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## EDITORIAL

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This issue is focuses on reports form the XVI International AIDS Conference held in Toronto in August.

It is 10 years since the conference was last held in Canada - then in Vancouver, and heralding the first data on PI-based combination therapy. The revolutionary nature of those studies, may turn out to be matched by early data on Merck integrase inhibitor - a new compound in a new class - which now has to pass broader safety testing but which probably generated most excitement at the conference.

A named-patient programme for MK-0518 is due to start in the UK in the next month.

Broader issues, of course, included many sessions looking at roll out programmes, and access to treatment for the majority of HIV-positive people, who are still mainly living in countries where there are few drugs.

Further coverage of the conference will follow in the next issue, together with coverage of the Lipodystrophy Workshop being held at the end of this month.

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## NEW i-BASE BOOK

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### **“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 been very lucky to develop links to many other advocacy projects outside the UK.

One recent meeting, held in Cape Town earlier this year, focused on how to raise the profile of treatment literacy.

One result from the meeting is a publication “Why we must provide HIV treatment information”.

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

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.

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## CONFERENCE REPORTS

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### **16th International AIDS Conference**

**13-18 August 2006, Toronto, Canada**

#### **Introduction**

The XVI International AIDS Conference is the largest meeting of its kind. This year around 24,000 people traveled to Toronto to choose from over 4000 studies covering all aspects of HIV including basic science, clinical science, epidemiology, prevention, behavioural and policy-related research. It is organised every two years by the International AIDS Society (IAS) and since 2000 has alternated between northern and southern countries.

The meeting also now reflects the urgency and inequalities of the global epidemic, and treatment access takes an increasingly high profile.

In this issue we report on durability of treatment in several access programmes and highlight several other aspects of treatment important in developing countries, especially paediatric treatment.

Much of the scientifically data was compressed into an extended Track B late-breaker session. This session included studies with several drugs with potential to treatment drug-resistant HIV including MK-010518 (an integrase inhibitor), maraviroc (a CCR5 inhibitor), TNX-355 (a monoclonal antibody), together with several lopinavir/r monotherapy studies and the head-to-head study between fosamprenavir and lopinavir/r. This generated an optimism for pipeline drugs, supported by studies on darunavir (TMC-114) and etravirine (TMC-125), presented in the main meeting.

While it is unlikely that the title for the conference 'Time to Deliver' - as with earlier meeting titles such as 'Bridging the Gap', 'Breaking the Silence' and 'Access for All' - will change the reality for most people living with HIV, the intention to focus on access issues is at the centre of the meeting.

Key lectures at the opening and closing ceremonies, together with many of the oral sessions, focused on treatment access. Stephen Lewis was one of the speakers to close the conference, giving his last speech as UN Ambassador for AIDS in Africa. He received a standing ovation, largely for broadening his talk to clear political and social concerns: the disproportionate of HIV on women, their own "abysmal" track record of equitable inclusion of women within the UN system, and political leadership most particularly from South Africa (see below).

However, while over 1.5 million people are now on treatment - half of the WHO target for the end of 2005 - most concerns about the goal of universal access by 2010, are linked to financial scale-up and sustainability. Repeated calls at the meeting were made for individual country to make clear national targets for their HIV programmes for 2010 – due to be set by December 2006, but not so far released by any government.

Other speakers at the meeting highlighted again and again, that we have everything we need to stop HIV and to treat people already living with the virus; what we lack is political will for change, and in this we are all responsible for positions taken by our own governments.

Three community delegates were also given unprogrammed 'one minute' slots to address the final closing ceremony. In perfect balance to the official positions driving towards access, Loon Gangte, from the Delhi Network of People Living with HIV was able to articulate a first-person demand that the audience would otherwise never have heard so clearly: 'we demand universal free access to all essential medicines'.

Given that first line therapy has only been possible because of generic manufacturers, and that newer drugs for second-line therapy are barely available and linked to new restrictions on patent use, he continued 'when you sign free trade agreements, you sign away our lives'.

Some of the excellent general sessions, debates and press conferences are also available online as webcasts, podcasts and transcriptions by Kaisernetwork.org.

[http:// www.kaisernetwork.org/aids2006](http://www.kaisernetwork.org/aids2006)

The conference website includes abstracts for all presentations, and powerpoint slides from many studies. These are available by viewing the online conference programme, and following the link to the session in which the study was presented.

<http://www.aids2006.org>

Our own reports relating to clinical studies from the conference covered in this issue of HTB include:

- Enough is enough: South African activists demand "fire Manto"
- Treatment access: more optimistic results from scale up programmes
- Integrase inhibitor MK-0518: early results show greater early potency than efavirenz
- Maraviroc results in R5/X4 mixed/dual tropic patients: unexpected safety data shows possible immunological effect
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- Fosamprenavir/r is non-inferior to lopinavir/r in treatment naïve patients
- Tenofovir/FTC maintains greater virological response and reduced lipotrophy compared to AZT/3TC after 96 weeks

- Paediatric studies in Toronto: Children face a serious service delivery gap; Accumulating data shows children from resource limited settings benefit from antiretroviral treatment (ART)
- Bioavailability study results for new paediatric tablets for oral suspension, and caution against splitting adult doses
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- Selected abstracts from Track A presentations at Toronto
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- Poor scientific or medical knowledge is a factor in increase in criminal charges for HIV transmission in the UK
- Online webcasts and debates

Further reports will be included in the next issue of HTB.

Many other community-based and medical websites produce rapid online reports from the meeting. These sites will cover a wide range of studies not reported in this issue of HTB. Particularly recommended include:

[www.aidsmeds.com](http://www.aidsmeds.com)

[www.thebody.com](http://www.thebody.com)

[www.natap.com](http://www.natap.com)

[www.clinicalcareoptions.com](http://www.clinicalcareoptions.com)

[www.aidsmap.com](http://www.aidsmap.com)

IAS TORONTO: TREATMENT ACCESS

## **Enough is enough: South African activists demand “fire Manto”**

**Polly Clayden, HIV i-Base**

Throughout the conference activists from the Treatment Action Campaign (TAC) demanded that their government “Fire Manto” Dr Manto Tshabalala-Msimang, their nonsense-talking Minister of Health.

TAC activists briefly occupied the South African booth (that they were later accused of trashing which would not have been unreasonable under the circumstances) that, with cruel irony, displayed garlic, lemon and African potato but typically no antiretrovirals.

Their frustrating struggle has not gone unnoticed by the international community, both at the conference and beyond. Stephen Lewis made his position very clear in his closing address: “South Africa is the unkindest cut of all. It is the only country in Africa, amongst all the countries I have traversed in the last five years, whose government is still obtuse, dilatory and negligent about rolling out treatment. It is the only country in Africa whose government continues to propound theories more worthy of a lunatic fringe than of a concerned and compassionate state. Between six and eight hundred people a day die of AIDS in South Africa. The government has a lot to atone for. I’m of the opinion that they can never achieve redemption.”

As did Mark Weinberg: “We went to the Durban meeting, expecting a South African government that would be on the same side as us. Instead, we found a denialist president who turned his back on us... and who began to convene committees that would articulate on his behalf that somehow it was in dispute whether or not HIV was truly the cause of AIDS ... We were all completely taken aback, we were all insulted. ... I for one am no longer prepared to take a back seat as a scientist and not express my personal concern that this situation seems to have continued unabated.”

And on 4 September 2006 a letter was sent to South Africa’s President Thabo Mbeki from over 80 leading HIV scientists “to support and endorse Dr Wainberg’s words.”

They write: “To deny that HIV causes AIDS is farcical in the face of the scientific evidence; to promote ineffective, immoral policies on HIV/AIDS endangers lives; to have as Health Minister a person who now has no international respect is an

embarrassment to the South African government. We therefore call for the immediate removal of Dr Tshabalala-Msimang as Minister of Health, and for an end to the disastrous, pseudo-scientific policies that have characterised the South African Government's response to HIV/AIDS."

TAC, which launched protests against the health minister last month welcomed the letter and continue to step up their national campaign for a united and rational South African response to AIDS.

TAC have asked for international support for their campaign. In the UK we can get involved or make donations through the Friends of TAC (FoTAC)

[www.fotac.org](http://www.fotac.org)

[www.aidstruth.org/letter-to-mbeki.php](http://www.aidstruth.org/letter-to-mbeki.php)

[www.tac.org](http://www.tac.org)

## Treatment access: more optimistic results from scale up programmes

Simon Collins, HIV i-Base

There were hundreds of posters relating to treatment access that were all very similar in describing successful results from roll-out programmes. All these studies are important. They document treatment success of local, regional or national significance, but contain few medical surprises. And as James McIntyre remarked in his rapporteur's report: "In addition to large scale high impact access programmes thousands of smaller programmes are treating hundreds of thousands of people successfully at a community level." What he called "the long tail of ART access". [1]

In summary, treatment works well for both adults and children in all settings. We just need a lot more of it and successful treatment is often limited by late diagnosis, poor nutrition, TB coinfection (though ARVs reduce the incidence of TB in HIV-infected patients), fees at point of access, and, increasingly, access to second-line treatment.

Adherence rates are often significantly higher than reported in Western studies, characterised in a meta-analysis presented by Mills and colleagues, comparing African and Western studies. [2]

They included 30 studies from North America (2 abstracts) and 22 studies (15 abstracts) from Africa (from 11 Sub-Saharan countries). All African studies were published after 2002. Patient self-report was used to assess adherence in 70% of US and 82% of African studies and similar thresholds for measuring appropriate adherence (eg. 100%, >95%, >90%, >80%) were used. In their pooled analysis, African patients had significantly greater levels of adherence: 77.1% [95%CI 67.3, 85.6] than North American patients: 54.7% (95% CI, 48.0, 61.3), comparison odds ratio 2.5, 95% CI, 2.2 to 2.8, P<0.0001.

Several of the earliest programmes also reported data on durability of treatment. For example, Goemaere and colleagues reported 5-year follow-up data from the Khayelitsha programme, which has been providing free treatment now for over five years. [3]

In this prospective cohort from three clinics outside Cape Town, a preliminary analysis from 1729 adults who started ARVs by the end of 2004, 76% of patients remain in care after four years, of whom 84% are still on their first-line regimen.

Median baseline CD4 count for new patients almost doubled from 46 cells/mm<sup>3</sup> in 2001 to 85 cells/mm<sup>3</sup> in 2004, and mortality over the first 6-months treatment fell from 13% to 7%. Two-thirds of the deaths in the programme occur in first six months. The proportion of patients with viral loads < 400 copies/mL at 6 months remained stable at between 88% and 91%. Toxicity-related treatment changes were reported as 16.7% and 8.3% cumulatively by 36 months, for patients starting with d4T or AZT respectively.

A second study from MSF presented by Sauvageot and colleagues reported >3-year follow-up from over 1,100 adults (>13 years old, 49% women) from 6 MSF programs in 5 countries (Cambodia, Cameroon, Kenya, Malawi, Guatemala). [4]

At baseline, 90% of patients were ART naïve, 89% in WHO stage III/IV, with a median age of 34 years (IQR: 29-41) and a median CD4 count of 62 cells/mm<sup>3</sup> (IQR: 18-136). Baseline median BMI was 20 kg/m<sup>2</sup> (IQR: 18-22). 94% received the 2003 WHO recommended first line regimens (94%).

At 3 years, 768 patients (68%) were still on treatment, 235 (21%) had died, 102 (9%) were lost to follow-up (LTF) and 31 (3%) had transferred care to a different centre. For patients still on treatment, median CD4 level had increased to 326 cells/mm<sup>3</sup> (IQR: 229-463) and BMI to 22 kg/m<sup>2</sup> (IQR: 20-25).

The probability of still being followed at 3 years was 0.71 [95%CI, 0.68-0.73] using death and loss-to-follow-up as endpoints, and 0.87 [95%CI, 0.84-0.89] among patients still on treatment at 1 year. The probability of not developing a new WHO stage IV or III condition was 0.72 [95%CI, 0.70-0.75] and 0.64 [95%CI, 0.61-0.67], respectively. The probability of changing a

single ARV drug because of intolerance or switch to a second line regimen was 0.29 [95%CI, 0.26-0.32] and 0.05 (95%CI, 0.04-0.06), respectively.

Just prior to the conference the WHO released new guidelines for treatment of HIV that included for the first time a caution against using d4T in first line treatment, because of the higher risk of side effects (see later in this issue of HTB). [5] While the virological durability reported in the MSF studies above is important and impressive, an indication of the impact of d4T on lipodystrophy in Africa was given in an MSF study from Rwanda. [6]

All patients (n=226) attending two MSF clinics in Kigali from November 2005-February 2006, who had been on WHO-recommended first line regimens for over one year were assessed for symptoms of lipodystrophy, using a Lipodystrophy Case Definition Study questionnaire and clinical examination

Of the 226 patients assessed, >90% used d4T/3TC-based regimens (187 with nevirapine and 20 with efavirenz). Only 19 patients used AZT/3TC-based regimens (n=13 with nevirapine and 6 with efavirenz).

Mean (SD) age/time on HAART was 38 (+/-8) years and 18.1 (+/-4.5) months; 77% were women. Body fat changes were reported by 65 patients and clinically confirmed in 56 cases, resulting in an overall prevalence of 24.8%. Fat loss was observed in 11.8% (n=24); fat accumulation in 4.5% (n=9), and mixed patterns in 10.7%(n=23);

Women were more likely to have lipoatrophy (fat loss) compared to men (p=0.01). Use of d4T was significantly associated with lipodystrophy in general (p=0.04) and fat loss in particular (p=0.02). Baseline and maximal weight on HAART were significantly higher in patients with lipoatrophy (7+/-2 and 8+/-2 kg difference, respectively (p<0.01)). Lipoatrophy was associated with recent onset weight loss (-5.1+/-2.9 kg vs -1.0 +/-0.9 kg p<0.001), occurring at a faster rate (0.52 +/-0.07 kg/wk vs 0.18 +/-0.02 kg/wk, p<0.001). No association of lipodystrophy/lipoatrophy was seen with clinical/immunological parameters, age of patients and time on HAART.

In Kevin de Cock's plenary from "3 by 5" to universal access he showed that the scale of treatment of women has run in parallel and sometimes exceeded the feminisation of the epidemic in high prevalence countries; and that 60% -70% of adults receiving treatment are women. [7]

TB is the leading cause of death in Africa and in many places the leading cause of death for people with HIV.

A very concerning study of "extensively drug resistant" (XDR) TB reported by Neel Gandhi from KwaZulu South Africa reported a high prevalence acquired both nosocomially and in the community with a very high mortality rate. [8]

A total of 10% of all positive TB isolates were not only resistant to INH and rifampicin (MDR TB), but also XDR, resistant to all first and second line TB drugs (INH, rifampicin, ethambutol, streptomycin, ciprofloxacin, kanamycin). Most people had no prior history of TB therapy and 36% had no prior hospitalisation. Two health care workers (and possibly four others were infected with XDR TB and died). Of all people with XDR TB, 98% died.

