies. By week 96, they were still comparable but had begun to show differences, but these were not statistically or clinically significant.

In an intent-to-treat "non-completer = failure" analysis at 96 weeks, 327 of 440 patients (74%) in the atazanavir/ritonavir arm achieved HIV RNA < 50 copies/mL, compared with 302 of 443 (68%) in the lopinavir/ritonavir arm ($P < 0.05$). Mean CD4 increases from baseline were comparable: +268 in the atazanavir/ritonavir arm and +290 in the lopinavir/ritonavir arm ($p=NS$). Rates of virological failure were low in both arms, at 7%. Discontinuation of study at 96 weeks was 16% of participants in the atazanavir/ritonavir arm and 21% in the lopinavir/ritonavir arm. Both measures in this intent-to-treat analysis were affected by the higher dropout rate in the LPV/r group.

Virologic failure in both groups was around 7%. The ATV/r arm showed better gastrointestinal tolerability. It also showed an improved fasting lipid profile over baseline (total cholesterol to HDL cholesterol ratio of >5; 23% at baseline and 17% at week 96), whereas the LPV/r group showed no improvement and was more likely to initiate lipid-lowering therapy (2% vs. 9%).

There were some concern previously that ATV/r may not do well in patients with high viral load and low CD-4 count. These data show that atazanavir is just as potent a drug as other PIs in all patient populations.

Another poster from the CASTLE study suggested no adherence benefit of protease inhibitor treatment given once compared to twice a day. [2]

Overall, adherence rates were above 80% throughout the study and did not differ between the two groups. Interestingly, more people reported forgetting to take ATV/r (11%) than LPV/r (6%).

In the past few years, once daily antiretroviral regimens have become more common particularly since the introduction of Atripla (tenofovir + FTC + efavirenz). While people with HIV commonly express a preference for simpler regimens, there's little comparative data to show how well they perform compared

to twice daily regimens. This CASTLE analysis suggests that once daily dosing did not lead to better adherence and might actually lead to slightly higher rates of forgotten doses.

C O M M E N T

Both the ARTEMIS study and the CASTLE study suggests that PI naïve patients (in the absence of PI resistance) do not have to take more than 100 mg of ritonavir when starting with PI.

Lopinavir/r (Kaletra) dosing includes 200 mg, which may lead to higher triglycerides, cholesterol and GI side effects.

Reference:

1. Molina J et al. CASTLE: atazanavir-ritonavir vs lopinavir-ritonavir in antiretroviral-naïve HIV-1 infected patients: 96 week efficacy & safety. 48th ICAAC, 25-28 October 2008. Washington. Abstract; H-1250d
2. Su J et al. Adherence in antiretroviral treatment-naïve subjects treated with once daily atazanavir/ritonavir or twice daily lopinavir/ritonavir, both in combination with tenofovir/emtricitabine: 48 week results from the CASTLE study. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-1242.

ICAAC: SIDE EFFECTS & COMPLICATIONS

Bone loss in SMART study

Mark Mascolini, for NATAP.org

People randomised to continuous antiretroviral therapy in the SMART trial lost more bone mineral density (BMD) than those randomised to intermittent therapy, according to results of a SMART substudy analysis [1].

After 2.8 years of follow-up in the overall 5472-person study group, 10 people on continuous antiretrovirals had grade 4 fractures, compared with 2 in the intermittent-therapy arm. The findings are surprising in light of recent cohort studies that saw no link between antiretroviral therapy (except perhaps tenofovir) and declining BMD in men [2] or women [3]. Also confounding expectation, the substudy did not correlate steady tenofovir use with waning BMD.

The SMART substudy used yearly DEXA scans to measure hip and spine BMD and quantitative computed tomography (QCT) to measure trabecular density in the spine. Among 98 substudy participants on continuous antiretroviral therapy and 116 on intermittent therapy, median age stood at 43 and 45 years, 25% and 15% were women, 51% and 41% smoked, and 5% and 3% used steroids. Median CD4 counts were similar in the two groups (525 on continuous therapy and 590 on intermittent therapy), and nadir CD4 counts were similar (268 and 235). About 40% in each group had low initial BMD by DEXA t-scores, and about 4% in each group already had DEXA-defined osteoporosis.

Compared with people taking intermittent antiretroviral therapy, those on steady treatment had significantly greater drops in femur BMD (0.9% per year), spine by QCT (2.9% per year), and spine by DEXA (0.4% per year). Estimated BMD change differences between the two groups (continuous therapy BMD minus interrupted therapy BMD) reflected significantly more BMD loss in the continuous-therapy group:

- 1.4% in femur (95% confidence interval [CI] 0.5 to 2.3, $P = 0.002$)

- 2.9% in spine by QCT (95% CI 0.7 to 5.1, $P = 0.01$)
- 1.2% in spine by DEXA (95% CI 0.02 to 2.3, $P = 0.05$)

In the treatment-interruption group, BMD remained stable in the first year of follow-up then began falling roughly in parallel with the drop in the continuous-therapy group. The investigators suggest that “this pattern is consistent with the increased antiretroviral therapy use after year 1 in the treatment-interruption group. “Higher viral loads during the first year did not appear to contribute to bone loss in the interruption group”.

Treatment with lopinavir/ritonavir, with abacavir, and with the two thymidine nucleoside analogues, stavudine and zidovudine, correlated with lower spine density by DEXA or QCT. Nevirapine use correlated with *greater* spine density by DEXA. Tenofovir did not affect BMD in the SMART analysis, though some studies of adults and children tied tenofovir to bone loss. [4-6]

The models used to make these associations considered race, gender, race-by-gender interaction, age, smoking (ever and time-updated current smoking status), history of alcohol abuse, body mass index (baseline and time-updated change), and baseline BMD. Alone among all these traditional risk factors, lower body mass index correlated with decreasing hip BMD.

Among all SMART participants, 10 of 2753 in the steady-therapy group and 2 of 2720 in the treatment-interruption group had a grade 4 fracture. Those numbers translated into rates of 0.13 per 100 person-years in the steady-therapy group versus 0.03 per 100 person-years in the intermittent group.

The SMART team did not speculate on why tenofovir did not threaten bones in their study group, as it has in others. They caution that SMART was not designed to assess the effects of individual drugs on bone density and that the trial did not dictate which drugs participants should take. The researchers list moderate sample size and follow-up as limitations of their BMD analysis.

The SMART investigators stress that these findings do not support intermittent antiretroviral therapy since overall trial results show a higher risk AIDS and death from AIDS and non-AIDS diseases in the intermittent-therapy arm. [7]

C O M M E N T

While several studies have generally documented significantly higher rates of osteopenia and osteoporosis in HIV-positive compared to HIV-negative groups, this is the first large study to report a negative effect of treatment, without a link to specific drugs or classes.

These findings highlight the importance of prospective studies of bone health in HIV-positive patients - increasingly important as the HIV-population ages - especially as the main finding of SMART still strongly supported the use of continuous treatment.

A sub-study from the GSK COL100758 study looking at either 100mg or 200mg boosting doses of ritonavir with 1400mg fosamprenavir plus abacavir/FTC (all once-daily) included results on BMD. Patients in both arms experienced reductions of -1.05% in total BMD and of -2.99 and -2.22 in L-spine BMD (in the 100mg and 200mg arms respectively). [8]

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bone mineral density: results from the SMART study. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-2312a.

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Non alcoholic Fatty Liver Disease (NAFLD) is common among HIV-positive patients

Satyajit Das, HIV i-Base

Non Alcoholic Fatty Liver Disease (NAFLD) is the most common form of liver disease among the general population. Crum-Cianflone and colleagues reported results from a cross-sectional study of 300 HIV-positive patients (who were not infected with hepatitis B or C, or reported significant alcohol use) to determine the prevalence and factors associated with NAFLD.

NAFLD was diagnosed by ultrasound examination and liver biopsies were performed on a subset of participants. Thirty-one percent (67/216) of HIV patients had NAFLD on ultrasound. Demographics included mean age 40 years; male 94%; 48% Caucasian, 27% African American, and 25% other. Mean duration of HIV infection was 10 years, mean CD4 count was 535 cells/mm³, and 65% were receiving antiretroviral therapy.

Factors associated with NAFLD in the multivariate model included increased waist circumference, elevated serum triglycerides, and lower HDL levels. African Americans were significantly less likely to have NAFLD compared to Caucasians (14% vs. 35%, $p=0.05$). Analyses were repeated for those with NAFLD on liver biopsy with similar results. HIV-specific factors such as CD4 cell count, viral load, HIV duration, and ART were not independent factors associated with NAFLD.

Increased waist circumference, elevated serum triglycerides, and lower HDL levels, all are markers of metabolic syndrome. These data suggest that weight and lipid management may be key factors for the prevention of liver disease due to NAFLD among HIV patients.

Ref: Crum-Cianflone NF et al. Nonalcoholic Fatty Liver Disease (NAFLD) among HIV-Infected Persons. 48th ICAAC, 25-28 October 2008. Washington. Abstract: H 2322.

ICAAC: TRANSMISSION

HIV reinfection reported in 10% of couples in Zambian study**Simon Collins, HIV i-Base**

A poster from C Kraft and colleagues from the Zambia Emory HIV Research Project reported on the incidence of HIV subtype C reinfection in heterosexual couples infected with genotypically different viruses.

The study aimed to see whether reinfection could be detected, together with the frequency, and any virologic consequences. Seventeen unlinked couples were screened with a gp41-based heteroduplex mobility assay for reinfection and the results were confirmed by phylogenetic analysis of single genome amplified *env* genes.

Three cases of reinfection were confirmed, only two of which occurred during early infection. In one case a newly infected partner was reinfected by their chronically infected spouse, and, in the second, reinfection of the seroconverting partner resulted from a second non-spousal transmission. In the third case, reinfection in a chronically infected partner occurred during acute infection of his partner's unlinked infection.

In two cases, reinfection was accompanied by a 10-fold increase in viral load. Phylogenetic analyses were consistent with rapid recombination between the reinfected strains in each individual.

The authors concluded "in this retrospective study of a limited number of HIV-1 infected cohabiting couples, superinfection appears to be a frequent event (3/34).

C O M M E N T

Similar rates of reinfection have been reported in several at least one other heterosexual study, although rates in MSM are still poorly studied.

It may be important that the case reinfection during chronic infection was from a partner in acute infection when viremia is highest.

Ref: Kraft CS et al. HIV-1 superinfection in cohabiting Zambian heterosexual couples. 48th ICAAC, 25-28 October 2008. Washington. Abstract H-4049.

CONFERENCE REPORTS

17th International AIDS Conference**3 - 8 August 2008, Mexico City****Introduction**

The IAS International AIDS conferences held every two years are the largest HIV meetings. This year approximately 25,000 delegates traveled to Mexico City to review 4,500 studies.

Although this conference has an increasingly stronger interest in social, political, prevention, treatment access over clinical and basic science there was still plenty to report for HTB.

Each year internet coverage improves and this year most oral presentations, many slide sets or poster PDF files and all abstracts are posted online. Webcasts are also available from many of the oral sessions.

<http://www.aids2008.org>

The direct URL for the online poster database is:

<http://www.aids2008.org/Pag/PosterExhibition.aspx?presType=PE&D=04&S=621>

The IAS have progressively provided the abstract books as free-access PDF files from the website – something that could hopefully set the standard for all HIV-related medical meetings.

