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## October 2007

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## EDITORIAL

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This issue leads with a report presented to the BHIVA conference from the latest BHIVA audit on treatment of naive patients in the UK. Some of the findings make uncomfortable reading.

One of the satellite sessions at the same meeting included a case study presented by Mervyn Tyrer, of a African woman, newly diagnosed with both TB and HIV. Her CD4 count was 120 cells/mm<sup>3</sup>, clearly with a medical need to treatment for both infections.

It was shocking to see that half the audience of several hundred well-informed healthcare workers would only be prepared to threat the TB within their Trust.

There have been reports of similar cases where an in-patient treated for TB and HIV is presented with a bill for HIV care that results in them discharging themselves, and then being lost to further healthcare.

It is also common for the Home Office to deny leave to remain in the UK on the basis that HIV treatment is available in someone home country - even though this will not be available to that individual. Even though the government is supporting universal access to care.

Doctors with patients in a similar situation are recommended to contact Joe Murray, a new policy officer at National AIDS Trust, focussing on immigration, on 20 7814 6756 for advice.

It would be helpful for BHIVA, perhaps in a future audit, to look at Trust policy and access to treatment by PCT.

Included with this issue of HTB is an i-Base report written by Winnie Sseruma on assessing the treatment information needs of African communities.

This report was commissioned to better understand the needs of HIV-positive Africans living in the UK and to evaluate i-Base's existing publications and services, and to inform our future direction.

The quotations throughout deserve a wider readership, and should inform healthcare professionals about aspects of accessing healthcare in the UK that rarely get a high profile.

The report is also available online.

### **ARV4IDUs – issue 2**

We will include a second supplement to people who receive the email distribution of HTB

This is the second issue of a new electronic publication called ARVs4IDUs. This quarterly summary of research relating to injecting drug users and HIV, with the first issue launched at the IAS conference in Sydney.

HTB readers who currently receive HTB by email will continue to receive this automatically as a supplement to future issues of HTB.

Print readers will need to subscribe for this new service electronic publication online:

<http://www.i-base.info/forms/esub.php>

This publication is available in English and Russian language versions.

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## CONFERENCE REPORTS

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### **BHIVA Autumn conference**

**11-12 October 2007, London**

This years Autumn conference was held on 11 and 12 October in London.

Presentations from many of the key talks (including results from the BHIVA audit reported below) are already available online:

<http://www.bhiva.org/cms1220897.asp>

## **Audit of treating naïve patients showed basic UK guidelines not followed in over 25% patients; 60% patients start with a CD4 count <200 cells/mm<sup>3</sup>**

**Simon Collins, HIV i-Base**

The annual BHIVA audits are one of the most important sources of information on current standards of care that HIV-positive people receive in the UK. Each audit is usually linked to BHIVA guidelines on a particular aspect of care. This year was the first prospective audit. The subject was treatment of treatment naïve patients, and results were presented by Emma Street at the Autumn conference.

Key conclusions from the audit included:

- 4% of patients were lost to follow-up within the first year
- 60% patients starting treatment at less than 200 CD4 count and starting at the lowest CD4 counts was associated with poorer outcome
- 1 in 6 patients still had a detectable viral load 5-12 months after starting treatment
- At least 16% patients did not have a resistance test prior to starting treatment
- 54% patients did not have a viral load result by week 4 and 26% did not have a result by week 6
- 25% patients with hepatitis B coinfection were using 3TC without tenofovir (HBV monotherapy)
- there were no apparent differences between results at larger and smaller treatment centres.

Results were collected on 1301 treatment naïve patients from 133 centres who starting first-line therapy from April to September 2006. 11 centres did not take part in the follow up phase, accounting for 86 patients and major discrepancies excluded a further 45 patients, leaving 1170 patients who were included in most analyses. The primary outcome was the viral load measurement closest to six months after starting treatment.

Baseline demographics included 54% men, 44% women (some not stated); almost 50% African, 38% White, 4% Caribbean; and 16% were pregnant women.

CD4 count when starting treatment, showed that the majority of patients already miss the minimum stage recommended for an optimal response to treatment: 19% were 0-50, 41% were at 50-200, 30% started between 200 and 350 and approximately 5% starting 350 to 500, and 5% at over 500 cells/mm<sup>3</sup>.

Approximately 70% of those starting <200 cells/mm<sup>3</sup> had been diagnosed within the previous 6 months (ie late diagnoses), but over 6% of those diagnosed for over 6 months started at a count lower than 50 cells/mm<sup>3</sup>. Baseline viral load was greater than 100,000 copies/mL in 43% patients.

Only 72% patients had resistance test results available prior to starting treatment, with 6% still waiting for results and at least 16% not having been tested. Of those tested 6% had evidence of single class resistance and 1% had multi-class resistance – a prevalence that is high enough to justify the recommendations for all patients to be tested on diagnosis or prior to starting treatment.

Approximately 35% of patients each used either tenofovir/FTC or abacavir/3TC as dual nukes, but 25% of patients still started treatment with Combivir, and even if all the women using treatment during pregnancy started with Combivir, this leaves at least another 10% of patients used this non-recommended option.

55% patients started an efavirenz-based combination, with just under another 20% using either nevirapine or lopinavir/r. Approximately 5% patients started with either saquinavir/r or fosamprenavir/r.

The primary outcome of suppression to <50 copies/mL was achieved by 68% 1215 patients. 14% were detectable (and not accounted for by 6% who stopped treatment used during pregnancy). 12% had no outcome reported. In an on-treatment analysis (patients still on treatment with a measurement at 6 months, 84% of these patients were suppressed to <50 copies/mL and 16% had detectable viral load (though for approximately 65% of these patients were suppressed below 500 copies/mL).

The percentages of patients suppressing to <50, 50-500 and >500 copies/mL were similar across all clinics (from those treating less than 50 patients to those treating more than 500 patients).

Time to first viral load result was also a concern with only 46% patients having a viral load result by the recommended maximum of 4 weeks after starting treatment. 75% of patients had a result by 6 weeks and 85% by 8 weeks.

Given the importance of confirming viral activity, and the opportunity to provide both adherence support and evaluation of side effects, this appears to represent one of the most shocking findings,

Results showed that approximately 25% patients with either baseline CD4 <50 cells/mm<sup>3</sup> or viral load >100,000 copies/mL did not reach than 50 cells/mm<sup>3</sup>.

Of the 151 patients who had no primary outcome result, 66 had transferred care, and a similar number were neither known to have transferred care or were untraceable – a poor outcome for patients starting first treatment. 11 patients died. Patients stopping treatment and not transferring care were disproportionately more likely to be African (72%) and female (60%), compared to the group as a whole.

The contribution of dispersal and being denied leave to remain in immigration cases was unclear in these results.

Several other secondary outcomes were briefly reported:

'No known issues' were reported for 85% of patients – a term that could cover healthcare indifference and ignorance – with 10% reporting 'some problems' and <5% 'substantial problems'.

Hepatitis B coinfection was reported in 53 (4.5%) patients, 13 of whom were using 3TC without tenofovir. Just 6% of patients were reported as being untested for HbsAg (although some clinics may have used HbcAb, which was not included in the survey).

However, 2.7% were hepatitis C antibody positive at baseline and 4.8% were untested.

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#### C O M M E N T

**Some of these results are disappointing – and it is therefore all the more important that this audit was commissioned and that the results were presented at this national meeting.**

**This audit seems to indicate that despite clear guidelines, suboptimal treatment is being delivered to a significant proportion of patients.**

**The results provide a snapshot of strengths and weaknesses but are unable to give much detail about the reasons that could be behind some results.**

**Early CD4 and viral load tests at 2-4 weeks have long been established as standard of care, and additionally provide the opportunity to monitor for side effects and support adherence. Some patients appear to be given three months treatment and told to come back when that is finished unless there is a problem.**

**It is not difficult to understand why someone would never start without a CD4 count, so why does resistance testing still prove such a hurdle.**

**It is disappointing that so many clinics who took part in the first part of the audit did not continue with the audit and produce follow up results. This, together with the missing and loss to follow-up data probably overestimates the success of treatment that was seen.**

**Although this exercise produces less rigorous data than would be available from a clinical trial, BHIVA should be commended for highlighting this picture of current clinical care.**

**These results should focus and inform clinicians, advocates, patients and purchasers alike.**

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## TREATMENT ACCESS

The following round-up of articles and links relates to treatment access news over the last month.

### **Donor governments pledge record amounts to the Global Fund**

#### **Global Fund Observer**

Donors are expected to give the Global Fund at least \$9.7 billion over the next three years, 57% more than they gave over the past three years.

Twenty-six donor governments and one foundation, gathering at a Replenishment Meeting in Berlin, Germany that ended on 28 September, promised that during the years 2008-10 they would give at least \$6.3 billion to the Fund. With the Fund projecting that other donors will give at least \$3.4 billion, this leads to a total of \$9.7 billion.

The G8 has declared that in the year 2010, the Fund will need to spend \$6 billion, or possibly as much as \$8 billion. (This compares with its likely expenditure this year of \$3.2 billion.) The Fund says that its total needs over the three years 2008-10 will be \$12-18 billion. Over the past few months, donor government studied the Fund's needs and effectiveness and deliberated over how much each would commit to for the three years 2008-10. They then came to Berlin last week to announce their decisions.