#### References

Unless stated otherwise, all references are to the Programme and Abstracts of the XVI International AIDS Conference, Toronto, Canada. 13-18 August 2006. ([www.aids2006.org](http://www.aids2006.org))

1. McIntyre J. Rapporteur Report, Track B. FRPL0102.
2. Mills E, Nachega J, Buchan I et al. Adherence to antiretroviral therapy in Africa versus North America: a meta-regression analysis. TUPDB03.
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4. Sauvageot D, Ferradini L. Clinical and immunological long-term outcomes on adults after 3 years of ART in "Médecins Sans Frontières (MSF)" programs: a multicentric analysis. Abstract WEPE0074.
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7. de Cock K. From "3 by 5" to universal access. Plenary session. Oral abstract WEPL01.
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IAS TORONTO: NEW ANTIRETROVIRALS

The most exciting new clinical science at the conference mainly occurred in the extended session for late breakers for Track B. This is one of the few clinical science sessions that is available as a webcast.

## Integrase inhibitor MK-0518: early results show greater early potency than efavirenz

Simon Collins, HIV i-Base

The most exciting data at this meeting probably related to the late breaker from Merck, that presented limited 24-week data from a phase-II study of their integrase inhibitor MK-0518 in treatment-naive patients. [1]

Marty Markowitz from the Aaron Diamond Institute presented results from a two-part, five arm, 48-week, dose-finding study. For the first ten days, 40 patients were randomised to receive MK-0518 monotherapy dosed at 100, 200, 400, or 600 mg or a placebo, twice daily. After an interim analysis (reported at CROI this year [2]), 150 new patients were randomised to either one of the MK-0518 doses plus tenofovir/FTC, or the comparator arm of efavirenz/TFV/3TC. Patients from part one continued the same dose of MK0518 in part two, adding TDF/FTC.

Mean baseline CD4 and viral load were 270-330 cells/mm<sup>3</sup> and 4.6-4.8 log copies/mL respectively, with 29-43% diagnosed with AIDS, across the groups. Approximately 80% were male, and 70-90% were Caucasian. Baseline characteristics are detailed in Table 1.

**Table 1: Baseline characteristics in MK-0518 phase II study**

			400mg	600mg	
n	39	40	41	40	38
% male	85	73	90	73	76
% Caucasian	18	35	34	35	32
Mean CD4	314	296	338	271	280
HIV RNA log	4.8	4.8	4.6	4.8	4.8
% with AIDS	31	33	29	43	37

Although the printed abstract included limited 16-week data, the oral presentation reported here included 24-week data on 202 patients.

In summary, all groups showed a -2.0 log drop in viral load by week 2, that was sustained out to week 24. Suppression to <50 copies/mL at week 24 was achieved by 90-95% of patients receiving higher doses of MK-0518 compared to 92% of patients receiving efavirenz and 87% of the low dose MK-0518. These differences were not statistically significant.

However, when looking at early response at weeks 4 and 8, a statistically significant difference in the percentage of patients reaching <50 copies/mL was seen in all MK-0518 groups compared to the efavirenz arm (p<0.001). The approximate differences were 60-70% vs 20% at week 4 and 70-80% vs 40% at week 8. The clinical implications are unclear, but this early higher potency compared to the current best standard of care, generated much of the excitement over this drug.

CD4 increases were similar in all arms: approximately +50-100 cells/mm<sup>3</sup> at week 2, increasing to +100-150 cells/mm<sup>3</sup> in all groups by week 24. Discontinuations and side effects were low in all groups and are summarised in Tables 2 and 3 respectively.

**Table 2: Discontinuations over 24 weeks**

	MK- 0518 100mg	MK- 0518 200mg	MK- 0518 400mg	MK- 0518 600mg	placebo/ EFV
n enrolled	41	40	41	40	41
n treated	39	40	41	40	38
D/c bywk24	0	5	1	2	2
Efficacy	0	2	0	0	0
Side effect	0	0	0	1	0
Other	0	3	1	1	2

**Table 3: Side effects reports >5% patients**

	MK-0518 (all doses)	EFV
Nausea	11	13
Headache	9	24
Dizziness	8	26
Diarrhoea	7	11
Insomnia	7	11
Abnormal dreams	6	18
Flatulence	6	-

Additional side effects seen at >5% in the efavirenz group included nightmares (11%), vomiting (8%), malaise (8%), fatigue (5%), disturbance in attention (5%), lethargy (5%), anxiety (5%)

Most clinical side effects were mild to moderate. There were 8 serious adverse events overall (7/160, 4% in the 4 MK-0518 groups, 1/38, 3% in EFV group); none were considered drug related. There was one discontinuation for increased AST/ALT. Grade 3 / 4 laboratory abnormalities were uncommon.

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C O M M E N T

**Integrase is one of three virally encoded enzymes that is essential for HIV replication. While reverse transcriptase and protease have proved effective targets for drug development, despite many years of research, largely led by Merck, compounds that target integrase, have only recently shown efficacy *in vivo*. It is very exciting to see this data.**

**Integrase regulates a two-step process including initial chain termination followed by strand transfer where RT-transcribed viral DNA becomes integrated into host cell DNA. MK-0518 is active at the second of these stages.**

**While MK-0518 will still need to be used in combination with other active drugs, *in vitro* resistance data suggests that there is not a particularly low barrier to resistance. At dosing 100mg twice daily, mean plasma concentrations at 12 hours produced drug levels over the IC95. Based on the results of this study, Phase 3 studies will go forward at 400mg BID dose. Lack of interactions with other drugs cleared by P450 pathway, or with food, is also important.**

**Although the FDA are fast-tracking the approval process for MK-0518, this is still very early data from a small number of patients. Other promising drugs have shown problems in Phase 3 studies due toxicity that only became apparent when studied in larger groups, and last years excitement over CCR5 inhibitors is tempered by later concerns in two of the three lead compounds. Nevertheless, other characteristics of MK-0518 suggest this may be appropriate for research into numerous strategies: treatment experienced patients, PEP, PrEP, and earlier initiation of treatment. Perhaps most importantly is an option for second-line therapy in resource-limited countries given the less complicated manufacturing process (and the potential to cost less than any protease inhibitor) and independence from ritonavir boosting.**

**An expanded access programme is scheduled to start in the US in September 2006, and EAP programmes are expected to start in Europe and the UK in the new few months.**

**For more details in the UK contact the medical information department at MSD on 01992-467272.**

**Patients can be registered for the expanded access programme at:**

**<http://www.earmrk.com>**

References

1. Markowitz M, Nguyen B-Y, Gotuzzo E et al. Potent antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, as part of combination ART in treatment-naïve HIV-1 infected patients. Late breaker abstract THLB0214.
2. Grinsztejn B et al. Potent antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. 13 CROI Abstract 159LB. See HTB March 2006.  
<http://www.i-base.info/htb/v7/htb7-3/Early.html>

## Maraviroc results in R5/X4 mixed/dual tropic patients: unexpected safety data shows possible immunological effect

Simon Collins, HIV i-Base

Of the three CCR5 inhibitors in development last year, only the Pfizer compound (maraviroc) is showing continued promise as a treatment for both naïve and treatment experienced patients. [1, 2]

The rationale for studying maraviroc (MRV) in patients with dual/mixed (D/M)-tropic infections includes the theoretical risk of outgrowth of X4-tropic HIV-1 when a patient with D/M-tropic HIV-1 is treated with a CCR5 antagonist and because X4-tropic HIV-1 has been associated with more rapid CD4 cell depletion and progression to AIDS.

Mayers and colleagues presented results from a double-blind placebo controlled study in 190 mixed/dual tropic patients who were randomised to optimised background regimen (OBT) including at least one sensitive drug, plus either maraviroc once-daily (n=63), maraviroc twice daily (n=61) or placebo (n=60). [3]

Over 90% patients were PI-experienced, with 50-60% currently using T-20. CD4 count and viral load were <100 cells/mm<sup>3</sup> and > 5logs respectively. >95% patients had dual/mixed tropism. Further baseline characteristics and tropism are detailed in Table 1.

**Table 1: Baseline characteristics and tropism**

	Placebo + OBT n = 62	MRV QD + OBT n = 63	MRV BID + OBT n = 61
Mean age (ys), (range)	44.6 (23–65)	42.7 (16–59)	42.5 (16–62)
Female, n (%)	9 (14.5)	10 (15.9)	6 (9.8)
Race, n (%)			
- White	40 (64.5)	46 (73.0)	44 (72.1)
- Black	18 (29.0)	17 (27.0)	13 (21.3)
- Other	4 (6.5)	0 (0)	4 (6.6)
Tropism, n			
- X4	2	2	4
- R5	0	1	0
- NP/NR	2	3	5
- D/M	58	57	52
CD4 (cells/mm <sup>3</sup> )			
Mean	99	85	96
Median	42	40	43
(min, max)	(2, 650)	(1, 442)	(0, 615)
HIV-1 RNA (log <sub>10</sub> c/mL)			
Mean	5.01	5.03	5.10
Median	5.10	5.10	5.17
(min, max)	(3.65, 6.15)	(3.43, 5.94)	(3.61, 6.67)

After 24 weeks, the mean decrease in viral load was similar between the maraviroc and placebo arms, but there was a statistically significant increase in CD4 counts in the maraviroc groups compared to placebo, which are detailed in Table 2.

There were 13 category C events: MRV QD (7), MRV BID (3), placebo (3). None of the 7 deaths in the study (MRV QD (2), MRV BID (2), placebo (3)) were considered MRV-related.

The study concluded that over 24 weeks, in treatment-experienced patients with D/M-tropic HIV-1 and advanced disease, maraviroc + OBT was generally well tolerated. There were no cases of hepatotoxicity, lymphoma or adenocarcinoma. Although the treatment arms did not demonstrate superior reductions in HIV-1 RNA compared with placebo, maraviroc + OBT was associated with greater increases in CD4 cell count than placebo + OBT.

Patients receiving maraviroc + OBT were more likely to fail with X4-tropic HIV-1 than those receiving placebo + OBT. However, patients treated with maraviroc and X4-tropic virus at treatment failure had increases in CD4 cell count consistent with the overall maraviroc-treated population.

**Table 2: Virologic and immunologic responses at week 24**

<i>All treated patients with D/M-tropic HIV-1</i>	Placebo + OBT n = 58	MRV QD + OBT n = 57	MRV BID + OBT n = 52
Mean decrease in HIV-1 RNA (log <sub>10</sub> c/mL)*	-0.97	-0.91	-1.20
Treatment diff (MVC-OBT) in HIV-1 RNA decrease (log <sub>10</sub> c/mL) (97.5% CI)	-	+0.06 (-0.53, +0.64)	-0.23 (-0.83, +0.36)
RNA < 400 c/mL (%)	24.1	24.6	30.8
RNA < 50 c/mL (%)	15.5	21.1	26.9
Mean decrease in RNA in pts using T-20** (log <sub>10</sub> c/mL)	-0.89	-1.26	-1.44
Mean CD4 change (cells/mm <sup>3</sup> , mean)			
All treated patients with D/M-tropic HIV-1	+36 (n=58)	+60 (n=57)	+62 (n=52)
Mean CD4 change (cells/mm <sup>3</sup> , mean)			
Pts with only X4-tropic HIV-1 detectable at time of virologic failure	-104 (n=2)	+48 (n=12)	+33 (n=12)

**C O M M E N T**

**While virological response in this study was similar to placebo, this was expected in dual-tropic patients. More significant is the lack of HIV progression in this group, which was the main safety concern.**

**The safety from short-term exposure to a CCR5 inhibitor in patients with mixed tropism at baseline, may also indicate a lower dependence on a tropism test prior to treatment, especially as the current test is relatively insensitive and expensive.**

**The CD4 increase in the maraviroc arm was unexpected and deserves further investigation.**

References

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3. Mayer H, van der Ryst E, Saag M et al. Safety and efficacy of maraviroc, a novel CCR5 antagonist, when used in combination with optimised background therapy for the treatment of antiretroviral-experienced subjects infected with dual/mixed-tropic HIV-1: 24-week results of a phase 2b exploratory trial. IAS Toronto, 2006. Abstract late breaker THLB0215.

## **Vicriviroc 24-week results in triple-class experienced R5-tropic patients**

**Mike Youle, for natap.org**

After the disappointment of earlier vicriviroc studies it was comforting to see some positive news with the late-breaker presentation by Trip Gulick of the ACTG5211 study assessing 3 doses of vicriviroc (VCV) against placebo in the highly experienced R5-tropic patient population.

One hundred and eighteen subjects (median VL 36,380 copies/mL and CD4 146 cells/mm<sup>3</sup>) were randomised within the study and viral load declines were significantly greater in all three vicriviroc arms compared to placebo at day 14 and week 24 (p<0.05; ITT analysis).

Although not statistically significant the lower dose of 5mg resulted in more virologic failures and greater X4 virus emergence in that arm. Thirty three per cent of participants were already experienced to T-20 (enfuvirtide). The group was 92% male, 66% Caucasian, 20% Black and 12% Hispanic.

Tropism at study entry was R5 only in 86% patients with only 10% with dual or mixed tropic. Considering that at screen, a few weeks before this, all were R5 only goes to show some of the limitations of the current technology to exactly decide the tropism of a patients' virus. However, emerging data that even mixed/dual tropic virus responds to R5 receptor blockers may make the use of such an assay less vital.

Viral load reductions of >-1.5 logs were seen in at all VCV doses at week 24 (compared to -0.2log in OBT alone with CD4 increases of +84-142 compared to no change in the OBT alone group, and are detailed in Table 1.

When the responses were broken down by baseline tropism, good suppression was seen even in the X4/R5 tropic populations.

In a poster from Angela Sanone from Schering-Plough the effect of combining the vicriviroc with a range of boosted protease inhibitors (atazanavir, saquinavir, indinavir, fosamprenavir and tipranavir; also unboosted nelfinavir) was evaluated in a pharmacokinetic study in healthy volunteers. It seems that the addition of any of these agents has negligible effect on the key VCV PK parameters and no significant adverse events were reported. Clearly, further data will be needed with boosted lopinavir and with TMC114 (darunavir).

**Table 1: Results of vivriviroc dose-finding study**

	5mg QD	10mg QD	15mg QD	OBT only
N	30	30	30	28

Mean log change in viral load

Day 14	-0.87	-1.15	-0.92	-0.08
Week 24	-1.51	-1.86	-1.68	-0.20
Change in CD4				
Week 24	+84	+142	+142	0
Tropism switch to X4/R5 or X4	27%	10%	7%	4%

This article is part of a longer report on new antiretroviral studies at the conferences, available at:

<http://www.natap.org>

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1. Gulick R, Su Z, Flexner C et al. ACTG 5211: phase II study of the safety and efficacy of vicriviroc in HIV-infected treatment-experienced subjects. Late breaker abstract THLB0217.
2. Sansone A, Keung A, Tetteh E et al. Vicriviroc (VCV) pharmacokinetics (PK): lack of impact of ritonavir (RTV)-boosted protease inhibitors (PI). Poster abstract TUPE0074.

