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EDITORIAL

As this issue went to press, named-patient programmes were about to start for both MK-0518 and TMC-125. Although the number of patients with multi-drug resistant HIV who are failing treatment in the UK is low - the 2006 BHIVA audit suggests that less than 3% of HIV-related deaths in the UK are related to lack of treatment options - for those patients these early access programmes clearly offer life-saving options.

Together with other recently approved or available drugs (T-20, tipranavir, darunavir), patients with multi-drug resistance (MDR) now have the strongest opportunity for many years of achieving and sustaining undetectable viral load. Both the new UK and US treatment guidelines have been updated to recognise this fundamental shift in aiming for maximal viral suppression in patients with MDR.

There is further optimism from new classes of drugs in the pipeline: CCR5 inhibitors, budding inhibitors and a monoclonal antibody that, as drugs in new classes, are expected to work against MDR HIV.

The BHIVA guidelines strongest caution is to always use at least 2 new sensitive drugs in any combination - and these choices mean some people will be able to use three sensitive drugs. A second caution relates to potential interactions. Currently, darunavir has fewer interactions than tipranavir. MK-0518 looks to have fewer interactions still - with a question only over TMC-125. Until the results of an interactions study between MK-0518 and TMC-125 are available, these drugs should not be used together.

NEW i-BASE BOOK:

“Why we must provide HIV treatment information”

Photography by Wolfgang Tillmans

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

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

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

We are asking for minimum donation price of £10.00 plus £2.50 p&p.

Please contact the i-Base office for more details:

T: 020 7407 8488

or email: bookoffer@i-Base.org.uk or post the donation form on the inside back page of this issue of HTB, using either ‘standing order’ or ‘one-off donation’ as appropriate.

Thank you for your support.

CONFERENCE REPORTS

8th International Workshop on Adverse Drug Effects and Lipodystrophy in HIV Infection (IWADELHI)

23-26 September, San Francisco

Introduction

This annual Workshop is the most important meeting for researchers, clinicians and advocates who focus on metabolic complications relating to management of HIV-positive patients.

While many studies reaffirmed the role of some ARVs in risk factors associated with lipodystrophy, cardiovascular disease and diabetes, there was further evidence on managing this risk by treatment choice. While lipodystrophy is now firmly linked to use of thymidine analogues and some degree of fat reversal occurs when switching to alternative drugs, notably tenofovir or abacavir, the mechanism to reverse fat accumulation is less clear.

Research into lipodystrophy over the last few years has increasingly focused on understanding adipogenesis as a dynamic process, and on the role of two major proteins produced by adipocytes: leptin and adiponectin, which act as hormones in their effect on different organs. At this years workshop, the role of inflammation by macrophage and lymphocyte activity in adipose tissue was also shown to be an increasingly important factor.

Although an interesting study suggested that leptin may be a useful treatment for reducing central fat accumulation, this research has been slow and leptin isn't a clinical option at the moment. Prevention, through choice of initial treatment, switching treatment when necessary and lifestyle modification, was still stressed as the take-home message.

Clinical discussions included the role of the metabolic syndrome, and the high incidence of risk factors for insulin resistance and progression to type-2 diabetes in patients with HIV - and the degree to which this risk is underestimated.

Reports in this issue include:

- The role of the metabolic syndrome in HIV
- Effect of lifestyle modification on risk factors for cardiovascular disease and metabolic syndrome
- Pioglitazone reduces peripheral lipatrophy and improves adipokines without reducing visceral fat
- Leptin reduces visceral abdominal tissue (VAT) without reducing limb fat
- Adipose tissue morphology improved after treatment discontinuation
- Incidence of lipodystrophy in Rwanda

For the first time, the organisers of the meeting have produced webcasts of many of the key presentations and discussions. This is a very positive and important step towards making medical research presented at the workshop available to a wider audience. Abstracts from the meeting together with webcasts of oral sessions and some slide presentations are posted on the conference website:

<http://www.intmedpress.com/lipodystrophy>

The Programme and Abstracts for the 8th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV Infection (IWADRLHI) are published as part of Antiviral Therapy, Volume 11, Issue 7.

The role of the metabolic syndrome in HIV

Simon Collins, HIV i-Base

The first session of the Workshop included several presentations and discussions about definition of metabolic syndrome (MS) in HIV-positive patients, and whether this a diagnosis of MS adds to risk greater than the sum of individual markers.