<http://www.aids2008.org/mainpage.aspx?pageId=174>

Articles in this issue include:

- Abacavir and heart disease: SMART study supports an abacavir-associated increased risk of cardiovascular disease
- HAART use in pregnancy and preterm delivery and low birth weight
- New paediatric formulations of ARVs

MEXICO: ANTIRETROVIRALS

Abacavir and heart disease: SMART study supports an abacavir-associated increased risk of cardiovascular disease**Simon Collins, HIV i-Base**

Jens Lundgren from the INSIGHT research group presented an analysis of nucleoside toxicity and cardiovascular disease from the SMART treatment interruption study. [1]

This issue was one of the most discussed topics of the meeting as GSK also presented an analysis from their clinical trial database. [2]

In February 2008, the D:A:D study showed an increased risk of cardiovascular risk from current or recent use of abacavir – a finding that that was unexpected and challenging for people skeptical of a cohort study identifying a new effect with an as

yet unexplained mechanism. [3] Cautious reactions to the D:A:D data looked for validation from other studies which were not allayed by GSK's more limited dataset, originally published as a letter to the Lancet in April. [4]

The SMART researchers analysed patients in the continuous treatment arm of the SMART study by NRTI use relating to the previous D:A:D findings: using abacavir (but not ddl) n=1019, using ddl (but not abacavir) n=643, and other NRTI combinations with neither abacavir nor ddl (n=2882). Baseline characteristics of these three groups were similar, including common cardiovascular risks (~4% prior CVD, 40% current smokers, 35% ischemic abnormalities and 7% diabetic). Lipid lowering drugs and blood pressure medications were each used by just under 20% of patients. 15% patients had ≥ 5 cardiovascular risk factors.

In multivariate analysis adjusting for CVD risk factors, all four categories of cardiovascular disease defined by the group showed increased hazard ratios (HR) for abacavir compared to other NRTIs (see Table 1).

Table 1: Adjusted HR of cardiovascular event with abacavir use vs. other NRTIs in SMART

CVD category	No. of events	Adj. HR (95% CI)
Clinical and silent MI, stroke, surgery for coronary artery disease (CAD), and CVD death	70	1.8 (~1.1-3.2)
Clinical MI as defined in D:A:D	19	4.3 (1.4-13.0)
CVD, major, expanded version (Major CVD plus peripheral vascular disease, Congestive heart failure (CHF), drug treatment for CAD, and unwitnessed deaths).	112	1.9 (1.0-3.1)
CVD, minor (CHF, peripheral vascular disease or CAD requiring drug treatment).	58	2.7 (1.3-2.9)

Importantly, the results were similar when patients receiving tenofovir were used as reference group and when the approximate 10% of patients with events in both D:A:D and SMART databases were excluded from the analysis.

The SMART study also showed a strong association between elevated levels of some inflammation biomarkers with levels of viral load rebound and risk of serious event. In this analysis, patients using abacavir had D-dimer and IL-6 that were 27% and 16% higher at study baseline than patients in the reference group using other NRTIs (both $p=0.07$).

These levels could have been higher for reasons unrelated to abacavir use and will need to be examined in a study looking prospectively at changes in these biomarkers in patients starting abacavir.

Similar to D:A:D, the clinical significance from abacavir use was greatest in patients with the highest underlying cardiovascular risk factors. Those patients with five or greater cardiovascular risks or ischemic abnormalities on ECG showed three-fold increased risk from using abacavir compared to other NRTIs (both HR 3.1).

Earlier in the conference, GSK, reported that their retrospective meta analysis from 54 phase 2 and 3 abacavir registrational studies did not find an association between cardiovascular events

and either abacavir or non-abacavir use. [2]

While this was important from a regulatory perspective – any safety signal requires a company to look at their own dataset – the limitations of both this database and the presented analysis were unlikely to be resolve the concerns highlighted by D:A:D and SMART.

Of the 54 trials, only 13 were randomised for abacavir use, 33 included abacavir in background regimens and 8 did not include abacavir. Just over 14,000 adults and 500 children were included. Events were identified by a search for cardiovascular-related events and rates in naïve and experienced patients were calculated per 1000 person years.

No differences were seen in the relative rates by abacavir use for any cardiovascular event (RR=0.59; 0.35-1.01; p -value=0.055) or any MI (RR=0.863; 0.40-1.86; $p=0.706$).

Myocardial infarctions (MI) were identified in 16 patients using abacavir (10 using non-PI and 6 on PI-containing regimens. Of the 11 MIs in the non-abacavir group, all used PI-based regimens except for one patient using an NNRTI-based combination.

Several limitations were raised concerning this data. Firstly, that there were too few events to have statistical power to detect an association either way. Many cardiovascular risks were not recorded at baseline, including smoking status, hypertension, HDL and LDL. Patient numbers were much lower (~7000 and 4500 PYFU in the abacavir and non-abacavir groups), and importantly median follow-up time was less than one year.

By comparison, D:A:D included 33,000 patients to be followed for seven years (160,000 PYFU) until there was sufficient power to make associations to a single-drug effect.

Secondly, patients in clinical trials are and were generally younger, healthier, with lower cardiovascular risks. Interestingly, GSK did not present an analysis relating to the comparator regimens used in these studies, which were PI-based, and therefore already carried a higher risk of CVD.

C O M M E N T

The significance of these results from the SMART study, which are already published as a fast track paper in the 12 September edition of AIDS [5], is that they support the earlier D:A:D findings in two ways. They report a similar association between current or recent abacavir use and cardiovascular disease; and they found that the clinical impact was most significant in patients with highest underlying CVD risk.

Taken together, the D:A:D and SMART results suggest that for patients at the highest CVD risk (>20% 10-year Framingham), abacavir should not be used unless alternative options are not available.

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MEXICO: PREGNANCY & PMTCT

HAART use in pregnancy and preterm delivery and low birth weight

Polly Clayden, HIV i-Base

An association between preterm delivery and use of HAART by HIV-positive mothers has been reported in some studies but not others.

A poster from Claire Townsend and co-workers showed findings from a comparison of three studies from the US, Europe and

the UK and Ireland undertaken to investigate explanations for reported differences in preterm delivery with HAART use. The three studies were: Pediatric Spectrum of HIV Disease (PSD), a medical record-based cohort study (1990-2004) conducted at seven sites in the US between 1990-2004; European Collaborative Study (ECS), a consented cohort study conducted at 26 centres in nine European countries between 1990-2006 and National Study of HIV in Pregnancy and Childhood (NSHPC), a national population-based surveillance study conducted at maternity units in the UK and Ireland between 1990-2006.

This comparison included singleton infants born to HIV-positive women during the respective study periods and compared maternal characteristics, including ART and mode of delivery, and prematurity.

Strategies to treat mothers and/or prevent mother to child transmission varied over time in all three cohorts.

The investigators reported substantial variation in maternal and pregnancy characteristics (see Table 1).

They noted that prematurity rates were stable over time in both the PSD and NSHPC, but increased in the ECS (elective caesarean sections at <37 weeks were excluded).

Adjusting for history of injecting drug use, maternal ethnicity, maternal age (except PSD), HIV-related symptoms at delivery (except ECS) and child's birth year, the investigators found the association between ART and prematurity compared to monotherapy across all three studies (see table 2).

Table 1. Maternal and pregnancy characteristics by study

	PSD n (%)	ECS n (%)	NSHPC n (%)	+2 p-value df=2
Maternal characteristics				
History of injecting drug use	1189 (13.1)	1460 (35.5)	295 (4.4)	<0.001
White ethnicity	869 (9.6)	2682 (65.4)	1009 (15.3)	<0.001
Born abroad	1477 (19.7)	1381 (34.5)	5473 (84.7)	<0.001
Pregnancy characteristics				
On HAART in pregnancy	2697 (29.7)	1626 (38.1)	4776 (73.5)	<0.001
Caesarean section delivery	3113 (35.9)	2490 (59.7)	4878 (76.6)	<0.001
Premature delivery <37weeks	1533 (17.3)	591 (14.8)	748 (11.6)	<0.001
TOTAL*	9078	4263	6665	

*denominators vary due to missing data

Table 2. Odds ratio for preterm delivery by type of ART

Study	ART	OR	95%CI	p-value	AOR	95%CI	p-value
PSD	Monotherapy	1.00			1.00		
	Dual therapy	0.79	0.64-0.97	0.025	0.77	0.58-1.03	0.077
	HAART	1.01	0.87-1.16	0.931	0.96	0.72-1.27	0.756
ECS	Monotherapy	1.00			1.00		
	Dual therapy	0.94	0.65-1.37	0.765	0.92	0.61-1.39	0.696
	HAART	1.64	1.3-2.07	<0.001	1.57	1.14-2.17	0.006
NSHPC	Monotherapy	1.00			1.00		
	Dual therapy	1.04	0.59-1.83	0.888	0.84	0.42-1.68	0.62
	HAART	1.47	1.15-1.87	0.002	1.67	1.26-2.23	<0.001

HAART use was associated with a significant increased risk of preterm delivery in ECS and NSHPC, but not in PSD. The investigators noted that there was evidence of interactions in the PSD between ART and ethnicity and ART and site of report, which they suggest require further analysis.

C O M M E N T

These data are interesting and it is very useful to have then analysed and presented so clearly. It is important to place the pre term delivery rates into the context of the background rate of 6 - 8% in an HIV-negative UK population. The UK/Ireland data would seem to give a rate with AZT prophylaxis approaching this. This raises the question of the equivalent rate for North America?

The data would seem to suggest that the rate of preterm delivery, even with AZT prophylaxis is very high, perhaps twice what we would see here.

An explanation of the data is that there are a number of factors that are associated with preterm delivery and that where these are strong, leading to high background rates, then the effect of HAART on preterm delivery is not seen, however where rates are lower, as in the UK with AZT prophylaxis, then an effect due to HAART can be detected.

One analysis that might be interesting is to compare the time on HAART during pregnancy in the three cohorts. Is it possible that HAART is started later in the PDS cohort?

Quite clearly, unless the impact of HAART is immediate, there is likely to be a lag between starting therapy and any associated PTD. HAART started after say 32 weeks will mean that no severe preterm delivery will be associated and the data will be biased to exclude the background rate of preterm delivery.

This will also be an important issue for resource limited settings as using HAART for prevention of mother to child transmission for women not indicated for treatment for their own health continues to be discussed (see also our article on low birth weight in Cote D'Ivoire study on page 26) .

Ref: Townsend CL, Schulte J, Thorne C et al. Differences in the association between ART in pregnancy and premature delivery: a comparison of three studies from the United States and Europe

MEXICO: PAEDIATRIC CARE

New paediatric formulations of ARVs

Polly Clayden, HIV i-Base

The complexities of using liquid formulations of paediatric antiretrovirals (such as transportation, storage, cost, taste and dosing) are a barrier to scale up of HIV treatment in children. The WHO and UNICEF have requested the development and registration of solid paediatric formulations. Four posters showed novel combination dose and single drug tablets suitable for paediatric use.

AZT and 3TC fixed dose combination tablet

GlaxoSmithKlein (GSK) have developed scored tablets of AZT 300mg/3TC 150mg (Combivir) for children >14kg and able to

swallow tablets. [1]

Ivy Song and co-workers showed pharmacokinetic modelling, performed to support manufacturers' dosing recommendations.

Doses were selected by weight bands using half and whole tablet regimens to provide daily AZT/3TC doses from -10% to +40% of those from the approved mg/m² (AZT) or mg/kg (3TC) dose of the liquid formulations (see table 1).

Table 1: Manufacturer recommended dose regimens of AZT/3TC scored tablets

Weight range (kg)	Number of tablets
14 to 21	Half BID
>21 to <30	Half am/whole pm
>= 30	Whole BID

Systemic drug exposures from these regimens were predicted using Monte Carlo simulations and reanalysis of historical data, and compared with historical exposure at approved doses in adults and children.

The investigators found the simulated AZT daily AUC for the scored tablet to be similar to historical controls while C_{max} is 30-80% higher. Simulated 3TC daily AUC is 10-50% higher than historical controls while C_{max} is higher than historical controls from BID dosing but similar to historical adult controls at approved 300 mg QD regimen.

