
EDITORIAL

This issue of HTB continues our coverage of the 15th Conference on Retroviruses and Opportunistic Infections with reports on antiretrovirals, treatment strategies, pregnancy and PMTCT, and hepatitis coinfection.

Further reports will follow in the next issue.

STOP PRESS: i-Base funding withdrawn: urgent request for letters of support

As this issue of HTB went to press we learned that the London Health Commissioners who fund the Treatment Information Providers Initiative (TIPI) have failed to renew funding for current projects or fund any other i-Base projects.

For the last two years we have received £50k (about 20% of our annual budget) towards the treatment helpline and information services, adherence support publications (including the BHIVA-recommended treatment passport) and for treatment workshops. This funding acknowledged that Londoners comprise approximately half our service users.

Public funding for these projects allowed i-Base to continue to provide other non-funded services such as HTB and the five i-Base treatment guides which are provided free to all individuals and clinics as well as expand our treatment workshops with community groups.

Now, no public funding is to be given to i-Base - not for publications, not for treatment workshops, not for advocacy training, not for helpline support, not for email services, not for online Q&A services, not for translations of treatment not for publications, not for the website. Nothing!

- * The i-Base helpline has been provided expert peer-advocacy support for over five years, and have the cumulative experience from having spoken to thousands of individual patients.
- * Over the last two years the UK-CAB has developed into a representative network of advocates and peer advocates.
- * We have distributed thousands of treatment guides - ordered by request from clinics.

The commissioners think that no patients or clinics in London want or need these services. Instead the Commissioners want London patients to access our services without paying for them.

We think this is unfair and is not reflective of the needs of London patients and clinics.

If you use or have used i-Base services as a London patient or clinic, please email letters of support to:

Ray.Appleby@kc-pct.nhs.uk

Hong.Tan@londonscg.nhs.uk

It would help us if you could copy any correspondence to:

Simon.Collins@i-Base.org.uk

i-Base employs three full-time and four part-time staff for all our projects. A majority of our staff are HIV-positive. The funding decision, for which we are told there is no appeal, threatens these posts and the services we provide.

We intend to challenge this but need your help.

Thank you for your support...

CONFERENCE REPORTS

15th Conference on Retroviruses and Opportunistic Infections

Boston, 2-6 February 2008

Introduction

This annual conference is one of the most important HIV-related scientific meetings.

Abstracts for the meeting are online as soon as the conference opens, and many of the most important oral abstract sessions and overview sessions are posted as webcasts within a day or so. We encourage readers to go directly to the source for many of these sessions.

www.retroconference.org

This issue includes reports on antiretrovirals and treatment strategies, prevention of mother to child transmission (PMTCT), hepatitis coinfection and oncology:

- Atazanavir/r vs lopinavir/r in treatment-naïve patients: 48 week results
- Baseline inflammation and coagulation markers and changes over four weeks during a treatment interruption are strongly linked to HIV viraemia and risk of mortality
- Restarting treatment after an interruption reduces the risk of serious events but CD4 recovery falls short of baseline
- Very low rate of MTCT in women on HAART in UK and Ireland who achieve viral suppression
- Predictors of mother to child transmission among women initiating HAART in pregnancy in a South African cohort
- Maternal and infant outcomes from the DREAM programme
- Nevirapine-resistant HIV present in the latent reservoir following single-dose nevirapine for MTCT prevention
- Tenofovir plus FTC reduce NNRTI resistance following single dose nevirapine
- Response to treatment after single dose NVP exposure in women
- Response to treatment after single dose NVP exposure in infants
- Other studies looking at birth outcomes
- Infant prophylaxis for postnatal transmission
- Antiretroviral drug concentrations in breast milk and breastfeeding infants
- Maternal breastfeeding prophylaxis
- Risk factors for breastfeeding transmission
- UK cohort reports sexual HCV reinfection in at least 5% HIV-positive gay men following sustained response to treatment
- MELD score predictive of pre-transplant mortality in HIV/HCV coinfecting patients
- Does abacavir decrease SVR rates with HCV treatment?
- No effect of interferon maintenance therapy on fibrosis progression in non-responders
- Stem cell transplant from HLA-matched CCR5-delta 32 deleted donor suppresses viraemia in recipient for eight months without HAART
- Risk factors for AIDS-defining and non AIDS-defining cancers

Further coverage will be included in subsequent issues of HTB.

CROI: ANTIRETROVIRALS

Atazanavir/r vs lopinavir/r in treatment-naïve patients: 48 week results

Simon Collins, HIV i-Base

Although widely used off-label, atazanavir/r is not currently approved in Europe for use in first-line combinations, nor recommended in European guidelines, due to limited data in naïve patients. Results from a large randomised international head-to-head study against lopinavir/r, sponsored by BMS, are therefore important to report.

Jean-Michel Molina from St Louis Hospital, Paris, presented the 48-week analysis from this 96-week CASTLE study. This was a non-inferiority study (10% margin) and the primary endpoint was the proportion of patients with HIV RNA <50 copies/mL at week 48.

The trial randomised 883 treatment-naïve patients to either atazanavir 300 mg / ritonavir 100 mg once-daily or lopinavir/ritonavir 400 mg/100 mg twice-daily, both in combination with fixed-dose tenofovir/FTC once-daily.

Baseline demographics and characteristics included median CD4 count 205 cells/mm³ (range 2-810) with 12% less than 50 cells/mm³; and viral load around 5 log copies/mL (range 2.6-5.9), with 50% patients starting above 100,000 copies/mL. Only around 5% had CDC class C diagnosis, and 12% were coinfecting with hepatitis B or C.

Only around 10% of patients discontinued prior to week 48, with a balance between each arm, detailed in Table 1.

Table 1: Patient disposition at week 48

	ATZ/r	LPV/r
Randomised (n)	440	443
Treated (n)	438	440
Discontinued	39 (9%)	58 (13%)
AE's	10 (2%)	14 (3%)
Death	4 (<1%)	4 (<1%)
Efficacy	5 (1%)	8 (2%)
LTFU	6 (1%)	6 (1%)
Adherence	6 (1%)	9 (2%)
Withdrew consent	4 (<1%)	13 (3%)
Other	4 (<1%)	4 (<1%)

The percentage of patients with viral load <50 copies/mL at week 48 in the atazanavir/r and lopinavir/r arms was 78% vs 76% (estimated difference 1.9, 95% CI -3.6 to 7.4), by intent-to-treat analysis.

Stratified by baseline viral load, the results were 82% vs 81% (<100,000 copies/mL) and 74% vs 72% (>100,000 copies/mL), in the ATZ/r and LPV/r groups respectively, with no statistical difference between arms.

A post-hoc analysis of results by baseline CD4 counts showed no impact for ATZ/r, but a statistically significant poorer response for the LPV/r arm, ranging from 80% <50 copies/mL in patients with >200 CD4 cells/mm³ to 63% for those starting with <50 cells/mm³, p = 0.0085.

CD4 response was similar in each arm (+203 vs + 219 cells/mm³).

Side effects generally reflected the known profile of each drug, with ATZ/r having higher incidence of jaundice, and LPV/r reporting greater GI-related ae's, that are detailed in Table 2.

Table 2: Adverse events in CASTLE study

	ATZ/r n=441 (%)	LPV/r n=437 (%)
Serious AE's	54 (12%)	42 (10%)
All grade 2-4	115 (26%)	129 (30%)
Jaundice *	16 (4%)	0
Nausea *	17 (4%)	33 (8%)
Diarrhoea *	10 (2%)	50 (11%)
Rash *	14 (3%)	9 (2%)
Renal (all grades)	14 (3%)	9 (2%)
Total bilirubin >2.5xULN	146 (34%)	1 (<1%)
Total cholesterol (>240 mg/dL)	30 (7%)	77 (18%)
Triglycerides (>750 mg/dL)	2 (<1%)	15 (4%)
Hyperglycemia (>251 mg/DL)	1 (<1%)	1 (<1%)

* Grade 2-4 in >3% of patients

With laboratory AE's, grade 3-4 ALT/AST elevations were low (<2%) in both arms.

Lipid profile favoured ATZ/r with fewer patients at week 48 having total cholesterol >240 mg/dL (7% vs 18%), and significantly lower changes from baseline for TC, non HDL and TG (all p<0.0001). Lipid lowering drugs were used by 2% and 7% of the ATZ/r and LPV/r arms respectively.

C O M M E N T

The study concluded that atazanavir/r is an appropriate treatment for first line therapy. Regulatory and guidelines committees will hopefully review these data carefully and promptly.

Ref: Molina JF et al. Efficacy and safety of once-daily atazanavir/ritonavir compared to twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine in ARV-naive HIV-1-infected subjects: the CASTLE study, 48-week results. Abstract 37.
<http://www.retroconference.org/2008/Abstracts/31137.htm>

This oral presentation is available to view online from the conference website (Monday 4 February).

CROI: TREATMENT STRATEGIES

Baseline inflammation and coagulation markers and changes over four weeks during a treatment interruption are strongly linked to HIV viraemia and risk of mortality

Simon Collins, HIV i-Base

Lewis Kuller presented further analysis from the SMART study. In summary, this international study randomised around 5,500 patients to CD4-guided treatment interruptions or continuous treatment, was stopped early because of excess death in the intermittent treatment group: with 55 vs 30 deaths over the first 16 months, most not related to opportunistic infections.

Baseline markers of inflammation and clotting as they related to total mortality, the changes of these variables, and how they related to outcome.

Two matched controls for each death prior to January 2006 when the study was stopped, were matched on a variety of variables. Logistic regression analysis was used to estimate odds ratios (OR) for mortality with adjustment for cardiovascular, HIV, co infection risk factors and other demographic factors. Baseline characteristics relating to deaths included lower CD4 counts, and a higher proportion of current smoker, diabetes, treated blood pressure and CVD, in the cases compared to the controls, all of which were adjusted for.

Markers analysed included inflammatory markers: serum amyloid A and serum amyloid P, C-reactive protein (CRP) – acute phase proteins (pentraxins), and IL-6 (a major inflammatory marker and stimulant of CRP and stimulant of release of tissue factor from smooth muscle cells in the endothelium).

The markers of coagulation that were measured were D-dimer (a measure of the breakdown of fibrogenesis that is a powerful risk factor for CVD) and prothrombin fragments 1+2 (F1.2).

All markers have been strongly associated with cardiovascular risk in HIV-negative patients.

Kuller first reported that many of these markers were elevated at baseline and that this was significantly associated with all cause mortality. Adjusted OR (4th vs 1st quartiles) showed an almost 12-fold increased risk associated with elevated IL-6 and a 26-fold increased risk associated with increased D-dimer (both $p < 0.0001$). CRP was associated with a 3-fold risk ($p = 0.03$).

IL-6 and D-dimer, but not the other markers, also increased over 4 weeks in patients not on treatment, compared to those on continuous treatment ($p < 0.0001$). Changes in both markers were strongly correlated with increases in viral load. Change from baseline to week four levels in IL-6 (OR 5.3, 95%CI 1.6-17.1; $p = 0.006$) and D-dimer (OR 5.0, 95%CI 1.3 -18.9; $p = 0.02$) were also strongly correlated with risk of death.

Kuller suggested that activation of coagulation and inflammation markers could impact multiple organs: the association with all cause mortality was stronger than to CVD.

This may occur as a consequence of a challenge to the endothelium. Viraemia affects vascular endothelium which increases production of tissue factor transcription, which activate the extrinsic clotting pathways. Elevated d-dimer and IL-6 clearly identified patients at highest risk of death, at a level unseen with any other marker in HIV-negative predictive biomarker studies (which report 1-2-fold increased risk). He concluded by suggesting that this opened the questions of whether this may be a useful marker to monitor in patient management.

These findings were initially presented to the IAS conference last July. [2]

References:

1. Kuller L et al. Elevated Levels of Interleukin-6 and D-dimer Are Associated with an Increased Risk of Death in Patients with HIV. Oral abstract 139.

<http://www.retroconference.org/2008/Abstracts/32757.htm>

This oral presentation is available to view online from the conference website (Wednesday 6 February).

2. See HTB August/September 2007

<http://www.i-base.info/htb/v8/htb8-8-9/HIV.html>

Restarting treatment after an interruption reduces the risk of serious events but CD4 recovery falls short of baseline levels

Simon Collins, HIV i-Base

Wafaa El-Sadr from the INSIGHT research network, presented an analysis of event rates from the large international CD4-guided treatment interruption study (SMART) that occurred in the 18 month period of follow-up since enrollment was stopped and patients were recommended to restart treatment.

The study was halted following a recommendation by the DSMB in January 2006 after only two of the planned seven years, due to significant benefits in terms of mortality and serious AIDS and non-AIDS morbidity, in favour of continuous treatment.

As well as providing sufficient power to look at the original study question, this trial dataset (5472 patients were randomised) is providing significant insight into other important aspects of HIV management.

Prior to January 2006, patients randomised to the treatment discontinuation arm (DC=drug conservation) spent 34% of follow-up time on treatment compared to 94% patients in the continuous treatment arm (VS=viral suppression). Post-January 2006 this increased to 71% vs 91% respectively, and when the study closed in July 2007, 83% and 95% of patients in each arm were on treatment,

It is important that after the recommendation to restart treatment, the rate of opportunistic infection or deaths all declined in the interruption arm (from 3.4 to 2.1/100 pt yrs) and stayed constant for patients in the continuous therapy group (1.4/100 throughout). This was a significant change in hazard ratio between the pre- and post January 2006 hazard ratios ($p=0.03$). Rates reduced in inverse proportion to time since restarting treatment.

Although similar trends were reported for other endpoints (death, OI, major CVD renal or hepatic disease) the p-value for the change in hazard ratio pre-and post January 2006 was not statistically significant.

Although the majority of patients in the DC group re-suppressed viral load, mean CD4 count noticeably failed to reach pre-interruption levels. Patients in either arm who had experienced a non-fatal serious event prior to January 2006 (113 in DC and 50 in VS arms) were at 5.8-fold increased risk of death during the follow-up (95%CI 3.2-10.8), $p<0.0001$).

These differences were not explained by patients in the DC not following the recommendation to restart treatment; an analysis of a subgroup of patients who all restarted treatment confirmed similar results.

Clinics where >85% patients followed the recommendation to restart treatment reported a drop from 3.8 to 1.1 in the DC arm ($p=0.02$, for difference in HR pre- and post- January 2006). The persistence of increased risk in the DC arm was largely explained by lower mean CD4 count and higher proportion of patients with uncontrolled viraemia.

When looking at the CD4 response to restarting treatment, the researchers found a significant difference between the two groups, even 18 months after restarting treatment: mean 507 vs 648 cells/mm³ in favour of the continuous treatment arm. Baseline CD4 counts in each group was approximately 600 cells/mm³.

This was not explained by patients within the DC group who chose not to restart treatment as an analysis of a sub group of patients who had all followed the recommendation to restart treatment found similar results.

The investigators concluded that these results further strengthened the earlier recommendation not to use CD4-guided treatment interruptions, as this was associated with long-term impact beyond the period of interruption.

C O M M E N T

This provides additional validation for the decision to stop the study early and for the recommendation to restart treatment.

Although the study provides some evidence that long-term clinical outcome may become normalised over time once treatment is restarted, the significantly lower CD4 count, even 18 months after treatment was resumed, was not expected.