The Replenishment Meeting was chaired by Kofi Annan, former UN Secretary General, and opened by German Chancellor Angela Merkel.

The pledges constitute the largest single financing exercise for health that has ever taken place. The amounts pledged were as shown in the full article online. Some highlights of the pledges were as follows:

- The three countries that pledged (or are projected to pledge) the most for 2008-10 were USA (\$2,172 m.), France (\$1,274 m.) and the UK (\$729 m.).
- The three countries that pledged the largest percentage of their Gross National Income (GNI) were Norway (0.087%), Ireland (0.076%) and Sweden (0.075%).
- The country that pledged the largest amount per capita was the Netherlands. (Of course, as one participant humorously pointed out, the Bill and Melinda Gates Foundation pledged considerably more per capita.)
- The three developed countries that pledged the smallest percentage of their GNI were Japan, Finland and Switzerland (0.004% each).
- The three countries whose pledges grew the most since from their pledges for the previous three years were Russia (increased 8.7 times), Saudi Arabia (3.6 times) and Spain (3.4 times).

Source: Global Fund Observer, Issue 77

<http://www.aidspace.org/gfo>

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## ANTIRETROVIRALS

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### **Atripla approved in Europe as switch option for suppressed patients**

On 18 October 2007, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion on the Marketing Authorisation Application for the fixed-dose triple combination Atripla (efavirenz600mg/FTC200mg/tenofovir300mg).

Specifically, the CHMP indication is for 'adults with virologic suppression to HIV 1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months'. Patients should not have experienced virological failure on 'any' prior ARV therapy, and not have resistance to any of the three individual drugs prior to starting their first regimen.

The CHMP's positive recommendation will be reviewed by the European Commission, which has the authority to approve medicinal products for use in the 27 countries of the European Union. The companies (Atripla is a result of a collaboration between BMS, Merck and Gilead) expect the European Commission to issue its decision on the marketing authorisation for ATRIPLA toward the end of the year.

In the US, the FDA also granted approval of an identical alternate formulation (it is a white rather than pink-coloured tablet) for distribution in developing countries. In March 2007, the World Health Organization added Atripla to its Model List of Essential Medicines.

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### C O M M E N T

**The option of a one-pill, once-daily combination is popular with patients, especially those who are more recently diagnosed, even though caution needs to be taken concerning the side effect profile of efavirenz.**

**The EMA have not made any public statement about why approval of Atripla seems to have been so problematic – it was approved by the FDA in the US in 15 months ago. The likely issue was the conflicting food recommendations for tenofovir.**

**In the US, Atripla is recommended to be taken 'on an empty stomach' and tenofovir is recommended to be taken 'without regard to food'.**

**In Europe, because food interaction data showing increased tenofovir levels (AUC by 40% and C<sub>max</sub> by 14%) when taken with a high fat meal (700-1000kcal, including 40-50% fat), the recommendation is to take tenofovir 'with a light meal or snack'. However, this information is actually inconsistent with pharmacokinetic data included in the tenofovir SPC, which shows that 'a light meal or snack' has no effect on drug levels.**

**For years the EMA and Gilead have therefore been providing inconsistent information about dosing. The potential importance of increased drug levels from taking tenofovir with a high fat meal for some patients is still unknown.**

**There is still no comparative data on the virological impact of higher drug levels when starting treatment, especially in experienced patients, or in those who have higher baseline viral load.**

Anecdotally, it seems that tenofovir is commonly taken without regard to food, following the US indication. This is less likely to matter in patients who are virologically suppressed.

There is therefore a theoretical basis for the approval of Atripla as a switch option in suppressed patients, though this too may be ignored in practice.

Someone at the EMEA needs to recognise that 'take with a light meal' and 'administration with a light meal did not have a significant effect on the pharmacokinetics of tenofovir' are incompatible in the same SPC.

Either that, or we should have studies to show the virological impact of not taking tenofovir with a high fat meal.

## Maraviroc approved in Europe for treatment-experienced CCR5-tropic patients

On 24 September 2007, maraviroc (trade name in Europe Celsentri) was approved in Europe for treatment-experienced patients who have CCR5-tropic HIV infection. Maraviroc is a CCR5 inhibitor manufactured by Pfizer with the trade name Celsentri in Europe and Selzentry in the US. Approved in the European Union, Providing a Novel Treatment Option for Treatment-Experienced HIV Patients

Maraviroc is the first member of a new class of oral HIV medicines (CCR5-antagonists) and works by blocking viral entry into human cells.

EU approval of maraviroc is based on 48-week data from the two ongoing double-blind, placebo-controlled MOTIVATE clinical trials, which showed that maraviroc plus optimised background therapy (OBT) provided substantially greater viral load reduction compared to patients receiving OBT alone.

Further details and product information are in the European Public Assessment Report on the web site of the European Medicines Agency:

<http://www.emea.europa.eu>

<http://www.emea.europa.eu/humandocs/Humans/EPAR/celsentri/celsentri.htm>

Source: Pfizer press release (24 September, 2007)

<http://www.pfizer.com>

## Paediatric formulation of fosamprenavir approved in Europe

On 13 September, the EMEA issued a decision to extend the indication for fosamprenavir (Telzir) in combination with ritonavir to include adolescents and children of six years and older.

For full prescribing information see:

<http://www.emea.europa.eu/humandocs/Humans/EPAR/telzir/telzir.htm>

The scientific opinion for this decision is included at the following link:

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/telzir/EMEA-H-534-II-18-AR.pdf>

Source: GSK press release

## Raltegravir approved in the US

On 12 October 2007, the Food and Drug Administration (FDA) granted accelerated approval for raltegravir (trade name Isentress), the first integrase inhibitors. Approval is based on efficacy and safety data from two double-blind, placebo-controlled studies (BENCHMRK 1 and 2) in 699 treatment-experienced HIV-1 infected adult patients (with documented resistance to at least 1 drug in each of NRTIs, NNRTI and PI classes), randomised 2:1 to receive either active drug or placebo, plus optimised background treatment.

The mean changes in plasma HIV-1 RNA from baseline were -1.85 log<sub>10</sub> copies/mL in the raltegravir 400 mg twice daily arm and -0.84 log<sub>10</sub> copies/mL for the control arm. The mean increase from baseline in CD4 cell counts were 89 cells and 35 cells/mm<sup>3</sup>, respectively.

The most common adverse events reported with raltegravir were diarrhoea, nausea, and headache. Blood tests showed abnormal elevated levels of a muscle enzyme in some patients receiving raltegravir. Caution is advised when using raltegravir in patients at increased risk for certain types of muscle problems, such as patients taking other medications that can cause muscle problems.

Source: FDA list serve

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### C O M M E N T

**Raltegravir has already been filed in Europe, and a decision is expected by the new year.**

## EMA recommends reinstating license for Roche's nelfinavir

On 20 September 2007, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the lifting of the suspension of the marketing authorisation for nelfinavir (Viracept, manufactured by Roche) and the re-introduction of the medicine onto the market in the European Union.

The marketing authorisation for Viracept was suspended on 6 August 2007, following the contamination during the manufacturing process of several batches of the active substance with ethyl mesilate, a known genotoxic substance.

See previous Treatment Alerts in the previous two issues of HIV Treatment Bulletin. [1, 2]

The CHMP has assessed the corrective and preventive measures put in place by Roche, and these have also been verified by an inspection of the manufacturing site. As a result, the CHMP has been reassured that the cause of the contamination has been eliminated and that future production of Viracept would meet the required quality standards.

The CHMP therefore decided to recommend to the European Commission the lifting of the marketing authorisation suspension. Once this decision has been issued - this is not expected before the end of October - Roche will be able to resume supply of Viracept to patients. It is likely to take several months for nelfinavir to become available again. Countries in most need will be prioritised for the first supply.

Source: EMA press release

<http://www.emea.europa.eu/pdfs/general/direct/pr/41816807en.pdf>

1. Roche recalls nelfinavir (Viracept) due to chemical impurity. HTB June/July 2007.

<http://www.i-base.info/htb/v8/htb8-6-7/Roche.html>

2. Update on nelfinavir recall. HTB August/September 2007

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

## Roche withdraw application for Biojector 'needle-free' option for T-20

On 3 October, Roche and Trimeris announced that they are withdrawing a supplement application for approval to market Biojector B2000 as a 'needle-free' option for delivery of T-20 (enfuvirtide). [1]

The reasons for not continuing with the applications was given as 'based on comprehensive assessment of the clinical program, as well a significant delay in achieving U.S. regulatory approval due to the time required to generate additional data'.

It has been over three years since the first studies showing similar pharmacokinetics and the potential for better tolerability using Biojector compared to regular injections. [2] Safety concerns in larger studies included an increased risk of nerve damage and haematoma.

Patients in the UK are not able to access Biojector as the manufacturer does not have a European license for this device. Patients currently using Biojector in the US through an expanded safety trial may be able to continue to use the device, as it is still commercially available there.