The interest in MS is that it is an equation of several measurable factors that can predict longer-term risk of cardiovascular disease (CVD) and type-2 diabetes mellitus (T2DM) than Framingham which deals with 5 and 10-year risk. Clinical guidelines in Europe and the US for management of pre-diabetes, in non-HIV-related, risk say that individual factors are sufficient to monitor and treat individually, but with HIV these may add more than individual factors alone.

Andrew Carr from St Vincents Hospital, Sidney, reported MS prevalence in the international cohort used for the Lipodystrophy Case Definition Study (approx 800 cases and controls) of 14% by International Diabetes Federation (IDF) and 18% by NCEP ATP III criteria (National Cholesterol Education Programme, Adult Treatment Panel), [1] which were both less than for the US general population.

The ATP III definition requires 3 or more factors from: waist (>88cm in women or >102cm in men, triglycerides >1.7 mmol/L, HDL <1.29 mmol/L in women or < 1.04 in men, glucose >6.1 mmol/L, SBP >130 and DBP > 85mmHg. The IDF criteria includes waist >80cm in women and >94cm in men, plus any two other parameters (with glucose set slightly lower at 5.6 mmol/L).

The concordance between the two definitions was significant but only moderate. 23% patients were positive for MS by one or more definition, but only 9% were positive by both ($k=0.46$, $p<0.0001$). ATP III criteria diagnosed 50% more men but 30% fewer women. Half the patients meeting metabolic criteria for MS had a normal waist circumference prevented diagnosis of MS by ATP III.

Those with MS by either definition had higher BMI, waist:hip ratio, total body fat, visceral fat, systolic and diastolic blood pressure, triglycerides, insulin resistance and diabetes, and lower HDL, as would be expected. Discordance focused on when waist circumference and waist:hip ratio prevented a diagnosis of MS in 50% of patients with objectively defined lipodystrophy, suggesting that both definitions may be insensitive tools for diagnosing risk of diabetes and cardiovascular disease in HIV-positive patients.

Patients with MS also had higher levels of C-reactive protein (CRP) (5.5 +/-7.0 vs 3.9 +/-6.0 mg/L, $p=0.03$), lower adiponectin (12 +/-8.0 vs 15 +/-10 mmol/L, $p=0.04$) and high leptin levels (+/-9 vs 4 +/- 6 mmol/L, $p<0.0001$).

Wand and colleagues from the same research group, also presented data on prevalence, incidence and progression to cardiovascular events or type-2 diabetes (T2DM) over 3 years in a separate cohort of 881 patients. [2]

Prevalence of MS in this group at baseline was 11% and 9% by ATPIII and IDF criteria respectively. In patients without MS at baseline, progression occurred in 32% (ATPIII) and 22% (IDF). Presence of MS at baseline was associated with a significantly increased risk of T2DM after 3 years: ATPIII: RR=4.37 (95CI 2.24-8.52, p<0.001); IDF: RR 2.89 (95CI 1.35-6.20, p=0.006). Developing new MS during the study was also associated with higher risk of progression to T2DM, though not as strongly as having MS at baseline.

Relative risk of CVD was 2.58, p=0.051 and 2.97, p=0.026 in the ATPIII and IDF criteria respectively.

The researchers concluded that rapid and frequent progression to MS after starting HAART was associated with development of diabetes (and non-significantly to CVD), and that diagnosis of MS at baseline was therefore a useful tool to identify patients for prevention strategies, especially as the predictive value of individual MS components for diabetes or CVD in this study was low.

References

1. Samaras K, Wand H, Carr A et al. Metabolic syndrome in HIV-infected patients using IDF and ATPIII criteria: prevalence, discordance and clinical utility. 8th IWADRLH, September 2006, San Francisco. Abstract 1.
2. Wand H, Calmy A, Carey D et al. Metabolic syndrome, cardiovascular disease and type-2 diabetes mellitus after initiation of antiretroviral therapy in HIV-infected adults. 8th IWADRLH, September 2006, San Francisco. Abstract 2.

Effect of lifestyle modification on risk factors for cardiovascular disease and metabolic syndrome

Simon Collins, HIV i-Base

Steven Grinspoon from Massachusetts General Hospital presented results from a study of lifestyle modifications on metabolic syndrome criteria and cardiovascular parameters in HIV-positive patients with the metabolic syndrome. [1]

Previous studies have indicated that 17-45% HIV-positive patients have metabolic syndrome and that the relative risk for developing cardiovascular disease of type-2 diabetes mellitus (T2DM) are also higher in HIV-positive compared to HIV-negative men diagnosed with metabolic syndrome.