References

1. El-Sadr W et al. Re-initiation of ART in the CD4-guided ART Interruption Group in the SMART Study Lowers Risk of Opportunistic Disease or Death. 15th CROI, 3-6 February 2008, Boston. Abstract 36.
<http://www.Retroconference.org:8888/2008/Abstracts/32784.htm>

This oral presentation is available to view online from the conference website (Monday 4 February).

CROI: PREGNANCY AND MTCT

Introduction to MTCT studies

There were many studies to report on relating to pregnancy and MTCT at CROI this year and the studies below will add to our understanding of how to move forward.

In the conference opening plenary, Doug Richman emphasised that, "regimens (including those for MTCT) that are slightly more costly on a daily basis might be much less costly over the long term for the individual and the population." We share his view.

Meanwhile, data, reported in a poster from Townsend et al. shows almost negligible transmission risk for a well-managed HIV-positive woman delivering in the UK today.

Very low rate of MTCT in women on HAART in UK and Ireland who achieve viral suppression

Polly Clayden, HIV i-Base

A poster from Claire Townsend and coworkers from the Institute of Child Health, St Thomas' Hospital and St Mary's Hospital looked at HIV mother to child transmission (MTCT) rates among women and infants in the UK and Ireland 2000 to 2006.

In recent years, transmission rates have declined to 1 to 2% in Western Europe. With the success of HAART in reducing transmission, women are increasingly opting for vaginal delivery, instead of elective caesarean section.

In the BHIVA guidelines AZT monotherapy with elective caesarean section is also offered as an option for some women who do not need HAART for their own health and who have very low viral loads.

In this analysis, HIV status was available for 5136/6127 (86.8%) infants. The authors reported that the overall MTCT rate was 1.1% (61/5316, 95% CI 0.9% - 1.5%), and 0.8% (40/5027, 95%CI 0.6 - 1.1%) in infants whose mothers received ART for at least 14 days.

They found no significant difference in MTCT rates between women receiving HAART who had an elective caesarean section (17/2337, 0.7%, 95% CI 0.4 to 1.2%) or a planned vaginal delivery (4/565, 0.7%, 95%CI 0.2 to 1.8%). Nor was there a difference for mothers receiving prophylactic AZT monotherapy who had an elective caesarean section (0 /467, 0%, upper 95%CI 0.8%; p=0.094).

In these three groups, the numbers of women with viral load <50 copies/mL were 59% 1341/2276 (59%), 508/634 (80%) and 105/447 (23%), respectively. They found only three transmissions reported among 2202 infants born to women on HAART with viral load <50 copies/mL (0.1%, 95%CI 0 to 0.4%): 2 were born by elective caesarean section (MTCT rate 0.2%, 2/1180) and 1 by planned vaginal delivery (MTCT rate 0.2%, 1/419).

Of the three HIV-positive infants, two had positive PCR tests at births, suggesting in utero transmission and the other was negative at birth suggesting intrapartum transmission.

The authors wrote: "There was no difference in MTCT rates according to the management strategies outlined in the BHIVA Guidelines: HAART with elective caesarean section or planned vaginal delivery, and zidovudine monotherapy with elective caesarean section. The risk of MTCT in appropriately managed pregnancies in the United Kingdom and Ireland is very low."

C O M M E N T

These data are very reassuring; with good management focusing on maternal health and choice, there is little risk of transmission to her child for an HIV-positive mother delivering in the UK today. The 1/1000 transmission rate for women receiving HAART with an undetectable viral load (<50 copies/mL) across both modes of delivery is the lowest reported and represents a significant advance in the information available to women planning a family or already pregnant.

The similarly low transmission rate seen in selected women with very low viral load who chose to receive AZT monotherapy and deliver by elective caesarean section is important too, as it confirms that this remains an option.

Ref: Townsend C, Cortina-Borja M, C Peckham C et al. Very low risk of MTCT in women on HAART who achieve viral suppression: The UK and Ireland, 2000 to 2006. 15th CROI. February 2008, Boston. Poster abstract 653.

Predictors of mother to child transmission among women initiating HAART in pregnancy in a South African cohort

Polly Clayden, HIV i-Base

There are limited data from Africa describing mother to child transmission (MTCT) in mothers initiating HAART in pregnancy.

A poster authored by Risa Hoffman and coworkers from the Reproductive Health and HIV Research Unit of the University of Witwatersrand and the UCLA Program in Global Health, Los Angeles presented findings from a retrospective analysis from a cohort of women in an antenatal antiretroviral clinic at Johannesburg Hospital looking at factors associated with infant HIV infection.

In this study 689 women indicated for antiretroviral treatment (CD4 \leq 250 cells/mm³ or WHO stage 4) were referred to the antenatal clinic between August 2004 and February 2007. The women had a mean baseline CD4 of 154 cells/mm³ and 82% received d4T/3TC/NVP. 302 mothers completed 6 weeks postpartum follow up; of these 15/302 (5%) infants had positive DNA PCR.

Using univariate analysis, the investigators found shorter duration of treatment ($p=0.001$) and lower CD4 baseline ($p=0.03$) to be associated with MTCT.

Analysis of variance (ANOVA) found a statistically significant difference in duration of gestational HAART in pregnancy among mothers whose infants were positive ($n=15$), negative ($n=287$) and of unknown status ($n=376$), $p=0.0005$.

Mothers with HIV-positive infants received HAART for a shorter duration than those with negative infants, 5.1 vs 11.2 weeks (OR, 0.730, 95% CI 0.612-0.879), $p=0.001$. The investigators noted that for each additional week of HAART during gestation, the odds of transmission were reduced by 27%. The transmission rate for women receiving >7 weeks HAART was 0.3%.

Lower CD4 baseline, 148 vs 106 cells/mm³ (OR, 0.991, 95% CI 0.982-0.999, based on change of 25 cells/mm³), $p=0.03$, was also predictive of MTCT in this analysis.

Viral load at baseline and follow up were not predictors of transmission in this analysis but the investigators suggest that this may be due to high variance in viral load and small numbers of women with complete viral load data.

Unsurprisingly, overall women receiving HAART in pregnancy in South Africa have low rates of transmission. The investigators wrote: "Strategies are needed to facilitate earlier treatment of HIV-infected pregnant women with advanced disease."

C O M M E N T

In the cohort described in the poster, lower CD4 count (ie women with more advanced disease in need of treatment for their own health) was associated with an HIV-positive infant, and this is consistent with the literature, which shows this over and over again.

The authors highlight the need to initiate treatment earlier in pregnancy and this deserves emphasis both for the health of the mother and the baby's HIV status.

The transmission rate of 5% at 6 weeks in this cohort of women with advanced disease (almost all with CD4 < 250) is far lower than the reported transmission rates for healthier women in South Africa who only have access to single dose NVP or other PMTCT regimens and breastfeed (18-25% at 6 weeks).

Ref: Black R, Hoffman R, Sugar C et al. Factors associated with MTCT in South African women with advanced immunosuppression initiated on HAART during pregnancy. 15th CROI, February 2008, Boston. Poster abstract 657.

Maternal and infant outcomes from the DREAM programme

Polly Clayden, HIV i-Base

A poster from the Drug Resource Enhancement and Malnutrition (DREAM) programme reported 12-month mother and infant data from women initiating HAART in pregnancy and continuing throughout 6 months of breastfeeding in Mozambique. [1]

In this prospective cohort study, 341 women were enrolled of whom two (0.6%) died during the period of follow up.

Of the 276/341 (81%) infants, with complete data available, 51 (15%) were lost to follow up and 14 (4.2%) died during the study period. Half of these deaths occurred in the first six months of life. Of the children who died, 13 were HIV-negative and one was HIV-positive. The investigators reported an infant mortality rate of 48.3 per 1000 live births (compared to a background rate for Mozambique in 2005 of 101 per 1000).

The majority of mothers (97.5%) in this cohort were antiretroviral naïve at initiation of treatment. The mothers received AZT/3TC/NVP if their CD4 was <250 cells/mm³ and mothers with >250 cells/mm³ received either LPV/r or NFV instead of NVP. Fifty-five mothers continued treatment after 6 months as they had CD4 count <200 cells/mm³ or clinical symptoms. There was one infection at 6 months among the group who continued treatment.

The investigators reported a cumulative total of 8 transmissions (2.9%) in this cohort; 4/341 (1.2%) at 1 month, 2/313 (0.6%) at 6 months and 2/276 (0.7%) at 12 months.

The median maternal viral load was 4.38 log at infant diagnosis for mothers with HIV-positive infants and 3.79 log for those with HIV-negative infants. There was no association with maternal CD4 count or viral load, or duration of HAART in this study. The investigators suggest this was due to the small numbers of transmissions overall.

A second poster from the DREAM programme looked at CD4 count, viral load, liver enzymes and haemoglobin at 12 months after treatment interruption (6 months after delivery), in women not indicated for treatment according to this programme.

At enrolment the median CD4 count among 220 women studied was 496 cells/mm³ (IQR 378 to 698), median viral load was 7850 copies/mL (IQR 2230-16,000), median haemoglobin 9.7g/dL (IQR 8.5-10.5) and liver enzymes were normal. The median duration of maternal HAART was 302 days (IQR 273-326).

Approximately 18 months after delivery, the median CD4 count was 536 cells/mm³ (IQR 367 to 669), median viral load was 5100 copies/mL (IQR 1125-14,450), median haemoglobin 11.1g/dL (IQR 10.0-11.9), median ALT was 12 (IQR 8-28). The

investigators reported that all parameters evaluated did not differ significantly from baseline, $p > 0.05$.

They wrote: "These data support the safety of discontinuation of antiretroviral prophylaxis for women not meeting the criteria for treatment."

References

1. Marazzi M, Palombi L, Liotta G et al. Decrease in HIV-1 mother-to-child-transmission in women receiving postnatal HAART: 12 month follow up data. Poster abstract 639.
2. Palombi L, Marazzi M, Germano P et al. Treatment interruption after HAART prophylaxis in HIV-1 infected pregnant women In Mozambique: The Drug Resource Enhancement and Malnutrition Programme. Poster abstract 668.

Nevirapine-resistant HIV present in the latent reservoir following single-dose nevirapine for MTCT prevention

Polly Clayden, HIV i-Base

Nevirapine (NVP) resistant virus often becomes undetectable in the months after discontinuation of NNRTI therapy and after single dose MTCT prophylaxis. Until now, investigators have not determined whether or not resistant virus remains present in the latent reservoir in resting CD4 cells after single dose NVP exposure in HIV-infected women.

A poster authored by Megan Wind-Rotolo and coworkers from Johns Hopkins University, Baltimore, United States and University of Witswatersrand, Johannesburg, South Africa, reported findings from a study investigating the presence of NVP resistant virus in the latent reservoir of women who had received a single dose at least six months before.

Sixty women with CD4 > 200 cells/mm³ were included in this study. The investigators collected plasma and peripheral blood mononuclear cell (PBMC) samples.

Purified resting CD4 cells were cultured in the presence of 3TC, tenofovir, efavirenz and raltegravir in order to prevent the completion of reverse transcription and integration in cells without integrated virus.

A highly sensitive mutation-specific assay (LigAmp) was used to identify virus containing any of three NVP resistance mutations (K103N, Y181C, G190A) among virus from the latent reservoir and virus present in a matching plasma sample. The cut off value for the assay was 1% resistant virus.

Plasma was analysed from 58 women; NVP mutations were found in 2/58 (3.4%) of women.

Virus from the latent reservoir was isolated from 50 women (24 from Soweto, South Africa and 26 from Rakai, Uganda). Four of these women (8%) had NVP mutations in virus from the latent reservoir. Three of four (6%) women did not have NVP resistant virus in the matching plasma sample. One woman had low levels of K103N in virus from plasma but not from the latent reservoir (see Table 1).

Table 1: NVP resistance mutations detected among virus from plasma and latent reservoir

Patient no.	NVP resistance in plasma virus	NVP resistance in latent reservoir virus
1	None	G190A
2	K103N	K103N, G190A
3	None	K103N
4	None	K103N
5	K103N	None

The investigators wrote: "NVP resistance mutations that arise following a single dose of NVP to prevent mother to child transmission of HIV-1 can be archived in the resting CD4+ T cell latent reservoir and persist for long periods of time and could provide a source of drug resistant virus that may contribute to future antiretroviral failure and development of new resistance mutations."

C O M M E N T

This poster provoked comment that finding the archived resistance in anyone is very significant, as the archive reservoir is so difficult to access and study and evidently represents over 3 years work.

Conversely, failure to detect archived virus with NVP associated mutations in 92% patients is encouraging.

Ref: Wind-Rotolo M, Durand C, Cranmer L et al. Identification of nevirapine-resistant HIV-1 in the latent reservoir following single-dose nevirapine. 15th CROI, February, 2008, Boston. Poster Abstract 634.

Tenofovir plus FTC reduce NNRTI resistance following single dose nevirapine Polly Clayden, HIV i-Base

Single dose nevirapine (NVP) still remains an important component in prevention of mother to child transmission (PMTCT). With short course AZT and “tail” coverage it is considered to be a reasonable option for women who do not need antiretroviral treatment to protect their own health.

Four presentations at CROI and a recent Lancet paper looked at using tenofovir (TDF) and emtricitabine (FTC) added to single dose NVP to reduce the emergence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI). Two of the presentations describe TDF and FTC maternal and infant pharmacokinetics.

Both drugs have long half-lives (approx 17 hours for TDF and 8 hours for FTC in plasma) and are category B for use in pregnancy.

Reduction in NNRTI resistance with one dose of TDF/FTC

A paper authored by Benjamin Chi and coworkers, published in the November 17, 2007 edition of the Lancet reported findings from a Zambian study to investigate whether the addition one dose of the co-formulation of 300mg TDF and 200mg FTC (Truvada) to single dose NVP in labour would be effective in reducing resistance [1].

In this study, conducted at two primary health care facilities in Lusaka, women screened that met WHO maternal criteria for antiretroviral therapy were referred and not enrolled.

All enrolled women received standard of care of AZT from 32 weeks gestation plus single dose NVP in labour. The women were randomised to receive TDF/FTC or no additional intervention above the standard of care.

All infants received single dose NVP plus seven days of AZT. The majority of women opted to breastfeed for six months.

The primary endpoint of the study was maternal NNRTI resistance at 6 weeks post partum. The secondary endpoints were NNRTI resistance at two weeks, other antiretroviral resistance (particularly to TDF, FTC and AZT) at two and six weeks post partum, HIV transmission rates and drug safety.

The investigators reported: 627 women were enrolled in the study, of those 227 were not eligible, 397 women were randomised between March 2005 and February and three others were excluded from the analysis, two due to incorrect dispensing of the study drug according to protocol and the third due to the randomisation envelope being incorrectly opened.

The mean maternal CD4 was 464 cells/mm³ (SD, 208) in the intervention arm (n=198) and 490 cells/mm³ (SD, 200) in the control arm. 83% and 79% received antenatal AZT, and the length of time on AZT was 39 (SD, 25) and 34 (SD, 20) days in the intervention and control arms respectively. 28% and 29% of women had a viral load <400 copies/mL at delivery. Among those not suppressed at delivery the mean log viral loads were 3.9 (SD, 0.8) and 3.7 (SD, 0.6) logs in the intervention and control arms.