References

1. Press release: Roche and Trimeris provide update on development of alternative administration options for delivery of FUZEON: Companies withdraw application to market Biojector® 2000 device for use with Fuzeon. (03.10.07)

<http://www.roche.com>

2. Needle-free injections for T-20 in the US. HIV Treatment Bulletin, April 2005.

<http://www.i-base.info/htb/v6/htb6-4/Needle.html>

3. T-20 studies presented at Rio. HIV Treatment Bulletin, September 2005.

<http://www.i-base.info/htb/v6/htb6-9/T20.html>

## WOMEN'S HEALTH

### Antiretroviral drug exposure in the female genital tract

Polly Clayden, HIV i-Base

A paper in the September 2007 edition of AIDS reported data from a study to evaluate antiretroviral exposure in the genital tract of HIV-positive women. Julie Dumond and coworkers from the School of Pharmacy, University of North Carolina looked at 11 commonly used antiretroviral medications in the three drug classes: nucleoside/tide analogue reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI).

The investigators hypothesised "to prevent sexual transmission of HIV in women, oral antiretroviral drugs that achieve high concentrations quickly in the genital tract after a first dose would be optimal candidates for PEP or PrEP regimens." The

study was undertaken as no human pharmacology data have been generated in either healthy volunteers or HIV-positive women “that allow rational selection of drugs used for this purpose.”

The study objective was to describe first dose and steady state antiretroviral exposure in the female genital tract and exposure in cervicovaginal fluid relative to blood plasma. It was a non-blinded, open label study of 27 women initiating combination therapy at a single centre from November 2002 to May 2006.

The women in the study were mainly African American (70%) with a median age of 35 (IQR 31-42) years, CD4 count of 307 (IQR 220-372) cells/mm<sup>3</sup> and viral load of 4.7 (IQR 4.0-5.0) log<sub>10</sub> copies/mL at entry. 67% of the women were drug experienced.

For both first dose and steady state (at least three weeks after first dose) concentration samples were taken at 0 (predose), 2, 4, 6, 12 and 24 hours after observed doses.

The drugs were ranked according to the genital tract concentrations achieved relative to blood plasma.

The investigators found the median rank order of highest to lowest genital tract concentrations relative to blood plasma at steady state were: 3TC (concentrations were 411% greater than blood plasma), FTC (395%), AZT (235%), tenofovir (75%), ritonavir (26%), ddI (21%), atazanavir (18%), lopinavir (8%), abacavir (8%), d4T (5%), and efavirenz (0.4%).

They wrote: “The results of this investigation support the use of 3TC, ZDV and TDF, and potentially FTC as excellent pre-exposure/post-exposure prophylaxis (PrEP/PEP) candidates. ATZ and LPV/r might be useful agents due to favourable genital tract concentrations in relation to HIV-1 wild-type susceptibility. We believe that agents that achieve less than 10% of blood plasma exposure, such as efavirenz and d4t, are less likely PrEP/PEP candidates.”

#### C O M M E N T

**For rational selection of PEP and PrEP agents, we must have a thorough understanding of the pharmacology of these drugs at the site of infection. This study was a first step in that direction.**

Ref: Dumond JB, Rosa, Yeh RF, Patterson KB et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. *AIDS* 2007, 21:1899–1907.

## **Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women**

**Polly Clayden, HIV i-Base**

There have been conflicting results from studies evaluating the effect of hormonal contraceptive use on the risk of HIV acquisition.

Recent data from a study conducted in Uganda and Zimbabwe found that women using hormonal contraception had an increased risk if they were herpes simplex virus type 2 (HSV-2) negative, but not if they were HSV-2 positive. This difference in risk was highly significant ( $p=0.003$ ).

A paper in the August 20 2007 edition of *AIDS* authored by Jared Baeten and coworkers reported findings from a study to examine the effect of HSV-2 on the relationship between hormonal contraception and HIV-1 in a high-risk population. [1]

This group had previously found in a study of female Kenyan sex workers, both oral contraceptive pill and depot medroxyprogesterone acetate (DMPA) use were associated with increased risk of HIV acquisition. [2]. HSV-2 was not assessed in that analysis. The investigators re-examined the data to evaluate the effect of HSV-2 on the relationship between hormonal contraception and HIV.

Data were from a prospective cohort study of 1206 HIV-negative sex workers from Mombasa, Kenya who were followed monthly. At enrollment, 171 (14.2%) women used oral contraceptive pills and 244 (20.2%) DMPA. 234 (19.4%) women were HSV-2 negative and 972 (80.6%) were HSV-2 positive. 84 women who were HSV-negative at enrollment seroconverted during the study period.

The investigators found 233 women acquired HIV-1 (8.7/100 person-years). HSV-2 prevalence (81%) and incidence (25.4/100 person-years) were high. In multivariate analysis, including adjustment for HSV-2, HIV acquisition was associated with use of oral contraceptive pills [adjusted hazard ratio (HR), 1.46; 95% confidence interval (CI), 1.00–2.13] and DMPA (adjusted HR, 1.73; 95% CI, 1.28–2.34).

The effect of hormonal contraception on HIV acquisition was not significantly different between HSV-2 negative versus positive women. HSV-2 infection was associated with increased HIV risk (adjusted HR, 3.58; 95% CI, 1.64–7.82).

The investigators concluded: “In this group of high-risk African women, hormonal contraception and HSV-2 infection were both associated with increased risk for HIV-1 acquisition. HIV-1 risk associated with hormonal contraceptive use was not

related to HSV-2 serostatus.”

#### References

1. Baeten JM, Benki S, Chohan V et al. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. *AIDS* 2007, 21:1771–1777
2. Lavreys L, Baeten JM, Martin HL et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. *AIDS* 2004; 18:695–697.

## **Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women’s Interagency HIV Study**

**Polly Clayden, HIV i-Base**

A paper in the August 20 2007 edition of *AIDS* authored by Phyllis Tien and coworkers looked at the incidence of diabetes mellitus (DM) in the Women’s Interagency HIV Study (WIHS). WIHS is an American, nationally representative cohort of HIV-positive women and a comparison group of HIV-negative women.

This was a prospective study between October 2000 and March 2006 of 2088 participants from the WIHS who did not have evidence of DM at enrollment (1524 HIV-positive and 564 HIV-negative).

The study defined Incident DM as either having fasting glucose  $\geq 1.26$  g/l, reporting antidiabetic medication, or reporting DM diagnosis (with subsequent confirmation by fasting glucose  $\geq 1.26$  g/l or reported antidiabetic medication). All were assessed at twice yearly study visits.

116 HIV-positive women and 36 HIV-negative women developed DM in over 6802 person-years.

HIV-positive women reporting no recent antiretroviral therapy (n=25) had a DM incidence rate of 1.53/100 person-years; those reporting HAART containing a PI (n=41) had a rate of 2.50/100 person-years. Those reporting non-PI containing (n=41) HAART a rate of 2.89/100 person-years.

HIV-negative women had a DM incidence rate of 1.96/100 person-years.

For HIV-positive women, longer cumulative exposure to NRTI was associated with an increased risk of DM incidence compared with no NRTI exposure: relative hazard (RH) 1.81 [95% confidence interval (CI), 0.83–3.93] for  $>0$  to 3 years exposure and RH 2.64 (95% CI, 1.11–6.32) for  $>3$  years exposure. In this study neither cumulative exposure to an NNRTI nor a PI was associated with DM incidence.

The investigators looked at the rate of DM among HIV-positive women receiving the four most frequently used NRTIs (AZT, abacavir, d4T and 3TC). They found cumulative exposure of  $>1$  year to 3TC was associated with a three fold increase in DM after adjustment.

They concluded: “NRTI are in the backbone of effective ART, and so regular monitoring of fasting glucose levels in HIV-infected patients is warranted. Study of the biological mechanisms by which NRTI might induce disorders in glucose metabolism is a priority.”

Ref: Tiena PC, Schneiderb MF, Stephen R. Coleb SR et al. Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women’s Interagency HIV Study. *AIDS*, 2007, 21:1739–1745.

## **PREGNANCY AND MTCT**

### **Pregnancy shows a positive impact on HIV disease progression**

**Polly Clayden, HIV i-Base**

Studies conducted in HIV-positive women receiving either no ART or AZT prophylaxis (HAART) showed that pregnancy either slightly increased the risk of HIV disease progression or had no effect.

A paper authored by Tai and coworkers from Vanderbilt University School of Medicine and Comprehensive Care Centre, Nashville, Tennessee, reported findings from an observational cohort study to evaluate disease progression in pregnant women receiving care between 1 January 1997 and 31 December 2004.

In this study HIV disease progression was defined as an AIDS defining illness or death.

The investigators found that 759 women met the inclusion criteria; 139 (18%) had at least one pregnancy during follow-up. There were 174 pregnancies during the study period; 30 women had two pregnancies and five women had three pregnancies. Altogether there were 124 live births, nine spontaneous abortions, three elective abortions, two stillbirths, and one ectopic pregnancy.

In this analysis pregnant women were younger (25, IQR 23-31 years vs. 36, IQR 30-42 years), had higher median baseline CD4 counts (450, IQR 312-660 cells/mm<sup>3</sup> vs. 352, IQR 177-560 cells/mm<sup>3</sup>) and had lower median baseline viral load (3.9, IQR 3.1-4.6 log<sub>10</sub> copies/mL vs. 4.2, IQR 3.2-4.9 log<sub>10</sub> copies/mL).

119 pregnant and 421 nonpregnant women received HAART and 20 pregnant and 55 nonpregnant women received non-HAART ART only (defined as dual or mono therapy). All pregnant women received ART. Pregnant women were more likely than nonpregnant women to receive HAART. Treatment duration was comparable for pregnant and nonpregnant women.