The study randomised 34 patients to an intensive 6-month lifestyle modification intervention, modeled on the Diabetes Prevention Programme, or to standard health advice. The intervention included 1-2-1 weekly counseling with a dietician, as part of a diet and exercise programme.

The dietary aims included reducing daily calories intake from fat to <35%, with <7% calories from saturated fat and at least 25-35 grams of soluble or insoluble fibre. Up to 10% and 20% calories could come from polyunsaturated and monounsaturated fats respectively. The exercise component included 3 hours of physical activity each week, and 10,000 steps daily measured with a pedometer.

Baseline characteristics of the study group included mean age of 45 (+/-2), 50% were smokers (39% in the control group), 50% were African-American, and over 60% were women, and are detailed in Table 1. Over 90% of patients were using RTIs, 50% were using PIs and 44% were using NNRTIs in their ARV regimen. While half the patients were using blood pressure medication, only 5-11% were using lipid lowering drugs (LLD). Waist circumference was the only statistically significant difference between the two groups at baseline.

Table 1: Baseline characteristics

	Intervention	control	p value
Age (yrs)	45 +/-2	46 +/-2	NS
African American	69%	56%	NS
Male/Female	37/63%	33/67%	NS
Smoker	50%	39%	NS
Duration HIV	128 mo	124 mo	NS
Current BP Rx	56%	50%	NS
Lipid Rx	6%	11%	NS
Waist (cms)	113	101	0.001
TG (mg/dL)	176+/-23	263+/-50	NS
HDL (mg/dL)	48+/-3	41+/-2	NS

Fast gluc mmol/L	5.05 +/-0.22	5.00+/-0.01	NS
Systolic BP	131+/-4	138+/-4	NS
Diastolic BP	79+/-2	83+/-2	NS
Current BP Rx	56%	50%	NS

NS: non significant

Six patients discontinued the study early: 4 in the intervention arm (2 LTFU, 1 pregnancy, 1 family death) and 2 in the control arm (1 LTFU, 1 anemia).

Table 2: Results at 6 months

	Intervention	Standard advice	p value
Waist circumference (cms)	-2.6 +/-1.1	1.2 +/-1.0	0.022
Blood pressure (mmHg)	-13 +/-4	4 +/- 4	0.008
Triglycerides	1+/-22	-25+/-34	0.550
HDL cholesterol	3+/-3	0+/-2	0.396
Fast gluc mmol/L	0.17+/-0.17	0.06+/-0.11	0.716
Systolic BP	-13+/-4	4+/-4	0.008
Diastolic BP	-2+/-3	1+/-3	0.489
HgbA1C	-0.1%	+0.2%	0.017

In the intervention arm, caloric intake reduced by approximately -350 kcal/day (p=0.068), with the percentage of calories from saturated fatty acids dropping by 2% (p=0.040) and fibre intake increasing by 4g/day (p=0.057), with no changes in the control group. Exercise increased by approximately +16 hours/week (p=0.014 compared to control). At month 6, significant improvements in some parameters included in the metabolic syndrome were reported in the intervention group and are detailed in Table 2.

C O M M E N T

Although this was a small study and lipid markers (TC, LDL and HDL) were not helped, lifestyle modification significantly improved some of the markers associated with metabolic syndrome. The study only had short-term follow-up for some benefits that would be expected to accumulate further over time if the programme was maintained.

For example, previous research with the Dietary Prevention Programme intervention with 3 year follow-up showed that lifestyle changes reduced cumulative incidence of diabetes by 58% compared to control patients. In this placebo controlled randomised study in older patients with impaired glucose tolerance, the reduction in risk from use of metformin was only 31%. [2]

Given current ARV choices, supporting lifestyle changes is currently one of the most optimistic interventions to reduce risk of CVD and T2DM in high-risk patients. It is disappointing that so few studies have focused on this area, as similar to smoking cessation programmes, these are also likely to have long-term cost benefit advantages.

References

1. Fitch KV, Anderson EG, Grinspoon S et al. Effects of a lifestyle modification programme in HIV-infected patients with the metabolic syndrome. 8th IWADRLH, September 2006, San Francisco. Abstract 24.
2. Knowler WC, Barrett-Connor E, Fowler SE et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. NEJM 2002 Feb 7;346(6):393-403. PubMed ID: 11832527.