Based on this model these dosing regimens of scored tablet are expected to provide similar safety and antiviral efficacy to 3TC and AZT at previously approved doses. The investigators note that there is a possibly of higher frequency of AZT-associated gastrointestinal effects (because of association with the higher C_{max}) in some patients. They suggest that taking the whole tablet before bedtime may improve tolerability.

The manufacturer recommended doses overlap with but are "slightly more conservative" than the WHO recommendations for AZT/3TC (see table 2).

Table 2: WHO recommended dose regimens of AZT/3TC scored tablets

Weight range (kg)	Number of tablets
14 to <20	Half BID
20 to <30	Whole am/half pm
>= 30	Whole BID

This formulation has been approved for use in the EU and review by the FDA is underway.

Dispersible fixed dose combination of 3TC/AZT/NVP

Ranbaxy laboratories have developed dispersible, scored 3TC/AZT/NVP fixed dose combination (FDC) Tablets for Oral Suspension (TFOS) for children. [2]

Raghuvanshi and co-workers summarised their findings from the prototype development. They describe the characteristics of this product as:

1. Dispersible into an oral suspension in 5 ml of water within 2 minutes.
2. Showing stability under accelerated conditions.

3. Similar in-vitro dissolution profile as that of three reference liquid products.
4. Complying to divisibility test.
5. Palatable and acceptable lemon flavor.
6. Having comparable pharmacokinetic parameters to individual reference liquid formulation under fasting conditions (n=18), (see table 3).

Table 3. Pharmacokinetic parameters of 3TC/AZT/NVP FDC compared to reference products

ARV	Cmax	AUCt	AUCinf
3TC	115.35	105.4	107.08
NVP	110.76	102.93	101.39
AZT	104	105.08	105.2

These investigations supported product feasibility for paediatric 3TC/AZT/NVP FDC. The investigators have completed the comparative bioavailability study for this product and it was filed for prequalification with WHO in November 2007.

Dispersible fixed dose combination of 3TC and d4T

Ranbaxy has also developed TFOS combining 3TC and d4T. [3]

They summarised the product characteristics:

1. Quickly dispersing into a suspension in 5 ml of water within 1 minute
2. Having similar in-vitro dissolution profile as that of two reference liquid products.
3. Showing stability under accelerated conditions.
4. Having palatable and acceptable orange flavor
5. Complying to divisibility test
6. Having comparable pharmacokinetic parameters to individual reference liquid formulation under fasting conditions (N=23). (See table 4)

Table 4. Pharmacokinetic parameters of 3TC/d4T FDC compared to reference products

ARV	Cmax	AUCt	AUCinf
3TC	94.3	100.94	100.91
d4T	87.21	98.03	97.11

The investigators concluded: "All the studied parameters of TFOS were satisfactory which support the product feasibility for paediatric therapy using lamivudine and stavudine FDC."

Bioavailability of the 100mg etravirine tablet dispersed in water and of the 25mg tablet formulation

Tibotec have developed a 25mg paediatric tablet of etravirine (TMC125). Additionally the 100mg tablet can be dispersed in water.

Schöller-Gyüre and co-workers evaluated the oral bioavailability of the 100mg tablet dispersed in water and of the compositionally proportional 25mg pediatric relative to the 100mg tablet swallowed whole. In addition to treatment in children, the investigators suggest this evaluation will support adult patients with swallowing difficulties. [4]

This study was an open-label, randomised, 3-period crossover trial in HIV-negative volunteers. Three single doses of etravirine were administered as:

- Treatment A (reference) - one 100mg tablet swallowed whole
- Treatment B - four 25mg tablets
- Treatment C - one 100mg tablet dispersed in 100mL water

37 volunteers participated (7 women). All treatments were received within 10 minutes of a standardised meal and were separated by 14-days wash-out periods.

Pharmacokinetics of etravirine were assessed over 96 hours after each administration and least square means ratios compared to reference (see table 5).

Table 5 Pharmacokinetic parameters and LSM ratios of etravirine

PK parameters	Tx A	Tx B	Tx C
N	37	35	33
AUClast (ng. h/mL)	1241+/- 642	1126+/- 542	1219+/- 712
AUCinf (ng. h/mL)	1412+/- 885	1286+/- 751	1409+/- 1109
Cmax (ng/mL)	130+/- 50	113+/- 44	131+/- 62
LSM ratio (90%CI)			
		B vs C	C vs A
AUClast (ng. h/mL)		0.91 (0.85-0.98)	0.97 (0.9-1.05)
Cmax (ng/mL)		0.85 (0.78-0.93)	0.95 (0.88-1.04)

The investigators noted that the decrease of Cmax by 15% when etravirine is received as four 25mg tablets is not considered clinically relevant.

They reported that etravirine was generally safe and well tolerated. The most frequently reported adverse event was headache (n=8). One volunteer discontinued prematurely because of Grade 3 lipase increase during Treatment B. No other Grade 3 or 4 adverse events were reported.

They concluded that the 25mg tablet of etravirine is suitable for paediatric use. Additionally paediatric or adult patients requiring an alternative to swallowing tablets can disperse etravirine tablets in water. They added that the stability of etravirine in liquids other than water has not yet been determined.

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CONFERENCE REPORTS

3rd International Workshop on HIV Transmission

1 - 2 August 2008, Mexico City

This workshop was held in Mexico City immediately prior to the International AIDS Conference. Thanks to Mark Mascolini and NATAP.org for these reports.

- Intermittent tenofovir/FTC PrEP offers monkeys some protection
- Tenofovir/FTC gel protects female monkeys from SHIV
- Common estimate of heterosexual HIV transmission risk sometimes far too low

For other online reports from NATAP please visit:

<http://www.natap.org>

Selection presentations from oral sessions at the workshop however are available at:

<http://www.HIVpresentation.com>

Unfortunately the workshop organisers have not made the abstracts from this workshop available online.

Intermittent tenofovir/FTC PrEP offers monkeys some protection

Mark Mascolini for NATAP.org

Two-dose intermittent pre-exposure prophylaxis (PrEP) with Truvada (tenofovir plus emtricitabine) protected male macaques from rectal exposure to a simian-HIV hybrid virus (SHIV) as well as daily Truvada did in an earlier study by scientists from the US Centers for Disease Control (CDC). [1]

But two-dose PrEP did not protect all animals in any of the four 6-monkey groups who got the drugs at different times relative to SHIV exposure.

Trials of daily Truvada PrEP are now under way in different human populations at high risk of HIV infection. An earlier monkey trial of emtricitabine alone and tenofovir/emtricitabine found better protection from SHIV with the two drugs. [2]

In the new study Gerardo Garcia-Lerma and CDC colleagues rectally exposed 24 male Rhesus macaques to SHIV, a simian immunodeficiency virus with an HIV coat, once weekly over 14 weeks. They split the monkeys into four groups of 6, giving human-equivalent doses of Truvada to each group through a mouth-to-stomach tube at different times:

- Group 1: 2 hours before and 22 hours after SHIV exposure
- Group 2: 22 hours before and 2 hours after SHIV exposure
- Group 3: 3 days before and 2 hours after SHIV exposure
- Group 4: 2 hours after and 26 hours after (postexposure prophylaxis, or PEP)

In a comparison group of 24 untreated monkeys, 23 became infected with SHIV (detected in plasma and blood cells) after a median of 2 rectal exposures (range 1 to 12). In contrast 3 of 6

group-1 animals did not pick up SHIV after 14 exposures, 5 of 6 group-2 animals remained free of SHIV after 14 exposures, 5 of 6 group-3 animals remained uninfected after 14 exposures, and (in an ongoing study) 3 of 6 group-4 animals are free of virus after 12 exposures.

Compared with the untreated macaques, group 1 had a 3.7-fold lower risk of SHIV infection ($P = 0.04$), group 2 had a 15.5-fold lower risk ($P = 0.008$), and group 3 had a 14.0-fold lower risk ($P = 0.01$). Risk of SHIV infection in these three groups did not differ significantly from infection risk in monkeys who received daily Truvada PrEP in the earlier trial. In animals that did become infected, viremia was about 10-fold lower than in control animals. Resistant virus did not emerge in animals whose PrEP failed.

Garcia-Lerma and coworkers speculated "the long intracellular drug half-life of tenofovir and emtricitabine may explain the extended window for protection by the pre-exposure dosing and provides opportunities for different intermittent PrEP regimens."

In a separate study also reported by NATAP, tenofovir/FTC formulated in a stable vaginally applied gel protected 6 of 6 female pigtail macaques from 20 SHIV exposures. [3]

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1. Garcia-Lerma J, Cong M, Masciotra S, et al. Intermittent pre-exposure prophylaxis (PrEP) with oral Truvada protects macaques against repeated rectal SHIV exposures. 3rd International Workshop on HIV Transmission: Principles of Intervention. 31 July -2 August 2008, Mexico City. Abstract 40.
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Tenofovir/FTC gel protects female monkeys from SHIV

Mark Mascolini for NATAP.org

Vaginal microbicide research in humans took a recent setback with reports that two products did not protect women from HIV infection. But neither of those microbicides (Carraguard and cellulose sulfate) used antiretroviral agents to ward off HIV.

Urvi Parikh and colleagues at the US Centers for Disease Control (CDC) and Emory University randomized 14 female pigtail macaques to three study groups: 2 received no gel, 6 received a placebo gel (hydroxyethyl cellulose only), and 6 got the tenofovir/FTC gel (5% FTC plus 1% tenofovir, which is equivalent to one Truvada dose, in 2% hydroxyethyl cellulose). [1]

The tenofovir/FTC gel was clear, odorless, viscous, and stable at 37 degrees Celsius for 6 months. Technicians applied the gels vaginally 30 minutes before challenging the monkeys with SHIV, a simian immunodeficiency virus with an HIV coat, at a dose of about 1,160,000 RNA copies. After exposure the investigators used blood tests and polymerase chain reaction to search for SHIV in plasma. The challenges occurred twice weekly for 10 weeks.

Both monkeys who got no gel and 5 of the 6 who got the placebo gel became infected after a median of 3.5 challenges (range 2 to 11). All 6 pigtailed treated with tenofovir/FTC before SHIV exposure remained free of infection after 20 challenges ($p < 0.005$ versus control groups). The CDC team could detect no viral RNA, no proviral DNA, and no viral antibody in any of the 6 tenofovir/FTC-treated animals.

Parikh and coworkers detected low levels of FTC (median 67 ng/mL) and tenofovir (median 22 ng/mL) in plasma samples 30 minutes after vaginal application. Those findings, the investigators proposed, suggest "rapid drug absorption with relatively higher levels of drug remaining in vaginal tissue."

Ongoing trials are testing oral tenofovir/FTC (Truvada) as pre-exposure prophylaxis in humans, and a separate study at this workshop showed that oral tenofovir/FTC partially protected male monkeys from rectal SHIV exposure. [2]

An earlier study of 1% tenofovir without FTC applied rectally in a single high dose found only a 60% protection rate. [3]

Double therapy clearly did better in this vaginal trial, but Charles Boucher (Erasmus University, Rotterdam) worried about the wisdom of developing drugs for both prevention and treatment because acquired resistance could compromise use of those and other drugs.

A vaginal tenofovir/FTC gel has yet to be tested in humans.

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Common estimate of heterosexual HIV transmission risk sometimes far too low

Mark Mascolini for NATAP.org

...In heterosexual couples with enough other risk factors, transmission risk can climb as high as 1-in-10 for penile-vaginal sex and 1-in-3 for penile-anal sex....heterosexual sex can be a remarkably efficient way to transmit HIV....

One commonly cited estimate of heterosexual HIV-1 transmission risk - 1 infection per 1000 sexual acts - is probably inaccurate because it fails to account for other factors that raise or lower the risk of HIV transmission. [1]

That conclusion emerged from a multi-study analysis by Kimberly Powers (University of North Carolina at Chapel Hill), who pinpointed five variables that have a potent impact on heterosexual HIV transmission. With enough cofactors in play, Powers estimated that men and women risk transmitting the virus once every three times they have insertive sex.