## **Etravirine (TMC-125) associated with -1 log viral load reduction at 48-weeks results in treatment experienced patients**

**Simon Collins, HIV i-Base**

Cal Cohen from Community Research Initiative of New England, Boston reported 48-week results from the Tibotec randomised, controlled, Phase II study of etravirine (TMC-125) in 199 treatment experienced patients with documented NNRTI resistance and 3 or more primary PI mutations.

Patients were randomised to TMC125 (400 mg or 800 mg bid) with an investigator selected background, or standard-of-care control regimen. Median baseline CD4 and viral load were 100 cells/mm<sup>3</sup> and 4.7 log copies/mL respectively.

Mean reductions viral load (ITT, NC=F) were -0.88, -1.01 and -0.14 logs for the 400mg, 800mg and control arms respectively (p<0.05 for both TMC doses compared to control). CD4 cell counts increased by +58, +61 and +13 cells/mm<sup>3</sup>, for the 400mg, 800mg and control arms respectively (see Table 1).

**Table 1: Results of etravirine (TMC-125) at 48-weeks**

	400mg	800mg	control
Mean VL change (log)	-0.88 *	-1.01 *	-0.14
Mean CD4 change	+58	+66	+13
VL failure	9%	9%	78%
Med. duration of Rx (wks)	48 wks	48 wks	18 wks

\* P <0.05 compared to control

The study design allowed patients with virological failure in the control group to leave the study after 16 weeks and access etravirine on an open-label basis. This confounded the comparison of safety by the lower median duration of treatment in the control arm of 17.9 weeks, versus 47.7 weeks in both TMC125 groups. Grade 3/4 side effects (all causes) were reported in 43% of patients on TMC125 and 17% patients discontinued etravirine due to side effects.

The principle importance of etravirine is the response to NNRTI-experienced patients. At baseline, patients had a median of 2 NNRTI mutations and the phenotypic median fold-change to efavirenz, nevirapine and etravirine was 41, 61, and 1.7-fold, respectively. The virologic response by number of NNRTI mutations at baseline is shown for the 800mg group is shown in Table 2.

**Table 2: Response to 800mg BID etravirine by baseline NNRTI resistance**

# mutations	0	1	2	3 or more
N (%)	14 (18%)	19 (24%)	16 (20%)	30 (38%)
Mean D VL	-1.67	-1.38	-0.90	-0.54

No single NNRTI mutation was associated with an arbitrary >10-fold mean change, although clinical cut-offs for etravirine still have to be established from larger trials. 12% patients had a combination of mutations that generated >10-fold reduced susceptibility to etravirine, always including one or more from K101P, V179E/F, Y181I/V G190S and M230L, and always with at least 4 other mutations.

The dose selected for Phase III studies is 800mg BID, which requires 2 x200mg pills, twice-daily.

Reference:

- Cohen C, Steinhart C, Ward D et al. Efficacy and safety results at 48 weeks with the novel NNRTI, TMC125, and impact of baseline resistance on the virologic response in study TMC125-C223. Abstract TUPE0061.

## Three-class experienced patients experience 1 log viral load reduction using monoclonal antibody TNX-355

Simon Collins, HIV i-Base

The late-breaker session also included a presentation of 48-week results from Tanox's monoclonal antibody, TNX-355, in 82 triple-class experienced patients (87% male, 46% Causasian, mean age 46. [1]

TNX-355 is a humanised monoclonal antibody that binds to domain 2 of the CD4 receptor, blocking entry of HIV-1 into target cells. This randomised, double-blind, placebo-controlled study used two doses of TNX-355 plus optimised background regimen (OBR) compared to placebo plus OBR. The primary endpoint was mean change in viral load at week 24 (reported at ICAAC last year [2]), with additional safety and efficacy data presented in this analysis through to week 48.

TNX-355 was given intravenously 10mg/kg once-weekly for 9 weeks followed by either 10mg/kg. 15mg/kg or placebo every 2 weeks. All patients received OBR. After virologic failure (< 0.5 log<sub>10</sub> drop from baseline after week 16), patients received 15 mg/kg open-label TNX-355 every two weeks in combination with new OBR. This was a generally male, Caucasian study, with CD4 counts 200-300 cells/mm<sup>3</sup> and viral load 4.8 logs. Further baseline characteristics are detailed in Table 1.

Both TNX-355 arms showed sustained viral load reductions of -0.7 to -0.9 logs at week 48 compared to placebo, which was matched by mean CD4 increases of around +50 cells/mm<sup>3</sup> (detailed in Table 1). Time to loss of virologic response (TLVR) was 230 and 253 days in the 10mg and 15mg arms respectively, compared to 0 days in the placebo group. Although all groups received OBR, T-20 was not allowed in the study, and details on the use of OBR drugs were not presented.

**Table 1: Baseline characteristics and ITT responses to TNX-355**

	15mg/k g+ OBR	10mg/kg +OBR	placebo + OBR
N	28	27	27
Age	47	44	46
% male/female	78/22	93/7	89/11
Baseline CD4 (%<200 c/mm <sup>3</sup> )	299 (26%)	223 (51%)	245 (43%)
Baseline VL (%>5log)	4.8 (26%)	5.0 (57%)	4.8 (33%)
Mean change in CD4+	+51 (p=0.016)	+48 (p=0.031)	+1
Mean VL change wk-48	-0.71 (p<0.010)	-0.96 (p<0.001)	-0.14

N (%) $\geq$ 1.0 log reduction	9 (32)	10 (37)	3 (11)
N (%) $\geq$ 0.5 log reduction	11 (39) (p=0.029)	12 (44) (p=0.014)	3 (11)
% <400 (%<50) copies/mL	7 (4)	4 (0)	0 (0)
Median TLVR (days)	253 (p=0.003)	230 (p=0.003)	0

#### References

- Norris D, Morales J, Godofsky E et al. TNX-355, in combination with optimized background regimen (OBR), achieves statistically significant viral load reduction and CD4 cell count increase when compared with OBR alone in phase 2 study at 48 Weeks. Late breaker abstract THLB0218.
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## New data on darunavir (TMC-114)

Mike Youle, [natap.org](http://natap.org)

Two posters in Toronto dealt with data for POWER 3 darunavir study. This is the follow-up study in treatment experienced patients, in which all subjects received TMC114/r 600/100mg from baseline, plus optimised background regimen (OBR).

POWER 3 was non-randomised, open-label and enrolled 327 patients: 75% Caucasian, 87% male, with a mean entry viral load of 4.62 log and CD4 count of 115 cells/mm<sup>3</sup>. To assess if there was any relationship between drug exposure and efficacy or safety, trough and peak PK samples were taken at week 4, and baseline resistance measurements was used to calculate the inhibitory quotient (IQ) of the drug. The IQ calculates how much drug is needed to deal with the amount of resistance that exists in an individual to that drug. [1]

It appears from these data that TMC114 IQ was a strong predictor of virologic outcome, which is not surprising, and that most of this is driven by the baseline resistance fold change to the drug and not TMC114 exposure levels. With regard to safety, there seemed to be no association of TMC114 drug levels with adverse events and it is comforting that any signature toxicity has not appeared with this compound. The second POWER 3 analysis presented by Jean-Michel Molina showed results to be broadly similar to the first two studies with 65% having a >1log drop in HIV RNA by week 24, 40% reaching <50 copies/mL and a mean VL reduction of -1.65log. [2]

The most common adverse events were diarrhoea (14%), nasopharyngitis (11%) and nausea (10%). Grade 3 or 4 triglyceride, cholesterol, and liver function enzyme elevations occurred in 6%, 4%, 2% and 2% of patients, respectively, similar rates to these seen in previous TMC114/r studies.

Finally Sharon Walsmley from Toronto gave an oral presentation on the week 48 combined analysis of the POWER 1 and 2 studies which included 241 subjects treated with TMC114 compared to 244 patients who received comparator PI (CPI) regimens. [3]

Ninety one TMC114 subjects were <50copies/mL compared to 22 given CPI (p<0.001) and the breakdown by baseline subgroups is shown in Table 1 below.

**Table 1: Virologic response (<50 c/mL) at Week 48 and use of T-20**

	TMC-114 600/100	OBR only
T-20 used (naive)	58%	10%
T-20 used (non-naive)	15%	5%
T-20 not used	45%	8%
0 sensitive ARV in OBR	20%	0
>1 sensitive ARV in OBR	54%	10%

Clearly the use of enfuvirtide (T-20) within the background regimen is important for those patients still sensitive to the agent. CD4 cell responses were good in the TMC114 groups +92/102 cells/mm<sup>3</sup> compared to +17/19 cells/mm<sup>3</sup> in the CPI group ; p<0.001 and P<0.05 respectively for Power 1 and 2). Adverse events were similar to those seen earlier with around 20% reporting diarrhoea and 15% headache; the majority of adverse events were grades 1 and 2. A word of caution is that it is always difficult to assess side effects in this group of late stage patients since immune reconstitution can produce many constitutional symptoms also.

## References

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3. Lazzarin A, Queiroz-Telles F, Frank I et al. TMC114 provides durable viral load suppression in treatment-experienced patients: POWER 1 and 2 combined week 48 analysis. Oral abstract TUAB0104.

IAS TORONTO: TREATMENT STRATEGIES AND APPROVED ARVS

## Lopinavir monotherapy: less potent than triple therapy with higher risk of resistance

Simon Collins, HIV i-Base

Four oral presentations - three of them late-breakers - and at least four posters presented results from various strategies looking at lopinavir/r monotherapy (see Table 1).

The most successful approach was reported for treatment naïve patients reducing to monotherapy after previous suppression <50 copies/mL for  $\geq 6$  months on triple therapy. However, results were not very dissimilar for treatment-naïve patients starting with monotherapy outright, though the numbers in these studies were also small.

While few patients failed outright, or showed lopinavir-associated mutations, at least one of the studies highlighted a major difference: a significantly greater proportion of patients receiving monotherapy experienced viral rebound to between 50-400 copies/mL, compared to patients receiving triple therapy. This is the one factor that has historically been shown to impact on long-term durability of other ARV triple regimens.

Bill Cameron from the University of Ottawa presented two-year results from 155 treatment naïve patients randomised 2:1 to lopinavir/r plus AZT/3TC for at least 6 months followed by lopinavir/r maintenance therapy, or to a control arm of efavirenz plus AZT/3TC triple therapy. In the primary analysis, 50% of the monotherapy arm compared to 61% of the triple therapy suppressed viral load to <50 copies/mL at week 96 (ITT,  $p=0.23$ ). [1]

However, Kaplan-Meier analysis showed that the proportion maintaining <50 copies/mL was 62% vs 91%, in favour of efavirenz-based triple therapy was statistically significant ( $p=0.002$ ). Although most patients on the lopinavir/r arm re-suppressed on continued monotherapy (11/12) or with addition of RTIs (1/12), new PI mutations (generally only very rarely reported with lopinavir/r triple therapy) were seen in (2/15) 13% lopinavir/r-blipping patients.

Also as a late breaker, Jean-Francois Delfraissy and colleagues from the Kremlin Bicêtre Hospital Paris, presented 48-week results from the Monark study that randomised 136 treatment naïve patients to initial lopinavir/r monotherapy ( $n=83$ ) or lopinavir/r plus AZT/3TC ( $n=53$ ). [2]

Similar to the first study, lopinavir/r monotherapy was associated with more episodes of viremia compared with triple-drug therapy, with approximately 10-15% patients at any point after week 16 having viral load 50-400 copies/mL, (84% vs 98% patients had viral load <50 copies/mL in the on-treatment analysis,  $p=0.03$ ).

CD4 responses and tolerability were similar between the two groups, but protease-associated mutations again occurred more frequently in the monotherapy arm (2/83) compared to a single RT mutation (M184V) in the triple therapy arm.

José Arribas presented results from a Spanish study that randomised 198 patients suppressed on current lopinavir/r-based treatment <50 copies/mL for the previous 6 months, and who had no previous history of protease resistance, to continue triple therapy or reduce to lopinavir/r monotherapy. [3]

After 48 weeks, there were no statistically significant differences between the monotherapy vs triple-therapy groups: the percentage of patients without therapeutic failure >400 copies/mL (94% vs 90%), % suppressed to <500 copies/mL (89% vs 90%) and <50 copies/mL (85% vs 90%). PI resistance however was detected in 2/2 monotherapy vs 1/3 triple therapy patients with confirmed viral rebound.

Several other smaller studies looked at boosted PI-monotherapy. In an oral presentation in the main conference programme, Nunes and colleagues reported on interim 48-week results of a 96-week reduction therapy trial in 60 patients in Brazil, with similar response rates to the studies above, but this study included no resistance data. [4]

Two small non-controlled studies from the UK reported on results from lopinavir/r monotherapy in specific patients with restricted options for triple therapy, and perhaps best described real world settings where individualised may show a role for lopinavir/r monotherapy.

A poster by L Waters and colleagues from the Chelsea and Westminster Hospital in London reported on 35 treatment-experienced patients in their database who were using lopinavir/r and who had previously had low adherence on triple combinations. [5]

At switch, patients had mean CD4 and viral load of 248 cells/mm<sup>3</sup> and 54,866 copies/mL respectively, and had used a median of 5 previous drug regimens. 14/28 (50%) achieved VL<50 copies/ml and 73% a >1 log reduction. Mean CD4 rise was +115 and +73 cells/mm<sup>3</sup> in the undetectable and viraemic groups respectively. Of the 5 patients with major PI mutations at baseline, 3 experienced satisfactory responses (CD4 increase; 2 undetectable, 1 <400 copies/mL). 2/10 patients with genotype results on monotherapy developed new minor mutations. 8/28 subjects switched therapy (3 virological failure, 2 for blips, 1 immunological failure and 2 unclear reasons) and 20 remain on lopinavir/r monotherapy, 12/20 remaining undetectable after a mean of 13.5 months (range 3-34).

In a second small study from London, N Martin and colleagues from Mortimer Market Centre, presented retrospective results from a database review of 13 patients using monotherapy with lopinavir/r (n=13) or atazanavir/r (n=3). [6]

Median age was 41 (range 3-54) years. Reasons for choosing monotherapy over alternative regimens included co-existing medical conditions [renal failure, TTP, lymphoma and hereditary mitochondrial toxicity (n=8)], drug toxicity (n=6), known genotypic resistance (n=6), and known poor adherence (n=2).

Median CD4 and viral load at baseline were 190 cells/mm<sup>3</sup> and 5,100 copies/mL respectively. Although at the start of monotherapy only 4/16 patients had VL<50 copies/mL, after 12 weeks 7/14 (50%) and 9/14 (64%) achieved virological suppression to <50 copies/mL and <400 copies/mL, respectively. Of the remaining five, 2 stopped therapy due to intolerance and 3 failed to suppress, with VL between 1000 and 8200 copies/mL after a mean of 10 weeks.