Pioglitazone reduces peripheral lipotrophy and improves adipokines without reducing visceral fat

Simon Collins, HIV i-Base

Jacqueline Capeau from Pierre and Marie Curie University and colleagues presented additional results from a French study showing benefits of pioglitazone, a thiazolidinedione, on peripheral fat loss and circulating adipokines. [1] The main results from this study were presented at the Retrovirus conference in February 2006. [2]

Although previous studies with rosiglitazone were widely reported for lack of benefit [3], these were largely confounded by continued use of thymidine analogues, which blocked the likely mechanism of action. [4]

In this study, 130 HIV-positive patients with lipodystrophy were randomised to 30mg pioglitazone once-daily or matching placebo. At 48 weeks, patients using pioglitazone (who were not using d4T) showed a mean increase of +0.45kg limb fat by DEXA compared to no change in the placebo arm.

Subcutaneous (SAT) and visceral adipose tissue (VAT) increased significantly but there was no significant differences between the two groups. Anthropometry measurements showed the increase in weight in pioglitazone patients (+1.7kg) was distributed mainly in increased thigh and arm circumference: thigh +1.4 cm (vs 0.2cm, $p=0.017$), and tripepal skin fold +0.9cm (vs 0.4cm, $p=0.047$).

No change occurred in glycemic parameters, triglycerides, total cholesterol or LDL cholesterol. However, HDL significantly increased (+0.09, SD 0.18 vs -0.08 mmol/L, SD 0.66, $p=0.0005$). New data from this study presented at the workshop related to changes in adipokine expression. Plasma adiponectin increased from 3.9 (SD 3.3) to 8.7 (SD 7.7) in the pioglitazone arm compared to no change in placebo ($P<0.0001$). However, no changes were seen in plasma leptin, resistin and soluble TNF-alpha receptor.

The change in limb fat correlated with both pioglitazone concentration ($r=0.476$, $P<0.001$) and leptin variation ($r=0.365$, $P<0.01$).

These results support the use of pioglitazone in the treatment of lipodystrophy in patients with HIV-related lipodystrophy who are no longer using thymidine analogues in their regimen.

References

1. Maachi M, Slama L, Capeau J et al. Effect of pioglitazone on limb fat and circulating adipokines in HIV-related lipodystrophy (ANRS113: Lipiot). 8th IWADRLH, September 2006, San Francisco. Abstract 23.
2. Slama L, Lanoy E, Valentin MA et al. Effect of Pioglitazone on HIV-1 Related Lipodystrophy: a Randomized Double-Blind Placebo-Controlled Trial (ANRS 113) with 130 patients. 13th CROI, 2006. Late breaker abstract 151LB. See HTB March 2006. <http://www.i-base.info/htb/v7/htb7-3/Interventions.html>
3. Carr A, Workman C, Carey D, et al. No effect of rosiglitazone for treatment of HIV-1 lipodystrophy: randomised, double-blind, placebo-controlled trial. *Lancet*. 2004 Feb 7;363(9407):4 29-38.
4. Mallon P, Unemori P, Bowen M, et al. Nucleoside reverse transcriptase inhibitors decrease mitochondrial and PPAR-gamma gene expression in adipose tissue after only 2 weeks in HIV-uninfected healthy adults. 11th CROI, 2004. Abstract 76.

Leptin reduces visceral abdominal tissue (VAT) without reducing limb fat

Simon Collins, HIV i-Base

Hootan Khatani and colleagues from University of California, San Francisco, presented results from an NIH funded, open-label, pilot study looking at the effects of leptin treatment on glucose and fat metabolism in patients with lipodystrophy and hypoleptinaemia. [1]

While interest in leptin has been discussed at many of these workshops, research into a therapeutic role has been very slow. For an overview of the role of leptin and potential role in HIV-related lipodystrophy, see the HTB report from the Lipodystrophy Workshop four years ago. [2]

The study enrolled eight HIV-positive men with lipodystrophy (5/8 severe, and two patients also had fat accumulation) with leptin levels <3 ng/ml (range 1.1-2.2ng/ml), dyslipidaemia and insulin resistance. Recombinant human leptin was dosed subcutaneously at 0.1mg/kg BID for the first 3 months and at 0.03 mg/kg BID for a further 3 months.