Using a genotype test with thresholds for detection to detect a mutant viral subpopulation of 20%, they found that women receiving the intervention were less likely than controls to have an NNRTI mutation at 2 weeks post partum: 6/187 (3%) vs 21/169 (12%) (RR, 0.27; 95% CI, 0.11-0.66), p=0.002; at 6 weeks, 20/173 (12%) vs 41/166 (25%), (RR, 0.47, 95% CI 0.29–0.76), p=0.002 and cumulatively, 22/167 (13%) vs 49/163 (30%), (RR, 0.44, 95% CI, 0.28-0.69), p<0.0001.

The investigators noted that when they stratified the women according to maternal viral load at delivery, they found the protective effect was greatest in women whose viral load was >10,000 copies/mL.

They did not detect any mutations associated with resistance to TDF, FTC or AZT.

The overall transmission rate at 6 weeks was similar in the two groups 10/180 (5.6%) and 14/175 (8%) in the intervention and control group respectively, p=0.403. this was consistent for in utero, 8/180 (4.4%) vs 10/175 (5.7%), p=0.635, and intrapartum/early post partum, 2/127 (1.6%), p=0.44.

Serious maternal adverse events were also similar in both groups, 7/198 and 9/199 in the intervention and control groups. The most common was postpartum anaemia, which was reported for four women in each group. 20/198 (10%) of infants in the intervention group and 23/199 (12%) in the control group had a serious adverse event, mostly septicaemia (n=22) or pneumonia (n=8), there was no difference between the groups and none were considered to be associated with the study intervention.

The investigators concluded that addition of a single dose of combined TDF and FTC to the prophylaxis regimen of short course AZT and single dose NVP was associated with a 73% reduction in resistance at two weeks and a 53% reduction at six weeks. They noted that in this setting the intervention did not result in a reduction of mother to child transmission compared to controls.

The frequency of the K103N mutation increased from 2 weeks to 6 weeks postpartum as has been described in other studies. The frequency of Y181C/I remained stable. None of the women in the intervention group developed a mutation at

codon 181 and the investigators were unable to explain this finding.

The investigators suggested that further reductions in resistance might be possible with the addition of a second dose of tenofovir and FTC but would also preserve the simplicity of the regimen.

A poster authored by the same group, showed findings from a secondary analysis from this study, in which they evaluated 122 random maternal samples using an oligonucleotide ligation assay (OLA) [2]. This assay can detect a mutant sub-population as low as 5% of circulating virus. Mutations found at codons 103, 106, 181, and 190 were considered to be NNRTI resistant.

Of the 122 maternal samples evaluated, 38 were taken at two weeks post partum (15 in the intervention arm and 23 in the control arm) and 84 were taken at six weeks post partum (43 in the intervention arm and 41 in the control arm). The investigators reported that the median \log_{10} viral load was not different between the study arms at two weeks post partum (3.53 vs 3.67; $p=0.27$), nor at six weeks postpartum (4.61 vs 4.54; $p=0.44$).

When NNRTI resistance was assessed by OLA, they found a 69% reduction at two weeks post partum, 2/15 (13%) vs 10/23 (44%), (RR 0.31, 95%CI 0.08-1.21), and a 58% reduction in NNRTI at six weeks post partum, 8/43 (19%) vs 18/41 (44%), (RR 0.42, 95%CI 0.21- 0.87).

The investigators concluded that the efficacy of single-dose TDF and FTC in reducing NNRTI drug resistance by population genotyping was confirmed with the more sensitive OLA. "These findings further emphasise the role of this simple intervention in settings that rely heavily on intrapartum NVP, alone or in combination with other drugs, for perinatal HIV prevention" they wrote.

Further reduction with seven days TDF/FTC postpartum

In an oral presentation, Elise Arrive from the TEMAA French National Agency for AIDS Research (ANRS) 12109 study conducted in Ivory Coast, Cambodia and South Africa presented findings from a similar strategy but using seven days TDF/FTC tail coverage [3].

This is an open label, phase II trial to look at safety in which all HIV-positive pregnant women received AZT from 28-38 weeks of gestation (median 33) single dose NVP at the onset of labour with two doses of TDF/FTC followed by once daily TDF/FTC for seven days post partum.

All infants received single-dose NVP syrup and AZT syrup for 7 days.

The study enrolled 38 women with a median age of 27, a median CD4 count 450 cells/mm³, and a median viral load of 4.08 \log_{10} copies/mL. The women received TDF/FTC at a median of 4.9 hours before delivery.

The investigators reported 9/38 (24%) women experienced Grade 3/4 biological events (anemia, leucopenia) postpartum. 9/39 (23%) live births (1 set of twins), had serious adverse events, including 4 deaths (meningitis, gastroenteritis, intestinal obstruction, and severe encephalopathy of unknown aetiology) and 2 had transient grade 3 anemia (5%).

They found that the mothers' viral load decreased by a median of 0.90 \log copies/mL at 2 days postpartum, and returned to baseline at 4 weeks. 2/39 (5.1%) infants had detectable virus at 3 days (confirmed at 4 weeks), suggesting in utero transmission. No genotypic viral resistance to AZT, NVP, FTC, or TDF was detected in either the mothers or infants in this small study.

The investigators wrote: "A TDF/FTC combination for PMTCT appears to be well tolerated in women and exposed newborns: 7 days of postpartum TDF/FTC exposure seem to extend the suppression of viral replication avoiding NVP-resistance mutations".

Tenofovir and FTC pharmacokinetics

In a pharmacokinetic substudy presented as an oral late breaker, Deborah Hirt and coworkers from the ANRS group evaluated tenofovir pharmacokinetics in pregnant women and in their infants. [4]

In this study, they measured maternal, cord blood, and neonatal tenofovir plasma concentrations.

The authors noted that absorption was faster and greater for women with caesarian section than with vaginal delivery (they suggested this was due to fasting administration of TDF before delivery). Following a 600-mg TDF administration, median population tenofovir AUC, C_{max} and C_{min} in pregnant women were 2.73 mg.L⁻¹.h, 0.31 and 0.056 mg/L, respectively.

They found at delivery, maternal and cord blood median tenofovir concentrations were 0.13 and 0.10 mg.L⁻¹ respectively. Neonatal plasma half-life was 8.3 hours (45%), suggesting low neonatal concentrations quickly after birth.

They concluded: "TDF 600 mg before delivery produces similar concentrations to those of HIV infected people taking 300 mg daily. If time elapsed between maternal administration and delivery is >12 hours, 2 tablets of TDF/FTC should be re-administered. Tenofovir was shown to have good placental transfer. Administering 13 mg/kg of TDF as soon as possible after birth should produce neonatal concentrations comparable to those observed in adults."

A poster from the same group presented findings from a similar pharmacokinetic study with FTC.

They report, after the 400-mg FTC administration, median population AUC, T_{max}, C_{max} and C_{min} in pregnant women were 15.5 mg.L⁻¹.h, 3.0 hours, 1.60 and 0.14 mg/L, respectively. At delivery, median (range) FTC maternal and cord concentrations were respectively 1.02 (0.035 to 2.04) and 0.74 (0.005 to 1.46) mg.L⁻¹.

They conclude: "FTC was shown to have good placental transfer. Administering 2 mg/kg of FTC 12 hours after birth or 1 mg/kg 6 hours after birth should produce neonatal concentrations comparable to those observed in adults."

C O M M E N T

These preliminary studies looking at TDF and FTC are useful in extending the possibilities to reduce the risk of maternal NNRTI resistance following single dose NVP. In the Chi et al study the investigators excluded women with CD4<200 cells/mm³ (who, quite rightly, received HAART), and 81% of women evaluated received antepartum AZT for a median of about 37 days, with 30% having undetectable viral load at delivery.

In contrast, in TOPS (which looked at AZT/3TC 'tail' coverage and provided evidence for this strategy to be included in the WHO guidelines), there was no AZT and all women received single dose NVP regardless of CD4 [6]. It is possible that the longer TOPS regimens were more successful in reducing resistance (from nearly 60% to 10% vs 30% to 14% in the Chi study) but there is no head-to-head comparison. TEmAA also evaluated healthy women who received AZT from a median of 33 weeks so, again, it is difficult to compare results between studies.

Chi's findings suggest that the single dose addition of TDF/FTC would be valuable where the WHO guidelines are being fully implemented ie where those indicated for HAART receive it. But perhaps some will caution, "not yet known" to the question of whether this strategy will be as effective where only single dose NVP is viable. But the simplicity would make it even more attractive for those programmes with very limited capacity.

Shahin Lockman and James McIntyre write in an accompanying editorial to the Lancet paper: "Chi's results do provide strong evidence that addition of single-dose tenofovir/FTC to short-course zidovudine and single-dose nevirapine in women with higher CD4+ cell counts is a new, effective, and feasible approach to reducing maternal nevirapine resistance, and one that should be seriously considered for implementation." [7]

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Response to treatment after single dose NVP exposure in women

Polly Clayden, HIV i-Base

In an oral presentation, Paul Weidle showed findings from a prospective cohort study of treatment response to an NNRTI-based regimen in women exposed or unexposed to single dose nevirapine for PMTCT. [1]

The study was conducted in Zambia (n=201), Thailand (n=87), and Kenya (n=67) between May 2005 and January 2007. The investigators looked at treatment failure (viral load \geq 400 copies/mL, not on NNRTI, died) at 6 months after initiation of HAART.

Of the 878 women, 355 were single dose NVP-exposed (including with short course AZT) and 523 unexposed. Single dose NVP-exposed women were younger (29 vs 33 years, $p < 0.001$), had a higher median CD4 (160 vs 139 cells/mm³, $p = 0.007$), and lower median viral load (97,300 vs 142,000 copies/mL, $p = 0.02$).

The investigators reported that at 6 months after initiation of HAART, 186 (21%) women had failed (76 had viral load \geq 400 copies/mL, 51 left the study, 48 died, and 11 had been switched to a protease inhibitor).

In a primary analysis looking at treatment failure at 24 weeks, they found women exposed to single dose NVP \leq 6 months before initiating NNRTI-based HAART, with baseline CD4 0 to 49 cells/mm³ or viral load $>$ 100,000 copies/mL responded less well to treatment (see table for odds ratios for treatment failure).

They also reported that women exposed to single dose NVP $>$ 12 months before NNRTI-based HAART did as well as unexposed women at time of analysis.

In a secondary on-treatment analysis, including only those still on NNRTI-based ART at 6 months, they reported similar results.

The investigators wrote: "These data do suggest an increased risk of treatment failure among women with recent single dose NVP exposure, but not with single dose NVP exposure $>$ 12 months before initiation of NNRTI-based ART. Treatment with ART or perinatal HIV prevention strategies other than single dose NVP should be considered for pregnant women who are likely to initiate ART within 1 year after delivery."

Table 1: Odds ratios for treatment failure at 24 weeks, primary analysis

Baseline characteristics (n=878)	Adjusted odds ratio (95% CI), also adjusted for age
Time since exposure:	
Unexposed	Ref
<6 mo	1.9 (1.1-3.1)
7-12 mo	1.6 (0.9-3.0)
>12 mo	0.9 (0.8-2.7)
Country:	
Thailand	Ref
Zambia	2.0 (1.2-3.2)
Kenya	1.5 (0.8-2.7)
CD4 $>$ 200 cells/mm ³	Ref
50-199	1.4 (0.9-2.2)
0-49	3.2 (1.9-5.5)
Viral load $<$ 10,000	Ref
10,000-99,000	1.9 (0.95-3.6)
\geq 100,000	2.3 (1.2-4.3)
WHO stage I or II	Ref
III	1.4 (0.85-2.1)
IV	1.7 (0.96-2.8)

C O M M E N T

The failure rates in Africa versus Thailand reported in this study are scary.

Following this presentation John Mellors remarked that, "24 weeks is not long enough for emergence of archived resistance". One problem now seems to be that we could be getting a false sense of security from some of these studies with short follow up and the "just wait 6 months" school-of-thought gains momentum. [2, 3, 4]

From the early days of denial, the emergence of resistance following single NVP to prevent MTCT story has swung past the alarmingly high rates of resistance seen if you looked early enough and hard enough to the most important question of "when does it matter?" Single dose NVP alone should not be given if there are sufficient resources to use more effective strategies. These would include HAART for pregnant women with advanced disease (some would say HAART for all) and short course AZT plus single dose NVP plus cover for the NVP tail for women not eligible for HAART.

Unfortunately, where resources are such that single dose NVP is the only option, the chances of initiating HAART in the mother less than 12 months later seem small.

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Response to treatment after single dose NVP exposure in infants

Polly Clayden, HIV i-Base

A poster from Linda Barlow-Mosha and coworkers showed findings from an analysis of treatment response to a NVP-based regimen in HIV-positive Ugandan children, who were exposed or unexposed to single dose NVP at birth.

There were 92 children enrolled in this study and they received 3TC/d4T/NVP. The children who had been exposed to NVP cohort were significantly younger than the NVP-unexposed children: median age 1.7 years (range 0.6 to 6.3) vs 7.8 years (range 2.9 to 12.4) ($p < 0.001$).

The investigators reported, both groups showed substantial increases in median CD4 percentage. Baseline 8.5%, 48 weeks 22.5% cells/mm³; Baseline 14.0%, 48 weeks 33.0% cells/mm³ in the unexposed and exposed children respectively ($p < 0.0001$)

The children's median baseline viral load was 650,568 copies/mL in the NVP exposed group and 239,027 copies/mL in the NVP unexposed group. Viral load response was similar in the two groups: 80% of the NVP unexposed and 76% of the single-dose NVP exposed group an undetectable viral load (< 400 copies/mL) at 48 weeks ($p = 0.74$).

The investigators concluded that their data suggest that prior single dose NVP exposure did not have a negative effect on treatment success for children placed on a NVP-based HAART at a median age of 1.7 years.

C O M M E N T

Data describing infant response to treatment following single dose nevirapine are even scarcer than those for mothers. These are encouraging. Findings from Lockman et al from the Mashu study were not: 10/15 exposed treatment infants having treatment failure at 12 months vs 1/15 unexposed. But these are tiny numbers. [2]

More studies are ongoing: the NEVEREST (Nevirapine Resistance Study) is evaluating response to treatment in women and children exposed to single-dose NVP; and IMPAACT 1060 is comparing the responses to initiation of NNRTI-based versus PI-based antiretroviral treatment in infants who have and have not previously received single dose NVP. Both are being conducted in South Africa.

This continues to be an areas in which we need more data.

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Other studies looking at birth outcomes

Polly Clayden, HIV i-Base

Two posters looked at incidence of low birth weight and preterm birth in infants born to women receiving HAART.

Ditrame Plus

Didier Koumavi Ekouevi and coworkers reported findings from an analysis of pregnancy outcomes in Ditrame Plus/MTCT Plus, Abidjan. [1]

Women in this study received either a PMTCT regimen of short-course AZT plus single dose NVP or short course AZT/3TC plus single dose NVP (n=190) or NVP-based HAART of AZT or d4T/3TC/NVP (n=168). All women in the ART group initiated treatment at least 28 days before delivery. The study evaluated the following: low birth weight (< 2500 g), stillbirth, and neonatal mortality. Only singleton births were included.

The investigators reported no difference between the rate of stillbirths in the HAART group and the PMTCT group: 3.1% vs 2.9% respectively, $p=0.85$. There was a significant difference between the rate of low birth weight: 22.3% in the HAART group and 12.4% in the PMTCT group ($p=0.02$).