An example of where lopinavir/r was clearly unsuccessful was in a small study by Falci and colleagues from Brazil, where 3/3 treatment experienced patients suppressed to <50 copies/mL for the previous 6 months, failed when switched to lopinavir/r once-daily compared to 2/12 (20%) on twice-daily lopinavir/r (p=0.02). Median time for failure was 10(6-16) months. [7]

**Table 1: Selected lopinavir/r monotherapy studies at Toronto**

Study reference	Design	no. pts in study	Tx experience	VL results (mono vs triple)	Follow-up	New PI Resistance
Cameron [1]	Triple Tx >6mo, randomised to monotherapy	155	Tx-naïve	50 vs 61% <50 c/mL (NS), but 62 vs 91% with no rebound (p=0.002)	96 weeks	Yes. New PI mutations in 2/15 (13%)
Delfraissy JF [2]	Mono vs triple	136	Tx-naïve	84% vs 98% (OT, p=0.03)	48 weeks	2/83 (mono) vs 1/53 (triple)
Arribas [3]	Reduction	198	Tx-experienced, no PI resistance	89 vs 90% <50 c/mL	48 weeks	2/2 failures
Nunes [4]	Reduction	60	On-treatment	86 vs 83% (NS) <80 c/mL	48 weeks	No data. IxVF in each arm
Waters [5]	Reduction	35	Tx-experienced	50% <50 copies/mL	13 mo (3-34)	2/10 (20%)
Matin [6]	Reduction Tx-exp	16	Tx-experienced	7/14 (50%) <50 c/mL	12 weeks	Not given
Falci [7]	Reduction	15	Tx-experienced	3/3 Tx-exp failed QD vs 2/12 LPV/r mono BID (20%) BID	10 mo (6-16)	No new PI Rx

#### C O M M E N T

These results are important because of the early hopes for lopinavir/r monotherapy and many people may still interpret these studies as not a bad option for 'some' patients. However, apart from cost, there are few reasons not to use the additional benefit from RTIs given the reduced pill count and side effect profile of recent formulations.

Reports from the Resistance Workshops in the July edition of HTB provided greater detail about the resistance for the M-613 and Monark studies. It was notable both that resistance to lopinavir/r occurred and that 20% patients experience viral rebound 50-500 copies/mL over during follow-up. The effect in the CNS and other compartments is unknown (see report on atazanavir/r monotherapy below).

The durability of other regimens has is limited by low level viral load <50-500 copies/mL and this is also likely to impact on longer term use of monotherapy. Although not yet shown in studies, this is likely to progressively increase the risk of resistance and treatment failure over several years.

Several commentators, including James McIntyre, the lead rapporteur for Track B studies, have suggested that these risks may be acceptable as a holding strategy, in resource-poor settings where access to second-line treatment is limited, even though additional nucleosides clearly provide optimal results. However, the higher cost of any second line treatment is currently prohibiting use of lopinavir/r in most settings, despite the reduced price of \$500 pa in the poorest countries.

The UK case reports, while uncontrolled and retrospective, provide examples of where monotherapy may provide an option in highly individualised care.

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## Atazanavir/r monotherapy and CNS penetration

Simon Collins, HIV i-Base

Vernazza and colleagues presented results looking at the compartmental effect of reducing treatment to ritonavir-boosted atazanavir monotherapy in 30 patients (28 male) suppressed to <50 copies/mL on triple therapy.

HIV viral load was measured every 4 weeks, and semen and cerebro-spinal fluid (CSF) samples were obtained from consenting patients at baseline (semen) and Wk24 (semen+CSF). The primary endpoint was defined as 2 consecutive viral load values >400 copies/mL.

One patient failed monotherapy at week 8 who was retrospectively shown to have previously failed a PI based HAART. One patient prematurely terminated treatment at week 20. All remaining 27 patients had suppressed viral load <100 copies/mL at week 24. 22 patients still remain on ATV/r with a median follow-up of 19 months (6–29) and a mean CD4 increase of 78 cells/mL.

19 CSF samples were obtained at week 24, 3 patients had detectable HIV-RNA in CNS (2.2, 2.9, 3.8 log<sub>10</sub> cp/ml) despite fully suppressed HIV-RNA in blood, although all three CSF samples were wild type. Viral load was undetectable in all semen samples (n=15).

The authors concluded “limited penetration of PI into CNS may result in replication of wild-type HIV in the CNS in a relevant subset of patients. As the consequence of low-level HIV replication in different compartments is not known, future monotherapy trials should include careful monitoring of compartments other than blood. Mono-maintenance, however, might be a valid option for future studies.”

Ref: Vernazza P, Daneel S, Schiffer V et al. Risk of CNS-compartment failure on PI monotherapy (ATARITMO-study). Poster abstract WEPE0073.

## Fosamprenavir/r is non-inferior to Kaletra in treatment naïve patients

Simon Collins, HIV i-Base

Joseph Eron from the University of North Carolina presented 48-week data from a large international randomised open-label study comparing fosamprenavir and lopinavir/r in 878 treatment naïve patients, which showed no significant differences between the two treatments in any analysis. [1] This study was published in the 5 August HIV/AIDS edition of the Lancet which has free online access. [2]

Both groups used twice-daily PI regimens and all patients also received fixed dose abacavir/3TC once-daily, with switching allowed for suspected abacavir hypersensitivity (HSR).

Median baseline CD4 and viral load counts were just under 200 cells/mm<sup>3</sup> (with 15-18% < 50 cells/mm<sup>3</sup>) and 5.1 log copies/mL (with half over 100,000 copies/mL) and are detailed in Table 1. Median age was 37 years; 78% were male; 58% were Caucasian; and 11% were CDC Class C.

**Table 1: Baseline characteristics in KLEAN study**

	FPV/r	LPV/r
N	434	444
Gender M/F %	78/22	78/22
Viral load log/copies/mL (IQR)	5.1 (4.6-5.5)	5.1 (4.6-5.5)
Viral load >100,000 c/mL (%)	55%	53%
CD4 cells/mm <sup>3</sup> (IQR)	188 (88-280)	194 (79-287)
CD4 <50 cells/mm <sup>3</sup> (%)	15%	18%

Primary endpoints were proportion of subjects with viral load <400 copies/mL at week 48, [time to loss of virologic response (TLOVR)] and treatment discontinuations due to adverse events (AEs). Protocol-defined virologic failure (VF) was failure to achieve viral load <400 copies/mL by week 24 or confirmed viral rebound >400 copies/mL.

The two groups had similar results from primary (% <400 c/mL, and discontinuations) and secondary endpoints (%<50 copies/mL, TLOVR, change in CD4), and are detailed in Table 2.

Approximately 71% and 65% in each group maintained viral suppression <400 and <50 copies/mL respectively after one year. Results of the two groups were similar when stratified by baseline viral load >5log or CD4 <50 cell/s/mm<sup>3</sup>,

77% patients (679/878) completed the study: around 100 patients withdrew from each arm before week 48. Discontinuations were similar: adverse events (27/25), lost to follow up (23/32), patients decision (16/9), non-adherence (13/10), virological failure (9/6), other (12/17) in the fosamprenavir/lopinavir groups respectively.

**Table 2: Fosamprenavir/r vs lopinavir/r in treatment-naive patients: 48-week results**

	FOS/r	LPV/r
N	434	444
% VL <400 c/mL, (%) *	73%	71%
% VL <50 c/mL (%)	66%	65%
Median CD4 change c/mm <sup>3</sup> (IQR)	+176 (106-281)	+191 (124-287)
Virological failure; n (%)	16 (4%)	24 (5%)
Drug-related Grade 2-4 AEs; n (%)	55 (13%)	46 (10%)
Discontinuations due to AEs; n (%)	53 (12%)	43 (10%)

\* (95% CI -3.26, 5.47)

The incidence of ABC HSR was 6 and 4% and rash was slightly higher in patients using fosamprenavir (3% vs <1%). Similar increases in median fasting lipid values (total cholesterol, LDL, HDL and triglycerides) were observed for both regimens.

Drug resistance in the 5% patients (n=40) with virological failure (>400 copies/mL) was very low. In 35 patients with baseline and week 48 genotype results only 4 showed minor PI-associated mutations (I54I/L, K20K/R, I62I/V) and 7 showed RTI-associated mutations.

This study also reported very high adherence rates (calculated by percentage of returned pills) of >= 98% for the protease inhibitors and 99.4% for abacavir/3TC.

**C O M M E N T**

**This was a non-inferiority study with 12% margin, but in these treatment-naive patients, dosed twice daily, the results were similar or the same in the two groups, in all analyses of primary and secondary endpoints: CD4 and viral load responses of the total population, and sub analyses for patients with baseline viral load </> 100,000, and baseline CD4 <50, 50-200, and >200 cells/mm<sup>3</sup>; ITT (E): TLOVR; discontinuations, side effects and laboratory abnormalities (including lipid changes).**

**Of note, this study reported very high adherence – and this may be one of the few differences that could appear in the clinic rather than trial setting. The pill count for fosamprenavir/ is 2 pills, twice-daily plus 100mg ritonavir, twice-daily, compared to 2 tablets twice daily for the new formulation of lopinavir/r.**

During the conference, GSK announced that it would reduce the net price of fosampranavir would be reduced by 30% to UK clinics.

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## Tenofovir/FTC maintains greater virological response and reduced lipoatrophy compared to AZT/3TC after 96 weeks

Simon Collins, HIV i-Base

Joel Gallant and colleagues presented 96-week data from Gilead's Phase III study comparing once-daily tenofovir/FTC to fixed dose twice-daily AZT/3TC (Combivir) in treatment naive patients starting on efavirenz-based regimens. [1]

Results from the primary endpoint (virological response <50 copies/mL at 48 weeks) have already been reported at earlier meetings, and showed advantages in favour of tenofovir/FTC both virologically (driven by higher discontinuations in the AZT/3TC group) and with reduced side effects. The 96-week data reported in Toronto maintained similar differences between the two groups, and included results from DEXA scans at week 96.

Baseline characteristics in the study (ITT, n=509) were similar between arms (median age 37, 14% female, 59% Caucasian, median viral load 5.0 copies/mL, median CD4 237 cells/mm<sup>3</sup>). Excluding patients (n=22) with baseline NNRTI mutations, 76% in TDF+FTC arm (n=244) vs 64% in CBV arm (n=243) achieved and maintained HIV RNA<400 copies/mL through to week 96 (TLOVR, 95% CI +4.3, +21.1%, p=0.004); 69% in TDF+FTC arm vs. 63% in CBV arm achieved and maintained HIV RNA<50 copies/mL (95% CI -2.0%, 14.7%, p=0.15). The mean increase in CD4 cell count from baseline was significantly greater in TDF+FTC arm (270 vs 237, p=0.036).

Adverse events leading to study regimen discontinuation (most common: anemia, nausea, fatigue, vomiting, rash) were fewer for TDF+FTC arm (5%) vs CBV arm (11%), p<0.001. The renal safety profile was also similar in both arms based on serum creatinine and Cockcroft-Gault GFR (p=0.51), but Glomerular Filtration Rate was significantly slightly lower in the tenofovir/FTC arm (p=0.006).

At week 96 patients in the tenofovir/FTC group had significantly greater increases in weight (2.7kg vs 0.5kg, p<0.001). In a subset of patients with DEXA data, median limb fat at week 96 was greater in TDF+FTC arm (7.7 kg, n=144) compared to CBV arm (5.5 kg, n=136), p<0.001.

In terms of resistance, no patient developed the K65R mutation, and significantly more patients on AZT/3TC developed M184V/I (9 vs 2, p=0.037).

#### Reference

1. Gallant J, Pozniak A, DeJesus E et al. Efficacy and safety of tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) compared to fixed dose zidovudine/lamivudine (CBV) and EFV through 96 weeks in antiretroviral treatment-naïve patients. XVI International AIDS Conference, Toronto, Canada. 13-18 August 2006. Poster abstract TUPE0064.

IAS TORONTO: PAEDIATRIC CARE

## Paediatric studies in Toronto

Polly Clayden, HIV i-Base

### Children face a serious service delivery gap

Access to paediatric HIV care and treatment in most resource limited settings remains inadequate, with few programmes meeting the WHO target that 10% of people receiving ART be children.

In her plenary talk Ruth Nduati gave a comprehensive outline of the global impact of HIV on children. [1]

She emphasised that a child's risk of death is halved if his or her mother remains alive, and she stressed, "Care of the infected and uninfected child must include treatment of their mothers and families." Dr Nduati outlined many of the obstacles to care and treatment, which have been recurrent themes throughout the conference, highlighting that the "WHO training package used in many countries does not include children, that is why many countries do not treat children."

And despite a growing paediatric evidence base in both industrialised and resource limited countries, “There has been a failure to translate the most successful clinical trials to a public health success.”

### **Accumulating data shows children from resource limited settings benefit from antiretroviral treatment (ART)**

However, albeit mostly on a small scale, many oral and poster abstracts including these from Zambia, Brazil and Médecins Sans Frontières report favourable outcomes for children receiving ART.

In Zambia 1,726 children of a median age of 6 years at initiation, receiving NNRTI-containing ART, achieved “dramatic increases” in CD4 response with concomitant reductions in mortality (8.7/100 child years), which was reduced to half the rate seen in adults. [2]

In Brazil, a cohort followed since 1983, showed decreases in mortality over time: whereas half of the children died within 20 months of diagnosis at the beginning of the epidemic, the median survival improved with more than half still alive by the end of the study and 75% of children diagnosed in 1997 and 1998 were still alive after four years follow-up. This was attributed to ART access and earlier age of diagnosis. [3]

Médecins Sans Frontières reported 80% of children still alive after 24 months of treatment in their multi-centre cohort and that survival is accompanied by substantial gains in CD4 counts [4]. Less than 1% of children failed and the majority of treatment switches (3.5%) were due to drug toxicities.

All presenting authors reported an under representation of very young children (below 18 months) in their cohorts due to difficulties accessing infant diagnostics, the lack of availability and cost of age-appropriate paediatric antiretroviral formulations, and the reluctance of healthcare workers to treat this age group.

UNICEF estimates that 660,000 children urgently require antiretroviral treatment, most of them in sub-Saharan Africa. Children need to be on national agendas and government-based targets must define treatment needs. And as the Brazilian investigators noted: “A free and universal access to ART, even in a country that lacks an ideal health infrastructure, can make a substantial difference in survival”. These results argue strongly for making such treatment available to children elsewhere in the developing world.”

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## **Bioavailability study results for new paediatric tablets for oral suspension, and caution against splitting adult doses**

**Polly Clayden, HIV i-Base**

All discussion concerning obstacles to paediatric scale up - both at this conference and to date - has highlighted the lack of easily stored, low cost, age appropriate antiretroviral formulations for children.

As an interim measure many programmes prescribe divided adult fixed dose combinations (FDCs) but this is not without problems, and can yield suboptimal levels of nevirapine, particularly in very young children (see below). Obviously FDCs for children will be a welcome development.