Pregnant women were more likely to achieve durable virologic suppression (defined as <400 copies/mL) and longer duration of follow-up.

Pregnant women were less likely to have intravenous drug use as a risk factor for HIV acquisition.

The investigators found 11(8%) pregnant and 149 (24%) nonpregnant women either progressed to AIDS or died. The AIDS-defining illnesses in pregnant women were Candida oesophagitis, cytomegalovirus retinitis, disseminated cryptococcosis, lymphoma, wasting syndrome, Pneumocystis jirovecii pneumonia and recurrent bacterial pneumonia.

In multivariate analysis, after adjusting for baseline CD4 count, and viral load, age, and durable virologic suppression, pregnancy was associated with a decreased risk of disease progression (HR, 0.40 [95%CI, 0.21–0.76]; p=0.005).

In a multivariate analysis that included the propensity score for pregnancy in addition to other significant predictors, the risk of disease progression was again significantly lower in pregnant women than in nonpregnant women (HR, 0.40 [95% CI, 0.20–0.79]; p=0.009).

The investigators performed an analysis of 81 matched pregnant and nonpregnant pairs according to age, baseline CD4 count, receipt of HAART, and date of cohort entry. Pregnant women had a lower risk of disease progression both before (HR, 0.10 [95% CI, 0.01-0.89], p=0.04), and after (HR, 0.44 [95%CI, 0.19-1.00], p=0.05) pregnancy.

The investigators wrote: "Our data suggest that, in a setting with high rates of HAART use, pregnancy is independently associated with a decreased risk of HIV disease progression. Further investigation into the responsible underlying biological mechanisms is warranted, particularly the interaction between ART and the immunological changes that occur during pregnancy."

In an accompanying editorial commentary Kathryn Anastos added: "...women can now have greater confidence that, in addition to protecting their children from MTCT with HAART, their own health will not be compromised by pregnancy, which would place their children at long term risk. For all women pregnancy is something of a gamble: there is no guarantee of a normal pregnancy or a healthy baby. For HIV-infected women becoming pregnant, the findings of Tai et al suggest that, at least for disease progression, the odds may be in their favour."

Ref: Tai JH, Mercy A, Udoji MA, Barkanic G et al. Pregnancy and HIV disease progression during the era of Highly Active Antiretroviral Therapy. Journal of Infectious diseases 2007;196. 1044-1052.

## **African infants' CCL3 gene copies influence perinatal HIV transmission in the absence of maternal nevirapine prophylaxis**

**Polly Clayden, HIV i-Base**

People with above the population median number of copies of CC chemokine ligand 3-like1 gene number (CCL3L1, also called MIP-1-alphaP) have been found to be less susceptible to HIV acquisition. [1]

In newborn infants reduced ability to produce CCL3 is associated with increased susceptibility to mother to child transmission (MTCT) of HIV. [2]

A paper authored by Louise Kuhn coworkers from Johannesburg and Soweto, South Africa and Columbia University, New York, USA reported findings from a study to investigate whether infants' and mothers' CCL3L1 gene copy numbers are associated with perinatal transmission. The investigators looked at infants born to mothers both receiving and not receiving single dose nevirapine for MTCT prophylaxis. [3]

This was a nested case-control study in which data was combined from four cohorts. This included 849 HIV-positive mothers and their infants followed prospectively at two hospitals in Johannesburg, South Africa.

The study compared HIV-positive mothers with HIV-positive infants (transmitting cases) to HIV-positive mothers with HIV-negative infants (non-transmitting controls).

The transmission rate across the cohorts was approximately 10%; 83 infants were HIV-positive. The CCL3L1 gene copy number was determined by real-time polymerase chain reaction (PCR) for mothers and infants from 79/83 transmitting pairs. 235 non-transmitting pairs matched by cohort were randomly selected as controls.

The use of antiretroviral drugs for MTCT prophylaxis varied across the cohorts (totals shown Table 1).

**Table 1: Use of maternal MTCT prophylaxis. In parenthesis are the numbers of pairs with genotype data available**

	intra-uterine	intra-partum	un-known	Child unin-fected	Total
Total all cohorts	21 (20)	33 (31)	29 (28)	766 (235)	849 (314)
No maternal ARVs	6 (6)	18(17)	1 (1)	183 (115)	208 (139)
Maternal s/d NVP	14 (13)	12 (11)	23 (22)	527 (98)	576 (144)
Other ARVs	1 (1)	3 (3)	5 (5)	56 (22)	65 (31)

The transmission rate among infants whose mothers received single-dose nevirapine was 8.5% (49/576). The rate among infants who received postexposure prophylaxis and whose mothers received no antiretroviral drugs was 11.9% (24/201) and among infants whose mothers received triple combination therapy was 4.9% (2/41).

Unsurprisingly, of the case controls, mothers that transmitted had higher viral loads (median 58,100 [IQR 5820-219,00] vs. 13,100 [IQR 1,950-55,400] copies/mL,  $p < 0.0001$ ) and lower CD4 counts (416 [std 223] vs 502 [std 264] cells/mm<sup>3</sup>,  $p = 0.01$ ) than non-transmitting mothers.

The investigators found that infant, but not maternal, CCL3L1 gene copies were significantly associated with perinatal HIV transmission ( $p = 0.004$ ).

After adjustment for maternal CCL3L1 copies, viral load, and CD4 cell count, there continued to be a significant association between higher numbers of infant CCL3L1 gene copies (continuous scale) and a lower risk of HIV transmission (OR 0.75, 95% CI 0.59–0.95,  $p = 0.018$ ).

The influence of infant CCL3L1 copies on transmission was attenuated if mothers received single-dose nevirapine or had low viral loads (irrespective of maternal drug regimens).

Additionally the investigators found that spontaneously released CCL3 ( $p = 0.007$ ) and phytohemagglutinin-stimulated CCL3 ( $p = 0.005$ ) was reduced for HIV-exposed, HIV-negative infants whose mothers took nevirapine, compared to those whose mothers took no antiretrovirals.

The investigators acknowledge that a limitation of this study is that they only investigated nevirapine. It is unclear whether similar attenuations of genotype transmission would be observed with other antiretroviral drugs.

In the discussion they wrote: “Our results have important implications for future studies of mother-to-child HIV transmission. First, for ethical reasons, it is unlikely in the future to find contexts in which vertical transmission can be studied in the absence of antiretroviral drugs. It appears, however, that some antiretroviral drugs currently used for prevention may obscure genotype–transmission relationships.”

They added: “Second, a vaccine to prevent breastfeeding HIV transmission would be extremely beneficial for settings in which avoiding all breastfeeding is neither safe nor acceptable. It is likely that studies of infant vaccines will include antiretroviral drugs given at least over the perinatal period. If these drugs influence CCL3 production they may affect the immunogenicity of vaccines that rely on appropriate support from this component of innate immunity. For these reasons, it is important that the indirect consequences of antiretroviral drugs used for the prevention of perinatal HIV transmission be investigated further.”

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1. Townson JR, Barcellos LF, Nibbs RJ. Gene copy number regulates the production of the human chemokine CCL3-L1. *Eur J Immunol* 2002; 32:3016–3026.
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3. Kuhn L, Schramm D B, Donninger S et al. African infants’ CCL3 gene copies influence perinatal HIV transmission in the absence of maternal nevirapine. *AIDS* 2007, 21:1753–1761.

## Low rates of mother to child transmission in the DREAM and MTCT-Plus programmes

Polly Clayden, HIV i-Base

There is ongoing discussion around the best way to manage pregnant women not indicated for treatment for their own health. Two recent publications reported findings from alternative approaches – offering treatment at all disease stages and

a “two tiered strategy”. Both report low rates of mother-to-child- transmission (MTCT).

### **The DREAM programme**

The Drug Resource Enhancement against AIDS and Malnutrition (DREAM) programme is a large ART programme with sites in sub-Saharan Africa. A major part of the DREAM programme is nutritional supplementation and prevention of mother-to-child transmission (PMTCT) of HIV.

A paper authored by Leonardo Palombi and coworkers published in AIDS supplement 4, 2007, presented findings from a comparison of two cohorts of pregnant women enrolled in the DREAM programme. The cohorts were followed prospectively and the investigators evaluated transmission rates and infant morbidity and mortality.

In this programme HIV-positive pregnant women receive HAART (3TC and nevirapine, plus either AZT or d4T) free of charge from 25 weeks gestation, at all clinical stages, CD4 counts, and viral loads. The infants receive post-exposure prophylaxis. The investigators explained: “Many PMTCT programmes fail to provide continuing treatment and care to mothers. It is difficult to have to tell a woman that she can avoid transmitting the infection to her child, but that little can be done for her own health. Under these circumstances, the refusal rates and no-return rates for those who are tested remain high.”

From 2004 to 2006, women in Mozambique, Tanzania, and Malawi received water filters and formula milk for the first 6 months of the infant’s life. In the second cohort starting in 2005 until 2006 in Mozambique, women received HAART for up to 6 months after delivery and were given the option to breastfeed.

In the first cohort, 879 live-born infants were delivered after 914 pregnancies, with 809 evaluable infants at 1 and 6 months. In the second cohort, 341 infants were delivered and evaluable at 1 month, and 251 infants were evaluable at 6 months. Follow up is ongoing in this cohort.