In a multivariate analysis ($n=309$), they found HAART was independently associated with low birth weight (OR 2.53, 95% confidence interval 1.20 to 5.35; $p=0.015$) after adjusting for CD4 count, WHO staging, maternal age, and maternal body mass index.

They found the 1-month probability of survival in HIV-positive infants was not statically different in those with and without low birth weight (94.3% vs 98.8, $p=0.13$).

They concluded: "ART initiated in pregnant women with advanced disease who are eligible for ART is associated with low birth weight. The relationship between maternal ART with advanced disease and infant outcomes, including child survival, requires further study."

Kisumu Breastfeeding Study (KiBS)

The Kisumu Breastfeeding Study (KiBS), is a phase IIB single-arm study evaluating maternal HAART for PMTCT in breastfeeding mothers in Kenya.

Rose Masaba and coworkers reported findings from analysis comparing rates of premature births and low birth weights among ARV-naïve HIV-positive pregnant women receiving different ARV regimens. [2]

Women in KiBs received either AZT/3TC/NVP or AZT/3TC/NFV from 34 weeks' gestation to 6 months post partum. In this study preterm delivery was defined as <37 weeks) and low birth weight as <2500g).

Of 403 women with CD4 ≥ 250 cells/mm³ 196(48%) received a NVP-based regimen and 207 (52%) received a NFV-based regimen. After 20 women withdrew from the study. Of 383 remaining women there were 384 (98%) were live births and 7 (2%) stillbirths.

The median duration of antenatal exposure to NVP was 5.1 weeks (Range 0.29 to 11.6) was lower than NFV, 6.0 weeks (Range 0.57 to 12.2) $p=0.008$. Of the live infants, 65 (17%) were preterm and 51 (13.3%) were of low birth weight.

The investigators reported, after controlling for baseline maternal viral load and duration on HAART before delivery, the rate of preterm deliveries was not significantly different between the two treatment groups: 19% vs 14% for those on NVP and NFV, respectively $p=0.08$. Nor did they find a difference in the rate of low birth weight: 14% vs 12% for NVP and NFV, respectively, $p=0.7$.

The investigators recommended: "Assessment of other safety features and tolerance should also be used to guide choice of NVP or NFV in PMTCT ARV regimens."

C O M M E N T

A lack of effect of HAART on preterm delivery when it is started as late as 34 weeks is not really very surprising. Not estimating gestational age at delivery to try to explain why babies have small birth weight when exposed to HAART from 28 weeks is.

References

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Infant prophylaxis for postnatal transmission

Polly Clayden, HIV i-Base

Two studies looked at giving prophylaxis to breastfed infants of HIV-positive mothers, who were negative at birth.

PEPI

In an oral presentation Taha E Taha showed data from the PEPI trial. PEPI is an open label, controlled phase III trial conducted in Blantyre, Malawi. [1]

In this trial all mothers received single dose NVP for PMTCT. The infants were randomised to one of three arms immediately after delivery: Arm 1 single-dose NVP + 1 week AZT (control arm); Arm 2 the control regimen plus extended daily NVP (ExtNVP) for 14 weeks; Arm 3 the control regimen plus extended daily NVP+AZT (ExtNVP/AZT) for 14 weeks.

The primary endpoint was HIV infection at 9 months in infants who were HIV-negative at birth. This analysis evaluated 3016

infants enrolled before August 7, 2007, HIV negative at birth, for whom information on HIV status were available (1003 control, 1016 ExtNVP, and 997 ExtNVP/AZT).

Mothers were counselled to exclusively breastfeed and wean at 6 months. Mothers' CD4 counts were similar in all three arms: control, median 401 cells/mm³ (IQR 263-587), n=921; ExtNVP, median 379 cells/mm³ (IQR 245.0-570.5), n=924; ExtNVP/AZT, median 400.5 cells/mm³ (IQR 280.0-581.0), n=902.

There was a very high rate of breastfeeding in this study from birth to 6 months. The investigators reported a reduction across all arms between 6 and 9 months (from 91% to 32% in control, 90% to 27% in ExtNVP, and 90% to 29% in ExtNVP/AZT).

At 14 weeks there were substantial differences in probability of infant infection: 8.4% in control arm, 2.8% in ExtNVP and 2.8% in ExtNVP/AZT. The differences continued to 9 months: 10.6% control, 5.2% ExtNVP and 6.4% ExtNVP/AZT. At 9 months the probability of death was 8.9%, 6.8% and 6.3% in the control, ExtNVP and ExtNVP/AZT arms respectively. And the probability of infection or death was 16.8%, 10.6% and 11.2% in the three arms respectively.

The protective efficacy in the extended arms vs the control arm was 67%/66% at 14 weeks in the ExtNVP and ExtNVP/AZT arms declining to 51%/40% at 9 months (and further decreasing over time: 23%/24% at 24 months). In a proportional hazards model, the risk factors for infant infection were ExtNVP vs control HR 0.56 (95% CI 0.41-0.76), p=0.0003; ExtNVP/AZT vs control HR 0.65 (95% CI 0.48-0.88), p=0.006 and maternal CD4 count (decrease of 100 units) HR 1.27 (95% CI 1.99-1.36), p<0.0001. Most deaths were caused by gastroenteritis and pneumonia. There was no difference in grade 2 or higher adverse events across all prophylaxis arms.

SWEN

The Six Week Extended dose Nevirapine (SWEN) study evaluated a similar strategy but of a shorter duration. In an oral presentation, Jayagowri Sastry reported findings from this study. [2]

SWEN is a group of three separate but coordinated, randomised controlled trials conducted in Ethiopia, India, and Uganda to evaluate whether daily NVP given to breastfed infants until 6 weeks of age can decrease HIV transmission through breastfeeding. This presentation was a combined analysis from the three trials.

HIV-positive women breastfeeding their infants were enrolled. There were two prophylaxis arms: Arm 1, single dose NVP to mothers and infants. Multivitamin placebo to the infants from day 8 to 42. Arm 2, the single-dose NVP regimen plus 5 mg NVP daily from day 8 to 42 to the infants (SWEN). This study looked at the risk of HIV infection and death at 6 weeks and 6 months of age in infants HIV-negative at birth.

Maternal baseline CD4 was 397 cells/mm³ in the single dose NVP arm and 394 cells/mm³ in the SWEN arm. This data was from a modified intent-to-treat analysis including 986 single-dose NVP infants and 901 SWEN infants (excluding infants lacking specimens and those with indeterminate or HIV-positive at birth).

The investigators found that 6 weeks of age, SWEN infants had a 46% lower risk of HIV infection than the infants in the single-dose NVP arm (2.5% vs 5.3%; RR 0.536, 95%CI 0.336 to 0.855; p=0.009). At 6 months of age, SWEN infants had a non-significant, 20% lower risk of infection than single-dose NVP infants (6.9% vs 9.0%; RR 0.800, 95%CI 0.584 to 1.096; p=0.164). At 6 months of the mortality risk for the SWEN arm vs single-dose NVP arm was 1.1% vs 3.6% (RR 0.471, 95%CI 0.256 to 0.867; p=0.016).

The combined risks of post-natal HIV transmission or death in the SWEN arm vs the single-dose NVP arm were 3.7% vs 6.8% (RR 0.583, 95%CI 0.391 to 0.870; p=0.008) at 6 weeks and 8.0% vs 11.6% (RR 0.729, 95%CI 0.549 to 0.967; p=0.028) at 6 months, respectively.

The estimated cumulative probability of death or HIV transmission were RR 0.58, p=0.008; RR 0.7, p=0.026 and RR 0.73, p=0.028 at 6 weeks, 14 weeks and 6 months respectively. Serious adverse events were similar in both arms.

Resistance in SWEN

Inevitably this strategy should cause concern about resistance in infants who become HIV-positive despite receiving nevirapine prophylaxis.

In a second oral presentation from SWEN, Anitha Moorthly showed data from the Indian study comparing NVP resistance in infants receiving SWEN vs single-dose NVP by timing of HIV-1 infection and receipt of maternal single-dose NVP. [3]

In this analysis, infant DNA PCR was performed at 48 hours, 1, 2, 4, 6, 10, and 14 weeks, and 6, 9, and 12 months of age. Timing of infection compared 4 groups: in utero (positive by 48 hours; n=22); peripartum/early breastfeeding (positive at week 1 to 6; n=19); late breast-feeding (positive at week 10 to 14; n=18), and very late breast-fed (positive at >=6 months; n=35).

Median maternal CD4 counts were 316 cells/mm³ (IQR 238,454) and 320 cells/mm³ (IQR 194,522) in the single dose NVP and SWEN arms respectively. 57% of the women received maternal single dose NVP. 83/89 (93%) infant plasma samples could be genotyped. 76 infants met the inclusion criteria (able to define timing of infection) with sample taken 28 days since

HIV diagnosis.

The investigators found higher rates of NVP resistance in SWEN infants infected within 6 weeks of life but lower rates of NVP resistance in infants infected after 6 weeks.

Table 1: Timing of infection

Timing of infection	S/D NVP n=51	ExtNVP n=25
Infected at \leq 6 weeks	38%	92%
Infected at $>$ 6 weeks	18%	15%
Infected in utero	50%	88%
Infected 1-6 weeks (Post partum/early BF)	27%	100%

The primary mutations were Y181C across both arms. There was no difference in mutations whether or not the mother had received NVP.

In multivariate analysis, the investigators found infants infected very late ($>$ 14 weeks) were 89% less likely to have NVP resistance than those infected earlier (in utero, peripartum, early breastfeeding, late breastfeeding) and these infants had mainly wild type virus.

With infection \leq 6 weeks as reference the adjusted odds ratios for NVP resistance during late or very late transmission (population or clonal level) were: OR 0.75 (95%CI 0.21-2.69), $p=0.658$ and OR 0.11 (95%CI 0.02-0.48, $p=0.004$ for late and very late transmission respectively.

Following this presentation Dr Jeff Stringer remarked that according to his “back of an envelope calculation” of 1000 HIV exposed babies 21 may be HIV-negative but 53 may have NVP resistance and asked whether this was “too high a price to pay.”

And a poster authored by Jessica Church and coworkers evaluated resistance in the Ugandan infants. [4]

In this study, samples were available from 49/69 (71%) infants with HIV infection by 6 weeks of age (24 in the single-dose NVP arm; 25 in the SWEN arm). Maternal CD4 cell count, infant viral load, and HIV subtypes were similar in the both arms.

At six weeks NVP resistance was detected using the ViroSeq assay in a greater number of infants in the SWEN arm compared to the SD NVP arm (21/25 84% vs 12/24, 50%, $p=0.01$). A higher percentage of infants in the SWEN arm also had at least one NVP resistance mutation detected using the more sensitive LigAmp assay (19/25, 79% vs 7/24, 35%, $p=0.004$).

In the SWEN arm, NVP resistance was not associated with the number of NVP doses received or the HIV status at birth. Among infants with resistance detected at 6 weeks, only 1 of 6 infants in the single-dose NVP arm had NVP resistance detected by ViroSeq at 6 months. All 7 infants in the SWEN arm still had detectable NVP resistance at 6 months.

Phenotypic resistance results were available for 42/49 (85.7%) of infants evaluated at 6 weeks. There was a higher percentage of infants with phenotypic resistance in the SWEN arm than in the single-dose NVP arm (19/22, 86.3% vs 9/20, 45%, $p=0.005$).

The Indian and Ugandan analyses were consistent in showing SWEN infants were more likely to have NVP resistance than those who received only single-dose NVP.

C O M M E N T

Isn't this all getting rather over evolved?

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3. Moorthy A, Gupta A, Sastry J et al. Timing of infection is critical for nevirapine resistance outcomes among breastfed subtype C HIV-1-infected infants exposed to extended vs single-dose nevirapine prophylaxis: The India SWEN Study. Oral abstract 44.
4. Church J, Omer S, Guay Let al. Analysis of NVP resistance in Ugandan infants who were HIV-infected despite receiving single-dose nevirapine vs single-dose NVP plus up to 6 weeks of daily NVP to prevent HIV vertical transmission. Poster abstract 635b.

Antiretroviral drug concentrations in breast milk and breastfeeding infants

Polly Clayden, HIV i-Base

A poster from the Breastfeeding, Antiretroviral, and Nutrition (BAN) study by Amanda Corbett and coworkers showed pharmacokinetic data in breast milk and plasma in mothers and breastfeeding infants.

BAN is enrolling >2400 pregnant women in Malawi to look at the effect on mother to child transmission of: 28 weeks of HAART given to mothers or daily NVP given to babies; weaning at 28 weeks; and nutritional supplementation.

In this study all mothers and infants receive single-dose NVP and 7 days' AZT/3TC "tail" coverage. Mothers with CD4 >200 cells/mm³ and infants with birth weight >2kg were enrolled. To better understand infant drug exposure from breast milk, the investigators performed a longitudinal pharmacokinetic study in mother–infant pairs.

Breast milk, and mothers' and infants' blood plasma samples were taken at the end of 12-hour dosing intervals at 6, 12, and 24 weeks post partum. Mothers' HAART regimens included a combination of AZT (or d4T), 3TC, and either NVP or NFV.

20 mother–infant pairs were enrolled in this study. Mothers were a median of 26 years old (range 19-35) and weighed 53kg (range 46-54) with CD4 counts 518 cells/mm³ (range 216 to 931) at delivery. Babies weighed a median of 3.1 kg (2.2 to 2.6) kg at delivery, and 75% were male. Samples were obtained at a median of 12, 15, and 17 hours post-dose at 6, 12, and 24 weeks post partum.

The investigators reported, <20% of samples had detectable AZT and d4T. They found, maternal plasma concentrations for other antiretrovirals were similar to previous reports.

For concentration ratios for 3TC, NVP, and NFV with all time points included see table below. The investigators noted that 3TC and NVP infant's plasma concentrations declined slightly from 6 to 24 weeks post-partum, while mothers' plasma and breast milk concentrations did not change significantly.

Table 1: Concentration ratios for 3TC, NVP and NFV

	3TC (n=47)	NVP (n=21)	NFV (n=26)
Breast milk/ mother's plasma	2.6 (1.1-3.5)	0.7 (0.5-0.9)	0.08 (0.04-0.14)
Infant's plasma/ breast milk	0.01 (0.004-0.03)	0.2 (0-0.3)	N/A
Infant's plasma/ mother's plasma	0.06 (0.01- 0.1)	0.12 (0 -0.3)	N/A

n=number of samples, median (IQR)

The investigators concluded that although 3TC concentrations in breast milk were 2.6-fold higher than in maternal plasma, infant plasma exposure was minimal (1% of breast milk). NVP concentrations in breast milk were 70% that of maternal plasma, with low exposure (20% of breast milk) in infants. They found NFV exposure in breast milk was minimal (8% of maternal plasma), with no drug detected in the infants.

Overall, infants' plasma concentrations for all antiretrovirals were well below therapeutic concentrations, which they suggested would have minimal toxicity risk. Both 3TC and NFV exposure in infants would suggest minimal risk for resistance in HIV-positive infants. But they noted, "low-level NVP exposure via breast milk may predispose HIV-infected infants to resistance."

Ref: Corbett A, Kashuba A, Rezk N, et al. Antiretroviral drug concentrations in breast milk and breastfeeding infants. 15th CROI, February 2008, Boston, USA. Poster abstract 64B.