### **Paediatric FDCs**

At the pharmacology (PK) workshop in Lisbon earlier this year, independent investigators presented bioavailability data for Indian generic manufacturer Cipla's Pedimune Baby and Pedimune Junior FDC tablets of NVP, 3TC and d4T, which led them to conclude that it would be acceptable to begin testing PK and dosing requirements of these formulations in African children even though the formal bioequivalence study by Cipla has not yet been completed. [1, 2]

Another Indian generic company, Ranbaxy has developed two new paediatric formulations of tablets for oral suspension (TFOS) “designed to disintegrate quickly into a uniform suspension in small volume of liquid media like water”.

A poster from Singla and co-workers from Ranbaxy described the formulation development of Triviro-LNS kid (3TC 20mg

/nevirapine 35mg/d4T 5mg) and Triviro-LNS kid DS (3TC40mg / nevirapine 70mg / d4T 10mg) – which will provide NIH recommended doses of the drugs for children weighing 9-31kg. [3]

And in an oral presentation Manish Vermer reported findings from the company’s bioavailability study of a single dose of the Triviro-LNS kids DS formulation compared to reference propriety liquid formulations. [4]

The investigators reported that the tablet has: a break line, “to enhance accuracy of dosing”; “a pleasant orange flavour” and requires no specific measuring device or refrigeration. Time to dispersion is 40 seconds in a small amount of water.

The bioavailability study was an open label, single dose crossover study conducted in 36 fasting HIV negative adult males.

The investigators reported that the geometric mean ratios (% Test/Reference) of log-transformed parameters of AUC, Cmax and 90% confidence intervals were within 80 -125% interval, see Table 1.

They wrote “Therefore the two treatments were considered to be similarly bioavailable and they concluded “Ranbaxy’s novel paediatric triple ARV TFOS could be used in place of individual liquid formulations.”

**Table 1: Ratio of LSM % (90% CI)**

	3TC	NVP	d4T
Cmax	115.27 (106.84-124.38)	105.11 (98.90-111.71)	88.73 (83.42-94.39)
AUC 0-t	107.90 (100.87-115.41)	99.56 (95.59-103.69)	91.87 (89.42-94.39)
AUC 0-oo	107.24 (100.54-114.39)	100.84 (96.77-105.08)	92.82 (90.95-94.73)

**Divided adult fixed dose combination can yield suboptimal nevirapine dose for very young children**

Several programmes reported favourable outcomes for children receiving adult fixed dose combination solid formulations of NVP, 3TC and NVP. [5, 6, 7, 8]

However, there are concerns with this strategy for very young children, for whom dose ratios for the different drugs are less analogous with those of adults, see Tables 1 and 2. Additionally smaller doses require quartered tablets and there are difficulties with accurate cutting.

**Table 2: Drug ratios in Triomune**

	NVP:3TC	NVP:d4T
Triomune 30	1.3	6.7
Triomune 40	1.3	5

**Table 2: examples of WHO (2006) recommendations for children of different weights**

Weight	NVP: 3TC	NVP:d4T
5kg	2.3	9
15kg	1.6	6.5
25kg	1.4	5.5

*Adult FDC will underdose NVP if 3TC and d4T doses are correct BUT overdose d4T and 3TC if NVP dose correct.*

In an oral abstract Veronica Mulenga presented findings from an updated pharmacokinetic study (first presented at the PK workshop in Lisbon and reported in HTB in more detail [9,10]) that again highlights the need for caution in very young children, but included some pragmatic recommendations [11].

This study was conducted in a group of 127 Malawian and Zambian children aged 8 months-18 years.

Dr Mulenga summarised that divided Triomune resulted in adequate nevirapine concentrations in nearly all children prescribed doses  $\geq$  300 mg/m<sup>2</sup>. But the youngest and smallest children were more likely to have subtherapeutic levels, particularly those receiving <300mg/m<sup>2</sup>/day, these children tended to receive quarter Triomune tablets.

She noted that malnourished children (with low BMI for age) had higher nevirapine concentrations. She suggested that these

children could be older for the same dose and therefore metabolise nevirapine more slowly. Stunted children had lower nevirapine levels due to lower volume of distribution. She emphasised the need for further study of the effect of malnutrition on nevirapine PK.

Dr Mulenga recommended caution with using part of FDC adult formulations in children <3 years old. If they are used, doses should be chosen to achieve adequate nevirapine dose (though this may result in some overdosing of 3TC and d4T). Therefore it is preferable to use Triomune 30 rather than Triomune 40 to achieve higher nevirapine doses relative to d4T.

She made the case once again for the need for child specific FDCs containing appropriate ratios of drug doses for children. This group is conducting in-depth pharmacokinetic and adherence studies in HIV-infected children of NVP, 3TC and d4T receiving the Cipla FDC, Pedimune in Zambia; they will further study the effects of nutritional status on PK parameters.

#### C O M M E N T

**It is important to note that the Ranbaxy Triviro-LNS kid and Triviro-LNS kid DS formulations still have lower amounts of nevirapine relative to the two NRTIs than required for very small children for whom dividing adult FDC is most problematic. Hence these formulations are not recommended for children <9kg.**

**The ratios of 3TC and d4T are also different also from those in Pedimune; this is because Pedimune was designed bearing in mind some recent data from the PENTA 13 pharmacokinetic study suggesting that the dose of 3TC may be rather low for children <6 years and that it may be better to keep the dose of d4T near the lower end.**

**Ranbaxy is not planning to do any PK studies in children and therefore the effects of malnutrition will not be assessed. Andrew Tomkins from the Institute of Child Health raised concerns about this in Toronto after the oral presentation. Although PK data from children is not a regulatory requirement from either WHO or FDA for paediatric FDCs, several researchers and paediatricians are concerned that this may be assuming the right dose when malnutrition raises complex issues around weight for age calculations. In conversation one paediatrician remarked that in any malnutrition ward in Africa about 60% children are likely to be HIV infected. This is a very common presentation of HIV in most resource-limited settings.**

**However, for children >9kg, it is likely that both Triviro-LNS kids and Pedimune (and dividing adult FDCs which has produced pretty good data for older children) will be reasonable.**

**Results from the CIPLA bioequivalence study conducted in HIV negative adult volunteers for registration requirements should be available very soon.**

**In summary:**

- **For youngest children liquid formulations or Pedimune baby are likely to be most reliable; PK studies using Pedimune will hopefully confirm this soon.**
- **For older children either the Ranbaxy, Cipla paediatric formulations or divided adult FDCs seem safe.**
- **We urgently need PK data from children with different degrees of malnutrition.**
- **We need these formulations to be licensed and pre-qualified by the WHO.**

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## **Pharmacokinetic and virological evaluations after stopping NNRTIs in children: a substudy of the PENTA 11 (TICCH) Trial**

**Polly Clayden, HIV i-Base**

There are currently limited paediatric pharmacokinetic (PK) data to guide stopping NNRTIs safely.

Marc Lallemand and co-workers from the PENTA 11 study group (evaluating the role of planned treatment interruptions) in Thailand and western Europe presented preliminary findings from a small substudy to assess the PK of antiretrovirals with long half lives and their association with development of resistance within this context.

In PENTA 11, children aged 2-15 years with viral load <50 copies/mL and CD4 percentage of >33% (ages 2-6 years) or CD4 percentage of >32.5% and CD4 >350cells/mm<sup>3</sup> (ages 7-15 years) are randomised to planned treatment interruption or continuous therapy.

Between November 2004 and January 2006, 70 children have been randomised of whom 13 (aged 5-15 years; 6 girls) have interrupted nevirapine-based ART and 9 (aged 5-14 years; 6 girls) have stopped efavirenz-based ART.

The choice of stopping strategy was at the discretion of the clinician and was to either "stagger stop" (stop NNRTI first, continue remaining regimen for 7-14 days) or replace the NNRTI (switch to PI and stop all drugs after 7-14 days).

Nevirapine and efavirenz plasma drug concentrations were measured by High Performance Liquid Chromatography (HPLC) with a limit of detection between 0.05 – 0.15mg/L for NVP and 0.05 – 0.2mg/L for EFV. In this evaluation  $\geq 0.15$  for NVP and  $\geq 0.2$  mg/L were considered detectable.

The investigators reported median pre-interruption drug levels of 4.8 mg/L (range: 2.2-15.1) in 11 children interrupting NVP and 3.2 mg/L (range: 0.9-3.5) in 7 children interrupting EFV.

They found that at week one, no children had detectable NVP levels, but they noted that of 2/5 samples tested with a more sensitive assay (lower limit of detection <0.05mg/L) had detectable levels, and three children had detectable EFV levels: 0.61, 0.54 and 0.2mg/mL. At week two, no children had detectable NVP levels and three had detectable EFV levels: 0.26, 0.32 and 0.29 mg/L. At week four no children had detectable levels of either drug.

The investigators also noted that following the results for the first 6 children interrupting EFV, the stagger stop/replace recommendation was increased to two weeks.

Additionally they found that viral rebound following treatment interruption was similar between stopping strategies and that the majority of children had detectable viral load by four weeks.

All 11 children receiving NVP were tested for resistance and one child was found to have detectable K103N mutations at four weeks. The investigators explained though that this child had detectable viral load (700 copies/mL) and detectable K103N at the time of interruption. The investigators reported no resistance in the eight children evaluated to date receiving EFV.

In their conclusion, they wrote that these preliminary data suggest that to avoid the development of resistance in children with undetectable viral loads interrupting an NNRTI based regimen, "the adoption of a staggered stop or replacement strategy of: 7-10 days of children interrupting nevirapine; and at least 2 weeks for children interrupting efavirenz; may be sufficient to prevent the selection of resistant mutations." However, they added that more sensitive assays may be required to detect very low level resistance.

The group are currently investigating NRTI mutations in the 22 children interrupting 3TC in PENTA 11.

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

**Data to guide stopping drugs with long half lives are important. There were concerns following the news from the SMART study of the short-term risk of intermittent therapy in adults that to continue PENTA 11 would be unwise.**

**The trial was stopped temporarily but its DSMB, having reviewed all the relevant data, recommended resuming enrolment to the study with a few safety amendments on the grounds that:**

- **Likely duration of treatment and immune reconstitution very different in children compared to adults.**
- **No data on planned treatment interruptions in children.**
- **PENTA 11 treatment interruption strategy uses CD4 criteria for restart/stop of ART, which are already higher than SMART so should have lower risk.**
- **In addition, the strategy can be modified to reduce risk of disease progression even further:**

- i) children with CD4 within 2% or 50 cells/mm<sup>3</sup> of the restart threshold should be monitored more intensely, to ensure that CD4 do not fall much below the restart thresholds;
- ii) children to spend no more than 48 weeks off ART, and at least 24 weeks back on ART after interruption;
- iii) children whose CD4 drop rapidly after first interruption and restart within 10 weeks of stopping ART should not re-interrupt;
- iv) detailed immunology and virology in children interrupting ART essential to understand viral and host dynamics.

Ref: Lallemand M, Burger D, Lyall H et al. Pharmacokinetic and virological evaluations after stopping NNRTIs in children: a substudy of the PENTA 11 (TICCH) Trial. XVI International AIDS Conference, Toronto, Canada. 13 - 18 August 2006. Poster abstract MOPE0206.

## **3TC/abacavir maintains virological superiority over AZT/ 3TC and AZT/abacavir beyond 5 years in children**

**Polly Clayden, HIV i-Base**

There have been few randomised trials in naïve children directly comparing ART combinations. Di Gibb presented findings from 5-year follow up of the PENTA 5 trial. This was a 48-week randomised controlled trial comparing three dual NRTI combinations with or without NFV as first line ART therapy.

128 children were randomised, one died and one was lost to follow up within two weeks of randomisation. Asymptomatic children (n=55) were also randomised to NFV or placebo; all other children received open-label NFV. 126 were followed after 48 weeks: AZT+3TC (n=36), AZT+ABC (n=44) or 3TC +ABC (n=46).

Median follow-up was 5.8 years (range: 3.1-7.8 years) and only 18 children (14%) had less than 5 years follow up. The authors reported 94% AIDS-free survival at 5 years in all arms.

The investigators found that, as expected, the proportion of child-time taking randomised antiretroviral drugs decreased over time. Between 2.5 to 5 years the proportion of children still taking their randomised NRTIs was lower in both AZT groups: AZT/3TC 61%, AZT/ABC 54% and 3TC/ABC, 69%.

By 5 years, 63/126 children (50%) were still taking randomised NRTIs; 19 (53%) AZT/3TC, 16 (36%) AZT/ABC and 28 (61%) 3TC/ABC. However, 18% (3/17) AZT/3TC, 50% (14/28) AZT/ABC and 50% (9/18) 3TC/ABC of the changes from randomised NRTIs were either early single drug substitutions for toxicity (<24 weeks after randomisation) or switches in children for viral suppression (HIV-1 RNA <400 copies/ml) for simplification, toxicity or carer/child request.

At year five viral load data were available for 105 children and 62% (65/105) of children were <400copies/mL. Of these 55%/32% AZT+3TC ; 50%/25% AZT+ABC; and 79%/63% 3TC/ABC had VL <400/<50 copies/ml respectively (p=0.03/p=0.003).

There were corresponding decreases in log<sub>10</sub> VL: 2.3, 2.5 and 3.4 respectively (p=0.001). The mean increase in CD4% was 12%, 9% and 12% (p=0.2); height-for-age 0.42, 0.68 and 1.05 (p=0.02); weight-for-age 0.03, 0.13 and 0.75 (p=0.02).

Reverse transcriptase resistance mutations were different between the arms:

AZT/3TC (n=4): 41, 67, 70, 184, 210 and 215; AZT/ABC (n=6): n=4 maintained wild-type virus, n=2 developed TAMs 41, 67, 70, 210, 215, 219; 3TC/ABC (n=6): 65, 74, 115, 184.

Of the 24 children randomised to dual NRTI only, 0/7 AZT/3TC, 3/11 AZT/ABC and 4/6 3TC/ABC were still taking only 2 drugs at year 5 (0, 1, and 3 with VL <400 copies/ml).

Dr Gibb concluded that 3TC/ABC sustained long term virological superiority; the short-term benefits in terms of growth persisted and lower rates of switching with detectable viral load were observed compared to the other two NRTI backbones.

She also noted that this backbone can be taken once daily in children >3years and once again made the case for a "combined scored baby pill."

Ref: Gibb DM, Green H, Saidi Y et al. 3TC +ABC maintains virological superiority over ZDV+3TC and ZDV+ABC beyond 5 years in children. Oral abstract WEAB0302.

IAS TORONTO: MALIGNANCIES AND HIV

## **French study raises importance of early screening for anal cancer in HIV-positive people**

**Simon Collins, HIV i-Base**

Christophe Piketty and colleagues looked at the impact of HAART on incidence of anal cancer diagnosed between 1992 and 2003 in HIV-positive patients from the French Database of HIV (FHDH). The analysis looked at pre-HAART, early HAART, and later HAART time periods. 92 cases were identified (84 men, 8 women) from almost 75,000 patients in the database.