Treatment increased serum leptin to approximately mean 7 ng/mL at month 3 and 20 ng/mL at month 6 ($p=0.03$ and 0.008 respectively).

Table 1: Effect of leptin on lipid metabolism

	Baseline	6 month	p value
Total cholesterol (mg/dL)	229 +/-16	187 +/-12	0.001
LDL cholesterol	140 +/-8	117 +/-8	0.002
Non-HDL	204 +/-15	158 +/-12	0.001
HDL	25 +/-2	29 +/-3	0.07
Triglycerides	333 +/-79	222 +/-51	0.16
Free fatty acids (mEq/L)	0.40 +/-0.04	0.30 +/-0.04	0.04
Lipolysis (mg/kg/min)	0.20 +/-0.05	0.15 +/-0.06	0.02

Visceral adipose tissue measured by MRI (L4-L5) decreased significantly in all patients, from mean 183 +/- 24 cm² to 129 +/- 24 cm² (p=0.001) compared to non-statistical changes in subcutaneous adipose tissue, 101 +/- 29 cm² to 90 +/- 19 cm² (p=0.45). The decrease in lipolysis suggested this was an effect in adipose tissue, and the lack of effect on lipoatrophy, that this may be a depot-specific effect.

Leptin also had a generally beneficial effect on lipids (TC, LDL, HDL, non-HDL and TG), see Table 1. Although insulin sensitivity improved in the liver, whole body glucose uptake did not achieve significance.

C O M M E N T

This small uncontrolled study clearly produced sufficiently optimistic results for this to be studied in larger trials. Similar questions may be as appropriate for leptin as for rHGH - ie cost, side effects, and particularly the durability of the effect after the treatment is stopped.

References

1. Khatani H, Schwartz JM, Sakkas GK et al. Effects of leptin treatment on glucose and lipid metabolism and fat distribution in HIV+ patients with lipoatrophy and hypoleptinemia. 8th IWADRLH, September 2006, San Francisco. Abstract 22.
2. Leptin, lipodystrophy and insulin resistance. HIV Treatment Bulletin, November 2002.
<http://www.i-base.info/pub/htb/vol3/htb3-9/index.html#Leptin>

Adipose tissue morphology improved after treatment discontinuation

Simon Collins. HIV i-Base

Jacqueline Capeau, one of the lead researchers into metabolic changes associated with lipodystrophy, and one of the organisers of the workshop, presented results showing an improvement in sub-clinical markers for lipodystrophy in virologically controlled patients who discontinued treatment for 6 months.

Subcutaneous abdominal fat biopsies were taken at baseline from 40 patients and after six months for the 33 patients who completed the treatment interruption, and adipose tissue morphology examined in 29 patients.

Of these, treatments used in combinations were PI+NRTI (10), NRTI without PI (19), d4T (8), AZT (13), other RTI (12). Samples from 23 patients were tested for mitochondrial DNA and from 20 patients for adipose tissue gene expression (8 PI-based; 12 using NRTIs without PIs; 1 using d4T, 8 using AZT and 11 using other RTIs).

The six month treatment break did not change clinical symptoms or levels of fibrosis. However, adipose tissue inflammation was significantly improved with reduced lipogranuloma and macrophages (p=0.003 and 0.002 respectively). TNF-alpha and IL6 was only increased at baseline in patients using d4T or AZT, and adipocytes and inflammatory cells positive for both markers were markedly reduced after 6 months discontinuation of d4T or AZT (PI use did not affect this). Other improvements at month 6 in patients discontinuing d4T and AZT included increased mitochondrial DNA and reduced COX4 RNA and COX2/COX4 ratio.

PPAR-gamma and SREBP-1 are markers for adipocyte differentiation that previous studies have shown to be significantly reduced in patients with lipodystrophy, and patients stopping PIs showed improved levels of PPAR-gamma, PGC-1-alpha and COX2), and mitochondrial alterations, though at different levels.

C O M M E N T

The study took place prior to the results from the SMART treatment interruption study, and the researchers were not recommending treatment interruptions in patients now.

Instead the results are interpreted as showing the beneficial effects from removing a drug that negatively impacts on fat metabolism, and as additional data supporting active switching away from drugs associated with symptoms of lipodystrophy.

Ref: Capeau J et al. A six month interruption in HIV-infected patients improves adipose tissue morphology and gene expression (ANRS EP29 Lipostop). 8th IWADRLH, September 2006, San Francisco. Abstract 5.