Maternal breastfeeding prophylaxis

Polly Clayden, HIV i-Base

The Kisumu Breastfeeding Study (KiBS), a phase IIB single-arm study evaluating maternal HAART for PMTCT in breastfeeding mothers in Kenya. In an oral presentation Timothy Thomas presented preliminary findings from KiBS. [1]

In this study, pregnant women received AZT/3TC and NVP (later changed to nelfinavir (NFV) for women with CD4 >250 cells/mm³) from 34 weeks' gestation to 6 months' postpartum. The mothers' treatment was continued after the breastfeeding period where indicated for their own health. Women were counselled to exclusively breastfeed and to wean rapidly at 6 months. Infants received single-dose NVP at birth.

522 women were enrolled in the study of which 500 delivered 502 live born infants. The mothers' median CD4 was 382 cells/mm³ and median viral load was 4.5 log copies/mL. HIV infection data were available for 497 infants live born: 27 (11

males, 16 females) became HIV-positive, 3 after 6 months.

Cumulative infant HIV infection rates per 100 infants and by maternal CD4 count and regimen are shown in the table. There was no difference in transmission rates by maternal CD4 ($p=0.89$) or by regimen ($p=0.83$). The overall rate at 12 months for female infants was 7.4 (95%CI 4.6 to 11.9) and male infants 4.5 (95%CI 2.5 to 8.1), $p=0.15$.

Only 3.5% of transmissions were attributed to breastfeeding at 12 months. The investigators noted that transmissions occurred after 6 months when weaning was recommended.

Table 1: Cumulative MTCT to 12 months, overall, by CD4 and NVP vs NFV

Age	0–7 dys	6 wks	3 mo	6 mo	12 mo
Transmissions	12	19	20	24	27
Overall (n=497)	2.4 (1.4-4.2)	3.9 (2.5-6.0)	4.1 (2.7-6.3)	5.0 (3.4-7.3)	5.9 (4.0-8.5)
CD4 \leq 250 (n=118)	3.4 (1.3-8.8)	4.3 (1.8-10.0)	5.2 (2.4-11.2)	5.2 (2.4-11.2)	6.7 (3.2-13.9)
CD4 \geq 250 (n=379)	2.1 (1.1-4.2)	3.8 (2.2-6.3)	3.8 (2.2-6.3)	4.9 (3.1-7.7)	5.5 (3.6-8.4)
Nevirapine (n=178)	1.1 (0.3-4.4)	3.4 (1.6-7.5)	3.4 (1.6-7.5)	5.2 (2.8-9.8)	5.9 (3.2-10.6)
Nelfinavir (n=201)	3.0 (1.4-6.5)	4.0 (2.0-7.9)	4.0 (2.0-7.9)	4.6 (2.4-8.6)	5.2 (2.8-9.5)

The investigators wrote: “Further assessment—adherence to antiretrovirals, the optimal timing for breastfeeding cessation, HIV-free survival, and drug resistance in maternal and infant HIV isolates—is necessary to determine whether HAART is a feasible, acceptable, safe, and efficacious strategy for PMTCT among breastfeeding women, particularly those not meeting WHO treatment criteria.”

In a previous analysis this group have reported that maternal NVP and 3TC are transmitted to the infant via breastfeeding in sufficient quantities to have biologic effect.

In a poster authored by Clement Zeh and coworkers, they showed findings from a study evaluating whether infants could acquire resistance in this way [2].

29/502 infants in this study (5.8%) were HIV-positive. In 24/29 (83%) the first positive HIV PCR was before 24 weeks ie during the period of maternal prophylaxis. Of these 24 infants, 14 (58%) of their mothers received NVP mothers and 10 (42%) received NFV.

The investigators found detectable genotypic resistance in 16 infants (see table 2). 6/14(43%) of infants of mothers receiving NVP and 10/10 (100%) of infants of mothers receiving NFV ($p = 0.006$).

Genotypic NRTI resistance mutations were: M184V (n=13), K65R (n=4), D67N (n=2), and T215Y (n=2), and NNRTI mutations were: Y181C (n=3), K103N (n=2), G190A (n=2), and K101E (n=1).

Of the infants exposed to maternal NVP, 4/6 (67%) of infants with resistance had a NRTI mutation and 6/6 (100%) had an NNRTI mutation. Of those exposed to maternal NFV, 10 (100%) of 10 infants had a NRTI mutation, but none had a major protease inhibitor mutation.

Table 2. Resistance in breastfed infants in KiBS

Week post-partum	N	First PCR-positive specimen		Week 14 and/or 24 specimen
		Not amplified	n resistant / n tested	n resistant / n tested
Delivery	12	3	0/9	11/12
2	2	1	0/1	1 /2
6	6	0	1/6	1 /6
14	2	0	2/2	2/2
24	2	0	1 /2	1 /2
36–72	5	1	0/4	NA
Total	29	10	3/19	16/24

The investigators noted that when they evaluated infants who became HIV-positive before 6 weeks of life, they did not

initially detect genotypic resistance, suggesting resistant virus may not have been transmitted from the mother in utero or during labour. But they found resistance emerged during the breastfeeding period, likely due to the transfer of ARV from breast-milk.

They wrote: "Differing HIV resistance patterns depending on the mothers' treatment may have implications for the choice of ARV for mothers during the breastfeeding period and for subsequent treatment of infants who become HIV-infected."

References

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2. Zeh C, Weidle W, Nafisa L et al. Emergence of HIV-1 drug resistance among breastfeeding infants born to HIV-infected mothers taking antiretrovirals for prevention of mother-to-child transmission of HIV: The Kisumu Breastfeeding Study, Kenya. 15th CROI, February 2008, Boston, USA. Poster abstract 84LB.

Risk factors for breastfeeding transmission

Two reports looked at risk factor for postnatal transmission.

Polled analysis from the Vertical Transmission Study and Ditrane Plus

In an oral abstract Renaud Becquet presented findings from an analysis of breastfeeding pattern and duration and their contribution to postnatal HIV transmission. [1]

Data were pooled from two studies: Ditrane Plus, conducted in urban West Africa, where breastfeeding cessation at 4 months was recommended and where exclusive breastfeeding was rare; and the Vertical Transmission Study which took place in rural South Africa, where promotion of safer breastfeeding means high rates of exclusive breastfeeding, but with longer duration.

This analysis assessed 18-month HIV postnatal transmission. The study included 1195 breastfed infants, HIV-negative at birth. 90% of the infants were breastfed for 3 months. At 6 months 83% of the South African and 38% West African infants children were still breastfed. At 12 months this had declined to 38% and 20% in South Africa and West Africa respectively.

At 3 months of age, 66% of the South African infants had been exclusively breastfed since birth and 55% of West African infants had been predominantly breastfed (defined as breastmilk plus water-based drinks).

The investigators reported the overall postnatal-transmission risk at 18-month in the South African infants was twice that of the West African infants, 9% (95% CI 7-11%) vs 5% (95% CI 3-8%), $p=0.03$.

In a competing risk analysis allowing for duration of breastfeeding and assuming that all children were breastfed for 18 months, the investigators found the postnatal-transmission risk would be 14% (95% CI 10-18%) in the South African infants and 16% (95% CI 8-28) in the West African infants $p=0.32$.

The 18-month postnatal-transmission risk was 3.9% (95% CI 2.3-6.5) for children breastfed for less than 6 months, and 8.7% (95% CI 6.8 to 11.0) for those breastfed for more than 6 months; crude HR 2.1 (1.2-3.7), 0.02; adjusted HR 1.8 (0.9 to 3.4), $p=0.06$ (adjustment included maternal CD4 count).

The investigators found no difference in transmission risk for infants exclusively breastfed to those predominantly breastfed for the same period. But infants receiving solids at least once during the first 2 months of life were 2.9 (1.1-8.0) times more likely to acquire HIV through breastfeeding than infants never exposed to solids in this period (adjusted competing risk analysis, $p=0.04$).

The investigators wrote: "Breastfeeding duration is a major determinant of postnatal HIV transmission, and safe alternatives to breastmilk beyond 6 months are urgently needed. The postnatal-transmission risk was not different in exclusively and predominantly breastfed children, and we confirm the negative effects of mixed breastfeeding with solids."

Mashi

A poster authored by Roger Shapiro and coworkers showed findings from an analysis of early breastfeeding and potential late risk factors for transmission in a randomised infant feeding trial. [2]

In the Mashi study, HIV-positive women were randomised to either breastfeed or formula feed for 6 months. The mothers received AZT from 34 months of gestation and either single-dose NVP or placebo. The infants received single-dose NVP or placebo, and AZT for 1 month (formula-feeding arm) or 6 months (breastfeeding arm). Maternal HAART became available mid-study for women with CD4 cell count <200 cells/mm³ or AIDS.

The investigators reported, of 1116 infants HIV-negative at birth, 6 (1.1%) formula-fed and 7 (1.2%) breastfed were HIV-positive by 1 month ($p=1.0$). They did not find maternal NVP predictive of MTCT either in the first month or later in this study.

Of 549 breastfed infants alive and HIV-negative at 1 month, there were 24 (4.4%) late transmissions: 15 by 4 months, 6 from 4 to 7 months, and in 3 later. Infant feeding patterns were similar from months 1 to 4 regardless of eventual HIV status.

In univariate analysis, associations with late MTCT included higher maternal plasma or breast milk viral load, $p=0.0002$ and $p=0.02$, respectively); lower maternal CD4 cell count, $p=0.005$; infant diarrhea, $p=0.03$; and infant anemia $p=0.001$). 3/109 (2.8%) exclusively breastfed infants were infected compared to 20/400 (4.8%) of 400 mixed-fed infants, $p=0.14$.

In multivariate analysis, excluding breast milk viral load, maternal viral load (OR 2.7, 95%CI 1.4-55, $p=0.005$), maternal CD4 cell count (OR 0.08, 95%CI 0.76-1.0, $p=0.06$), no electricity in the home (OR 0.1, 95%CI 0.02-1.0, $p=0.05$), infant diarrhea (OR 3.0, 95% OR 1.2-7.9, $p=0.02$) and infant anemia (OR 4.1, 95% CI 1.5-11.9, $p=0.008$) predicted late MTCT.

The investigators reported there were no transmissions in the 34 breastfed infants whose mothers started HAART before delivery. The median baseline maternal CD4 cell count for late transmitters was 225 cells/mm³. There were no late transmissions when baseline maternal viral load was <3500 copies/mL. They noted, "Reverse causality may explain associations between infant illness and late MTCT when HIV testing is infrequent."

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1. Renaud Becquet R, Bland R, V Leroy V et al. Duration and pattern of breastfeeding and postnatal transmission of HIV: Pooled analysis of individual data from a West and South African cohort study. 15th CROI. February 2008. Boston USA. Oral abstract 46.
2. Shapiro R, Smeaton L, Lockman S et al. Risk Factors for mother-to-child transmission of HIV-1 from breastfeeding in a randomised clinical trial in Botswana: The Mashi study. 15th CROI. February 2008. Boston USA. Poster abstract 637.

CROI: HEPATITIS COINFECTION

UK cohort reports sexual HCV reinfection in at least 5% HIV-positive gay men following sustained response to treatment

Simon Collins, HIV i-Base

Rachel Jones from Chelsea and Westminster Hospital presented an analysis of failed treatment of HCV in HIV-positive gay men. Describing the characteristics of individuals with a second episode of HCV viraemia following SVR post-treatment of HCV, using molecular phylogenetic analysis to determine whether viraemia was due to treatment relapse or secondary infection.

Patients were identified from the databases of Royal Free Hospital and Chelsea and Westminster Hospital from 2002-2008. SVR was defined as undetectable HCV PCR on at least two measurements, at least six months apart.

Notes review looked for evidence of risk behaviour, including STIs and HIV characteristics, and then compared paired RNA from the first and subsequent episodes of hepatitis C viraemia.

211 individuals were identified with acute HCV, 16 of whom had a second episode - all detected following a peak in ALT (median peak 413, range 49-2727 I/U).

All were HIV+ gay men with no documented IDU. Mean duration of HIV 4 years (range 2-17) and mean age 38 (range 26-51). Mean CD4 476 cells/mm³ (range 195-834). At second episode of viraemia patients were slightly older with a similar CD4 count. The mean duration of SVR was 28 months.

All but two individuals had at least one documented STI during the period of SVR: syphilis (10, predominantly secondary), NSU (2), gonorrhoea (6, 3 urethral and 3 rectal), herpes (3, 1 new case and 2 recurrent). This incidence may have been underestimated as STI treatment in the UK is frequently accessed at a different centre to HIV care.

Only 8/16 had paired samples, all genotype 1. 6/8 had very divergent samples and even the 2/8 that were closely related were separated by a temporal difference of four and five years indicating this was unlikely to be a relapse so late and more likely to reinfection from a common source.

In summary, supported by evidence of STI, the researchers suggested that in this small but significant cohort, reinfection rather than relapse explained the new infected in at least 6 cases, and probably in all eight cases.

In addition to highlighting the importance of stronger health prevention messages, the researchers suggested that identifying patients who had perhaps cleared HCV spontaneously and generated protection against future infection could help identify immune correlates that might help with prognosis of this group of patients.

Treatment responses were all reported as being as effective with second treatment as the initial HCV treatment. However, two of these patients have since been reinfected a third time.

C O M M E N T

A recent presentation from a European cohort containing these cases at the recent AASLD meeting in Boston showed an international spread of a few HCV-strains in patients experiencing an acute hepatitis C in Germany, France and UK after high risk sexual engagements.

Some reviewers suggest that this supports the idea that HCV is not an increasing STI in the wider gay community, but is limited to a HIV-positive men who serosort to eliminate the risk of HIV transmission. Risk factors reported in previous studies included not using condoms, group sex, some recreational drug use and longer and more physical activity.

Others have suggested that HCV is not being picked up outside of HIV-positive cohorts because no-one is looking for it. Acute HCV in HIV-positive men is generally only detected due to routine liver enzyme monitoring.

A research letter in the 12 March issue of AIDS reported case reports of two HIV-positive gay men who had been reinfected (superinfected) with a second HCV strain following sexual exposure.

References:

1. Jones R et al. Hepatitis C viraemia following sustained virological response to pegylated interferon and ribavirin in HIV+ men who have sex with men-re-infection or late relapse? Oral abstract 61LB.
<http://www.retroconference.org/2008/Abstracts/33444.htm>

This oral presentation is available to view online from the conference website (Monday 4 February).

2. Ghoshn J et al. Sexually transmitted hepatitis C virus superinfection in HIV/hepatitis C virus co-infected men who have sex with men. AIDS: Volume 22(5)12 March 2008p 658-661.

MELD score predictive of pre-transplant mortality in HCV coinfecting patients

Simon Collins, HIV i-Base

Aruna Subramanian from Johns Hopkins University looked at determining incidence, cause, and time to pre-transplant mortality in transplant candidates compared to HIV-negative patients in a prospective cohort study at 20 US sites, with particular reference to the MELD score.

The MELD score (Model for End Stage Liver Disease) incorporates creatinine, bilirubin and INR checked at the same visit. MELD is validated as predictor of mortality in HIV-negative patients. It is used as a basis for organ allocation, so that sick patients get earlier access to transplant.

Patient in this study needed to fulfil local criteria to be included on a transplant list, with CD4 count of >100 cells/mm³ within 16 weeks of transplant (>200 if a recent OI), and to have undetectable viral load (except in cases when ART was discontinued due to hepatotoxicity, and a resistance profile indicated that HIV suppression post transplant would be likely. Clinical follow-up was at least every three months from joining the list until transplant.