Among men, 74% were men who have sex with men. The median age at diagnosis was 42.4 years [IQR: 36.0-49.3]; the median CD4 cell count was 247 cells/mm<sup>3</sup> [IQR: 135-420]; the median nadir CD4 cell count was 80 cells/mm<sup>3</sup> [IQR: 21-174] and 39% of the cases had presented an AIDS defining event prior to the anal cancer diagnosis. At diagnosis, 71 patients (77%) had been receiving HAART for over five years (median 65 months [IQR: 44-77]).

**Table 1: Changes in incidence rate or anal cancer**

	1992-Mar 96	Apr 1996-1998	1999-2003
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Whole database

Pt/yr follow-up	104,648	102,798	204,298
No. cases	9	12	69
Incidence 100,000 Pt/yr	8.6 [3.0, 14.2]	11.7 [5.1, 18.3]	33.8 [33.8, 41.7]
Relative risk	1.0	1.36 [0.57, 3.22]	3.93 [1.96, 7.87]

MSM

Pt/yr f/u	37,923	37,046	72,647
No. cases	6	10	44
Incidence 100,000 py	15.8 [3.2, 28.5]	27 [10/3, 43.7]	60.6 [42.7, 78.5]
Relative risk	1	1.71 [0.62, 4.69]	3.83 [1.63, 8.98]

The incidence of anal cancer increased, in both the whole HIV-cohort, and in HIV-positive men who have sex with men (MSM), though the risk in MSM was approximately twice as high, and is detailed in Table 1. The increase in all rates was explained by the investigators by longer life expectancy conferred by HAART, in that people are living long enough for malignancies to develop. The survival probability after the anal cancer diagnosis was 74%+/-6% at 3 years.

The conclusion drawn by the researchers was that as HAART exhibited no favorable effect on the incidence of anal cancer, this 'supported the urgent need for developing anal cancer screening programs for HIV-infected individuals'.

Reference

1. Piketty C, Selinger-Leneman H, Grabar S et al. Dramatic increase in the incidence of anal cancer despite HAART in the French hospital database of HIV. XVI International AIDS Conference, Toronto, Canada. 13 - 18 August 2006. Oral abstract TUAB0305.

## Prognostic index for risk of progression of Kaposi's Sarcoma

Mark Bower and colleagues from the Chelsea and Westminster Hospital London, presented a prognostic score for patients diagnosed with Kaposi's Sarcoma (KS), derived from analysing covariates predictive of overall survival in a cohort of 326 HIV+ patients who developed KS since 1996.

The score in these patients, ranged from 0 to 15 and was calculated starting at the number 10. It incorporated:

S stage - other ADI	+3	(any other HIV-related illness)
age	+2	(if > 50 years old at diagnosis)
KS as a first ADI	-3	(If KS is the ADI), and
CD4 cell count	-1	(per 100 cells/mm <sup>3</sup> at diagnosis)

Individuals with a prognostic score of 0, 5, 10 and 15, had 1 year survivals of 99.4%, 96.7%, 83.4% and 37.8% and 5 year survivals of 98.4%, 91.8%, 63.1% and 8.4% respectively. Increasing the prognostic score by 1 increased the risk of death by 40% (HR 1.4, 95% CI 1.28-1.53, bootstrapped HR 1.39, 95% CI 1.25-1.51) and the index has a concordance of 76.8% (95% CI 71.7-82.3%). The prognostic index, validated internally using a bootstrap procedure with resampled data, applied to individuals on and off HAART at KS diagnosis.

The study concluded that this score can be used to guide therapeutic options.

Ref: Bower M, Sanitt A, Mazhar D et al. A prognostic index for AIDS-associated Kaposi Sarcoma in the era of highly active antiretroviral therapy. Poster abstract TUPE0046.

## Tenofovir did not increase the incidence nephrotoxicity in limited numbers of HIV-positive patients using chemotherapy or HCV-coinfected patients using ribavirin

Simon Collins, HIV i-Base

Two posters from the Chelsea and Westminster used their database of over 5,000 patients to look prospectively at patients using tenofovir in their ARV combination, who were also using potentially nephrotoxic chemotherapy for haematological malignancies, or retrospectively at HCV coinfected patients using ribavirin for HCV treatment.

Tenofovir was included in the regimen for 50/142 patients (35%) treated with anthracycline-based combination chemotherapy and concomitant HAART. [1]

At the start of chemotherapy, 8 (6%) had CTC grade 1-4 renal toxicity (elevated serum creatinine (Cr) >110  $\mu\text{mol/L}$ ), including one patient on chronic haemodialysis. These included 3 patients on TDF and 5 not on TDF ( $p=0.93$ ). The median peak serum Cr for these patients was 152  $\mu\text{mol/L}$  (range 137-234), and did not differ between TDF group and non TDF group ( $p=0.48$ ). During the course of chemotherapy, a further 9 patients developed renal impairment; 2/50 on TDF and 7/92 not on TDF ( $p=0.38$ ). The median peak serum Cr in this group was 274  $\mu\text{mol/L}$  (range 166-581), this was lower in the TDF group (median 176  $\mu\text{mol/L}$ , range 166-187) than the non-TDF group (median 277  $\mu\text{mol/L}$ , range 207-581) (Mann Whitney U  $p=0.04$ ).

In the second analysis, 350 HIV/HCV coinfected patients with at least two recorded creatinine values of >120  $\mu\text{mol/L}$  were identified, of which had been exposed to tenofovir and/or ribavirin, and creatine clearance was compared by treatment use. [2]

The prevalence of abnormal creatinine was 32.1 per 1000 patients (95% CI: 10.4 to 73.2) and 19.2 per 1000 patients (95% CI: 4.0-55.1) in patient exposed to either tenofovir or ribavirin respectively, and 12.8 per 1000 patients (95% CI: 1.5-45.6) in patients using both drugs,

Although these analysis do not comment on channelling bias (for example, treatment choice may have been affected in patients with any pre-existing renal concerns), it is important that no signal of increased toxicity were reported.

### References

1. Jones R, Low E, Nelson M et al. Tenofovir does not increase the incidence of chemotherapy related nephrotoxicity. Poster abstract TUPE0047.
2. Jones R, Bower M, Mandalia S et al. Renal toxicity in HIV/Hepatitis C co-infected individuals exposed to tenofovir and/or ribavirin. Poaster abstract CDB0734.

## Selected abstracts from Track A presentations at Toronto

Svilen Konov, HIV i-Base

The conference included several important posters and presentations in the basic science Track A, particularly related to viral entry and genetic responses to treatment.

On the first day, Goto and colleagues from the Kyoto and Osaka Universities presented a detailed structural analysis of the attachment of HIV to the cell membrane at the nanoscale level. [1]

In order to clarify the process of attachment, they used automated electron microscopic tomography. HIV was inoculated into culture lymphocytes, and after a designated time the cells were harvested, fixed, and embedded for microscopy. The images were recorded automatically with a CCD (charged-coupled device) camera and the data was 3-D constructed for tomography. The results revealed that at the first contact point, the distance between the virus and the cell membrane corresponds closely to the length of the extended gp41 molecule. Further stages of attachment are currently under investigation.

Bosch and colleagues from Fundacio IrsiCaixa (Spain) and LaboRetro (France) investigated the cell-to-cell HIV-1 transmission and reported that it probably occurs through a caveolin independent but clathrin-dependent endocytic process, that results in the formation of endosomal vesicles containing complete HIV-1 particles. [2]

They localised internalised virus particles in large intracellular vesicles in cocultures of primary CD4+ T-cells with T-cells continually infected by either one of three HIV-1 isolates (NL4-3, Bal, and CI-1-SI-clinical). The non-stimulated CD4+ cells expressed only residual levels of the early endosomal marker EEA-1 or the late endosomal marker CD63 (as they have a very low metabolism). The HIV-1 infected cells, on the other hand, were strongly CD63 positive. Coculture of infected and uninfected cells produced a translocation into T CD4+ cells of both the HIV-1 *Gag* antigen and the CD63 marker (seen using immuno-confocal microscopy). Internalised virus was colocalised with clathrin-mediated endocytosis EEA-1 marker, but not with the caveolin-1 marker. The CD63 staining was observed by flow-cytometry after cell-to-cell contacts and viral transmission. Importantly, CD63 was present in the transferred viral particles, which explains the presence of a late endosomal marker in EEA-1 positive, *Gag* positive endosomes. The dependence on CD4 and the transmission of complete viral particles was confirmed by an analysis of CD4 and envelope subcellular localisation, which revealed their colocalisation with *Gag* in the polarised phenotype. Even though this finding does not have an immediate clinical impact, it may be important in the identification of new targets for novel compounds.

Pugach and colleagues from Cornell University, USA, studied how HIV-1 escapes from small molecule CCR5 inhibitors in vitro, by creating resistant viruses and examining their properties. [3]

Their results showed that the drug-resistant virus acquired the ability to utilise CCR5 in its inhibitor-bound form. Consequently, the resistant viruses are sensitive to inhibition by PSC-RANTES, but they are considerably resistant to this chemokine derivative when a small molecule inhibitor is also present. This finding may have implications on the research and possible future clinical use of maraviroc and vicriviroc.

Maeda and colleagues reported that CXCR4 antagonist induced co-receptor switching from X4 to R5 phenotype in vitro was determined by a single amino acid substitution in the V3 region of HIV-1 gp120. [4]

An R5/X4 variant (89.6 strain) was passaged in the presence of a CXCR4 antagonist T140 using a cell line highly susceptible to R5 variants, in order to select coreceptor switch mutants. The mutant harboured an amino acid substitution in the V3 region of the *Env* (Arginine 308 to Serine, R308S). The substitution conferred total resistance to CXCR4 antagonists when luciferase-reporter HIV-1 pseudotyped with the mutant *Env*. At the same time sensitivity to the CCR5 antagonist TAK-779 increased in both CCR5 and CXCR4-expressing cells. The analysis demonstrated that the virus with the mutation largely utilised CCR5 while retaining CXCR4 usage.

Humbert from Georg-Speyer-Haus, Molecular Virology, Frankfurt, Germany and colleagues successfully applied phage display technology to identify HIV-1 specific mimotopes for neutralising antibodies that are expected to have protective role in the long-term non-progressors (LTNP). [5]

Sera of LTNP and a control group of regular progressors were analysed and in the former, the titers of the neutralising bodies against HIV-1 were logically significantly higher. The team selected more than 1400 phage clones with LTNP IgG (analysed by ELISA) and more than 700 phage inserts were sequenced. They identified motifs related to the immunodominant epitopes in HIV-1 *Env*, but also conformational epitopes overlapping with receptor binding sites on the surface of gp120. Sera from mice immunised with ceratin phage groups showed neutralising activity against HIV in vitro, proving that the phage mimotopes indeed mimic epitopes for neutralising antibodies. These mimotopes may represent candidates for derivation of vaccine-relevant immunogens.

Several very interesting small studies dealing with polymorphisms were presented as posters. De la Tribonniere and colleagues reported that a polymorphism in MDR-1 alleles that is associated with virological efficacy in HIV-positive naive patients treated with non-boosted PI-containing HAART, regimens but not in those treated with boosted PI-containing regimens. [6]

The MDR-1 genetic single nucleotide polymorphism (SNP) in exon 26 (C3435T) regulates P-gp expression. The study assessed the influence of the above-mentioned SNP on the virological responses to first-line PI-containing regimens. They included 182 HIV-infected subjects who received HAART from 1997 to 2002 and were followed through December 2004. The proportion of subjects with MDR-1 exon 26 genotypes CC, CT, and TT were 37%, 44%, and 19% respectively. Female patients and patients from sub-Saharan Africa had more frequently exon 26 genotype CC ( $p < 0.05$ ). A multivariate Cox model showed that time to first undetectable viral load when the patients were on an unboosted PI regimen was shorter in the subgroup with the CT genotype ( $p = 0.01$ ) and not those with TT genotype [HR=0.69; 95% CI, 0.41-1.17 and  $p = 0.17$ ] and CC genotype. When comparing the subgroups on boosted PIs, however, the difference disappeared. The difference may be a result of the higher concentration achieved with the boosted PIs.

Two other polymorphisms studies were performed in geographically specific regions and in particular populations. Pavia-Ruz and colleagues analysed the T303A CCR5 gene polymorphism in Mayan and Mestizo populations of Yucatan, Mexico. [7]

Other CCR5 gene polymorphisms that cause premature termination of translation apart from T303A are the CCR5 delta-32 and 893delC. T303A, however, poses particular interest as it occurs in variable allele frequencies (e.g in 0.014 of Afro-Americans, 0.07 in French populations and is completely absent in three Brazilian ethnic groups). To determine the frequency of T303A in Mayan and Mestizo populations in Mexico, 100 samples were analysed (50 of each ethnic group). DNA was extracted from whole blood. Surprisingly, T303A (wildtype genotype) was present in all Mayan individuals, but only in 90% of the Mestizo samples. The heterozygous genotype was present in 10% of the Mestizo participants but in none of the Mayan population.

Tumanov and colleagues studied the distribution of CCR5-delta-32 and CCR2-64I alleles among the basic ethnic groups of Mongolian population. [8] 253 samples were analysed by PCR-restriction fragment length polymorphism assay. No subjects homozygous for CCR5-delta-32 genotype were found, while the percentage of the heterozygous genotype was 2.4% (6/253). The CCR2-64I allele frequency was 0.246. Both these results match the currently available data about the population in the East Asian region.

References:

Unless stated otherwise, all references are to the Programme and abstracts from the XVI International AIDS Conference, Toronto, Canada, 13-18 August 2006.

1. Goto T, Hasegawa T, Kajimura N et al. Attachment in HIV entry process by electronic microscopic tomography. Oral abstract MOAA0101.
2. Bosch B, Grigorov B, Senserrich J et al. Cell-to-cell HIV-1 transmission through a clathrin-dependent endocytic pathway. Oral abstract MOAA0102.

3. Pugach P, Kuhmann S, Ketas T et al. The mechanism of HIV-1 escape from small molecule CCR5 antagonists. Oral abstract MOAA0105.
4. Maeda Y, Yusa K, Harada S. CXCR4 antagonist-induced coreceptor switch from X4 to R5 phenotype in vitro determined by a single amino acid substitution in the V3 region of human immunodeficiency virus type 1 gp120. Oral abstract MOAA0104.
5. Humbert M, Antoni S, Landersz M et al. Vaccine relevant mimotopes selected with neutralising IgG present in plasma from long-term non-progressors (LTNP) by phage display. Oral abstract MOAA0204.
6. Tribonniere X De la, Broly F, Burban Deuffic S et al. Polymorphism in MDR-1 alleles associated with virological efficacy in naïve HIV-infected patientstreated with non-boosted PI-containing HAART regimensbut not in those treated with boosted PI-containing regimens. MOPE0012.
7. Pavia-Ruz N, Quintal-Ortiz I, Valadez-Gonzalez N et al. Analysis of the CCR5 gene T303A polymorphism in Mayan and Mestizo populations of Yukatan, Mexico. Poster abstract MOPE0007.
8. Tumanov A, Amarjal Y, Munkhtuvshin N et al. Polymorphism of CCR5 and CCR2 genes associated with HIV-1 resistance in Mongolia. Poster abstract MOPE0005.