At 1 month, HIV transmission rates (TR) were 4/341 (1.2%) among breastfed infants and 7/809 (0.8%) among formula-fed infants. At age 6months, TR was 2/251 (0.8%) among breastfed infants of women receiving HAART and 15/809 (1.8%) among formula-fed infants (p=0.38).

The cumulative incidence rate at 6 months was 2.7% for formula-fed infants and 2.2% for breastfed infants (p=0.60). The investigators noted a trend for TR to be slightly greater among formula-fed infants. They suggested that this is probably explained by some mixed feeding in this cohort. Overall, mother-to-child transmission rates in both cohorts were extremely low.

Most infants did well on both feeding regimens. Observed Z scores were greater than among the general infant population. Z scores  $\leq -2.0$  for weight by age occurred in 92/809 formula-fed infants (11.4%) and in 28/251 breastfed infants (11.1%).

The rates of anaemia in the infants were also lower than that of the general population. 40/809 (4.9%) formula-fed infants and 17/251 (6.8%) breastfed infants (p=0.33) had a hemoglobin value  $<8\text{g/dl}$ .

Infant mortality rates were similar in the two cohorts. At 6 months 27 per 1000 person years among formula-fed and 28.5 per 1000 person years among breast- fed infants. (Compared to 100 per 1000 person years observed in Mozambique).

The investigators wrote: “Our data clearly demonstrate that decreasing the rates of transmission of HIV from mother to child in Africa to those reported by high-income countries is feasible, efficacious, safe, and highly achievable even in the poorest of settings. Prenatal administration of HAART, starting as early as 25weeks of gestation in our programme, was highly tolerable and was safe for mothers.”

### **The MTCT-Plus programme**

A paper in the PLoS medicine authored by Besign Tonwe-Gold and coworkers reported an evaluation of the two-tiered PMTCT strategy of The MTCT-Plus Initiative in Abidjan, Cote D’Ivoire.

In this programme women receive either HAART if indicated for their own health or short-course antiretroviral (scARV) PMTCT. The study included all HIV-positive pregnant women and their live-born infants enrolled between August 2003 and April 2005 and followed until their HIV status was confirmed.

261 HIV-positive pregnant women were enrolled and 250 were prescribed ARVs before and/or during delivery.

The majority of women eligible for HAART (102/107), received AZT+3TC+ NVP Treatment was initiated at a median of 30 weeks gestation. The median CD4 count of eligible women was 189 cells/mm<sup>3</sup> (IQR 135-266 cells/mm<sup>3</sup>).

Of the 143 women who received scARV for PMTCT, the median CD4 count was 467 cells/mm<sup>3</sup> (IQR 368–602 cells/mm<sup>3</sup>). Median gestational age at prophylaxis initiation was 34 week (IQR 32–36 wk) and median number of days on scARV drug regimens was 46 days (IQR 31–65 days); 103 women (72.0%) received sc(AZT+3TC) with sdNVP during labour, 26 (18.2%) scAZT with sdNVP, and 14 (9.8%) sdNVP alone.

All infants received AZT syrup for 7 days and sdNVP syrup on day 3. Most (75%) of the infants were breast-fed for a median of 5 months.

Overall HIV status could be determined for 225 infants (97.4%); 12 were diagnosed HIV-positive. The overall probability of HIV infection was 2.2% (95% CI 0.3%–4.2%): 1.0% (95% CI 0.0%–3.1%) in the HAART group and 3.1% (95% CI 0.1%–6.1%) in the scARV for PMTCT group. At 12 months, 5.7% (95% CI 2.5%–9.0%) of the infants were diagnosed HIV-positive: 3.3% (95% CI 0.0%–6.9%) in the HAART group and 7.5% (95% CI 2.8%–12.3%) in the scARV for PMTCT group ( $p = 0.18$ ).

In multivariate analysis, low birth weight (<2,500 g) was the only factor associated with HIV infection, with an adjusted hazard ratio of 5.63 (95% CI 1.62–19.49,  $p = 0.006$ ).

191 infants were thus included in a post natal transmission analysis (87 in the HAART group and 104 in the scARV for PMTCT group) including 138 breast-fed infants (52 in the HAART group and 86 in the scARV for PMTCT group).

The median duration on HAART in breast-feeding women was 14.9 months (IQR 14.5–16.2 months) when the final infant diagnoses were determined. Overall, four infants had a confirmed postnatal infection (2.3% [95% CI 0.8%–7.3%]). In the HAART group, one case of postnatal infection was identified from 52 infants (1.9% [95% CI 0.04%–10.2%]) breast-fed for a median 4.7 months (IQR 3.3–6.3 months). In the scARV for PMTCT group, three cases of postnatal infection were identified from 86 infants (3.5% [95% CI 0.7%–9.9%]) breast-fed for a median of 5.7 months (IQR 4.3–7.1 months).

The investigators hypothesised that if the three cases with unknown timing were postnatal cases, this would give a rate of postnatal transmission of 3.8% (0.4%–12.9%) in the HAART group and 5.7% (1.8%–12.7%) in the PMTCT group.

No case of postnatal infection was identified among the 53 infants who were formula fed (upper limit of 95% CI, 6.7%). One death of an HIV-positive, formula-fed infant was reported.

The overall probability of HIV infection or death among all infants aged 12 months was 11.7% (95% CI 7.5%–15.9%); the probability was 11.2% (95% CI 5.0%–17.4%) among infants born to HAART-treated women, and 12.1% (95% CI 6.4%–17.9%) among infants whose mothers received scARV for PMTCT only ( $p = 0.90$ ).

In multivariate analysis ( $n = 231$ ): low birth weight (AHR 3.71 [95% CI 1.53–9.03],  $p = 0.004$ ) and female sex (AHR 0.35 [95% CI 0.14–0.88],  $p = 0.035$ ) were associated with HIV infection or death.

There were 18 deaths in this cohort: 10/99 (10.1%) infants born to woman who had initiated HAART during pregnancy and 8/132 (6.0%) infants who were born to women who received short-course antiretroviral prophylaxis.

This report also included some data on maternal health. 9/107 (8.4%) pregnant women initiating HAART required one switch in their regimen before delivery. One woman switched from NVP to efavirenz after 6 weeks of treatment (32 weeks gestation) following diagnosis of tuberculosis.

There were a number of toxicities. Eight women (7.5%) developed grade 3 or 4 adverse events associated with HAART: five women developed grade 3 rash attributed to NVP and were switched to nelfinavir, and two women developed grade 4 liver toxicity attributed to NVP, with alanine aminotransferase levels over 50 times and over 5 times the upper limit of normal value, respectively in the two groups of women; one woman developed severe anaemia attributed to AZT.

All adverse events were resolved with drug switches and no deaths were reported. In the cohort of women receiving scARV for PMTCT, no grade 3 or 4 toxicities were observed and no ART changes were made.

Stillbirths and neonatal deaths in the first 28 days of life were comparable in the HAART and scARV for PMTCT groups: 6.7% and 5.6%, respectively ( $p = 0.80$ ). There was no significant difference in the rates of premature births (gestational age <37 week) between the two groups (7.8% and 7.9% respectively,  $p = 1.00$ ).

A higher proportion of low birth weight (<2,500 g) was observed in infants whose mothers had received HAART, 26.3% compared with 12.4% among those having received a scARV for PMTCT regimen ( $p < 0.001$ ).

#### C O M M E N T

**Caution over giving HAART to all pregnant women irrespective of disease stage has been driven by concerns about maternal toxicity – particularly associated with nevirapine – and preterm delivery and other complications with the infant. Investigators from the DREAM programme previously reported low incidence of grade 3–4 adverse reactions associated with nevirapine toxicity (hepatotoxicity, skin rashes and Stevens–Johnson syndrome) of 6.5, 2.4 and 1.1%, respectively. Their data did not confirm an association between hepatic toxicity and high CD4 cell count. [3]**

**Concerning preterm deliveries, miscarriage and still birth the DREAM investigators suggest that these events appear to be significantly reduced in women receiving HAART in pregnancy in this programme [personal communication]. They are currently preparing to present these findings.**

**The MTCT-Plus study also found that HAART was relatively safe during pregnancy, although these numbers are small do not offer any information about women receiving HAART with higher CD4 counts. 7.5% of women receiving HAART developed side effects requiring a change in their medications.**

**There was no significant difference in the rate of preterm delivery between the two groups but infants born to women receiving HAART were more likely (26.3%) to have low birth weight than babies born to women who received short course ARV (12.4%).**

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## PAEDIATRIC CARE

### **Risk factors for early mortality for children receiving divided adult fixed dose combination tablets in Malawi**

**Polly Clayden, HIV i-Base**

National treatment scale up in Malawi initially did not serve children well due to concerns about using divided adult fixed dose combination (FDC) tablets and a shortage of healthcare workers trained in paediatric HIV.

Since 2006, national guidelines include more information about the management of children on ART, health workers have been trained and regional pharmacokinetic and clinical studies have provided reassuring data for divided FDCs. By September 2006, 4612 children aged 14 years or younger had started ART in the Malawi state programme.

A paper published in the August 20, 2007 edition of *AIDS*, authored by Bong and coworkers from Malawi and the Taiwan Medical Mission reported findings from a study that looked at risk factors for early death in children initiating ART.