Each case was matched (by age, gender, race, time of listing and HCV coinfection) with up to five controls, and compared by time to death, transplant and reaching MELD >25.

During follow-up the cohort included 167 HIV-positive patients (51% were not transplanted, 14% died and 35% received a transplant) and 792 controls (41% not transplanted, 11% died and 48% transplanted).

Median baseline CD4 was lower in patients who died compared to those who received a transplant (median 237 vs 315, p=0.01). There was no difference in the percentage with undetectable viral load, use of PI-based treatment or percent with HCV coinfection.

Cause of death pre-transplant were broadly similar in the HIV-positive vs control group, including sepsis (25% vs 20%), multi-organ failure (17% vs 26%), GI haemorrhage (13% vs 6%), other causes (29% vs 27%), and unknown (17% vs 20%).

Comparative time to death was similar in cases and controls, as was time to transplantation and to elevated MELD >25.

However, in multivariate model baseline MELD score showed the strongest risk (HR=21.8 95% CI 6.3, 75.7, p<0.0001). CD4 count <200 had only borderline significance (HR 2.6, 95%CI 0.98, 6.9, p=0.05), and viral load was not predictive.

The researchers concluded that low CD4 count at time of listing may be predictive of greater risk of death, but that after controlling for CD4 and viral load. MELD had excellent predictive value for pre-transplant mortality, and should be used routinely for patients with cirrhosis to help guide decisions for early transplant referral.

The group plans to develop a scoring method that incorporates CD4 count and MELD to predict mortality that could be validated for all patients, not just at transplant listing, and to determine optimum CD4 count for transplantation, and to determine any relationship between MELD score and post-transplant outcomes (which limited data indicate may be poorer in coinfecting patients).

An online MELD calculator is available at:

<http://www.unos.org/resources/MeldPeldCalculator.asp?index=98>

<http://hivtransplant.com>

C O M M E N T

These results should not be a surprise as MELD is well validated for assessing liver failure. MELD is used by European and US transplant centres, The post-transplant data are very important, because MELD score at the time of transplant may be an accurate indicator of post-transplant survival.

There are clearly concerns that 'standard' criteria for listing urgency may not apply for HIV-positive patients due to faster risk of progression and re-thinking listing priorities in this group of patients may be important. It is re-assuring that 'standard' MELD criteria still apply.

Ref: Subramanian A et al MELD is the best predictor of pre-transplant mortality in HIV-infected liver transplant candidates. Oral abstract 64.
<http://www.retroconference.org/2008/Abstracts/31927.htm>

This oral presentation is available to view online from the conference website (Monday 4 February).

Does abacavir decrease SVR rates with HCV treatment?

Simon Collins, HIV i-Base

Three studies from Spain reported on the relationship between nucleoside/tide analogues and response to HCV treatment. [1, 2, 3] Last year at CROI, a poster from French researchers reported that abacavir use was significantly associated with poorer outcome to HCV treatment, through a possible intracellular competition between abacavir and ribavirin. [4]

Jose Mira and colleagues from Hospital University de Valme, Seville presented a retrospective analysis comparing sustained virological response (SVR) rates among HIV/HCV-co-infected patients treated with peg-IFN plus ribavirin, who were taking a NRTI backbone consisting of either abacavir + 3TC or tenofovir + 3TC/FTC. [1]

In an intention-to-treat analysis, sustained virological response (SVR) was seen in 20/70 (29%) individuals receiving abacavir and 83/186 (45%) patients using tenofovir, ($p=0.02$). NRTI backbone containing TDF was an independent predictor of SVR in the multivariate analysis (adj odds ratio, 95%CI: 2.6; 1.05 to 6.9); $p=0.03$).

HCV genotype 2 or 3, baseline LDL cholesterol levels ≥ 100 mg/dL, lower baseline plasma HCV viral load and undetectable baseline HIV viral load also predicted SVR. The association between abacavir use and lower SVR rate was mainly seen in patients with plasma HCV viral load $>600,000$ IU/mL, HCV genotype 1 or 4 and in patients who received lower doses of ribavirin. (those less likely to respond to HCV treatment)

Of patients using a daily dose of ribavirin of less than 13.2 mg/kg, 3 (20%) of those under abacavir vs 22 (52%) under tenofovir achieved SVR ($p = 0.03$), whereas the rates were 31% and 38% ($p = 0.4$), respectively, in those receiving RBV dose higher than 13.2 mg/kg.

A second retrospective cohort analysis, from Juan J Gonzalez-Garcia and colleagues from the GESIDA 50/06 Study Group looked at all HIV/HCV coinfecting patients treated for HCV while on HAART between January 2003 and November 2005 from 35 sites. [2]

Patients were categorised in 2 groups: tenofovir, used with 3TC or FTC ($n = 238$); and non-tenofovir ($n = 481$) that included patients using AZT + 3TC ($n = 265$), d4T + 3TC ($n = 164$), or abacavir + 3TC ($n = 52$). They excluded patients receiving ddI or tenofovir with AZT/d4T or abacavir from the analysis.

The two groups were well matched in baseline characteristics except for a lower CD4 cell count mean (535 vs 601; $p=0.003$), exposure to more HAART regimens (7.2 vs 5.7; $p < 0.001$), and a higher mean GOT/GPT quotient (0.84 vs 0.77; $p=0.04$). Safety analysis revealed no differences between the groups in relation to death, hepatic decompensation and interruption of HCV treatment due to side effects.

Ribavirin dose-reductions were more frequent in non-tenofovir treated patients (12.8 vs 19.5%; $p=0.03$), particularly in patients treated with AZT (23.2%; $p = 0.003$). No significant differences were found in the SVR among patients in the tenofovir and non-tenofovir groups, by ITT analysis (45% vs 39%; $p= 0.12$).

In a multivariate analysis, adjusting for HCV genotype, HCV viral load $<500,000$ IU/mL, baseline HIV viral load <50 copies/mL, GOT/GPT quotient, and alcohol intake >50 g/day, SVR was positively associated with use of tenofovir (OR 1.70 95%CI 1.05 to 2.77, $p=0.03$) and negatively associated with use of AZT, related to anaemia (OR 0.60, 95%CI 0.37 to 0.99, $p=0.05$), detailed in the Table 1.

The study concluded that the use of TDF + 3TC/FTC was associated with an improved response to peg-IFN plus ribavirin, and that, as shown in previous studies, AZT is associated with a worse tolerability and effectiveness.

Table 1: Odds ratios of SVR by nucleoside backbone

NRTI use	OR of SVR	95%CI	p
TDF+3TC or FTC	1.70	(1.05 to 2.77)	0.03
AZT+3TC *	0.60	(0.37 to 0.99)	0.05
d4T+3TC	1.09	(0.65 to 1.82)	0.73
ABC+3TC	0.80	(0.32 to 2.08)	0.68

*including patients with AZT+3TC+ABC

In the third study, Ana Moreno and colleagues from Hospital Ramon y Cajal, Madrid looked at use of abacavir or tenofovir in 174 HIV/HCV coinfecting patients starting their first cycle of peg-IFN plus weight-adjusted ribavirin. Approximately half the patients used Pegasys and half used PegIntron [3]

Most subjects were male (76%), prior intravenous drug users (87%), with a median age of 40 years (28 to 63). The median duration of HCV infection was 21 years, and 102 (59%) had HCV-genotype 1 or 4. 82% were on HAART (49% PI, 32% NNRTI, and 18% triple-nuke). Tenofovir was used in 69 (48%), abacavir in 56 (39%). The mean ribavirin dosage was 14.7±2.4 mg/kg/day.

Baseline CD4 count, and HCV viral load were 513 cells/mm³ and 5.8 log IU/mL respectively, and two-thirds of the patients entered the study with undetectable HIV viral load.

SVR was reported in 79/174 (45%) patients. After each adjusted regression analysis however, neither abacavir (p = 0.59), nor tenofovir (p = 0.92), nor triple NRTI use (p = 0.12) had any significant effect on SVR.

By multivariate analysis, HCV genotype 1 or 4 (OR 7.8, 95%CI 2.6 to 22.93, p = 0.0001), and higher baseline HCV RNA levels (OR 3.5, 95%CI 1.7 to 7.3, p = 0.001) or fibrosis scoring (OR 1.7, 95%CI 1.2 to 2.6, p=0.003) remained independently associated with failure to achieve SVR.

They concluded that in this cohort, use of abacavir, tenofovir or triple nucleosides did not significantly influence the rate of SVR in patients receiving peg-IFN + weight-adjusted-RBV.

C O M M E N T

The first study from Mira et al. is a merger of data from Madrid and Seville. The data from Madrid were already presented at IAS and AASLD 2007 with similar findings. The study from Moreno et al. is considerably smaller which may explain the negative finding for abacavir.

The GESIDA cohort took a different route by including abacavir in the group of AZT, ddl and d4T – all of which are known to have toxicities limiting treatment efficacy in coinfecting patients.

In summary, these data are no surprise and do not tell us much about abacavir.

References:

- Mira J, et al. Efficacy of pegylated interferon + ribavirin treatment in HIV/HCV-co-infected patients receiving abacavir + lamivudine or tenofovir + either lamivudine or emtricitabine as nucleoside analogue Backbone. 15th CROI, Boston 2008. Abstract 1074.
<http://www.retroconference.org/2008/Abstracts/30917.htm>
- Gonzalez-Garcia J, et al. The use of TDF+ 3TC/ FTC is associated with an improved response to pegylated interferon + ribavirin in HIV/HCV-co-infected patients receiving HAART: the Gesida 50/06 study. 15th CROI, Boston 2008. Abstract 1076.
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No effect of interferon maintenance therapy on fibrosis progression in non-responders

Simon Collins, HIV i-Base

One aspect of HCV management that is informed by little data, is whether continued treatment of virologic non-responders with maintenance peg-IFN therapy can reduce the rate of clinical HCV progression.

This question was addressed in a study presented by Kenneth Sherman and colleagues in a multicentered US study that treated a mixed group of 329 patients (68% naïve and 32% refractory to previous treatment) with peg-IFN-alpha-2a plus weight-based ribavirin for 12-18 weeks. Median age was 48 years; 83% male; 43% white, 37% black, non-Hispanic and 15%

Hispanic; baseline median HCV viral load was 6.6 log IU; CD4 was 498 cells/mm³; 74% had HIV RNA <50 copies/mL.

Early virologic response (EVR) was defined as achieving undetectable HCV viral load (<600 IU) or 2-log drop at week 12. Patients without an EVR received biopsy and were randomised to peg-IFN 180ug alone or observation for 72 weeks.

Liver biopsies obtained at start and end of therapy were blinded, and read by a single pathologist. The study design required 134 subjects to show whether maintenance treatment produced 0.18 unit/year reduction in the rate of Metavir fibrosis progression.

EVR was observed in 55.6% patients (95%CI 50 to 61%; ITT analysis) and was strongly associated with expected factors (gender, race, degree of fibrosis, AST, absolute neutrophil and haemoglobin levels).

86 patients without EVR were then randomised to peg-IFN vs observation. Median entry Metavir score was 2; 28% had advanced fibrosis (F3, F4).

However, lack of fibrosis progression in both groups, lead to DSMB-recommended early closure of the study, when 62 patients had completed 72 weeks of follow-up, only 45 of who had paired biopsy results for this analysis (24 in the IFN, 21 in observation arm).

Compared to the expected rate of 0.18 units/year, median fibrosis change was 0.0 (Q1,Q3: 0.0, 0.69) in the maintenance groups and 0.0 units/year (Q1,Q3: -0.69, 0.61) in the control group.

The authors concluded that, in contrast to recent reports, this randomised controlled trial failed to identify significant change in hepatic fibrosis among untreated non-early virologic responses over 72 weeks. They also commented that weight-based ribavirin achieved higher levels of EVR (55.6% vs. 41%) than the ACTG 5071 study, which used lower doses of ribavirin, and that race (Causasian>Hispanic>Black) appears to be an important independent factor in early virologic response.

C O M M E N T

Right from the early registration studies for interferon and ribavirin, investigators had noted a slight reduction in hepatic fibrosis scores and also decreases in activity/inflammation, which drives fibrosis in patients who did not have a virological response to therapy. A question that had been asked was does this therapy have an anti-fibrotic effect over and above its anti-viral effect?

This phenomenon was recently explored in the HALT-C study (AASLD 2007, De Bisceglie et al), where HCV mono-infected patients with Child-Pugh A cirrhosis and previous non-response, were randomised to continue pegIFN-alpha 2a at half-dose (90mg) or placebo over 3.5 years. The end-points were death, de-compensation, HCC or an increase in fibrosis by two points. The results, presented by the authors at AASLD, suggested that for all individual end-points, there was no significant difference between the pegIFN arm and the placebo arm, thus suggesting that in clinical terms, pegIFN maintenance therapy did not prevent progression in cirrhotic patients.

This study, also called the SLAM-C study, included HIV/HCV co-infected patients, 15% of whom had cirrhosis. After a lead in period of treatment with pegIFN and weight-based ribavirin, patients with no EVR were randomised to maintenance therapy with pegIFN 180mcgs/week or no therapy. Liver biopsies were evaluated after 72 weeks. There was no fibrosis progression in either arm. However, there was a greater reduction in inflammatory scores in patients on pegIFN arm. Clearly this begs the question of whether maintenance therapy will help reduce fibrosis progression in non-virological responders. From this study, evidently not, although these were small numbers, therapy and follow-up was only for 72 weeks and that these patients had good CD4 counts and well-controlled HIV disease, and were therefore likely to have slow progression of HCV related fibrosis.

Taking HALT-C and SLAM-C results into account, current evidence does not support pegIFN maintenance in patients with no virological response.

Ref: Sherman K, et al. Sustained Long-term Antiviral Maintenance with Pegylated Interferon in HCV/HIV-co-infected Patients: Early Viral Response and Effect on Fibrosis in Treated and Control Subjects. 15th CROI, Boston 2008. Abstract 59.
<http://www.retroconference.org/2008/Abstracts/31871.htm>

CROI: BASIC SCIENCE

Stem cell transplant from HLA-matched CCR5-delta 32 deleted donor suppresses viraemia in recipient for eight months without HAART

Simon Collins, HIV i-Base

One of the most interesting and intriguing posters at the conference was a case study presented by Gero Hutter from the Medical University of Berlin.

The patient, a 40-year-old man diagnosed in 1995, experienced a relapse of acute myeloid leukemia (AML) that was first

diagnosed in 2006. He underwent allogeneic transplant of peripheral stem cells (alloSCT) with an HLA-matched donor, selected to be homozygous for CCR5-delta 32.

A bone marrow registry search identified 232 individuals who had matched HLA, and PCR identified homozygosity for CCR5-d32. HAART was stopped on the day of the transplant. GvHD prophylaxis followed standard regimens and engraftment was achieved on day 13. Complete chimerism as detected by competitive PCR was observed on day 60.

Viral load was measured both by RNA-PCR and proviral DNA-PCR. DNA-PCR was negative from day +68.

Previous attempts to use stem cell transplantation as HIV therapy have failed. Here, the investigators claim to have demonstrated the first successful allogeneic stem cell transplantation in an HIV-positive patient with a donor selected to be homozygous for the CCR5-delta-32-allele.