3rd Transmission Workshop, Mexico City

The investigators suspected the 1-per-1000 ratio may be too low to explain raging heterosexual HIV epidemics in many countries, partly because it does not factor in sexually transmitted infections (STIs), HIV disease stage, circumcision, and other variables known to boost or blunt transmission risk. Yet that ratio gets cited time and again in government reports, peer-reviewed studies, and media offerings, leaving the impression that heterosexual coitus is a highly inefficient way of infecting a partner. To get a better handle on sexual transmission dynamics, the North Carolina team systematically searched published studies estimating heterosexual infectivity of HIV-1. Then they used statistical tools to sort out infectivity differences according to risk cofactors.

Powers found 27 studies involving 15 distinct populations. Transmission estimates varied strikingly from one study to the next, depending on these cofactors. Estimates ranged from 0 transmissions after more than 100 penile-vaginal contacts to 1 transmission for every 3.1 episodes of heterosexual anal intercourse. The multistudy statistical analysis weighing the impact of cofactors identified five variables that boosted risk of HIV transmission:

- Transmission 33.8 times more likely with penile-anal sex than penile-vaginal sex.
- Transmission 8 times more likely for uncircumcised versus circumcised men.
- Transmission 6 times more likely with than without a genital ulcer disease.
- Transmission 2.5 times more likely with early versus mid-stage HIV infection.
- Transmission 1.85 times more likely with late versus mid-stage HIV infection.

Powers and colleagues concluded that the 1-in-1000 estimate adequately represents transmission risk only in stable couples with low rates of other transmission risk factors. In other words, 1-in-1000 "represents a lower bound" of a capacious risk spectrum. In heterosexual couples with enough other risk factors, transmission risk can climb as high as 1-in-10 for penile-vaginal sex and 1-in-3 for penile-anal sex.

The investigators encouraged researchers to consider such cofactors in future infectivity estimates, and they advised public health officials and clinicians to emphasise that heterosexual sex can be a remarkably efficient way to transmit HIV. The study will be published next week in *Lancet Infectious Diseases*.

Reference

1. Powers K, Poole C, Pettifor A, Cohen M. Rethinking the heterosexual infectivity of HIV-1: A systematic review and meta-analysis. 3rd International Workshop on HIV Transmission: Principles of Intervention. July 31-August 2, 2008, Mexico City. Abstract 14.

TREATMENT ACCESS

A summary of news links to stories relating to ARV access issues.

FDA approval of generic ARVs

The US Food and Drug Administration (FDA) has granted tentative approval for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
3TC 150 & 300mg	Macleods, India	7 October 2008
ddl delayed release capsules (125, 200, 250 and 400 mg)	Aurobindo, India	24 September 2008
Retrovir syrup, capsules and tablets	Matrix, India	19 September 2008

"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 programme for use outside the United States.

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

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=3D021360&TABLE1=3DOB_Rx

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 76 since the programme started. An updated list of generic tentative approvals is available on the FDA website:

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

Source: FDA list serve:

<http://www.fda.gov/oashi/aids/listserve/archive.html>

Brazil rejects Gilead patent on tenofovir

The Brazilian Patent Office has rejected a patent application filed by Gilead Sciences for tenofovir (Viread), currently one of the key antiretrovirals needed in resource-limited countries. The application was opposed by a coalition of Brazilian NGOs and a government pharmaceutical laboratory.

A statement from Gilead stated that previous patent rejections, including in the US had been overturned on appeal and that the company "remain confident in the strength of our intellectual property for tenofovir and plan to vigorously defend the patent and the scientific innovation on which it is based".

Several companies in India already make tenofovir (including an WHO-approved version for \$158 per year) after Gilead reached agreement with several generic manufacturers not to enforce its

patents. Some companies object to Gilead's patent claim that under the Indian patent system.

Gilead's tenofovir currently costs \$1,387 in Brazil and is used by almost 40,000 patients.

Source: www.pharmalot.com (3 September 2008)

<http://www.pharmalot.com/2008/09/brazil-rejects-gilead-patent-on-hiv-drug/>

ANTIRETROVIRALS

Antiretrovirals calculated to extend life expectancy by 35 years

Simon Collins, HIV i-Base

An analysis from a large international cohort study from the Antiretroviral Therapy Cohort Collaboration (ART-CC) has calculated that antiretroviral treatment currently extends life expectancy for HIV-positive people to an average of 65 years. Their model used patients who start treatment when either 20 or 35 years old.

Using data from 43,000 patients from 14 cohorts from Canada, Europe and the US, the researchers estimated the life expectancy since 1996 on the basis of reported deaths within the cohorts and compared rates in treatment-naïve patients starting treatment in the 1996–99 period to patients starting treatment from 2003–05.

Compared to the earlier treatment group, life expectancy for patients starting treatment in 2003-05 increased by 13 years.

Although life expectancy increased similarly in all groups there were significant absolute differences between different groups of patients,

Women had higher life expectancies than men (overall mortality rates/1000 patient years [95%CI]: 9.1 [8.2-10.1] vs 12.9 [12.3-13.6]).

Patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups (32.6 [1.1] years vs 44.7 [0.3], based on starting treatment aged 10).

Life expectancy was lower in patients with lower baseline CD4 cell counts than in those with higher baseline counts (32.4 [1.1] years for CD4 cell counts below 100 cells/mm³ vs 50.4 [0.4] years for counts of 200 cells/mm³ or more).

C O M M E N T

One of the most common responses to an HIV-diagnosis, and one of the key unanswered questions even for long-term survivors relate to life expectancy. It is therefore important to draw on the most recent studies to inform these discussions.

Antiretroviral therapy since 1996 has dramatically reduced mortality and extended life in all countries where there is access treatment, and as experience with treatment and availability of new and better drugs improves, projected life expectancy has similarly increased.

Every few years a new study produce more optimistic figures – 12 years, 25 years and now 35 years in the latest studies. [1, 2] It likely that future studies will close the gap between HIV-positive and HIV-negative populations.

But it we are not there yet. The paper from ATCC still shows 10-20 year differences due to HIV status. Patients starting at lowest CD4 levels have 10–20 years lower life expectancy and injecting drug use also impacts by 10 years.

ARV treatment, if used carefully, does not appear to have a built-in shelf life. Once virus is suppressed to below 50 copies/mL, ongoing viral evolution is stopped, rather than slowed, and resistance is related to poor adherence, or more rarely, re-infection with a resistant strain.

Experience with HAART over ten years suggests that initial concerns about compartmental sites, especially in relation to drug penetration and compartmental resistance has not led to systemic virological failure on a significant or measurable level. There are little data to predict whether this will become an important concern with longer use of treatment.

However, real concerns related to HIV-positive patients and aging include the greater risks for neurological complications, brain disorders (including alzheimer's and parkinsons), reduced bone mineral density, bone disease and fractures, virally-mediated cancers, diabetes, and heart disease.

The extent to which an extended period of uncontrolled viraemia prior to starting treatment may explain some of these increased risks is one of the questions addressed by several research groups, including the START study, due to enrol later this year. [3]

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<http://www.annals.org/cgi/content/abstract/146/2/87>
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FDA approves new paediatric AZT dosing

On 19 September 2008, the FDA approved a paediatric efficacy supplement for AZT syrup, capsules and tablets allowing for a twice-daily dosing regimen in children 6 weeks to 18 years of age. It also provides for dosing by weight in addition to dosing by body surface area.

Previously, AZT dosing recommendations for the treatment of HIV in children included three times daily dosing with dose calculated using body surface area. The new label has recommendations for twice daily or three times daily dosing by weight or by body surface area. The new recommendations should allow for more convenient dosing (twice daily) of AZT (zidovudine, Retrovir) in children. The main changes include revisions to the Dosage and Administration section to include twice daily dosing in children as follows.

Paediatric Patients (6 weeks to <18 years of age): Healthcare professionals should pay special attention to accurate calculation of the dose of AZT, transcription of the medication order, dispensing information, and dosing instructions to minimize risk for medication dosing errors.

Prescribers should calculate the appropriate dose of AZT for each child based on body weight (kg) and should not exceed the recommended adult dose.

Before prescribing AZT capsules or tablets, children should be assessed for the ability to swallow capsules or tablets. If a child is unable to reliably swallow an AZT capsule or tablet, the AZT Syrup should be prescribed.

The recommended dosage in paediatric patients 6 weeks of age and older and weighing >4 kg is provided in a dosing table (see FDA list serve sit or new prescribing information). AZT Syrup should be used to provide accurate dosage when whole tablets or capsules are not appropriate.

Alternatively, dosing for AZT can be based on body surface area (BSA) for each child. The recommended oral dose of RETROVIR is 480 mg/m²/day in divided doses (240 mg/m² twice daily or 160 mg/m² three times daily). In some cases the dose calculated by mg/kg will not be the same as that calculated by BSA.

The complete revised label will be available at:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda>

Baseline renal insufficiency and mortality risk in HIV-positive adults in Lusaka, Zambia

Polly Clayden, HIV i-Base

Renal insufficiency has been found to be a risk factor for mortality in people with HIV. Understanding the prevalence and clinical implications this condition will have particular relevance in resource limited settings as programmes begin to introduce tenofovir as part of first line therapy.

A paper published in the September 12, 2008 edition of *AIDS* authored by Lloyd Mulenga and co-workers examined the association between baseline renal insufficiency and mortality in adults initiating ART in Lusaka, Zambia.

In this study, the investigators used the Cockcroft–Gault (CG) method, the Modification of Diet in Renal Disease (MDRD) equation, and serum creatinine to assess renal function. Creatinine clearance of at least 90ml/min was considered normal. Having a creatinine clearance of 60-89ml/min was categorised as mild renal insufficiency; 30-59ml/min as moderate and less than 30 ml/min as severe.

This analysis included 25,779 patients enrolled in the Lusaka district programme, who started ART from May 2004 to September 2007, and who has a documented creatinine measurement at baseline.

When the investigators calculated creatinine clearance by the CG, they found a third of their patients (33.5%; 95%CI: 32.9%, 34.1%, n=8,456) had renal insufficiency. Of these, 6216 (73.5%) were mild, 1976 (23.4%) were moderate and 264 (3.1%) were severe.

In a multivariate analysis, the investigators found several covariates were associated with higher adjusted Hazard Ratios (AHR) of renal disease including: female sex (AHR=1.2; 95% CI: 1.1, 1.2), older age (AHR=1.5 per 10 years; 95% CI: 1.4, 1.5), hemoglobin less than 8 g/dl (AHR=1.5; 95% CI: 1.4, 1.6), BMI less than 16 kg/m² (AHR=1.7; 95% CI: 1.6, 1.8), and WHO stage 3 (AHR=1.2; 95% CI: 1.2, 1.3) or stage 4 (AHR=1.3; 95% CI: 1.2, 1.4).

Additionally, they found a modest increase in the risk for renal insufficiency as CD4 cell counts declined.

In Kaplan-Meier analysis, renal insufficiency correlated with 2-year survival: 91% for patients with normal creatinine clearance, 85.8% for mild, 78.8% for moderate, and 61.2% for severe ($p < 0.001$).

In an adjusted Cox proportional hazards model, risk for mortality less than 90 days increased for patients with mild (AHR=1.7; 95% CI: 1.5, 1.9), moderate (AHR=2.3; 95% CI: 2.0, 2.7), and severe (AHR= 4.3; 95% CI: 3.1, 5.5) reduction in creatinine clearance.

When compared with patients with normal renal function, the investigators noted similar risk in post-90 day mortality: mild insufficiency (AHR=1.4; 95% CI: 1.2, 1.6), moderate (AHR=1.9; 95% CI: 1.5, 2.3), and severe insufficiency (AHR=3.6; 95% CI: 2.4, 5.5).