In Malawi treatment outcomes for patients on ART are monitored monthly using ART patient “master cards”. As of September 2006, according to the Ministry of Health figures, 7983/69547 patients (11%) started on ART had died. In adults, 70% of these deaths occurred in the first three months of treatment.

The study was conducted at the Mzuzu Central Hospital, which is the main referral hospital in the northern region of Malawi. HIV-positive children eligible for ART by WHO criteria receive a thorough clinical assessment before starting treatment. Their guardians receive counseling and education about how to give children divided tablets.

For the first two weeks children receive a single daily divided tablet, FDC, of d4T 30 mg (T30) or 40 mg (T40)/3TC 150 mg/nevirapine 200 mg in the morning followed by a single daily divided tablet of d4T 30 mg or 40 mg/3TC 150 mg in the evening. If there are no nevirapine side effects, the children will then receive divided tablets, FDC, T30 or T40 twice a day.

Doses are based on body weight in accordance with national guidelines. Since December 2005, all children have been treated with the d4T

30 mg formulation only, as these provide a higher dose of nevirapine compared with d4T for all weight bands: pharmacokinetic studies in Malawi showed that children were underdosed with nevirapine when half to quarter tablets of T40 were used. Children also receive cotrimoxazole preventive therapy.

Of 439 children enrolled in the study, 220 (50%) were boys. The median age was 6 years (IQR 2.9–9.7 years). 37 children (8%) were aged less than 18 months (range 3.6–16.9 months; IQR 12–15.6 months), 172 (39%) were aged 18 months to 5 years (range 1.5–5.9 years; IQR 2.2–4.5 years) and 230 (52%) were aged 6–14 years (range 6–14 years; IQR 7.5–11.5).

The very young children, aged less than 18 months, were significantly more likely to have an advanced WHO clinical stage and severe wasting compared with the other children.

By September 2006, the outcomes of the 439 children were: 306 (69%) alive and on ART; 38 (8.6%) lost to follow; and 46 (10.4%) transferred to another ART clinic.

The investigators reported, of the live children, the percentage with a CD4 cell count indicating that they were not severely immunodeficient increased from 54% at baseline (n=408) to 75% at 3 months (n=209) to 85% at 6 months (n=138). 49 children (11%) died; 35 (71%) died in the first 3 months and 44 (89%) in the first 6 months of treatment. The cumulative incidence of death at 3, 6, 12 and 24 months after ART was 8, 12, 13 and 15%, respectively.

By multivariate analysis, children in WHO clinical stage 4, with severe wasting and with a CD4 cell count below the threshold for severe immunodeficiency had a significant risk of early death at 3 or 6 months.

In the discussion, the investigators note the limitations of this operational research study:

- Bacterial infections, particularly presumed sepsis, in most cases could not be confirmed because of a lack of sophisticated laboratory facilities. Therefore some children might thus have been incorrectly staged.
- Exact causes of death could not be determined as there are no postmortem facilities available.
- Previous studies in tuberculosis patients lost to follow up identified that a significant proportion had died and they probably underestimated the mortality rate in this study.
- There is concern that Malawi's current ART split-tablet regimen underdoses children with nevirapine and this might be a risk factor for early death. There is no pharmacokinetic information on nevirapine levels in children in this study.

They identified reasons for early mortality as: late diagnosis - particularly in the youngest children; late presentation at health facilities; and life-threatening complications such as bacteraemia.

In order to prevent these early deaths they recommend that:

- HIV testing and simple diagnostic tests, as an entry point to care, must be scaled up for infants and and better links made with PMTCT programmes.
- In Malawi, approximately 40% of children with malnutrition are HIV-positive. Controlled studies of nutritional interventions to see if this can impact on reduction of early mortality are required.
- Cotrimoxazole prophylaxis for children must be scaled up and integrated with PMTCT.

In conclusion they wrote: "The final challenge is to scale up PMTCT to prevent children becoming HIV infected in the first place."

Ref: Bong C, Yua JK, Chiang H et al. Risk factors for early mortality in children on adult fixed-dose combination antiretroviral treatment in a central hospital in Malawi. *AIDS* 2007, 21:1805–1810.

## HEPATITIS COINFECTION

### Risk of antibody negative HCV infection in four US HIV cohorts: risk linked to IDU, elevated ALT and low CD4 count

Simon Collins, HIV i-Base

Although HCV antibody screening is recommended in HIV management guidelines, false negative results can occur in both acute and chronic HCV infection. This has led to recommending wider use of HCV RNA screening in patients with HIV coinfection who have a negative antibody result.

Gabriel Chamie from University of California and colleagues reported an analysis in the February 2007 edition of *Clinical Infectious Diseases*, on the prevalence of HIV-positive patients who were HCV antibody-negative/PCR-positive, in four US cohorts.

The four cohorts (FRAM, Los Angeles, Iowa and REACH) included around 1800 patients, 37 of whom were Hcv antibody-negative/PCR-positive, and reported a pooled seronegative prevalence of 3.2% (95%CI 2.2-4.3%) Prevalence in individual cohorts ranged from 1.3% (FRAM) to 4.6% (IOWA).

Standard variables in the multivariate analysis included age, ethnicity, sex, alcohol use, history of IDU, ALT, CD4 and viral load. In the combined data, three independently predictive factors of chronic seronegative HCV infection: history of IDU [OR 5.8 (2.7-12.8),  $p < 0.0001$ ], CD4 count  $< 200$  cells/mm<sup>3</sup> [OR 2.3 (1.1 - 4.8),  $p = 0.025$ ] and ALT [OR 2.0 per doubling (1.3-3.2,  $p = 0.002$ ], see Table 1. A similar pattern of OR were reported in each of the cohorts, looked at individually. For HCV antibody-negative patients, with a history of IDU and either raised AT or CD4  $< 200$  cells/mm<sup>3</sup> a pooled prevalence of 24% was reported for testing HCV RNA-positive.

**Table 1: Factors associated with higher rate of antibody-negative HCV infection**

Factor	OR	95%CI	p-value
History of IDU	5.8	2.7-12.8	$< 0.0001$
CD4 count $< 200$ cells/mm <sup>3</sup>	2.3	1.1 - 4.8	0.025
ALT level	2.0 (per doubling)	1.3-3.2	0.002

This is the largest study so far to look at prevalence of HCV antibody-negative/PCR-positive results in HIV-coinfection. Among US blood donors, the prevalence by comparison is estimated to be as low as 1 in 250,000, largely explained by acute HCV infection.

The researchers concluded that HCV PCR testing should be recommended in antibody-negative, HIV-positive patients, especially those with a history of IDU and either a low CD4 count or a raised ALT.

#### C O M M E N T

**This is an important study in that it highlights the issue of antibody negative chronic HCV infection in the context of HIV-co-infection.**

**The important message here is that in patients with 'risk factors' and persistent unexplained hepatic transaminase elevation an HCV-RNA by RT-PCR is mandatory in order to rule out chronic HCV infection.**

**The BHIVA guidelines on HIV/HCV co-infection (2004) suggest that consideration should be given to HCV RNA testing in patients with a negative HCV-antibody test and unexplained raised hepatic transaminases.**

Ref: Chamie G, Bonacini M, Bangsberg DR, et al. Factors associated with seronegative chronic hepatitis C virus infection in HIV infection. Clin Infect Dis. 2007;44:577-583.

## ARV4IDUs

These two articles are reprinted from the October 2007 edition of ARV4IDUs, a new electronic quarterly bulletin from i-Base about antiretroviral treatment for injecting drug users. See HTB introduction for free subscription details.

### Survival of HIV-positive IDUs in the era of HAART

Polly Clayden, HIV i-Base

Mortality rates among injection drug users (IDUs) have been historically high and are still significantly higher than the rates for the general population. HIV-positive IDUs have an additional increase in mortality risk.

A paper authored by Roberto Muga and coworkers from the Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, and Department of Statistics and Operations Research, Universitat Politècnica de Catalunya, Barcelona, Spain, published in the 1 August 2007 edition of Clinical Infectious Diseases, looked at survival of HIV-positive IDU in the era of HAART.

In this study they evaluated the mortality rates for a cohort of HIV-positive and negative IDUs who were admitted to a substance abuse treatment programme in a tertiary hospital between January 1987 and December 2004. The investigators divided the follow up period into: 1987-1991 (the antiretroviral monotherapy era), 1992-1996 (the dual-combination treatment era and the introduction of methadone maintenance), and 1997-2004 (the era of HAART and established methadone programmes).

The investigators noted that during follow-up, several IDUs who were HIV-negative at admission became HIV-positive. They defined the time of infection by the midpoint of the interval from the last negative test result to the first positive test result. People that seroconverted contributed survival times to both groups of HIV infection: as seronegative subjects, the (right-censored) survival time lasted from admission until HIV infection; as seropositive subjects, the survival time lasted from the duration after admission to HIV infection, until either death or the end of follow-up.

During the study period, 1209 IDUs were admitted for the first time to a substance use treatment programme. Twenty-eight (2.3%) of the total study group were excluded from the study cohort because their HIV status was unknown. The calendar periods of admission, for the remaining 1181 IDU included were as follows: 490 (41.5%) for 1987-1991, 393 (33.3%) for 1992-1996 and 298 (25.2%) for 1997-2004.