This switch of CCR5 genotype was not associated with any increased transplant risk. The patient developed a functional reconstitution of his T-cell immunity. Finally, although HAART was discontinued for over a period of 285 days, HIV-1-load could not be detected, as determined by RNA and proviral DNA PCR assays of peripheral blood, bone marrow, and rectal mucosa. The researchers concluded that disruption of viral replication appeared to have been disrupted similar to initial CCR5-dependent infection.

C O M M E N T

If viraemia remains suppressed during long-term follow-up of this patient, this may be the most important report relating to immune/genetic therapy in many years. While viral load usually rebounds quickly when treatment is stopped, it is important to remember that this is still one uncontrolled case study.

It is unclear whether the latent virus is likely to include CXCR4 tropic strains, though this may not be the case in people treated earlier in infection.

Ref: Hutter G et al. Treatment of HIV-1 infection by allogeneic CCR5-D32/D32 stem cell transplantation: a promising approach. Poster abstract 719.

<http://www.retroconference.org/2008/Abstracts/31704.htm> (abstract)

<http://www.retroconference.org/2008/PDFs/719.pdf> (PDF poster)

CROI: ONCOLOGY

Risk factors for AIDS-defining and non AIDS-defining cancers

Simon Collins, HIV i-Base

Two oral presentations, one from France and one from Germany, presented cohort data on risk factor for cancers in one of the first oral presentation sessions.

Bruyand presented an analysis of the impact of CD4 count, viral load and duration of immunodeficiency and viraemia on risk of 109 AIDS-defining and 142 non AIDS-defining cancer diagnoses in 4194 patients followed in the French Aquitaine cohort from 1998-2006. [1]

For AIDS-defining cancers, a higher incidence (relative risk) was independently associated with longer time (per year of exposure) with detectable viraemia >500 copies/mL (1.20, 95%CI 1.10-1.31) and CD4 count <200 cells/mm³ (1.35, 95%CI 1.20-1.53). Duration of exposure to combination therapy had a reduced risk (0.82, 95%CI 0.74-0.91). All associations were statistically significant with a p-value <0.001.

The group also reported an association with CD4 counts and non AIDS-defining cancers. Higher incidence was associated with length of time with CD4 <200 cells/mm³ (RR 1.16, 95%CI 1.03-1.30; p=0.01) or duration with <500 cells/mm³ (1.11, 95%CI 1.01-1.22, p=0.02) and a lower incidence was associated with female gender (0.58, 95%CI 0.37-0.92, p=0.02). No association was found between viral load or use of treatment for non-AIDS defining cancers.

In the German study, Alexander Zoufaly presented data collected prospectively and retrospectively from 6,458 patients on three-drug HAART being followed in the Clinsurv cohort. [2]

They identified 94 lymphomas (78 AIDS-related NHL and 16 primary CNS) during 28,125 years of follow-up (incidence 3.3/1000 patient years).

Multivariate regression analysis identified MSM (1.86, 95%CI 1.19-2.90), age/10 years (1.40, 95%CI 1.17-1.68), CD4 count <200 cells/mm³ (3.64, 95%CI 2.08-6.40) or CD4 200-350 cells/mm³ (3.08, 95%CI 1.74-5.73) and ongoing viraemia (at least 75% viral load measurements >500 copies/mL), (HR 3.68, 95%CI 2.17-5.35) as increased risk factors (hazard ratio, HR all p<0.001).

When primary CNS lymphoma was analysed separately, there was a stronger effect of CD4 <200 cells/mm³ and less impact of ongoing viraemia.

C O M M E N T

These studies support the growing interest in use of earlier treatment to increase and/or maintain patients CD4 counts >500 copies/mL, and the particular importance of suppressed viraemia, in order to reduce long-term risk of serious AIDS and non-AIDS events.

References

1. Bruyand M et al. Immunodeficiency and Risk of AIDS-defining and Non-AIDS-defining Cancers: ANRS CO3 Aquitaine Cohort, 1998 to 2006. 15th CROI, 3-6 February 2008, Boston. Abstract 15.
<http://www.Retroconference.org:8888/2008/Abstracts/31415.htm>
2. Zoufaly A et al. Insufficient Virus Suppression during HAART Is a Strong Predictor for the Development of AIDS-related Lymphoma: German CLINSURV Cohort. 15th CROI, 3-6 February 2008, Boston. Abstract 16.
<http://www.Retroconference.org:8888/2008/Abstracts/31284.htm>

These oral presentations are available to view online from the conference website (Monday 4 February).

TREATMENT ACCESS

FDA approval of generic ARVs: first atazanavir approval

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

Drug and formulation	Manufacturer, Country	Approval date
Atazanavir (100, 150, 200mg)	Emcure, India	4 February 2008
AZT (300mg)	Matrix, India	14 February 2008
efavirenz (600mg)	Hetero, India	29 February 2008
d4T (15, 20, 30, 40mg)	Hetero, India	29 February 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 program for use outside the United States.

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

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

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 54 since the programme started. An updated list of generic tentative approvals is included as a table on the i-Base website:

<http://www.i-base.info/itpc/fdageneric.html>

This is the first approval of atazanavir and it is the first approval of a protease inhibitor. Tenofovir was approved in November 2007 and the slow inclusion of second-line treatment options under this programme is clearly essential.

Source: FDA list serve:

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

An archive of past list serve announcements is available on the FDA web site:

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

A list of FDA approved generic antiretroviral drugs for the treatment of HIV is available on the web at

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

New PMTCT guidelines for South Africa

On the 11 February 2008 the South African National Department of Health finally released their new PMTCT guidelines, which had not been revised since 2003.

The main change to the protocol is the addition of short course AZT from 28 weeks to the current single dose NVP regimen for women CD4 >200 cells/mm³ (unless they are severely anaemic, Hb<7g/dl). Unlike the World Health Organisation (WHO) guidelines they do not recommend maternal "tail" coverage of AZT/3TC for 7 days post partum.

Additional recommendations are:

- Women attending antenatal clinics with unknown status to be routinely offered an HIV test and a CD4 test on the same day if positive diagnosis. Women testing negative to be offered a repeat test at 34 weeks and women refusing the test offered again at subsequent antenatal visits.
- Women \leq 200 CD4 cells/mm³ or WHO stage 4 are indicated for HAART and should start as soon as possible. This too differs from the WHO, who recommend initiation at <350 cells/mm³ for women in WHO stage 3. The guidelines also recommend women with <200 cells/mm³ who have not initiated HAART in pregnancy do so immediately post partum – which may be the worst possible scenario for treatment failure, in the absence of a strategy to protect women from NVP resistance.
- Women initiating HAART will receive the South African regimen 1B – d4T/3TC/NVP. This again goes against most guidelines, which recommend an AZT containing regimen where possible for pregnant women.
- Pregnant women already receiving EFV-containing HAART should be switched to NVP if identified early enough. If identified after the first trimester they should continue the EFV and receive foetal anomaly scans.
- Infants whose mothers received the recommended regimens should receive single dose NVP and 8 days AZT. Infants of mothers receiving no only maternal NVP, <4 weeks AZT or HAART, or no maternal prophylaxis or treatment should receive 28days AZT.

Although pleased that the guidelines had been updated the Treatment Action Campaign (TAC) wrote:

"We regret that the Department of Health's new protocol, while better than the 2003 one, is still out of sync with WHO's strongest recommendations for the prevention-of-mother-to-child-transmission of HIV. Specifically, the revised protocol fails to include any mention of the antiretroviral drug 3TC, a safe, effective and inexpensive addition to AZT. The 2006 WHO guidelines for preventing HIV infection in infants recommend that 3TC be administered to the mother, in conjunction with AZT, both during birth as an HIV prophylaxis as well as postpartum as a means of reducing the risk of nevirapine resistance...Another serious shortcoming in the new PMTCT policy guidelines is that pregnant women who test positive for HIV will only be started on antiretroviral therapy once their CD4 count has dropped to or below 200 cells/mm³. Once again this puts the new guidelines out of step with current international best practice. Compelling scientific evidence points to significant health advantages for pregnant women who initiate antiretroviral therapy at CD4 cell counts of 350 cells/mm³ rather than 200 cells/mm³."

Meanwhile the Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults are due to be released at the end of March. These guidelines include recommendations for ART in special populations. Notably they recommend all identified HIV-positive pregnant women should be initiated on HAART irrespective of CD4 count and viral load.

The recommendations include:

- HIV testing with the aim to initiate treatment within two weeks of first visit.
- NVP based HAART for women <250 CD4 cells/mm³.
- Boosted PI (LPV/r) based HAART for women with >CD4 250 cells/mm³.
- Women initiating HAART with <350 cells/mm³ to continue treatment indefinitely.
- Women initiating HAART with >350 cells/mm³ who elect to formula feed should stop treatment after delivery. Those who choose to breastfeed should continue until after the infant is weaned.
- Women presenting in labour should receive single dose NVP with 7 days "tail" coverage.

Francois Venter, president of the Southern African HIV/AIDS Clinicians Society said: "South Africa is a middle income country; we have the resources to treat below CD4 <350 cells/mm³ and it is a lost opportunity not to increase this bar. It is also unclear why 3TC and the tail are being omitted and again seems to be a confused reaction to pressure to change the guidelines. I think the new Society guidelines set an international bar we can aim for - the South African ones are nowhere near aspirational enough."

References:

Policy and guidelines for the implementation of the PMTCT programme. South African National Department of Health:
<http://www.doh.gov.za/docs/policy/pmtct-f.html>

TAC statement

<http://www.tac.org.za/nl20080130b.html>

Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults

<http://www.sahivsoc.org>

ANTIRETROVIRALS

FDA approve 600mg darunavir tablet

On 26 February, the FDA approved a 600mg tablet formulation of the protease inhibitor darunavir (Prezista). Tibotec, manufacturers of this drug, say that they expect the new formulation to be widely available in the US from May 2008, requiring fewer daily pills than the current 300mg formulation.

Source: FDA list serve/Tibotec PR

US study changes use of abacavir/3TC in naïve patients with viral load >100,000 copies based on DSMB recommendation

On 28 February, a press release from a leading US research group, detailed recommendations from the Data and Safety Monitoring Board (DSMB) of ACTG 5202 study, to change the use of abacavir+3TC in treatment-naïve patients in this trial. [1]

The trial, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, involves a randomised comparison of efavirenz (EFV) with atazanavir boosted with ritonavir (ATV/r), and a double-blind, randomised comparison of co-formulations of FTC/TDF with abacavir/3TC. The DSMB has recommended changes to the study on the basis of new findings in a subset of participants who have been receiving ABC/3TC.

Investigators enrolled 1,858 eligible men and women into the Phase III efficacy study between September 2005 and November 2007 at 64 sites in the United States. Participants were divided into two groups based on HIV levels at the time of screening: those with high viral loads (100,000 or more copies of HIV RNA per milliliter of blood) and those with lower viral loads (fewer than 100,000 copies/mL). Each volunteer was assigned at random to one of the four treatment groups.

All regimens effectively reduced the amount of virus in most participants. However, the DSMB found that among participants with high viral loads at the time of screening, treatment combinations that included ABC/3TC were not as effective in controlling the virus as those on regimens containing FTC/TDF. This was the DSMB's primary concern. Secondly, the DSMB found that among participants with a high viral load at screening, those receiving ABC/3TC experienced a shorter time to developing non-specific side effects, such as body aches, and laboratory test abnormalities, such as elevated cholesterol and triglyceride levels, than those receiving FTC/TDF. In general, these side effects were obvious to participants or the study physicians and would have been readily managed or treated.

The DSMB had no safety concerns regarding EFV or ATV/r and recommended that study participants in the lower viral load group who were taking ABC/3TC should continue with their assigned treatment regimen.

Based on its findings, the DSMB recommended that all participants who had high viral loads at screening be told which treatment regimen they are receiving and stop taking their placebo pill. The DSMB also recommended that those participants receiving ABC/3TC who had high viral loads at screening be counseled on what the DSMB findings might mean for them and possibly be shifted to another regimen, if appropriate. Finally, the DSMB recommended that the remainder of the study continue as originally designed. NIAID concurred with the DSMB recommendations.

GSK issued a press release on the same day stating that previous abacavir trials have not reported lower virological responses in patients starting with higher baseline viral load, and that these results may be explained by sub-optimal use of baseline resistance testing prior to enrolling patients in this study. [2]

Sources:

1. NIH, NIAID new release: NIAID Modifies HIV antiretroviral treatment study: combination therapy that includes ABC/3TC found less effective in subgroup of antiretroviral-naïve individuals. (Feb 28, 2008)

<http://www3.niaid.nih.gov/news/newsreleases/2008/actg5202bulletin.htm>

2. GlaxoSmithKline comments on data concerning Epzicom from ACTG study. (Feb 28, 2008)

http://us.gsk.com/html/media-news/pressreleases/2008/2008_us_pressrelease_0005.htm

IMMUNOLOGY AND BASIC SCIENCE

A gutsy talk, and a new paper: report from third workshop on HIV persistence

Richard Jeffreys, TAG basic science log

In December 2007, the third workshop on HIV persistence during therapy took place on the Caribbean island of St. Maarten, where the weather is sunnier than prospects for eradicating HIV infection currently appear to be. [1] The meeting is the brainchild of French researcher Alan Lafeuillade and aims to bring together researchers interested in the topic of curing HIV infection, either by eradication or inducing lifelong control or tolerance of the virus without the need for ongoing drug therapy.

The submitted abstracts ranged widely in both subject matter and quality, with much attention focused on the struggle to accurately assess residual HIV replication in people on long term ART and the best methods for measuring levels of integrated, replication-competent virus in both the blood and body tissues.

One highlight of the meeting was a presentation on the last day by NIH researcher Tae-Wook Chun. Chun has been studying the latent HIV reservoir in people on therapy for over a decade now, and he offered a pithy summation of his views on the subject in a provocative talk entitled "10 questions you might have been afraid to ask at this workshop." This is a brief summary of his fear-inducing questions, along with his current thoughts as to the answers. Chun's recent work on HIV persistence in gut CD4 T cells has just been published online by the Journal of Infectious Diseases, along with an accompanying commentary by Steven Yukl and Joseph Wong; abstracts and links are appended below.

Tae-Wook Chun's 10 questions you might have been afraid to ask at the 3rd Workshop on HIV Persistence During Therapy

1. Does the reservoir of HIV in the body decline on effective antiretroviral therapy (ART)?

Yes. In a cohort of individuals treated early with combination ART, Chun observed that the half-life of HIV-infected cells was 4-6 months. [2] He explained that this observation was restricted to resting memory CD4 T cells, suggesting that this reservoir of HIV could potentially be eradicated after around 7 years of treatment. However, he stressed that this would not necessarily apply to infected cells of other types (e.g. macrophages, stem cells).

2. Is there ongoing viral replication on ART?

Yes. Some researchers think viral replication can be completely shut down by ART, but in Chun's experience there is always some ongoing low-level replication that can be difficult to detect.

3. Does ongoing HIV replication contribute to the reservoir?

Yes, but activation of CD4 T cells also contributes. He cited a study published by his research group several years ago showing that HIV DNA is detectable in both activated and resting CD4 T cells in people on long term ART. [3]

Chun also noted that the gut contains more activated CD4 T cells than other sites in the body and is therefore a major reservoir of HIV; he has found HIV DNA in activated CD4 T cells from the terminal ileum (see JID cites, below). Chun also showed several images showing the presence of lymphoid aggregates in the gut of HIV-infected individuals on ART and mentioned that these were "a little different from previously published papers" (likely an oblique reference to a notorious single image from the gut of an HIV-infected individual lacking lymphoid tissue, shown by Danny Douek several years ago in support of this theory that gut CD4 T cell depletion is central to HIV pathogenesis). To investigate whether viruses sampled from the gut were different from those found in the blood, Chun compared the genetic sequences and found that they overlapped, meaning that there was no evidence that HIV was somehow compartmentalized in the gut.