IAS TORONTO: OTHER UK STUDIES

## **Use of complementary alternative medicine that could interact with ARV treatment reported by 20% patients in the UK**

**Simon Collins, HIV i-Base**

A poster presented by David Laddenheim and recorded the use of complementary and alternative medicine (CAM) by patients using antiretroviral therapy at three specialist HIV clinics in London to look for potential serious interactions, relative or absolute contra-indications and warnings issued when potential health risks were identified.

They used a cross-sectional survey in 253 randomly selected patients using a multiple choice questionnaire exploring use of herbal remedies, supplements and physical complementary treatments.

Of these 154 (60.9%) were taking herbal remedies or supplements and 88 (34.8%) were using physical treatments. 67 patients (26.5%) used a combination of both. If a potential interaction or contraindications was identified, a warning or caution was given to the patient.

Twenty-five patients (9.9%) were asked to stop their CAM because of potential serious drug interaction with their ARVs or adverse effects of the remedy used. Thirty patients (11.9%) were advised to use their remedies with caution and adequate monitoring. Of those taking CAMs, only half had discussed CAM use with a healthcare professional.

The study highlighted a high use of CAM, comparable to other reports for other countries, and that ten percent of these examples were potentially compromising their ARV treatment.

Ref: Laddenheim D, Phillpot M, O. Horn et al. Potential health risks of complementary alternative therapy (CAM) in HIV positive patients taking antiretroviral drugs (ARVs). XVI International AIDS Conference, Toronto, Canada. 13 - 18 August 2006. Poster abstract MOPE0219.

## **Poor scientific or medical knowledge is a factor in increase in criminal charges for HIV transmission in the UK**

**Simon Collins, HIV i-Base**

Lisa Power presented a poster with an analysis of 24 cases of criminal prosecutions related to HIV transmission reported to the Terrence Higgins Trust between June 2005 and June 2006. This is a large recent increase in such reports, and many cases received high media attention.

Sources of the reports (n) were the accused person (9), the complainant or immediate family (5), the police (3), another NGO (3), a solicitor (2) and from a doctor (2). Of the 9/24 cases that resulted in court action, there were 4 convictions, 2 case dropped after initial hearing (following THT/legal interventions), 1 awaiting trial, 1 under appeal and 1 outcome unknown.

All 4 convictions were from guilty pleas, however, police and prosecution media statement significantly mis-stated the offence as 'deliberate' instead of 'reckless'. The two dropped cases were where no transmission had occurred, although prosecution was being pursued, despite English law being clear that no offence had taken place. In one case, the accused was the victim of assault by the complainant, but charges were still followed.

Although the study recognised limitations of some case details, they identified that 8/24 investigations involved poor scientific or medical knowledge, and substantial investigations took part in 8/24 cases before transmission was known.

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

**A draft of the Crown Prosecution Service (CPS) policy for prosecuting cases involving sexual transmission of infections which cause grievous bodily harm is available online for public comment. The document covers the intentional or reckless sexual transmission of HIV, as well as other sexually transmitted infections. The deadline for comments is 3 November, 2006.**

[http://www.cps.gov.uk/news/consultations/sti\\_policy.html](http://www.cps.gov.uk/news/consultations/sti_policy.html)

The consultation document is also available to view on the UKC website which also includes an anonymous online response form for individuals who would like the UKC to respond on their behalf.

<http://www.ukcoalition.org>

Further information on the criminal prosecution of HIV and other STIs as well as guidelines for commenting on the CPS consultation document are available on the THT and NAT websites.

Ref: Power L, Ward P. AIDS assassins? The impact of introducing criminal charges for transmission of HIV in the UK. XVI International AIDS Conference, Toronto, Canada. 13-18 August 2006. Poster abstract MOPE0910.

IAS TORONTO: TREATMENT ACCESS & COMMUNITY RESPONSES

## Online webcasts and debates

Many of the important sessions relating to healthcare policy and treatment access are available as webcasts, podcasts and transcriptions from kaisernetwork.org. The selected edited quotes below give an indication of the speeches and wider discussions, and are all available online:

<http://www.kaisernetwork.org/aids2006>

### *Loon Gangte*

"Let me hear the voice of people living with HIV/AIDS. Universal access and health is a human right. It's immoral, unacceptable, unjust and outright genocide, when the rich people can buy life, while poor people are condemned to unnecessary, untimely and unjust death. We demand universal and free access to all essential medicine. People before trade! To all the government officials here, please remember that when you sign for free trade, our lives are at stake."

Loon Gangte, Delhi Network of People Living with HIV

Closing session - 'one-minute' address

Friday 18 August, 2006

### *Gregg Gonsalves*

"Peter Piot told the New York Times earlier this year that „2005 was the least bad year in the history of the AIDS epidemic." But I am telling you today that we are losing the struggle against this disease. 5 million new infections last year, and 3 million dead, among them half a million children gone. It was the worst year yet for those we've lost.

I shan't offer attempt a comprehensive analysis of 25 years of HIV/AIDS in seven minutes and thus I will make three brief points hopefully to start a conversation rather than end one. The first is about the often misdirected energies and efforts, and the paralysing effects, of the international AIDS bureaucracy; the second is the familiar but indispensable point that AIDS is both a consequence and a symptom of wide and deep global injustice; the third is to take issue with some dear colleagues, and others I respect, about the push to 're-medicalise' AIDS and why we must be careful in this regard not to cast AIDS as yet another intractable social ill, drain it of political significance and give up the fight when we really need to be taking the struggle to the next level.

...We need to reinscribe the fight against AIDS as part of a larger movement for social and economic justice. Our heroes knew and know this. It's no surprise that where we find HIV/AIDS, we often find other infectious and chronic diseases, including TB, diabetes, obesity, heart disease, asthma, mental illness and social epidemics of crime, violence and poverty. Unless we start looking at the factors, the root causes that drive health disparities - in other words, why some of us get sick and some of us don't - broadly within our communities, we will be always treating one illness, while the 'patient' dies of another. It's also no coincidence that these multiple epidemics exist among marginalised communities across the globe, among the poor, women, drug users, sex workers, gay men, prisoners, migrants - the social, economic and political policies that create this marginalisation in the first place also push us into the path of oncoming epidemics. Yet, we continue to place our hopes in prevention programs that narrowly construct risk around individual behavior or in some new technology that will save us....

...We are at a terrible anti-political moment right now, where the powers-that-be have taken our rhetoric and told us that everything is fine-we're on your side-you can demobilise and leave the epidemic to us. That is the pernicious message of this conference. Don't believe a word they say."

Gregg Gonsalves, AIDS and Rights Alliance for Southern Africa

Session: 25 Years of AIDS ^ Reflecting Back and Looking Forward

Wednesday, 16 August 2006, 12:45 - 13:45

*Stephen Lewis*

“...we must continue to roll out treatment. Treatment is keeping people alive; treatment is bringing hope; treatment is stimulating prevention; treatment is meshing more and more frequently with community-based care; we cannot let the process slow.

While I am on the issue of treatment, I am bound to raise South Africa. South Africa is the unkindest cut of all. It is the only country in Africa ... whose government is still obtuse, dilatory and negligent about rolling out treatment. It is the only country in Africa whose government continues to propound theories more worthy of a lunatic fringe than of a concerned and compassionate state. Between 600-800 people a day die of AIDS in South Africa. The government has a lot to atone for. I'm of the opinion that they can never achieve redemption.

There are those who will say I have no right, as a United Nations official, to say such things of a member state. I was appointed as Envoy on AIDS in Africa. I see my job as advocating for those who are living with the virus, those who are dying of the virus ... all of those, in and out of civil society, who are fighting the good fight to achieve social justice. It is not my job to be silenced by a government when I know that what it is doing is wrong, immoral, indefensible.

...Unbeknownst to many, we are on the cusp of a huge financial crisis in response to the pandemic. I think we have been lulled into a damaging false security by the fact that we jumped from roughly \$300 million a year from all sources in the late 1990's, to \$8.3 billion in 2005. And indeed it sounds impressive. But, we need \$15 billion this year, and \$18 billion next year, and \$22 billion in 2008. Any straight line projection will take us to \$30 billion in 2010 ... the moment of universal access to treatment, prevention and care. We're billions and billions short of those targets. If these circumstances continue, universal access is doomed. All governments, as they continue to expand their treatment and prevention initiatives, are spooked by worries of financial sustainability. They're right to be spooked. The financial promises made at the G8 Summit in Gleneagles one year ago, are already unraveling. We will never accumulate the extra \$25 billion for Africa by 2010 as was committed.

PEPFAR has not yet announced its extension beyond 2008; when it does (as it surely will), the annual contribution, given the other demands on the US Treasury, will probably remain at \$3 billion a year. That large amount was a very significant percentage of the total expenditure on AIDS back in 2003/2004. But as a percentage of what is needed for global AIDS programmes in 2008 - \$22 billion - \$3 billion seems pretty paltry from the world's superpower.

The Global Fund to Fight AIDS, Tuberculosis and Malaria is still half a billion short this year and more than a billion short next year. At the moment, there is no obvious way to close the shortfall. It is almost inconceivable that the extravagant promises of Gleneagles are revealed as so fatuous that the Global Fund is now compromised. No one is asking for any more than that which was promised. But the Pavlovian betrayal of the South has already begun. Everything in the battle against AIDS is put at risk by the behaviour of the G8. Yesterday, Dr. Julio Montaner characterized that behaviour as genocide. I remember back in 2001, in an op-ed for the Globe and Mail, I used the phrase mass murder. It's hard, in the face of the annihilating human toll, not to be driven to linguistic extremes. This issue of resources makes or breaks the response to the pandemic. It is imperative that the delegates here assembled never let the G8 countries off the hook.”

Stephen Lewis, UN Special Envoy for HIV/AIDS in Africa,  
Closing session, Friday 18 August 2006

*Mark Wainberg*

“...I also want to remind you all that this conference cannot be deemed a success unless we collectively realise our theme of Time to Deliver. Indeed, we will have failed unless we dramatically and rapidly expand by millions the numbers of people around the world with access to antiretroviral drugs. Clearly, progress cannot be achieved if more people continue to become infected by HIV each year than the numbers that are able to access treatment.

In this context, we also recognise the problem that is sadly posed by HIV denialists. And it is correct that we ask how many additional millions of HIV cases are attributable to the failure of certain world leaders to directly and honestly address issues of HIV/AIDS with their people.

In South Africa, as an example, which has more cases of HIV than any country in the world, it is unconscionable that government leaders still do not speak openly about HIV and instead talk about lemon juice as a key prevention strategy. We all know that such talk about lemon juice as a mode of HIV prevention is scientific nonsense. Why don't the government leaders who need to impart critical messages to the vulnerable people of their country also understand this basic fact?”

Mark Wainberg, President IAS, Conference Co-chair  
Closing session, Friday 18 August 2006

## TREATMENT ACCESS

### FDA tentative approvals of generic ARVs

Simon Collins, HIV i-Base

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

Drug/formulation	Generic manufacturer	Date
ddl tablets, 100 mg	Aurobindo, India	10 July 06
3TC/AZT copackaged with abacavir	Aurobindo, India	26 July 06
nevirapine 200mg	Strides Acrolab Ltd	11 Aug 06
stavudine capsules, 30mg & 40mg	Strides Acrolab Ltd	28 Aug 06
3TC/AZT 150mg/300mg	Pharmacare, S Africa	23 Aug 06

Tentative approval means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, though it may not be marketed in the U.S. because of existing patents and/or exclusivity rights. Tentative approval, however, does make the product eligible for consideration for purchase under the PEPFAR program.

#### C O M M E N T

**This brings the total of FDA approved generic drugs and formulations to over 24 since the programme was launched.**

**An updated list of generic tentative approvals is included as a table on the i-Base website:**

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

**Whilst generic approval and competition have produced a side range of NNRTI-based options for first-line therapy, protease inhibitors and second-line RTIs, or other drugs effective for treatment experienced patients, are clearly missing from this list.**

Source: FDA list serve

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

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

### Patent oppositions filed on three essential drugs

In the continuing struggle to ensure that patents are not granted at the cost of human lives, health groups in India recently filed three more pre-grant patent oppositions against essential medicines.

Copies of these oppositions can be obtained at the Lawyers Collective website at:

[http://lawyerscollective.org/lc\\_hivaids/amtc/folder.2005-12-20.2101894352](http://lawyerscollective.org/lc_hivaids/amtc/folder.2005-12-20.2101894352)

In the Patent Office in Chennai, the Indian Network for People Living with HIV/AIDS (INP+) and the Karnataka Network of People Living with HIV/AIDS filed an opposition against Novartis's patent application for atazanavir (subsequently licensed to Bristol Meyers Squibb), a critical second-line protease inhibitor.

The opposition is based on four grounds: (1) that a prior patent discloses the compound that is claimed in the atazanavir application, and thus is not "new" under Indian law; (2) that the application is not "inventive" and is not patentable under Indian law; (3) that the application describes a "new form of a known substance" and is thus not an "invention" under Indian law; and (4) that the applicant has failed to provide the Patent Office with certain information that it was required to submit. If successful, this opposition will pave the way for generic companies to produce affordable versions of this critical second-line drug.

INP+ and the Uttar Pradesh Network for People Living with HIV/AIDS filed an opposition against GSK's patent application for amprenavir in the Delhi Patent Office. Amprenavir is the base molecule for the important protease inhibitor fosamprenavir, and thus the grant of patent for amprenavir could allow GSK to prevent other manufacturer from producing generic versions of fosamprenavir. This opposition is also based on the ground that the application is not "new," that it is not "inventive," and that it is just a "new form of a known substance." Additionally, the opposition is based on the grounds that the application is merely a "new use of a known substance," and thus not patentable under Indian law, and that it is, at most, a "mere admixture" and is thus unpatentable.

Finally, INP+ and the Tamil Nadu Network People Living with HIV/AIDS filed an opposition against valganciclovir, a critical treatment for CMV retinitis, a common AIDS-related opportunistic infection that can cause blindness. This opposition is based on the procedural grounds that the application concerns an invention from before 1995 and is thus unpatentable in India. India incurred its obligations under TRIPS as of 1 January 1995, and thus any inventions that pre-date 1995 are considered "public domain" in India and thus are not patentable.

We are hopeful that the PLHA groups will prevail in their struggle for access to the medicines that sustain their health. We are also hopeful that other health-related groups will take this information and broaden the fight against patents on essential drugs by opposing patents on their own.

Source: Press release from Lawyers Collective HIV/AIDS Unit

## WHO GUIDELINES

### New WHO guidelines for ARV treatment in resource limited settings

In the week prior to the Toronto conference, the World Health Organization published new online guidelines for adult antiretroviral treatment in resource-limited settings. These revisions are the first changes to guidelines first produced in December 2003.