The majority (81.3%) of patients were men. The mean age was 27.8 (+/- 5.6) years, and the mean duration of injection drug use was 7.6 (+/- 5.0) years. The prevalence of HIV infection and hepatitis C virus infections was 59.0% and 92.3%, respectively, and the total duration of follow-up was 10,116 person-years.

The investigators reported that although survival duration for HIV-negative IDUs in 1997-2004 was similar to the duration in earlier periods, the duration for HIV-infected IDUs improved significantly since 1997 ( $p=0.01$ ). Additionally, among patients admitted in the last period, there was no significant difference between the survival durations for HIV-uninfected and HIV-infected IDUs (HR 0.89; 95% CI 0.44-1.81).

They found that survival for HIV-positive IDUs improved substantially since 1997, reaching similar rates to those for HIV-negative IDUs who accessed the health care system in the era of HAART and methadone.

They noted that because only one-third of the HIV-positive IDUs in this study received HAART, other factors are likely to have contributed to their improved survival including: access to substitution therapy with methadone, prophylaxis for opportunistic

infections, harm reduction interventions, and regular clinical care.

They wrote: "HAART has been proven to be an extremely effective therapy for HIV-infected individuals. We have shown that HIV-infected IDUs who received health care during the period 3 exhibited mortality rates comparable to those for IDUs who were not infected with HIV."

Ref: Muga R, Langohr K, Tor J et al. Survival of HIV-Infected Injection Drug Users (IDUs) in the Highly Active Antiretroviral Therapy Era, Relative to Sex- and Age-Specific Survival of HIV-Uninfected IDUs. *Clinical Infectious Diseases* 2007;45, 1 August 2007.

## **Current or former injecting drug use is not related to earlier switch or discontinuation of HAART compared to non-IDU patients since 1999**

**Simon Collins, HIV i-Base**

A combined analysis from three prospective US cohorts, published in 6 June issue of *AIDS Research Therapy* reported that injecting drug use was not related to earlier changing, reducing or switching treatment – discussed as a marker for poorer long-term treatment success – after adjusting for other factors.

The three cohorts – AIDS Link to IntraVenous Exposure (ALIVE), Women's Interagency HIV Study (WIHS) and Multicentre AIDS Cohort Study (MACS) – were used to select approximately 1400 patients with no history of injecting drug use and compare treatment outcome to just under 850 former or current IDUs. These 1588 patients contributed 2,358 patient-years with 713 events.

The IDU group had a lower nadir CD4 count and higher proportion of patients who were unemployed, on low income, had lower educational level and a higher proportion of Black, non Hispanic patients. Use of treatment and choice of drugs was similar between the two groups.

All three cohorts collect similar follow-up data, and reported similar trends in ARV prescribing (generally with a similar shift from PI- to NNRTI-based therapy over the time of the study (April 1996 – April 2004).

The median time to a first report of discontinuation was 1.1 years vs 2.5 years for people without vs with a history of IDU, and overall the relative hazard (RH) of HAART discontinuation was higher for any IDU use when looking at the whole time period (pre- and post-1999) ([HR]1.24 (1.03-148)], However, when looking at the pos-1999 period alone (852 people contributing 382 events over 1,396 person years) this association disappeared in the multivariate analysis [HR = 1.05 (0.81-1.36), after adjusting for previous health, race, income and employment. For patients switching treatment, HR was 0.96 (0.82-1.14) and 1.09 (0.89 – 1.34) in the pre- and post 1999 periods respectively.

Over time, the proportion of patients using the same HAART regimen increased in both group: from 55% in 1997 to 70% by 2004 (in the non-IDU group) vs increasing from 35% to 65% at the same time points in the IDU group.

Similar results were seen when looking at current vs former IDU: in the post-1999 analysis: HR = 1.32 (0.90 – 1.94) vs RH = 1.00 (0.77 – 1.31).

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### **C O M M E N T**

**These results are particularly useful to challenge the common assumption that drug users are not able to be adherent.**

Ref: Morris JD, Golub ET, Shruti H et al. Injection drug use and patterns of highly active antiretroviral therapy use: an analysis of ALIVE, WIHS, and MACS cohorts. *AIDS Research and Therapy* 2007, 4:12 doi:10.1186/1742-6405-4-12.

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## **VACCINE RESEARCH**

### **Merck HIV vaccine trial halted by DSMB for lack of efficacy**

**Richard Jeffreys, TAG**

Extremely grim news for the HIV vaccine field: The phase IIb efficacy trial of Merck's adenovirus-based HIV vaccine candidate (MRKAd5, also recently referred to as V520) has been stopped after an interim analysis by the trial's Data Safety Monitoring Board (DSMB) found no differences between the placebo and vaccine groups for either of the trial's primary endpoints: acquisition of HIV infection or post-infection viral load levels (in this case, the geometric means of two viral load measurements taken 8 and 12 weeks after infection).

The details are contained in Merck's press release:

“The study evaluated two primary efficacy endpoints: whether the vaccine prevented HIV infection and whether the vaccine reduced the amount of virus in those who developed infection. As planned, an interim efficacy analysis was conducted in the approximately 1,500 volunteers expected to have the best response to the vaccine because they had low levels of pre-existing immunity to adenovirus 5.

The vaccine did not prevent infection: in volunteers who received at least one dose of the three-dose vaccine series, 24 cases of HIV infection were observed in the 741 volunteers who received vaccine and 21 cases of HIV infection were observed in the 762 participants in the placebo group. In the subgroup who had received at least two vaccinations and who were HIV negative for at least the first 12 weeks of the trial, 19 cases of HIV infection were observed in the 672 volunteers who received vaccine and 11 cases were observed in the 691 volunteers who received placebo. In addition, the vaccine did not reduce the amount of virus in the bloodstream of those who became infected; HIV RNA levels approximately 8 to 12 weeks after diagnosis of infection were similar in the vaccine and the placebo arms. The geometric means of the HIV RNA levels in the blood of infected individuals, the standard measure of ongoing HIV replication, were approximately 40,000 copies/mL in the vaccine group and approximately 37,000 copies/mL in the placebo group. Additional analyses will be conducted on the entire study population and will be shared with the scientific community.”

Like Merck’s vaccine, most HIV vaccines in the developmental pipeline are designed to induce memory T cell responses, because these immune responses have consistently offered some degree of enhanced post-infection control of viral load in animal models. The apparent failure of the HIV-specific memory T cell responses induced by Merck’s Ad5 vaccine to offer any benefits could therefore have devastating implications for the overall field. However, there are issues that still need to be explored, such as:

- Any longer term differences in outcome between vaccinees and placebo recipients that became infected (e.g. in terms of viral load levels, CD4 T cell counts and immune activation levels)
- Correlations (if any) between the functional properties of the HIV-specific CD4 and CD8 T cell responses induced by the vaccine and the outcomes in the trial
- The immune system genetics of trial participants, particularly HLA types which are an important genetic determinant of the ability to mount a T cell response against a given pathogen.
- The genetics of the infecting viral strains
- The timing of the infections (there is some basic immunology data which might suggest that there is a period immediately after immunization when activation of CD4 T cells could enhance susceptibility to HIV infection, before their differentiation into memory CD4 T cells is completed).
- The finding that the difference between vaccine and placebo recipients in terms of acquisition of infection seemed to widen after two immunizations (19 vaccinees vs. 11 placebo recipients) but skewed the other way in people that received only one immunization (5 vaccinees vs. 10 placebo recipients)

A second efficacy study of the same Merck vaccine construct that was slated to start in South Africa has been placed on hold until a more detailed review of these data can take place.

A press release from the Treatment Action Group expanded on the implications of these disappointing results:

HIV vaccine researchers have long sought a vaccine candidate that can reliably induce a type of immune defense called a killer CD8 T cell response, because CD8 T cells have been consistently associated with control of viral replication in animal models. Merck’s vaccine represented a breakthrough because it was able to induce HIV-specific CD8 T cell responses (and the supportive HIV-specific CD4 T cells that are needed to sustain them) in the majority of people who received it. Hence there were sound reasons to hope that the vaccine might reduce viral load and slow disease progression to a significant degree.

The interim STEP study results show that this hope has not been borne out, raising critical and difficult questions for the HIV vaccine field as a whole. It will be crucial to analyze the outcomes in the STEP study in detail and assess how they might impact other HIV vaccine candidates in development. [ .... ]

While the failure of Merck’s HIV vaccine represents extremely discouraging news for T cell-based HIV vaccines, it would be premature at this juncture to conclude that all such approaches are doomed to failure. Due to the difficulty of inducing effective neutralising antibodies against HIV, most HIV vaccines currently in the pipeline aim to induce T cell responses.

The next planned HIV vaccine efficacy trial involves two constructs developed by the Vaccine Research Center (VRC) at the National Institutes of Health. Like Merck’s vaccine, it includes an adenovirus component, but there are several differences in the approach that could potentially be important, including a “priming” immunization using a different DNA-based vaccine, plus several additional proteins (the envelope proteins derived from three different subtypes or clades of HIV).

These differences highlight some of the near-term options for HIV vaccine researchers in the light of Merck’s results: exploring whether the quality – in other words, the functionality - of the T cell response induced by a vaccine is an important

factor (i.e. DNA priming may lead to a qualitatively different T cell response) and also whether the parts of HIV included in the vaccine influence the outcome. Merck's vaccine included the HIV proteins Gag, Pol and Nef because these proteins are most frequently targeted by T cells in infected people. Strategies targeting additional structural and regulatory proteins from HIV also need to be evaluated.