They also found similar trends in secondary analyses when renal function was estimated with MDRD or serum creatinine.

The investigators noted that although these observational data do not establish a direct casual relationship between renal insufficiency and mortality they do suggest a need to further evaluate ART eligibility criteria.

They suggest that wherever feasible, screening for renal function should be instituted as part of ART programmes, particularly with the introduction of tenofovir. They add: "Algorithms for more aggressive assessment and management of renal insufficiency should also be developed specifically for settings with limited diagnostic capabilities."

Ref: Mulengaa LB, Krusea G, Lakhil S et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. *AIDS* 2008, 22:1821-1827.

Inflammatory and coagulation biomarkers linked to mortality in large treatment interruption trial

Richard Jefferys, TAG

The strong association between immune activation and disease progression in HIV infection has been demonstrated and confirmed by multiple studies over the past 25 years. In several reports, expression of the CD38 activation marker by CD8 T cells has correlated more closely with progression than viral load or CD4 T cell counts. Elevated levels of immune activation were even noted in the first AIDS case reports published in December 1981 in the *New England Journal of Medicine* (NEJM) [1]; at that time, CD38 was known as the thymocyte-associated antigen T10. Research has also shown that immune activation significantly increases the levels of pro-inflammatory cytokines in people with HIV infection compared to uninfected controls. Suppression of HIV replication by antiretroviral therapy (ART) typically causes an immediate and precipitous decline in immune activation, but levels tend to remain slightly higher than in controls even after several years of treatment.

What has been relatively unclear until recently is the degree to which the immune activation and inflammation caused by HIV infection can impact health. This under-appreciated aspect of disease pathogenesis was highlighted by the outcome of a large,

5,472-person randomized trial known as SMART (Strategies for the Management of AntiRetroviral Therapy), which compared continuous ART with an intermittent, CD4-guided ART strategy. Smaller studies had suggested this approach might be a safe and potentially toxicity- and cost-sparing approach to treating HIV and the primary risks were thought to involve drug resistance, increased possibility of transmission and acute infection symptoms after interruption. Only a few clinicians, such as Diane Havlir, voiced concern that the inflammatory consequences of HIV replication might cause treatment interruptions to be harmful. It was thus a surprise to many when in late 2006, it was announced that the intermittent therapy arm of SMART was being halted due to a doubling of the risk of illness and death compared to the continuous ART arm.

The results, published subsequently in NEJM, showed that the intermittent arm did worse on every endpoint, and the increased risk of clinical events and death was seen across all CD4 strata, not just among individuals with low baseline counts or nadirs. The majority of the events involved cardiovascular, liver and kidney disease and not opportunistic infections, suggesting that immune activation and inflammation had played a larger role in the outcomes than immunodeficiency. [2]

Now, in the latest *PLoS Medicine*, the SMART researchers report that analyses of biomarkers of inflammation and blood coagulation offer strong evidence that this was indeed the case. [3]

The study authors begin by noting that prior studies have demonstrated links between HIV replication and endothelial cell dysfunction (endothelial cells line the interior surface of blood vessels), and that this was associated with elevations in markers of hypercoagulability (a tendency for the blood to clot inappropriately) which were reduced by ART. Levels of the pro-inflammatory cytokine IL-6 have also been shown to be elevated in cross-sectional studies of HIV-infected individuals compared to uninfected controls, and IL-6 levels correlate with viral load in advanced disease. Similarly, levels of the pro-inflammatory marker C-reactive protein have been shown to increase over the course of HIV infection, with the highest levels reported among individuals progressing to AIDS.

In the SMART trial, a pre-planned substudy regularly measured four inflammatory biomarkers: high sensitivity C-reactive protein (hsCRP), IL-6, amyloid A, and amyloid P, and two coagulation markers: D-dimer and prothrombin fragment 1+2. To evaluate the impact of these biomarkers on the risk of death among SMART participants, the researchers conducted a case-control study in which two controls were matched with each of the 85 participants who died during the trial in order to compare biomarker levels using the samples taken prior to death. A second analysis was also conducted to look at levels in a larger random sample of 250 participants from each trial arm. Additional analyses looking at links between these biomarkers and specific clinical events are also being conducted, but results will be published separately.

The results showed that IL-6, D-Dimer and C-reactive protein levels were significantly higher among individuals that died compared to the matched controls.

In the larger analysis of a random sample of 250 participants from each arm after one month on study, the researchers found that individuals randomized to interrupt ART showed significant increases in IL-6 and D-Dimer levels: the median increase in IL-6 was 0.60 pg/ml (a 30% increase) and for D-Dimer 0.05 μ g/ml (a 16% increase). In comparison, the continuous ART group showed median increases of 0.0 μ g/ml and 0.12 pg/ml (a 5%

increase) for D-dimer and IL-6, respectively. The researchers report that changes in hsCRP and amyloid A were in the same direction but did not differ significantly between the two groups. The largest increases were seen among individuals in the interruption group who entered the study on ART with viral loads below 400 copies/ml (a 27% increase in D-Dimer and 43% increase in IL-6).

In discussing their results, the authors note that elevated IL-6 and D-Dimer levels have been associated with all-cause mortality in studies of uninfected elderly and critically ill individuals, lending plausibility to the associations observed in SMART. [4, 5]

They also point out that while inflammation is the most likely factor driving these biomarker elevations, the study does not formally prove this, and other potential contributors could involve microbial translocation (which elevates LPS, which in turn can elevate D-Dimer and provoke IL-6 production by monocytes) and direct effects of HIV proteins or HIV replication. One implication of the data highlighted by the researchers is that "specific therapies that reduce the inflammatory response to HIV and decrease hsCRP, IL-6, and D-dimer levels may warrant investigation as an approach for reducing risk of death among HIV-infected individuals."

A potentially important and worrying issue raised by these results which isn't discussed in the paper is that studies of treatment interruptions are likely more dangerous to people's health than has previously been appreciated. The general consensus has been that restricting this type of research to individuals with high CD4 counts and regularly monitoring CD4 counts and viral load during ART interruption is sufficient to ensure safety. These new data indicate that, at the very least, IL-6 and D-Dimer levels should be evaluated in order to exclude those at highest risk from treatment interruption trials. Clear information about these findings also needs to be added to the informed consent of any ART interruption protocol.

One example is a recently initiated trial of a therapeutic vaccine made by Bionor Immuno. [6]

This study involves a six month ART interruption and is enrolling people with CD4 counts over 400 and nadirs over 200. The SMART data show that, absent additional safeguards, this type of trial is likely to put participants at unnecessary risk of illness and death.

Source: TAG Basic Science Blog (22 October 2008).
http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/10/inflammatory-an.html

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OPPORTUNISTIC INFECTIONS

Single high dose fluconazole for oropharyngeal candidiasis (OPC) comparable to standard 14-day treatment

Simon Collins, HIV i-Base

Results of a randomised, double-blind, placebo controlled trial in Tanzania of single high-dose oral fluconazole was reported by Omar Hamza and colleagues from Muhimbili University, Tanzania.

The trial randomised 220 HIV-positive patients with clinical and mycological evidence of oropharyngeal candidiasis to receive oral fluconazole doses of either 750-mg single dose or standard dose of 150 mg once-daily for 2 weeks. Each arm included 110 patients.

Results were similar in each group are detailed in Table 1 with no statistically significant differences between the two groups. Approximately 95% patients were clinically cured (OR, 0.825; 95% CI, 0.244–2.789; $p=0.99$) and 85-75% mycologically cured (OR, 1.780; 95% CI, 0.906–3.496; $p=0.129$).

Table 1: Results from single dose vs 2-week fluconazole

	750mg single dose	14-day 150mg dose
Clinical cure	104 pts (94.5%)	105 pts (95.5%)
Clinical improvement	2 pts (1.8%)	4 pts (3.6%)
Treatment failure	4 pts (3.6%)	1 (0.9%)
Mycological cure	93 pts (84.5%)	83 pts (75.5%)
Mycological failure	17 pts (15.5%)	27 pts (24.5%)

Overall, clinical cure was not achieved in 11 patients, and for all of these, *Candida* species were isolated from patient specimens at baseline and on day 14. In 33 patients (15.0%), clinical cure was obtained despite persistent positive culture results on day 14 (mycological failure).

No differences were observed in relapse rates (OR, 1.073; 95% CI, 0.456–2.523; $P=0.99$). The average time to relapse after clinical cure was 18-20 days. Twenty-two (91.7%) of 24 patients who experienced relapse during follow-up had CD4 cell counts <200 cells/mm³, 16 (66.7%) had CD4 cell counts <100 cells/mm³, 17 (70.8%) were not receiving HAART, and 14 (58.3%) had had previous episodes of OPC.

The mean plasma fluconazole concentrations on days 1, 4 or 5, 7, and 14 in the 14-day fluconazole group were 13.35, 5.46, 1.37, and 0.32 mg/L and 4.18, 6.88, 7.94, and 7.62 mg/L, for the single-dose and 14-day groups respectively. These differences were statistically significant for days 1, 7 and 14.

Overall, adverse events were mild, and no differences in frequency of adverse events were noted between patients in the 2 treatment regimens. Because most of the study patients were in an advanced stage of HIV infection and AIDS, abnormalities in full blood count and liver function tests were common.

In this study, the mycological cure rate, with a single-dose treatment of 750 mg fluconazole, was much higher (84.5%) than the 6%–41% mycological cure rates reported from studies using 150mg single dose treatment.

The authors concluded “The use of a single high dose of fluconazole ... presents the advantages of simplicity and convenience, thus improving compliance and reducing the cost of therapy. A single dose of five 150-mg tablets is less costly than fourteen 150-mg tablets taken over a 14-day course and, therefore, could be used, especially in resource-limited settings like in sub-Saharan Africa. In addition, administration of the single-dose therapy can be observed directly by medical personnel, thereby assuring patient compliance.”

Ref: Omar J et al. Single-Dose Fluconazole versus Standard 2-Week Therapy for Oropharyngeal Candidiasis in HIV-Infected Patients: A Randomized, Double-Blind, Double-Dummy Trial. *Clinical Infectious Diseases* 15 November 2008, Vol. 47, No. 10: 1270-1276.

PREGNANCY & PMTCT

Tenofovir safe in pregnancy in macaque model

Polly Clayden, HIV i-Base

A paper authored by Koen Van Rompay and coworkers published in the September 2008 edition of *Antimicrobial Agents and Chemotherapy* showed findings from animal studies of tenofovir use from infancy to adulthood including pregnancy. [1]

Tenofovir is highly effective in the simian immunodeficiency virus (SIV) macaque model of HIV infection.

This paper reports extended safety and efficacy data from a study of 32 animals that received prolonged (>1- to 13-year) daily subcutaneous tenofovir regimens.

The authors report that the likelihood of renal toxicity (proximal renal tubular dysfunction [PRTD]) correlated with plasma drug concentrations, which were dose and age-dependent. They found that below a threshold AUC for tenofovir in plasma of 10g h/ml, (an exposure several fold higher than that in humans receiving 300 mg oral formulation tenofovir disoproxil fumarate [TDF]), prolonged tenofovir administration was not associated with PRTD using urinalysis, serum chemistry analyses, bone mineral density, and clinical observations.

When they looked at low-dose maintenance regimens, they found plasma tenofovir concentrations and intracellular tenofovir diphosphate concentrations were similar to or slightly higher than those found in humans receiving TDF. The authors note that no new toxicities were identified in this study and the available evidence does not suggest teratogenic effects of prolonged low-dose tenofovir treatment.

Despite the presence of the reverse transcriptase mutation K65R in all SIV-infected animals, 6 animals suppressed and maintained undetectable viral load for up to 12 years of TFV monotherapy.