Changes to this edition include:

- caution against use of d4T (stavudine)-based fixed dose combinations, because of the higher risk of toxicity (peripheral neuropathy, lactic acidosis and facial lipoatrophy)
- that first line treatment should include and NNRTI plus two RTIs or a include three RTI's, especially when comedications indicate a risk of drug interactions with NNRTIs
- recommending 3TC (lamivudine) or emtricitabine (FTC) plus either AZT or abacavir or tenofovir as preferred dual-nucleoside combinations
- more detailed discussion about risk of prescribing nevirapine to women with CD4 counts over 250 cells/mm<sup>3</sup>, or to men with CD4 counts >400 cells/mm<sup>3</sup>
- support for wider availability and use of CD4 count tests, and stronger caution that total lymphocyte counts are not an effective surrogate marker for either risk of disease progression, or optimum time for starting or changing treatment.

## C O M M E N T

**The decision to drop d4T is undoubtedly a better decision for patients receiving treatment, and inclusion in WHO guidelines will provide a stronger basis for advocates to change treatment choices.**

**Given the significantly higher cost of the new alternatives, and that many treatment access programmes still only treat a small percentage of people who need treatment, these recommendations are only likely to be effective if the cost of alternative RTIs approaches the current low price for d4T.**

Ref: WHO Guidelines: Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access:

<http://www.who.int/hiv/pub/guidelines/adult/en/index.html>

Additional WHO guidelines include:

<http://www.who.int/hiv/pub/guidelines/en/>

- Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access  
<http://www.who.int/hiv/pub/guidelines/adult/en/index.html>
- Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings: towards universal access  
<http://www.who.int/hiv/pub/guidelines/pmtct/en/index.html>
- Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings  
<http://www.who.int/hiv/pub/guidelines/ctx/en/index.html>
- WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children  
<http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html>
- WHO recommendations for clinical mentoring to support scale-up of HIV care, antiretroviral therapy and prevention in resource-constrained settings  
<http://www.who.int/hiv/pub/meetingreports/clinicalmentoring/en/index.html>

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## ANTIRETROVIRALS

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### Antiretroviral effect of foscarnet in patients with multiple drug resistance in late stage HIV disease

Simon Collins, HIV i-Base

In Volume 11, issue 5 of Antiviral Therapy, Ana Canestri and colleagues reported the results of using foscarnet as additional therapy in 11 multi-drug resistant French patients with late stage HIV disease, failing their current treatment.

Inclusion criteria for this open-label, single-arm, add-on pilot study, included viral load >50,000 copies/mL and CD4 counts <100/mm<sup>3</sup>, and documented three-class resistance. Foscarnet induction therapy consisted of 5 g intravenously twice daily for 6 weeks, in addition to their antiretroviral combination, and the primary endpoint was virological response at week 6. Patients with at least 1 log decrease in viral load at week 6 (W6), were given foscarnet 5 g intravenously twice daily on two consecutive days each week.

Median baseline CD4 and viral load were 10 cells/mm<sup>3</sup> and at 5.16 log copies/mL respectively, with a median of 9 (RTI), 2 (NNRTI) and 12 (PI) associated mutations.

In an intent-to-treat analysis, the median change in viral load was almost -2.0 logs at week 2 and -1.79 logs at week 6. 8/11 patients had at least 1 log reduction at week 6. One patient discontinued foscarnet at week 2 because of renal toxicity.

Six patients started maintenance therapy. Change from baseline after 12 weeks of maintenance therapy was -0.85 log in the four patients who reached W12, and the median increase of CD4+ T-cell count was 60 cells/mm<sup>3</sup>.

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#### C O M M E N T

The study noted that 'foscarnet markedly reduced plasma HIV load and improved immunological status'. Given the toxicity associated with foscarnet, and the difficulty of administration (twice-daily IV administration, often requiring a Port-a-Cath or Hickman line for anything treatment lasting longer than a few days) this is clearly a treatment of last resort.

It may nevertheless be suitable for a limited number of patients, particularly part of a short-term strategy to maximize virological response, and particlular if they also have active CMV.

Ref: Canestri A, Ghosn J, Wirden M et al. Foscarnet as salvage therapy for patients with late-stage HIV disease and multiple drug resistance. Antiviral Therapy 2006; 11: 561-566. (Volume11, Issue 5)

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#### ON THE WEB

##### *Online medical journals:*

### **"AIDS Issue" of the British medical journal The Lancet online**

The "AIDS Issue" of the British medical journal The Lancet is now online at [www.thelancet.com](http://www.thelancet.com). Many of the articles are available for free, after registering on the site.

The Lancet, Volume 368, Number 9534, 05 August 2006

<http://www.thelancet.com/journals/lancet>

<http://www.thelancet.com/journals/lancet/issue?volume=368&issue=9534>

Contents include many articles, opinion and discussion articles in addition to research papers, including

- AIDS in 2006 marks the time to deliver - Gayle HD
- HAART's first decade: success brings further challenges - Dore GJ, Cooper DA
- Microbicides: stopping HIV at the gate
- HIV/AIDS harm reduction in Iran
- Scaling up antiretroviral treatment in resource-poor settings (3 articles)
- Russia, the G8, and HIV

- Informing children of their HIV status
- ESPRIT trial – 4 letter and authors reply
- Heart disease in Africa

#### Primary Research

- HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy
- CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV.
- Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials
- The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial

#### Department of Ethics

- Circumcision and HIV prevention research: an ethical analysis
- AIDS: from crisis management to sustained strategic response – Peter Piot
- An examination of the Global Fund at 5 years

### **TAG pipeline drugs report: July 2006**

Three new reports from TAG were published on-line this week and distributed at the AIDS conference in Toronto.

#### **What's in the Pipeline? New HIV Drugs, Vaccines, Microbicides, HCV and TB Treatments in Clinical Trials:**

<http://www.aidsinfonyc.org/tag/tagline/pipeline2006.pdf>

#### **OSI/TAG report on civil society involvement in TB/HIV**

Including six case studies of civil society involvement in TB/HIV advocacy by Agua Buena Human Rights Association (Dominican Republic, El Salvador, Guatemala, Honduras, Jamaica, and Nicaragua), Fundación Mexicana para la Lucha contra el Sida (Mexico), Gender AIDS Forum (South Africa), Salvation (Ukraine), The Shepherd's Hospice (Sierra Leone), and Yayasan Spiritia (Indonesia).

The report summarises the advocacy activities, lessons learned, and next steps. It was ably written by Jeff Hoover and jointly published by OSI's Public Health Watch and TAG's TB/HIV Project.

<http://www.aidsinfonyc.org/tag/tbhiv/ositagreport.pdf>

#### **Tuberculosis R&D Investments: A Preliminary Assessment**

A documented review of current levels of spending on tuberculosis research and development (R&D) by the top 30 reporting donors, including basic science, research on new tools (diagnostics, drugs, and vaccines), and operational research.

30 respondents reported spending \$348 million on TB R&D in 2005, 70% of it by the public sector, 23% by philanthropies (mainly the Gates Foundation, 6.5% by industry (only 4 companies disclosed investments), and 0.5% by multilateral agencies.

\$93 million (27% of investment) went to basic research, \$15 million (4%) to diagnostics, \$67 million (19%) to vaccines, \$100 million (29%) to drugs, \$48 million (14%) to operational research, and \$23 million (7%) unspecified. The report reveals that research spending lags behind targets specified in The Global Plan to Stop TB: 2006-2015 by \$700 million per year.

A full report will be released at the IUATLD 37th World Conference on Lung Health 31 October - 4 November 2006.

<http://www.aidsinfonyc.org/tag/tbhiv/tbrandd2006.pdf>

#### *Other resources:*

#### **Resource for HIV-positive travelers: HIV/AIDS regulations**

[http://doc.ilga.org/ilga/publications/other\\_publications/hiv\\_aids\\_regulations](http://doc.ilga.org/ilga/publications/other_publications/hiv_aids_regulations)

As a resource for HIV-positive travelers, the German AIDS Federation and International Lesbian and Gay Association, have published an online overview of travel and entry restrictions in different countries: *'Quick Reference: Travel and Residence Regulations for People with HIV and AIDS 2005'*.

The regulations and restrictions for people with HIV/AIDS can be drastically different from country to country, and the guide is being updated as quickly as possible to reflect these changes. The latest edition reflects the most up-to-date information available in 2005, and a new version of the survey is tentatively slated for publication after the summer of 2007.

Nonetheless, some notable policy changes have already occurred including positive changes in Canadian entry policy, introduced to support delegates attending the IAS conference in Toronto this summer. Canada does not now require people applying for a visa to enter Canada as a short term visitor to disclose known HIV infection, does not routinely impose mandatory HIV testing on short-term visitors, nor does it categorically bar visitors based on their HIV-positive status.

Other updated information is available in French, German, and English:

<http://www.aidsnet.ch/linkto/immigration>

Updates in English are available at:

[http://www.aidsnet.ch/modules.php?name=Content&pa=list\\_pages\\_categories&cid=5](http://www.aidsnet.ch/modules.php?name=Content&pa=list_pages_categories&cid=5)

If you have any comments or information about individual countries, please contact Peter Wiesser at: [peter-wiesser@tonline.de](mailto:peter-wiesser@tonline.de).

Policy surrounding HIV/AIDS can be ambiguous or politically volatile, and it may be wise to compare information from a variety of sources before traveling abroad.

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## FUTURE MEETINGS

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### **8th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV**

**24 – 26 September 2006, San Francisco.**

<http://www.intmedpress.com/lipodystrophy/Home/home.cfm>

### **46 ICAAC**

**27-30 September 2006**

<http://www.icaac.org/>

### **IAPAC European Sessions 2006**

**12-13 October 2006, Budapest**

The International Association of Physicians in AIDS Care (IAPAC) and the European AIDS Clinical Society (EACS) will co-host the third annual IAPAC European Sessions in Budapest.

IAPAC European Sessions is a symposium that allows HIV-treating healthcare professionals to learn from each other while working toward solutions to on-going clinical questions.

This year's Sessions include:

- Implications of a decade of HAART
- Navigating ARV drug resistance
- Sociobehavioural aspects of HIV care
- Emerging issues in HIV care

To see the full program and faculty presenters, visit the [iapac](http://www.iapac.org) web site:

<http://www.iapac.org>

### **BHIVA Autumn Conference**

**Friday 13 – Saturday 14 October 2006, London**

<http://www.bhiva.org>

The BHIVA Autumn Conference will once again be held at the Queen Elizabeth II Conference Centre. T

The BHIVA Foundation Lecture will be delivered by Professor Paul Sharp from Nottingham and he will be presenting on 'Where AIDS came from'.

## 14 Retrovirus Conference (CROI)

February 25-28, 2007, Los Angeles

The 14th Conference on Retroviruses and Opportunistic Infections will be held February 25-28, 2007 at the Los Angeles Convention Center in Los Angeles, California.

<http://www.retroconference.org>

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## PUBLICATIONS & SERVICES FROM i-BASE

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### i-Base website

The website has been designed 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>

To coincide with the new publicity material for the treatment phoneline, we launched a web-based Q&A section for people to ask questions about their own treatment:

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

The site is also more accessible for those with impaired sight, with all pages conforming to at least the W3C-WAI Level A and most to level AAA.

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.

There is a new section on Education, Advocacy and Training. This 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 on the website, 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).

A new page has been added on how to adapt and translate treatment resources, and included examples from projects we have worked with outside the UK.

An average of 2000 pages a day are served from the site.

### 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 every three months since May 2002. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

Reading material, reports and presentations from these meetings (the 16th meeting was on 24 February 2006) are posted to the i-Base website.

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

<http://www.i-base.info/ukcab/feb06/index.html>

## **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 are available online.

The latest report is from a meeting held in January 2005 with four Indian generic manufacturers.

An earlier report is from a meeting in February 2004 with three major brand manufacturers.

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

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

## **Introduction to combination therapy**

**June 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 Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. Please see the 'translations' page or the website for more details.

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

**April 2005 edition**

Also updated and revised in April 2005, this is a non-technical patient guide to changing treatment and what to do if treatment fails. This booklet helps patients in discussions with doctors, and covers what can be done if viral load starts to rise, and the importance of considering or finding out why the current combination failed, treatment strategies and new pipeline treatments.

## **Guide to 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.

Chinese, French, Italian and Spanish translations of the previous edition are still available.

## **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.

Chinese, French, Italian and Spanish translations of the previous edition are still available.

## Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in 27 languages.

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

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

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>

### *Chinese*

- Avoiding & managing side effects PDF [3.8 Mb ] Aug 02
- Changing treatment: second line & salvage therapy PDF [284 Kb] Aug 02
- Introduction to combination therapy PDF [236 Kb] Aug 02

### *Bulgarian*

- HIV, pregnancy & women's health PDF [304 Kb] Mar 06

### *French*

- HIV, pregnancy & women's health April 06 [1 MB ]
- Avoiding & managing side effects PDF [344 Kb]
- Introduction to combination therapy PDF [132 Kb] Jun 01

### *Greek*

- Changing treatment: second line & salvage therapy PDF [180 Kb] Mar 03
- Introduction to combination therapy PDF Nov 01 [ 1 Mb ]

### *Italian*

- Avoiding & managing side effects PDF [1 Mb ]
- Changing treatment PDF [1 Mb ]
- HIV, pregnancy and women's health PDF [1.2 Mb ]
- Introduction to combination therapy PDF [1 Mb ]

### *Portuguese*

- Introduction to combination therapy PDF [696 Kb] Sep 05

### *Russian*

- Introduction to combination therapy PDF [448 Kb]
- HIV, pregnancy and women's health PDF [668 Kb]

### *Serbian*

- Introduction to combination therapy PDF [227 Kb]

### *Spanish*

- Avoiding & managing side effects PDF [210 Kb]
- Introduction to combination therapy PDF [192 Kb]
- HIV, pregnancy & women's health PDF [180 Kb]

## 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:

- How long will I live if treatment is working?
- What can I do about weight loss and hair loss since starting treatment?
- How quickly with my CD4 and viral load change after starting treatment?
- Which age group is more infected by HIV than others?
- Can I get HIV from kissing?
- I have symptoms of HIV, what do I have to do next?
- When is cotrimoxazole contraindicated (not recommended), in a pregnant HIV-positive woman, with a CD4 less than 200 cells/mm<sup>3</sup>?
- Brazil I have free medicine, so I like to now how do I do to buy my remedy while I'm in London.
- I am a newly diagnosed HIV+ man and my wife is still HIV-negative. How can we have an HIV-negative baby.
- What is the proof that HIV causes AIDS?
- What are fusion inhibitors and how do they work or suppress the virus?

## 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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## ***h-tb***

### *HIV Treatment Bulletin*

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

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

by sending an email to:

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

or by fax or post using the form on the back page.

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Dr Martin Fisher, Brighton & Sussex University Hospitals.

Dr Gareth Hardy, Case Western Reserve Univ. Cleveland.

Gregg Gonsalves, AIDS and Rights Alliance for Southern Africa.

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Dr Stefan Mauss, Düsseldorf.

Dr Graham P Taylor, Imperial College, London.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

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

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

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## HIV i-Base

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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I do not wish to make a regular donation but enclose a one-off cheque in the sum of \_\_\_\_\_ instead.

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### GIVE AS YOU EARN

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

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

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# HIV i-Base

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