Sources:

Richard Jeffreys Vaccine Prevention Blog

For ongoing coverage and commentary of this and other issues in HIV science, visit TAG's Michael Palm Basic Science, Vaccines and Prevention Project blog.

<http://tagbasicscienceproject.typepad.com>

Merck press release: Vaccination and Enrollment Are Discontinued in Phase II Trials of Merck's Investigational HIV Vaccine Candidate (21.09.07)

[http://www.merck.com/newsroom/press\\_releases/research\\_and\\_development/2007\\_0921.html](http://www.merck.com/newsroom/press_releases/research_and_development/2007_0921.html)

Treatment Action Group (TAG) press release

<http://www.treatmentactiongroup.org>

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## ON THE WEB

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### *Conference abstracts and presentations:*

#### **2007 AIDS Vaccine Conference**

Abstracts from the 2007 AIDS Vaccine Conference, which took place in August in Seattle, are now online in PDF format:

<http://www.hivvaccineenterprise.org/conference/archive/2007/abstracts.aspx>

#### **2nd International Workshop on HIV Transmission**

26 - 28 August 2007, Washington DC, USA

Presentations from this recent workshop on HIV transmission are now available online.

<http://www.hivpresentation.com>

The following earlier workshops from 2007 are also online at the same site.

- 5th European HIV Drug Resistance Workshop, Cascais
- 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, Hungary
- 1st International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings, Kampala, Uganda
- 3rd International Workshop on HIV & Hepatitis Co-infection, Paris, France

### *Free full text articles:*

The September issue of the journal Immunity is offering free access to several commentaries and reviews regarding immunity to viral infections, including HIV.

The journal editors could not have anticipated the timeliness and topicality of the issue, which includes pieces on factors associated with immunological control of HIV infection, correlates of vaccine-induced immunity and memory CD8 T cell differentiation during viral infection.

<http://www.immunity.com>

**The challenge of viral immunity** - Doherty PC, Turner SJ.

<http://www.immunity.com/content/article/fulltext?uid=PIIS1074761307004165>

**Correlates of immune protection and the development of an HIV vaccine** - Letvin NL

<http://www.immunity.com/content/article/fulltext?uid=PIIS1074761307004190>

**Antibodies and B cell memory in viral immunity** - Dörner T, Radbruch A

<http://www.immunity.com/content/article/fulltext?uid=PIIS1074761307004207>

Heterogeneity and cell-fate decisions in effector and memory CD8+ T cell differentiation during viral infection - Susan M. Kaech SM, John Wherry EJ

<http://www.immunity.com/content/article/fulltext?uid=PIIS1074761307004104>

HIV controllers: mechanisms of durable virus control in the absence of antiretroviral therapy - Deeks SG, Walker BD

<http://www.immunity.com/content/article/fulltext?uid=PIIS1074761307004104>

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## FUTURE MEETINGS

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### 2007-8 conference listing

The following meetings are taking place during 2007-2008.

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

24-27 October - 11th European AIDS Conference (EACS)

<http://www.eacs.eu>

31 October - 1 November - 2nd Intl Workshop on Hepatitis C, Resistance and New Compounds, Boston

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

2-3 November - 3rd Intl Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston

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

7-8 December - 3rd International Workshop on Targeting HIV Entry, Washington

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

3-6 February 2008, 15th Conference on Retroviruses and Opportunistic Infections. Boston

<http://www.retroconference.org/2008/>

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.informedhorizons.com>

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

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

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

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

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

<http://www.hiv8.com>

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## PUBLICATIONS & SERVICES FROM i-BASE

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### i-Base website

The website has been redesigned to be faster, easier to use, and simpler to navigate.

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

A new section has been added about adapting and translating i-Base materials in other countries:

<http://www.i-base.info/education/adapting.html>

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.

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).

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

## **New 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 with advocacy projects outside the UK.

A 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](mailto: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.

### **Treatment training for advocates**

i-Base have produced a training manual for advocates that is available online as a PDF document. It provides a basic entry-level curriculum relating to HIV and treatment. Each module includes non-technical review material, test questions, an evaluation and a glossary.

The manual is available in English, Russian, Portuguese, Hindi and Nepalese.

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

<http://www.nkplus.org>

### **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. The 22nd meeting was on Friday 13 July, and included training on tests (CD4, viral load, resistance and tropism), and strategies for monitoring.

<http://www.ukcab.net>

<http://www.ukcab.net/jul07>

### **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>

## **NEW: 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.

## **Introduction to combination therapy**

### **June 2006 edition**

This non-technical patient guide to treatment is available in 12 languages. It explains what combination therapy is, 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 HIV, pregnancy & women's health**

### **Spring 2005 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>

### **Bosnia Herzogovenia**

Introduction to combination therapy May 07 PDF File [452 Kb]

### **Bulgarian**

HIV, pregnancy & women's health - Mar 06

Introduction to combination therapy - May 06

### **Chinese**

Avoiding & managing side effects - Aug 02

Changing treatment: second line & salvage therapy - Aug 02

Introduction to combination therapy - Aug 02

### **Croatian**

Introduction to combination therapy May 07

### **Czech/Slovak**

Introduction to combination therapy - Jun 07

Changing treatment: second line & salvage therapy - Jun 05

### **French**

HIV, pregnancy & women's health - April 06

Avoiding & managing side effects - Jun 06

Introduction to combination therapy - Jun 01

### **Greek**

Changing treatment: second line & salvage therapy - Mar 03

Introduction to combination therapy - Nov 01

### **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

Further treatment information in Indonesian

<http://www.spiritia.or.id>

### **Italian**

Introduction to combination therapy - Jun 06

Avoiding & managing side effects - Oct 03

Changing treatment - Oct 03

HIV, pregnancy and women's health – Jun 04

### **Macedonian**

Introduction to combination therapy - May 07

### **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

### **Portuguese**

Introduction to combination therapy - Sep 05

Treatment training for advocates: a manual – 2006

### **Romanian**

Guide to Starting Treatment - 2007

Guide to Changing treatment 2007

Side Effects Guide - 2005

HIV, pregnancy & women's health - 2007

### **Russian**

Introduction to combination therapy - May 2006

HIV, pregnancy and women's health - Apr05

Treatment training manual – 2006

Hepatitis C for people living with HIV - May 07

### **Serbian**

Introduction to combination therapy - 2007

### **Spanish**

HIV, pregnancy and women's health - May 06

Avoiding & managing side effects - Nov 02

Introduction to combination therapy - Nov 00

## **Treatment 'Passports'**

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

## **HIV Treatment Bulletin (HTB)**

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

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

## **Treatment information request service - 0808 800 6013**

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

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

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

## New 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/index.html>

Recent questions include:

Is taking nevirapine a risk factor for heart disease?

- Will a test for recreational drug use show that I am HIV-positive?
- How long can I be delayed with a dose?
- Is there and HIV risk from blood on cotton balls?
- What protection do I need to have oral sex with an HIV-positive man?
- What is safe sex if my partner is HIV-positive?
- Is a negative test after 3 months accurate?
- A quick drop in the CD4 count
- What lifestyle changes can help with HIV?
- Do I need to test again?
- A sudden drop in the CD4 count
- What are the physical implications of non-adherence to ART?
- Literature about people who refuse to take ARVs
- Can a woman with HIV have a healthy baby?
- What does a CD4 count of 696 mean?
- Can I be late with Atripla?
- My clinic want to change viral load and CD4 monitoring - aren't both tests needed?
- Will I get resistance or live to 50?
- Can I test and use drugs immediately after exposure?
- What is combination therapy?
- Is massage safe if you are HIV-positive?
- Question about Imuno CIII
- Pain and drug switching
- Oral sex with another man who is HIV-positive?
- Can I continue to get treatment in the UK if I leave the UK?

## 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.

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

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

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

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

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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](mailto:subscriptions@i-Base.org.uk)

Editor: Simon Collins

Commissioning Editor: Polly Clayden

Medical Consultants:

Dr Karen Beckerman, New York.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Paul Blanchard, British School of Osteopathy, London.

Dr Martin Fisher, Brighton & Sussex University Hospitals.

Prof. Diana Gibb, Medical Research Council, London.

Gregg Gonsalves, AIDS and Rights Alliance for Southern Africa.

Dr Gareth Hardy, Case Western Reserve Univ. Cleveland.

Dr Saye Khoo, University of Liverpool Hospital.

Prof. Clive Loveday, International Laboratory Virology Centre.

Prof. James McIntyre, Chris Hani Baragwanath Hosp. South Africa

Dr Graeme Moyle, Chelsea & Westminster Hosp, London.

Dr Stefan Mauss, Düsseldorf.

Dr Graham P Taylor, Imperial College, London.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

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

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

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HIV i-Base  
Third Floor East  
Thrale House  
44-46 Southwark Street  
London SE1 1UN  
T: +44 (0) 20 7407 8488  
F: +44 (0) 20 7407 8489

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

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## HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

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

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

# HIV i-Base

Third Floor East, Thrale House, 44-46 Southwark Street, London SE1 1UN  
T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489



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