With regards to tenofovir exposure in utero, the authors report that one female macaque had been started at birth on continuous low-dose tenofovir. Her plasma TFV AUCs were four- to six fold higher than those observed with the oral TDF regimen in humans. After 10 years, this animal has not demonstrated any signs of toxicity and has delivered three healthy offspring that showed normal pre- and postnatal development (including renal parameters and bone development) for up to 5 years of age.

They explain that although the number of animals studied is small and further investigation is warranted, these preliminary findings with tenofovir during pregnancy are consistent with the available human data from the Antiretroviral Pregnancy Registry, which show no indications of an increased risk of birth defects after in utero exposure to tenofovir. [2]

The authors conclude that their findings show the safety and sustained benefits of prolonged tenofovir-containing regimens throughout development from infancy to adulthood, including pregnancy.

They write: "These observations support the long-term treatment of HIV-infected humans with TFV-containing regimens. Continued monitoring of these animals as they progress toward geriatric age

will provide further valuable information on prolonged treatment with TFV-containing regimens, with the ultimate goal of giving HIV-infected persons a normal life span."

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2. Antiretroviral Pregnancy Registry Steering Committee. 2007. Antiretroviral Pregnancy Registry interim report for 1 January 1989 through 31 July 2007. Registry Coordinating Center, Wilmington, NC.

Antiretroviral therapy in pregnant women and pregnancy outcomes in Abidjan, Cote D'Ivoire

Polly Clayden, HIV i-Base

The association between HAART use in pregnancy and adverse infant outcomes, particularly preterm delivery (PTD) is controversial. An association has been demonstrated in some studies but not others and data from Africa is lacking.

Didier Koumavi Ekouevi and co-workers compared pregnancy outcomes in two sequential programmes conducted at the same antenatal clinic in Abidjan. The programmes were: the ANRS Ditrane Plus study, conducted between March 2001 and July 2003 (when HAART was not yet available and not recommended by WHO) and the MTCT Plus programme between August 2003 and August 2007.

In Ditrane Plus women eligible for HAART, by WHO criteria, received a short-course of either AZT from 36 weeks or AZT+3TC from 32 weeks plus single dose NVP for mother-to-child transmission prophylaxis (PMTCT group). The women who met the criteria for starting treatment in MTCT Plus received HAART (HAART group).

The HAART group included both women who had started treatment before they became pregnant and women eligible for HAART who started during pregnancy.

All infants received AZT for 7 days and single dose NVP. Women were counselled either to replacement feed or exclusive breast feed for 4-6 months. Formula was provided free in the PMTCT group but not in the HAART group.

There were 358 HIV-positive women eligible for HAART enrolled in this study. Their median age at enrolment was 28 years (IQR, 25–32 and median CD4 cell count 179 cells/mm³ (IQR 120–252). The median maternal BMI at delivery was 23.8 kg/m² (IQR 21.8–26.3).

The women in the PMTCT (n=190) and HAART (n=168; 34 starting HAART before pregnancy) groups had similar characteristics except more women were at WHO stage 3 and 4 in the PMTCT group (59.4%) than the HAART group (39.7%), p=<0.001 and there was a difference in parity, p=0.001 and age, p=0.039.

The median duration of HAART before delivery was 11.9 weeks and the median duration of prophylaxis was 4.9 weeks. The most frequent regimens were: AZT+3TC+NVP (87%) in the HAART group and AZT+sdNVP in the PMTCT group.

Of 326 singleton infants (175 in PMTCT and 151 in HAART groups), the overall rate of stillbirth (fetal death any time after 20 weeks of pregnancy) was 3.1% (CI 1.5–5.6). There was no significant difference between the HAART and PMTCT groups (3.3 vs. 2.9%, $p=0.85$).

Among the 309 infants for whom data were available, the investigators found the median birth weight was 3000g (IQR 2700–3250). There were 52 (16.8%) infants with low birth weight (LBW) (<2500g). The frequency was higher in the HAART group than the PMTCT group (22.3 vs. 12.4%, $p=0.02$). The frequency was similar in the PMTCT group between the two regimens (12.3% with short course AZT+3TC+sdNVP and 9.4% with short course AZT+sdNVP, $p=0.60$). It was also similar between women who started HAART before and during pregnancy in the HAART group (25.0 vs 21.5%, $p=0.68$). There was no difference between the rate of very low birth weight (VLBW) (<2000g) between the two groups, $p=0.279$.

There were 28/305 infants identified as HIV-infected at 12 months (9.6%, 95% CI 6.7–13.7%). The estimated transmission risk was 2.3% (95% CI 0.7–6.9%) in the HAART group, and 16.1% (95% CI 11.2–22.9%) in the PMTCT group $p<0.001$. In the HAART group 65% of the women breast fed for a median of 4.7 months (IQR 3.3–6.3), compared to 48% in the PMTCT group for a median of 4.3 months (IQR 3.5–6.5).

In multivariate analysis, the authors found HAART initiated before pregnancy (AOR 2.88, 95% CI 1.10–7.51) and during pregnancy (AOR 2.12, 95% CI 1.15–4.65) and maternal BMI (<25 kg/m²) (AOR 2.43, 95% CI 1.20–4.91) to be associated with LBW.

The overall infant survival rate among uninfected infants was 0.93 (95% CI 0.87–0.96) and was similar in the two groups, $p=0.78$. Neither LBW (AOR 1.5, $p=0.38$) nor maternal HAART exposure (AOR 1.1, $p=0.85$) were associated with infant mortality in these infants. The only factor associated with infant mortality in this analysis was paediatric HIV infection (AOR 11.9, 95% CI 4.8–29.5); after adjustment for infant feeding, LBW, exposure to HAART regimens, and maternal characteristics at enrolment.

The authors note that they were unable to study PTD rates to try and explain rate of LBW because the majority of HIV-infected women did not know the date of their last menstruation and did not have an ultrasound examination in the first trimester.

They wrote: "Further larger scale international pharmacovigilance systems should be established to access pregnancy outcomes in the context of this wider use of antiretroviral regimen in pregnant women."

suggest possible associations between maternal disease status, HAART, and adverse pregnancy outcomes and this calls, as Ekouevi et al stress, for the establishment of good pharmacovigilance systems as HAART becomes more available and widely used in pregnancy in resource limited settings .

Ref: Ekouevi DK, Patrick A. Coffiea PA, Becquet R et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. AIDS 2008, Vol 22 No 14. 1815-1820.

C O M M E N T

The controversy surrounding HAART and preterm delivery should not obscure the need for careful assessment of birth weight and gestational age at delivery in all babies exposed to HAART in pregnancy. In this study low birth weight was not associated with infant mortality - only HIV infection. This is the most important point, but as rates of HIV infection become lower, determining the safest way to achieve this becomes even more important. In European studies a significant proportion of preterm deliveries have been before 32 weeks and such babies frequently require special care facilities that may not always be available.

So far there are limited data from Africa. Preliminary data from a review of obstetrical records in Botswana also

PAEDIATRIC CARE

Antiretroviral therapy in HIV-positive children in Southern Africa

Polly Clayden, HIV i-Base

An article in the August edition of the *Lancet Infectious Diseases* reported findings from a literature review, conducted by Catherine Sutcliffe and co-workers, looking at 30 paediatric HIV studies or treatment programmes in sub-Saharan Africa.

In this assessment, the authors found that children receiving antiretroviral therapy (ART) ranged from infants aged two months to adolescents aged 15 years. Out of 26 studies that reported age at ART initiation, 19 (73%) showed a mean or median age at starting treatment of >5 years. Only two studies reported a median age of starting treatment of <2 years.

The majority of children had severe immunosuppression at initiation of ART. The proportion of children with a CD4 percentage <15% ranged from 56% to 96%.

Only two studies reported how children were referred for treatment. In a Kenyan programme 69% of children were referred following admission to hospital and the remaining children were from other outpatient clinics. In Cote D'Ivoire, the paediatric department or other healthcare settings referred 64% of children, 24% were referred through the people living with HIV/AIDS network and 12% through prevention of mother to child transmission (PMTCT) programmes.

24/30 studies reported the antiretroviral regimens used, the majority (92%) of which included two NRTI inhibitors plus one NNRTI. Typically a regimen of: AZT or d4T plus 3TC with either EFV or NVP.

In the 17 studies that provided information on clinical outcomes, children gained 1.8-3.6 kg in the first year of treatment. There were improvements in weight for age Z scores with a median or mean -2 below baseline with a 1 SD improvement by 3 months. These improvements were sustained 2-3 years after start of treatment in those studies with longer follow up.

There was also significant immunological improvement reported in 28 studies, with a median gain in CD4 percentage of 7.0-13.8% at 6-8 months and 10-16% at 12-15 months of starting ART. And virological data from the 17 studies with the capacity to measure viral load showed a median 2.0 log₁₀ reduction within 1 year. Undetectable viral load was defined differently across studies but for those reporting <250 copies/mL, 400 copies/mL or unknown, 54-55% of children were suppressed at 3 months, 46-81% at 6 months and 49-81% at 12 months after starting treatment.

In the studies reporting <50 copies/mL, undetectable viral load was achieved in 64% and 84% of children at 6 months and 67-100% at 12 months. The authors noted that the explanation for the higher level of suppression in studies using the more sensitive assays was unclear but this trend continued among the small number of children with longer follow up.

Overall mortality during follow up was mostly low with a probability of survival at one year after initiation of ART of 84-97%. A study from Cote D'Ivoire reported over 3 years of follow up, with 92-3% survival at six months, 91% at 12 months, 88% at 18-36 months and 86% at 42 months from initiation of ART.

The majority of deaths were within 6 months of starting treatment. The most commonly reported risk factor for death was low CD4 percentage at initiation of treatment. Age >12-18 months was among the other risk factors.

One study from Mozambique compared mortality among children receiving ART and those ineligible for treatment. This comparison found that mortality was higher (HR 3.8, 95% CI 1.9-7.5) for the untreated group despite having better immunological and virological conditions at baseline.

Loss to follow up was generally low: 0-11% and 0.1-7.3% transfers among studies of <1 year; 1-9% and 6.0-11.2% transfers, studies of 1-2 years and 5.0-7.6% and 15% transfers among studies of up to 3 years.

The authors wrote: "Older children with slower disease progression are more likely to gain access to antiretroviral therapy in sub-Saharan Africa. By contrast, nearly two thirds of HIV-infected children who would have benefited from life prolonging treatment before reaching age 5 years are not being diagnosed or treated."

C O M M E N T

This assessment gives a very useful picture of children receiving antiretroviral therapy in sub-Saharan Africa. As the new WHO recommendations of universal treatment for all infants <12 months begin to be implemented, hopefully the picture should change considerably.

WHO recommendations:

http://www.who.int/hiv/pub/meetingreports/art_meeting_april2008/en/index.html

Ref: Sutcliffe CG, van Dijk JH, Bolton C et al. Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *Lancet Infect Dis* August 2008; 8: 477-89].

TRANSMISSION

Implications of transmission with undetectable HIV viral load: lower limit for HIV transmission excluded from model

Simon Collins, HIV i-Base

An Australian research group, lead by David Wilson, published a study in the Lancet modeling the potential impact of a low-level residual transmission risk. [1] This was in response to the Swiss Statement relating to low-to-zero risk of HIV transmission when an HIV-positive partners had shown a durable response to treatment (> 6 months with viraemia suppressed to <50 copies/mL) and other conditions are met (good adherence, no other STIs etc). [2]

The model looked at the risk of unprotected sexual transmission per act and cumulatively over many exposures, within couples where one partner is HIV-positive and the other is HIV-negative.