4. Is there a specific mechanism for HIV latency in resting CD4 T cells?

Probably not. This topic was addressed by a number of other presentations at the workshop, some of which suggested there may be specific mechanisms HIV uses to make itself quiescent or latent (as opposed to actively replicating). Chun stated that while he admired these presentations, he actually doubted that HIV had evolved such a mechanism. Rather, he believes that viral latency occurs as a byproduct of the physiology of the infected cell; for example, when an HIV-infected activated CD4 T cell returns to a resting state (a normal occurrence when an immune response is ending).

5. Do you think reactivation of the latent reservoir on ART would be sufficient to lead to eradication?

Probably not. At least two studies have investigated activating resting CD4 T cells to try and reduce the HIV reservoir, but the results were disastrous because the treatment (a T cell-depleting antibody called OKT3) led to severe decreases in CD4 T cell counts and illness.

6. Is early ART a good thing?

Yes, in terms of reservoir reduction, but Chun acknowledged the question is not so straightforward from the perspective

of an HIV-infected individual or a clinician, because of the potential for drug toxicities and the challenge of long term adherence.

7. Is eradication possible?

Chun stated that five years ago, his answer would have been no. Now he is “cautiously optimistic in a subset of patients.” He has studied some individuals on long term ART who started relatively soon after becoming infected, and in one he can’t find virus anywhere (including the gut), by any technique (RNA or DNA). This individual has not tried stopping ART yet, however. Chun has also compared the proviral burden (amount of integrated HIV DNA) in small groups on long term ART (>7yrs) that started early vs. during chronic infection. The early group averaged 4.6 copies HIV DNA, with 44% of the group having levels of less than 1.5 copies, while the group that started later averaged 949.4 copies of HIV DNA and only 11% showed levels

8. Is intensification a good idea for trying to reduce reservoir?

Yes. He is starting a randomized raltegravir (Isentress) intensification study that will recruit 24 people who have been on ART for over 4 yrs with viral loads less than 50 copies. Twelve will add raltegravir while 12 will receive placebo and the HIV reservoir will be measured regularly during follow-up.

9. Should “mild immunosuppressants” be studied?

Yes. Chun showed a DNA microarray analysis (which measures the activity of different genes) of CD4 T cells from people on long term ART (started in chronic vs. acute infection) and there were more activation and proliferation related genes upregulated in the former group. He suggested that mild immunosuppressants should be studied as part of a multi-pronged attack on HIV reservoirs that could potentially include ART intensification, enhancement of HIV-specific immunity, and drugs which activate HIV transcription in resting cells.

10. Which is more important, the latent HIV reservoir or cells supporting low-level HIV replication?

Equally important. Chun believes both have to be addressed if the aim is to work toward a cure. In response to questions from the audience, Chun said the western blot HIV antibody test was “very faint” in the person he’d mentioned where no virus could be detected. He also described this individual’s CD4/CD8 T cell ratio as “normal.” He hasn’t yet measured immune activation levels in his cohort of individuals treated early in infection, but he described their gene expression profiles as “calm.”

References

1. Third International Workshop on HIV Persistence during Therapy, St Maarten, West Indies, December 4-7, 2007
<http://www.informedhorizons.com/persistence2007>

The abstract book is available to be downloaded from:
http://www.ihlpress.com/gaj_issues_new.html

2. Chun T-W et al. Decay of the HIV Reservoir in Patients Receiving Antiretroviral Therapy for Extended Periods: Implications for Eradication of Virus. *Journal of Infectious Diseases* 2007;195:1762–1764.
<http://www.journals.uchicago.edu/doi/abs/10.1086/518250>
3. Chun T-W et al. HIV-infected individuals receiving effective antiviral therapy for extended periods of time continually replenish their viral reservoir. *J. Clin. Invest.* 115(11): 3250-3255 (2005).
<http://www.jci.org/cgi/content/full/115/11/3250>

See also:

Chun T-W et al. Persistence of HIV in Gut-Associated Lymphoid Tissue despite Long-Term Antiretroviral Therapy. *JID* 2008;197:000–000. DOI: 10.1086/527324.
<http://www.journals.uchicago.edu/doi/abs/10.1086/527324>

Editorial commentary: Yukl S and Wong JK - Blood and Guts and HIV: Preferential HIV Persistence in GI Mucosa
<http://www.journals.uchicago.edu/doi/full/10.1086/527325>

Source: TAG Basic Science Web Log

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/02/a-gutsy-talk-an.html

Posted: 21 Feb 2008 03:02 PM CST

OTHER NEWS

Managing stigma – report into gay and bisexual African men with HIV released

The first study into the lives of gay and bisexual African men living with HIV in London describes the challenges they face in dealing with the complex and sometimes contradictory realities of life.

The report, entitled ‘I count myself as being in a different world: African gay and bisexual men living with HIV in London’,

has just been released by the Centre of Sexual Health and HIV at Homerton University Hospital NHS Foundation Trust. It highlights that the additional stigma of being gay or bisexual and HIV positive is difficult for African men. However, life in London offers some benefits to men in this situation, including access to healthcare and more liberal sexual attitudes in the Capital.

The report shows that the dual stigma of being gay or bisexual and having HIV causes a dilemma when African men consider disclosing their condition. Author Professor Lesley Doyal said: "Our study shows that being HIV and gay or bisexual has created very complex social lives for African men, with many developing and having to manage different groups of friends who will either know some, all or nothing about their situation. Those who are open about being gay or bisexual and HIV tend to only go where this is accepted, sometimes losing contact with their own communities."

The report highlights that African gay or bisexual men with HIV face additional difficulties to other gay/bisexual men with HIV, because of the expectations surrounding their cultural identity. This has created a new set of practical and emotional needs, which sometimes cannot be met, particularly for those with little money or insecure immigration status.

This report is third in a series of projects describing the experiences of African people living with HIV in London. It is available to download from:

<http://www.homerton.nhs.uk/education/11924649825796.html>><http://www.homerton.nhs.uk/education/11924649825796.html>

Researchers from City University London and Homerton are now appealing for African men who have sex with men to take part in a major new national study. The project, Men and Sexual Health (MESH), will investigate whether sexual health services in Britain meet the needs of ethnic minority men who have sex with other men (MSM) including men of African origin. The questionnaire can be found online at:

<http://www.meshproject.org.uk/>

The two previous reports in this project are:

Doyal, L & Anderson, J (2003) 'My heart is loaded': African women with HIV surviving in London

Doyal, L, Anderson J & Apenteng, P (2005) 'I want to survive, I want to win, I want tomorrow': an exploratory study of African men living with HIV in London

Online versions of both reports are available at

<http://www.homerton.nhs.uk/education/11604037592768.html>>www.homerton.nhs.uk/education/11604037592768.html

FUTURE MEETINGS

2008 conference listing

The following meetings are taking place during the next year.

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

26-28 March 2008, 6th European HIV Drug Resistance Workshop, Budapest

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

7-9 April 2008, 9th International workshop on Clinical Pharmacology of HIV Therapy, New Orleans

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

9-11 April 2008, 3rd International workshop on Clinical Pharmacology of Hepatitis Therapy, New Orleans

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

23-25 April 2008, 14th BHIVA Annual Conference, Belfast

<http://www.bhiva.org>

10-14 June 2008, 17th International HIV Drug Resistance Workshop, Sitges

<http://www.intmedpress.com>

19-21 June 2008 (dates tbc), 4th International workshop on HIV and Hepatitis Coinfection, Madrid

<http://www.intmedpress.com>

1-2 August 2008, 3rd International workshop on HIV Transmission, Mexico City

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

3-8 August 2008, 17th Intl AIDS Conference, Mexico City

<http://www.aids2008.org>

25-28 October 2008, Washington, DC, ICAAC and IDSA joint meeting

<http://www.icaac.org>

October 2008, 3rd International workshop on Hepatitis C, Resistance and New Compounds, Washington DC

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

6-8 November 2008, 10th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, London, UK

<http://www.intmedpress.com>

9-13 November 2008, 8th Congress on Drug Therapy in HIV Infection, Glasgow

<http://www.hiv8.com>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

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

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

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

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

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

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

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

NEW: Training manual – revised, updated and now fully online

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

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

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

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

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

Sections include:

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

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

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people

who want to know more about aspects of their healthcare.

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

NEW: French side effects guide is now online

The French translation of the i-Base Guide to Avoiding and Managing Side Effects is now available online. Previously this could only be accessed by access a downloadable PDF file.

The new web resource can be used by non-French speaking healthcare workers as pages easily navigate between French and English, with the same layout and file structure.

<http://www.i-base.info/guides/fr/side>

NEW: Generic clinic forms, December 2007

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

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

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

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

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

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

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

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

Photography by Wolfgang Tillmans

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

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

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

We are asking for minimum donation price of £10.00 plus £2.50 p&p. Please contact the i-Base office for more details: T: 020 7407 8488 or email: bookoffer@i-base.org.uk or post the donation form on the inside back page of this issue of HTB, using either 'standing order' or 'one-off donation' as appropriate.

Thank you for your support.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting for three years. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted.

<http://www.ukcab.net>

World CAB - reports on international drug pricing

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

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

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

Introduction to combination therapy

November 2007 edition

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

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

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

May 2007 edition

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

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

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

April 2007 edition

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

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

Guide to HIV, pregnancy & women's health

July 2007 edition

Updated and revised in April 2005, this patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether on therapy or not and includes information for the mothers health and for the health of the baby.

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

Guide to avoiding & managing side effects

February 2005 edition

This is a comprehensive 44-page guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

New sections are included on heart disease, lipodystrophy, and information relating to newer drugs including T-20, atazanavir, tenofovir, FTC and fosamprenavir.

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 30 languages.

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

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

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

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

Bosnian

- Introduction to combination therapy, 2007

Bulgarian

- Introduction to combination therapy, 2006
- Avoiding & managing side effects, 2006
- Changing treatment: second line & salvage therapy, 2006
- HIV, pregnancy & women's health, 2006

Chinese

- Avoiding & managing side effects, 2002
- Changing treatment: second line & salvage therapy, 2002
- Introduction to combination therapy, 2002

Czech/Slovak

- Introduction to combination therapy, 2007
- Changing treatment: second line & salvage therapy, 2005
- Treatment training for advocates: a manual, Czech 2005
- Treatment training for advocates: a manual, Slovak 2005

Croatian

- Introduction to combination therapy, 2007
- Treatment training for advocates: a manual, 2007

French

- HIV, pregnancy & women's health, 2006
- Avoiding & managing side effects, 2006
- Introduction to combination therapy, 2001

Greek

- Changing treatment: second line & salvage therapy, 2003
- Introduction to combination therapy, 2001

Hindi

- Treatment training for advocates: a manual, 2006
- Introduction to combination therapy, 2006
- Guide to changing treatment, 2006
- Avoiding & managing side effects, 2006
- HIV, pregnancy & women's health, 2006

Indonesian

- HIV, pregnancy, & women's health, 2006

Italian

- Introduction to combination therapy, 2006
- Avoiding & managing side effects, 2003
- Changing treatment, 2003
- HIV, pregnancy and women's health, 2004

Kosovo

- Introduction to combination therapy, 2007

Macedonian

- Introduction to combination therapy, 2007

Nepali

- Treatment training for advocates: a manual, 2006
- Guide to Starting Treatment, 2006
- Guide to Changing treatment, 2006
- Side Effects Guide, 2006
- HIV, pregnancy & women's health, 2006

Polish

- Treatment training for advocates: a manual, 2007

Portuguese

- Side Effects Guide, 2008
- Guide to Changing treatment, 2007
- Introduction to combination therapy, 2005
- Treatment training for advocates: a manual, 2007

Romanian

- Treatment training for advocates: a manual, 2007
- Guide to Starting Treatment, 2005
- Guide to Changing treatment, 2005
- Side Effects Guide, 2005
- HIV, pregnancy & women's health, 2005

Russian

- ARV4IDUs Russian version from 2007
- Introduction to combination therapy, 2006
- HIV, pregnancy and women's health, 2005
- Treatment training for advocates: a manual, 2005
- Hepatitis C for people living with HIV, 2007

Serbian

- Introduction to combination therapy, 2007
- Treatment training for advocates: a manual, 2007

Spanish

- HIV, pregnancy and women's health, 2006
- Avoiding & managing side effects, 2002
- Introduction to combination therapy, 2002

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether

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

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

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

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Online Q&A service

A new 'question and answer' service has been added to the i-Base website. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- I kissed an HIV-positive man
- Will a bloated stomach on saquinavir/ritonavir improve?
- Why would test results change so much in a short time?
- How do I access treatment in the UK - I am from India?
- Recently diagnosed with HIV-2
- Can HIV cause a red face in the winter?
- What is the difference between HIV-1 and HIV-2?
- Is rapid finger prick test accurate?
- How accurate is the DUO test 27 days after a possible exposure?
- Can I have a baby if I have AIDS?
- Can I do something to reduce the side effects of my combination?
- What is the longest late detection of HIV-infection?
- Chances of infecting partner if I have an undetectable viral load?
- What are my Dad's chances of recovery?
- Why do some answers on i-Base use different words for similar testing questions?
- Is it true that HIV doesn't survive long outside the body?
- I am worried by a recent news report
- Can I take Atripla as a first line treatment?
- If you are infected by a viral disease, does that mean your CD4 counts are always low?
- Do you feel ok again after seroconversion?
- Do antibiotics interact with HIV meds?
- How long after a potential exposure can I donate blood?
- Anxious question after kissing an HIV-positive person...
- How is HIV transmitted by breastfeeding?
- What is seroconversion and what are the symptoms?
- Are enlarged lymph nodes painful, or related to HIV?

- I had a cut on my finger. Am I at risk?
- Which test is used to detect an infection within 6 months?
- Can mouthwash or antibiotics affect HIV results from a mouth swab?
- Is a test after 3 months conclusive?
- Is a 'non-reactive' result different from 'not-detected'?

Find HTB on AEGiS

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

<http://www.aegis.org/pubs/i-base/2006>

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

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

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

Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), Treatment 'Passports' and all our guides to managing HIV and additional reports.

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:

<http://www.i-base.info>; by fax or post using the form on the back page by sending an email to: subscriptions@i-base.org.uk

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HIV i-Base

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However, any donation that your organisation can make towards our costs is greatly appreciated.

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

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

REFUNDS FROM THE TAX MAN

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

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

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Guide To HIV, Pregnancy and Women's Health (July 2007)

1 5 10 25 50 100 Other

NEW: Introduction to Combination Therapy (November 2007)

1 5 10 25 50 100 Other

Changing Treatment - Guide to Second-line and Salvage Therapy (April 2007)

1 5 10 25 50 100 Other

Guide To Avoiding and Managing Side Effects (February 2005)

1 5 10 25 50 100 Other

Guide To HIV and hepatitis C coinfection (May 2007)

1 5 10 25 50 100 Other

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

Phoneline support material (pls specify required number of each)

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

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

1 Sheet 1 pad 5 pads 10 pads Other

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