Incidence of lipodystrophy in Rwanda

Simon Collins, HIV i-Base

As treatment access programmes, still largely reliant on d4T-based combinations, roll out in resource-limited settings, it is important that safety data are collected and reported, in order to influence access to and use of more modern, tolerable treatment.

Mutimara and colleagues from the Kigali Health Institute reported an incidence of lipodystrophy of 34% in a cohort of 571

patients from Rwanda with >6 months treatment experience. This rose to over 70% in patients who had received HAART for longer than 17 months. In this study, 80% of patients were using fixed dose combination of d4T/3TC/nevirapine.

Selected metabolic parameters from 100 HIV-positive patients with lipodystrophy were compared to 50 non-lipodystrophic patients and 50 HIV-negative controls. Waist circumference and median total cholesterol were higher in patients with lipodystrophy, and impaired glucose tolerance (fasting glucose >5.6 mmol/l) was higher in all patients on HAART compared to the HIV-negative control group (see Table 1).

Table 1: Metabolic parameter of patients on HAART with or without lipodystrophy (LDS) compared to HIV-negative controls

	LDS+	LDS-	HIV-negative
Waist circumference	86.3+/- 6.0	75.9 +/-6.1	-
Median TChol	3.60	3.19	3.31
Fasting glucose >5.6	18%	16%	2%

In addition to the high rates of lipodystrophy observed in patients using this WHO recommended first-line combination, the study highlighted the importance of anthropomorphic and metabolic parameters in resource poor countries and in particular these markers of risk for future cardiovascular disease and type-2 diabetes mellitus.

Ref: Mutimara E, Stewart A, Crowther NJ. The prevalence and metabolic consequences of antiretroviral-associated lipodystrophy in a population of HIV-infected African subjects. 8th IWADRLH, September 2006, San Francisco. Abstract 28.

CONFERENCE REPORTS

46th Interscience Conference on Antiretroviral Agents and Chemotherapy (ICAAC)

27-30 September 2006, San Francisco

Introduction

This US-based annual conference has generally reversed its trend for reduced HIV coverage, by including several important studies of new drugs.

Reports from this meeting include:

- MK-0518 demonstrates potent efficacy in patients with triple-class resistant virus: 24 week results
- Lipid profile of integrase inhibitor MK-0518: 24 week results compared to efavirenz in treatment naive patients
- Cell studies predict cross-resistance among integrase inhibitors
- HIV may use different coreceptors in blood and brain
- Critical interactions between darunavir (TMC114), lopinavir, Viagra, and oral contraceptives
- NRTI elvucitabine active against HIV in a 7-day monotherapy study
- Efavirenz/tenofovir fails as 2-drug maintenance regimen
- Nucleoside inhibitor MK-0608 mediates suppression of HCV replication for >30 days in chronically infected chimpanzees

MK-0518 demonstrates potent efficacy in patients with triple-class resistant virus: 24 week results

Edwin DeJesus, for thebody.com

This is the third major international HIV-related conference this year (including 13th Conference on Retroviruses and Opportunistic Infections [CROI] in Denver and the XVI International AIDS Conference this past August in Toronto) in which impressive data have been presented on the safety and efficacy of MK-0518 on various patient populations.

Integrase is an HIV enzyme that allows the virus to insert its genetic material into the DNA of human T cells. Integrase inhibitors block this important step in the viral life-cycle, preventing the virus from replicating. This new target makes this

drug extremely attractive for use in patients who already have preexisting resistance to other HIV drug classes.

MK-0518 has an in vitro activity (IC95) of 33 nM +/-23 nM in 50% human serum. The primary metabolism is via glucuronidation (UGT1A1), and it is not a potent inhibitor or inducer of CYP3A4; thus it does not require ritonavir (RTV, Norvir) boosting. For the same reason, the expected pharmacokinetics interactions are minimal. In fact, several pharmacokinetic drug interaction studies presented at this conference demonstrated very small changes on the MK-0518 pharmacokinetics when coadministered with efavirenz (EFV, Sustiva, Stocrin), ritonavir, tipranavir (TPV, Aptivus) or tenofovir DF (TDF, Viread), which did not require dosing modification. [1-3]

But the most relevant information presented at this conference on MK-0518 is a follow up of the study of MK-0518 in treatment-experienced patients. The results of this trial had been initially presented at CROI this past February. In fact, I also reported on that study. [4] At ICAAC we had the opportunity to view the 24-week results of this multicenter, international study [5] in which almost 200 heavily treatment-experienced patients with widespread HIV drug resistance were randomised to three different twice-daily dosages of MK-0518 (200 mg, 400 mg, 600 mg) versus placebo, plus an optimised background regimen.