They assumed that each couple had 100 sexual encounters per year, and calculated a cumulative probability of transmission to the HIV-negative partner each year. Transmission risk assumptions were based on the Rakai data (a heterosexual Ugandan study from 1991 looking at transmission risks in 415 sero-defferent couples). The Rakai group report that each ten-fold increase in viral load is associated with a 2.45-fold (95% CI 1.85–3.26) increase in the risk of HIV transmission per sexual contact. [3]

The model used per-transmission rates (from studies that hadn't factored the impact of viral load) from 0.001 to 0.0005 per exposure and an assumption that on-treatment viral load was 10 copies/mL (see Table 1). Current transmission rates were estimated assuming 80% condom use, and 95% effect protection from condom use.

This modelling suggested per exposure risk rates from an HIV-positive partner on ARV treatment from 1 in 43,000 for anal sex to less than 1 in 220,000 for vaginal sex.

This modelling suggested an approximate four-fold increase in risk across all three groups if sero-different stopped using condoms.

While this is interesting, it didn't closely relate to the motivation

behind the Swiss Statement, nor the clinical situations in which they suggested it be applied. These were i) ability to safely conceive a baby without dependence on sperm-washing (a procedure that is difficult to access or afford and which carries a reduced conception rate) and ii) to allay anxiety and worry over perceived risk of infection during regular sex (using condoms) and in the event of a condom break.

For many HIV-negative partners, single exposure risks of between 1 in 43,000 for anal sex to less than 1 in 220,000 for vaginal sex may often be acceptable in the context of general quality of life for family planning or a healthy less anxious sex life.

Importantly, a weakness in the model, from assuming a linear relationship between viral load and transmission was raised both in the original article and in an accompanying comment by Geoffrey Garnet from UCL and Brian Gazzard from the Chelsea and Westminster Hospital, published in the same issue of the Lancet. [4]

Assuming a log-linear relationship that supposes a risk at every level of viral load they argued "extrapolates the model beyond the available data, assuming that there is a continuous reduction in risk rather than a threshold below which no transmission is possible".

The model doesn't address the likelihood that most sero-different couples are likely to continue to use both ARVs and condoms, or the additional reduction in transmission risk from ARVs in this setting.

The comment concludes "In many ways, the Swiss statement provides the opportunity for positive public-health messages, by promoting adherence to treatment and concern over other sexually transmitted infections. The use of condoms, in addition to antiretrovirals, to further reduce risk and prevent other sexually transmitted infections can then also be promoted."

COMMENT

More than ten years after HAART has been able to reduce viral load to very low levels, it is notable that we have no prospective trial results looking at its impact on transmission, on either a population or individual level. Lack of data on whether treatment brings most people below a minimum threshold for transmission is clearly key to any further discussion.

The lack of data on transmission risk for anal sex (heterosexual and MSM) is also worryingly sparse, although

Table 1: Modelled cumulative transmission risk by type of exposure

	Estimated probability per exposure when NOT on ARVs	Estimated risk per single exposure when on ARV	Annual transmission risk based on 100 exposures/year (95% CI)	Current rates with condom use (95%CI)	Estimated number of new infections over 10-year period in 10,000 couples with viral load 10 copies/mL if condoms never used
Female-to-male	0.0005	0.000022 (1 in 220,000)	0.0022 (0.0008–0.0058)	52 (19–138)	215 (80–564)
Male-to-female	0.0001	0.000043 (1 in 430,000)	0.0043 (0.0016–0.0115)	104 (38–275)	425 (159–1096)
Male-to-male	0.001	0.00043 (1 in 43,000)	0.043 (0.0159–0.1097)	990 (376–2433)	3524 (1477–6871)

some research groups are looking to address this, hopefully with sufficient funding for sufficiently powered conclusions, and with some urgency.

The focus on ARVs as a prevention strategy, also a key topic at the Mexico conference, is long overdue. Many research groups have highlighted that 25-50% of new diagnoses are likely to be driven by people who are undiagnosed, especially those recently infected when viraemia is highest by a magnitude of several logs. [5, 6, 7, 8]

Many groups have also reported that risk behaviour generally falls after diagnosis especially once patients are within care. [9]

Increased testing, reducing late diagnosis and seeing treatment as protective of both health and transmission risk - rather than as something to delay until as late as possible - are likely to develop as increasingly important themes for managing the HIV epidemic in the 21st century.

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HIV RNA is detectable in semen in 5% patients with undetectable blood plasma viral attending fertility clinic

Simon Collins, HIV i-Base

In the context of quantifying levels of risk relating to natural conception in serodifferent couples in relation to the recent Swiss Statement relating to undetectable viral load and risk of transmission [1], Anne-Geneviève Marcelin from Hôpital Pitié Salpêtrière and colleagues reported rates of discordance between levels of HIV RNA in blood and semen in a cohort of 145 HIV-positive men enrolled in an assisted reproductive (sperm-washing) programme in Paris. [2]

The group, writing in a research letter to the August 2008 issue of *AIDS*, found that 5% of men in this group had detectable HIV RNA in semen.

264 paired blood and semen samples were collected between January 2002 and January 2008 with some patients providing up to six samples. Viral load was quantified using tests sensitive to 40 copies/mL and 200 copies/mL in blood and in seminal plasma respectively.

Thirty-two blood plasma samples were detectable (median 6,325 copies/ml (range = 222-28,300). Sixteen seminal plasma samples were detectable and the median level of HIV-1 RNA in semen was 1770 copies/ml (range = 255-25,100).

Overall, 234 paired samples were concordant, with 225 samples with undetectable HIV-1 RNA both in blood and semen (85.3%) and nine with detectable HIV-1 RNA in blood and semen (3.4%). However, 23 blood samples had detectable HIV-1 RNA although the seminal viral load was undetectable and seven seminal samples had detectable HIV-1 RNA although the blood viral load was undetectable (range 257-1230 copies/mL).

These seven discordant paired samples corresponded to seven distinct patients who had undetectable viral load in blood for greater than six months and no current STI's. Interestingly, 6/7 had undetectable concordant results in blood and semen on at least one occasion during follow-up indicating variability over time. Antiretroviral drug levels in semen showed no relationship between choice of drug and viraemia: 3TC, FTC, tenofovir and indinavir showed higher penetration but were also included in many of the regimens that these seven patients were using.

The researchers concluded that their findings justify measuring HIV-1 RNA in semen when sero-different couples are planning a pregnancy. They also cautioned that a residual risk of transmission relating to these discordant results should be included in the information available to couples who would like to have unprotected sexual intercourse in the context of conceiving a baby.

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C O M M E N T

It is interesting that level of discordance was intermittent in the seven patients with detectable viral load in semen, and that levels of viral load were generally low (maximum 1200 copies/mL).

As with the previous article, establishing whether a minimum threshold exists for transmission remains a crucial research question.

RNA testing of semen to minimise risks in the context of conceiving a baby without sperm-washing is clearly an additional safety measure that should be used whenever possible – along with limiting conception attempts to the most fertile days of the woman's cycle and possibly use of single-doses of tenofovir/FTC PrEP and PEP.

Tenofovir gel as a rectal microbicide: evidence for protection and priming of T cell responses in the SIV challenge model

Richard Jeffreys, TAG

The new PLoS Medicine features a study conducted by Martin Cranage and colleagues evaluating tenofovir gel as a potential rectal microbicide in the SIV challenge model. The researchers report that application of the gel two hours prior to exposure to the SIVmac251/32H challenge virus protected six out of nine macaques. Of the remaining three, two showed lowered viral loads post-infection compared to controls. Interestingly, most of the protected animals also displayed detectable SIV-specific T cell responses even though sensitive assays could find no trace of virus.

The PLoS editor's summary raises the concern that these SIV-specific T cells may be associated with enhanced susceptibility to infection upon re-exposure; however, Cranage et al note in their discussion that transient tenofovir treatment immediately post SIV infection has been shown to lead to induction of SIV-specific T cell responses, and macaques <<http://jvi.asm.org/cgi/content/full/75/21/10187>> in this study subsequently resisted both homologous and heterologous SIV challenges. The question of whether the SIV-specific T cell responses observed in Cranage's study have the potential to be protective can only be definitively addressed by another experiment in which the macaques are re-challenged with SIV.

An additional implication of these data is that human trials of microbicides and pre-exposure prophylaxis (PrEP) should include monitoring for HIV-specific T cell responses.

Source: TAG Basic Science Blog 06 Aug 2008

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/08/tenofovir-gel-a.html

Ref: Cranage M et al. Prevention of SIV Rectal Transmission and Priming of T Cell Responses in Macaques after Local Pre-exposure Application of Tenofovir Gel. PLoS Medicine Vol. 5, No. 8, e157 doi:10.1371/journal.pmed.0050157

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Genetic protection against malaria may increase susceptibility to HIV infection in people of African descent

Richard Jeffreys, TAG

A new and complex study has identified a possible genetic influence on susceptibility to HIV acquisition that preferentially impacts Africans and people of recent African descent. [1] The paper is available free on the website of the journal Cell Host & Microbe (link below).

The major points are as follows:

- The Duffy Antigen Receptor for Chemokines (DARC) [2] on red blood cells can bind a slew of different chemokines and also HIV itself (X4-using HIV isolates much more than R5-using isolates).
- A genetic change (called a single nucleotide polymorphism or SNP) can lead to a lack of DARC receptors on red blood cells. This SNP is very common in Africans and people of recent African descent, because it once protected against a form of malaria caused by the pathogen *Plasmodium vivax*.
- In a large cohort of African American individuals from the US military, having the DARC-negative SNP was associated with a significantly increased risk of having HIV infection, even in multivariate analyses controlling for various confounding variables. However, the confidence intervals on the multivariate analyses appear to approach a relative risk of 1.0 at the low end (in other words, based on the numbers in this study, it is within the bounds of possibility that the SNP has little impact on susceptibility). The result appears to rest on the finding that perhaps ~60% of 814 HIV-negative African Americans lacked the DARC receptor compared to ~70% of 470 HIV-infected African Americans. [3]
- If the result holds up, the fact the SNP is nearly ubiquitous among African populations could contribute to the higher incidence of HIV infection on that continent (the researchers estimate it might explain ~11%).
- The absence of the DARC receptor is associated with lower levels of CCL5 (formerly called RANTES), a chemokine with strong anti-HIV activity, providing a possible mechanistic explanation of the finding. A prior study has reported that persistently exposed, uninfected sex workers have ten-fold higher levels of CCL5 in the genital tract compared to both infected individuals and uninfected study participants who had recently started sex work and thus had little prior exposure to HIV. [4] Higher CCL5 production has also been reported in highly exposed but uninfected gay men. [5]
- Although at first blush it might sound paradoxical, the absence of DARC was also associated with a slight but significant slowing of disease progression in the HIV-infected members of the study cohort. The researchers suggest that this is likely explained by the association between the presence of DARC and higher levels of pro-inflammatory chemokines such as CCL2. Once infection occurs, the authors propose, the presence of DARC may exacerbate immune activation due to this association with elevated levels of pro-inflammatory chemokines (immune activation is the single strongest predictor of the pace of disease progression in people with HIV). While this hypothesis remains speculative, the authors argue it is supported by an association they have reported

previously; in that case, a SNP that increases CCL2 levels in European Americans was shown to be linked to reduced susceptibility to acquisition of HIV infection and also faster disease progression in infected individuals. [6] Another non-exclusive possibility raised by the authors is that the absence of DARC slows progression by preventing transfer of DARC-bound HIV particles to CD4 T cells.

In discussing their results, the study authors acknowledge that there is a possibility that the associations they have observed are connected to an unknown factor or factors that are linked to the DARC SNP, and stress that confirmation of these results in other cohorts will be necessary to ensure they are valid. If it does turn out that there is a protective effect mediated by elevated levels of CCL5, this information could potentially assist vaccine development, as it would suggest that using adjuvants that elevate CCL5 levels and/or inducing HIV-specific T cell responses that produce CCL5 could be useful strategies for HIV vaccines.

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BASIC SCIENCE & VACCINE RESEARCH

US cancel Phase 3 HIV vaccine trial

Following the failure of the STEP Phase 3 vaccine, and after broad consultation, including with community groups (see HTB July/August 2008), the US-funded follow-on Phase 3 study (called PAVE 100) has been cancelled. [1]

Detailed in a press statement, the US National Institute of Health (NIH) said that although a scaled down version of the study may still run to see whether this new but similar adenovirus candidate could impact on viral load in people who are infected post-vaccination, the shift in NIH funded vaccine research is towards supporting the basic research and vaccine discovery needed to design promising vaccine candidates.

Source: NIAID press statement: NIAID Will Not Move Forward with the PAVE 100 HIV Vaccine Trial. (17 July 2008)

Information about clinical HIV vaccine research supported by NIAID: <http://clinicaltrials.gov/ct2/results?term=HIV+vaccine+and+NIAID&recr=Open>

Microbial translocation in immunological non-responders to ART

Richard Jeffreys, TAG

A research letter in the journal *AIDS* reports that translocation of bacteria across the gut mucosa is associated with a failure to reconstitute CD4 T cells despite viral suppression by antiretroviral therapy (ART). [1]

The authors report that plasma levels of lipopolysaccharide (LPS), an indirect measure of microbial translocation, were significantly higher in both immunological non-responders (INRs) and individuals with untreated, advanced HIV infection compared to individuals on ART who experience good CD4 T cell reconstitution.

The researchers also offer the first published direct evidence of microbial translocation in HIV infection by measuring bacterial 16S DNA in samples and then conducting sequencing experiments to show that the DNA was derived from gut bacteria species. Using this technique, they found that 16S DNA could be isolated from five out of seven INRs and six out of 12 individuals with advanced, untreated HIV infection but none of the seven individuals with a good CD4 T cell response to ART.

In discussing their results, the authors state: "by showing an association between LPS and bacterial DNA fragments in plasma, our study is the first to directly demonstrate bacterial translocation in both naïve and HAART-treated HIV-infected patients through the direct demonstration of enterobacteria genome sequences." They also raise the issue of uncertainty regarding cause and effect, noting that microbial translocation may contribute to the lack of an immunological response to ART seen in INRs but also that, conversely, "bacterial translocation might be favoured in INRs by reduced T-cell-mediated competence failing to provide full immune control in mucosa and mesenteric lymph nodes, thus permitting peripheral egress and survival of bacteria."

In support of this possibility, they cite a paper from 1980 showing that microbial translocation occurs in athymic mice and can be reduced when the mice receive thymic grafts. The full text of this paper is available online. [2]

Interestingly, this is the same suggestion made by the recent murine study from Brigitta Stockinger's group which found that reduce naïve T cell levels were associated with microbial translocation and immune activation (reported on the blog previously). [3]

Source: TAG Basic Science Blog (Sep 2008)

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/09/microbial-trans.html

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Control of a superinfecting virus in an elite controller

Richard Jefferys, TAG

A free access article in the journal *Clinical Infectious Diseases* describes the case of an individual controlling HIV to below 50 copies/ml in the absence of treatment (classified as an "elite controller") who became superinfected with another virus. [1]

The researchers were able to document the source of the superinfecting HIV strain and report that after a brief increase in viral load to a maximum of 25,000 copies, the elite controller was able to regain his unusual degree of control of viral replication and has since shown viral loads consistently around 2,000 copies/ml over two years of follow-up. CD4 counts have remained in the normal range throughout.

In contrast, the individual's previously uninfected partner who was infected with the same virus showed high viral loads and decreasing CD4 counts, as did the individual who was the source of both infections. The researchers note that the elite controller possesses the HLA B*57 allele, which has been consistently associated with immunological control of HIV replication, and conclude that at least in some cases "host mechanisms seem to be able to repeatedly control HIV-1 replication, halting disease progression."

However, it's perhaps worth noting that the implications of the somewhat higher viral load levels observed after superinfection for the individual's clinical course remain to be determined.

Source: TAG Basic Science Blog (28 October 2008).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/10/control-of-a-superinfecting-virus-in-an-elite-controller.html

Ref: Rachinger A et al. Recovery of Viremic Control after Superinfection with Pathogenic HIV Type 1 in a Long-Term Elite Controller of HIV Type

1 *Infection. Clinical Infectious Diseases* 2008;47 DOI: 10.1086/592978 (free access to full text).

<http://www.journals.uchicago.edu/doi/full/10.1086/592978>

Second-oldest HIV-1 sequence identified

Richard Jefferys, TAG

A new study published in *Nature* reported the identification of the second-oldest known HIV-1 sequence. [1]

The sequence was recovered from a stored lymph tissue sample taken at a hospital in Kinshasa in 1960. The authors, led by Michael Worobey, were able to sequence around 5% of the HIV-1 genome and their analyses suggest that the virus began to spread and diversify in Africa around the turn of the century. The authors speculate that the growth of cities like Leopoldville facilitated an increase in transmission and the ultimate spread of HIV-1 across the globe.

Due to the many potential pitfalls associated with attempting to recover viral sequences from ancient samples, the work was confirmed by an independent laboratory, and the long lag time between the submission of the paper to *Nature* and publication also suggests that a great deal of rigor went into assuring the paper's reviewers that the findings were accurate.

In a news article for *Science*, Jon Cohen provides some additional background, noting that the tissue sample came from a 28-year old woman and was part of a group of samples taken from individuals with illnesses that had defied diagnosis, including lymph node abnormalities. Many more such samples are available for study, and Michael Worobey hopes to continue shedding light on HIV-1's early spread into the human population.

Source: TAG Basic Science Blog (01 October 2008).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/10/second-oldest-h.html

References:

1. Worobey M et al. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. *Letter. Nature* 455, 661-664 (2 October 2008) <http://www.nature.com/nature/journal/v455/n7213/abs/nature07390.html>

2. Cohen J. A viral blast from the past. *Science Now Daily News* (1 October 2008).

<http://sciencenow.sciencemag.org/cgi/content/full/2008/1001/1>

Why do we not yet have an HIV vaccine?

Richard Jefferys, TAG

In the online ahead of print section of *J. Virology*, Arnold Levine from Princeton University (who chaired a well-known, comprehensive 1996 critique of AIDS research at the National Institutes of Health) offers a thoughtful, personal review of a recent meeting that set out to address the question: why do we not yet have an HIV vaccine? Levine covers a range of territory, from the recent failure of Merck's T cell-based candidate in the STEP trial to concerns regarding how the HIV vaccine research field is currently structured. There follows some selected highlights and commentary, but the article is well worth reading in its entirety.

Beginning with a review of STEP, Levine notes that the grimmest

interpretation of the results – which came on the heels of the failure of a prior antibody-based vaccine called AIDSVAX - is that adaptive immunity is insufficient to repel or control HIV infection; he argues, however, that “there is good evidence that this is not correct and that more needs to be learned.” He cites the strong associations between specific class I and II HLA alleles and elite control of HIV replication (such associations have also been reported among exposed, uninfected individuals) and suggests that: “a clinical trial of a vaccine using individuals with this HLA group could be instructive in learning from the few to apply to the many.” Recent analyses of the STEP trial suggesting trends toward better control of viral load in recipients of the Merck vaccine possessing favorable class I HLA alleles (such as HLA B*57 and B*27) may offer additional support for this idea. Levine also stresses the need for a better understanding of the functional readouts that should be captured by immunological assays used in clinical trials, such as CD8 T cell-mediated killing of HIV-infected cells and antibody-mediated neutralization. Citing advances in gene analyses and systems approaches to interpreting data, Levine offers his view that “the modern tools of molecular biology now permit the human to be the best model organism to study biology.”

Addressing advances in understanding innate cellular mechanisms for interfering with DNA and RNA virus replication, Levine laments that attempts to incorporate this knowledge into HIV vaccination strategies remain in their infancy, and suggests “an organized effort in this area of research carried out in human beings is needed.”

Discussing the role of animal models, Levine touches on an area where he may be gratified to learn there has recently been some significant progress. Raising the issue of the relative resistance of HIV-infected chimpanzees to the development of AIDS, Levine argues that the phenomenon should by now be better understood. As it turns out, the < <http://69.7.74.112/publication.aspx?id=2514>> recent findings that a selective sweep has occurred at the level of chimpanzee class I MHC and that present-day alleles mirror the specificity of human HLA alleles associated with elite control of HIV offers a compelling explanation of the results obtained in chimpanzee HIV challenge studies, and one that further reinforces Levine’s earlier comments regarding the importance of HLA.

Levine concludes his discussion of the scientific challenges facing the field with a pithy summation: “The fact is we have failed to make some vaccines (HIV, Hepatitis C virus) because we don’t understand the immune system, the virology and the host in sufficient detail. We must carry out the hard work of doing good, even great science; if we continue just taking “shots on goal” in the hope we might get a small response to a vaccine, we will not be able to understand it or even improve it.”

Toward the end of his review, Levine also makes some pointed observations regarding how HIV vaccine research is currently organized. He notes: “the HIV field of basic and translational research has two structural properties that are not optimal for real novelty and progress. Because of the very large funding opportunities that come from several sources, laboratory sizes of some groups are very big. Having one leader and many researchers can narrow the direction and questions being asked in a field. A truly original and gifted scientist would not like to spend his or her career working on research problems formulated by others. The large groups compete well for funds, which may tend to drive talented new young researchers into other fields where they will have a greater chance to make an impact. Another

consequence of large laboratories dominating a field is that research efforts become stale.” He also points out that advances in virology and immunology that occur outside of the HIV field are often only belatedly acknowledged by researchers working within it, greatly slowing progress – a criticism leveled in the past by many other commentators, including TAG. Levine goes on to conclude: “there is a need to attract smart and interested young scientists into HIV virology, immunology, vaccine research, and systems biology. Not enough effort has been put into the planning of this component of the future of the HIV field. That is the best chance to gain the insights required for a larger group to develop a vaccine against HIV.”

Source: TAG Basic Science Blog (17 October 2008).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/10/why-do-we-not-y.html

References

1. Arnold J. Levine. Why do we not yet have an HIV vaccine? *J. Virol.* doi:10.1128/JVI.01953-08
<http://jvi.asm.org/cgi/content/abstract/JVI.01953-08v1>
2. Jefferys R. AIDS research in chimps. TAGline Summer 2008 (Vol. 15 No.3).
<http://treatmentactiongroup.org/publication.aspx?id=2514>

ABOUT 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:

- Do I need to start treatment?
- Is the treatment different for older people?
- Are the medications in Eritrea the same as the medications in the UK?
- Is impetigo a reason to start treatment?
- Do HIV-positive people get free dental treatment in the UK?
- Am I infective if I am passive and undetectable?
- What does a CD4 count of 0 mean?

- Can I use PEP if I am HIV-positive?
- Will I use the same meds for my treatment that I used in pregnancy?
- Can stress cause the same symptoms as HIV?
- What is diet advice if you are just diagnosed?
- Will my baby have HIV if we do not go for sperm washing?
- Is treatment in 2008 better than 10 years ago?
- Am I infectious if I am passive and my viral load is under 50c/mL?
- What do you know about raltegravir (Isentress)?
- Does PEP extend the window period?
- What is the possibility someone re-infected with HIV to go on new medication that will work for them again?
- How detrimental it is to stop treatment while on NNRTI?
- Is oral candida an early symptom of HIV-infection after 50 days?
- Are the women at the same risk?
- Is the reinfection something that is true or another myth?
- Is this a significant drop in my CD4 count?
- Options if I am getting efavirenz side effects?
- What are the risks of non-HIV cancers?
- Am I doing OK after TB and HIV treatment?
- Can I use the same medications in Thailand as in the UK?
- How do I handle adherence times in a different time zone (Australia)?
- Can you test for the CCR-5 delta 32 deletion that reduces the risk of infection?
- How much does the treatment cost?
- Is creatine safe with HIV drugs?

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>



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