The phenotypic susceptibility score in almost 50% of patients was 0, and 20-28% of the patients used enfuvirtide (EFN, T-20, Fuzeon) for the first time as part of their optimized background regimen. Approximately 17% of the patients in the treatment groups discontinued the study due to lack of efficacy in comparison to 67% in the placebo arm. Discontinuation due to adverse events was rare.

Table 1: Virological responses at 24 weeks

Week 24	MK-0518			Placebo
	200mg	400mg	600mg	
N	43	45	45	45
% > 1 log10	77	80	80	18
% <400 copies/mL	70	73	71	16
% < 50 copies/mL	65	57	67	14

This chart above summarizes the proportion of patients achieving HIV RNA below 50 copies/mL in an ITT analysis. The responses seen with all dosages studied are superior to the responses seen with placebo and an optimised background regimen.

On the 400-mg twice-daily group, which is the dose that has already been selected for further development, 69% of the patients with a PSS = 0 achieved viral loads below 400 copies/mL (in comparison to none in the placebo group). When these results are further stratified by the use or not of enfuvirtide, it appears that enfuvirtide improved the MK-0518 response by an approximate 20% in all groups studied. All dosages were very well tolerated.

These are remarkable results for a drug that appears to be not only extremely well tolerated, but has minimal drug interactions. Merck already opened an early expanded access to make this very promising agent available for the most needed population. The efficacy and safety of MK-0518 is also being evaluated in a head-to-head naive study against efavirenz, both using tenofovir DF/emtricitabine FDC (Truvada as backbone). This drug has a lot of potential to change treatment paradigms in the next few years. Its efficacy is clear; but data is now needed on sustained virologic responses beyond 24-weeks, resistance, sequentiability and safety. While we all wait for these data to come, it is extremely difficult not to get too excited about this promising drug.

Source: www.thebody.com

Slides:

<http://www.thebody.com/confs/icaac2006/pdfs/H-1670b.pdf>

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Lipid profile of integrase inhibitor MK-0518: 24 week results compared to efavirenz in treatment naive patients

Simon Collins, HIV i-Base

One of the highlights from last months IAS conference in Toronto was the late-breaker results from the Phase II dose-finding MK-0518 integrase inhibitor vs efavirenz, with tenofovir/FTC. [1]

Similar virological responses were seen in all arms at week 24, but of note, significantly faster suppression, and greater decreases in viral load were seen in all MK-0518 arms at weeks 4-8. As a result of this study, the 400mg BID dose was selected. Ongoing EAP programmes already started in the US, and starting in October in the UK, will collect additional safety data for the fast-track approval application.

Further details from this treatment-naive study were presented at ICAAC, showing that MK-0518 had a better lipid profile over 24 weeks in treatment naive patients than efavirenz. [2]

Total cholesterol dropped slightly (by approximately -5mg/dL over the first 12 weeks and was sustained out to week 24, compared to increases of +20 mg/dL in the efavirenz arm.

LDL (bad cholesterol) dropped slightly (by around -5mg/dL over the first 12 weeks sustained out to week 24, compared to increases of +5 mg/dL and +10 mg/dL at 12 and 24 weeks in the efavirenz arm. Differences compared to efavirenz were statistically significant, but were probably too modest to lead to clinical benefit.

HDL (good cholesterol) increased more rapidly in the efavirenz arm (approximately +6 mg/dL vs +1 mg/dL at 12 weeks) but differences reduced to approximately +4 and +2 respectively at week 24, and were not statistically significant.

Serum triglycerides remained close to baseline for the 100, 200 and 400 mg BD doses of MK-0518 out to week 24 and fell by ~50mg/dL in the 600mg BID arm, compared to an increase of approximately +50mg/dL over the first 12 weeks in the efavirenz, arm that were sustained out to week 24.

Table 1: Lipid changes after 24 weeks of MK-0518 or efavirenz

Drug/dose	0518 100mg BD	0518 200mg BD	0518 400mg BD	0518 600mg BD	EFV 600mg QD
B/line Chol mg/dL	168	161	168	162	170
Change Chol (95%CI)	-7* (-14 to 0)	-2* (-11 to 8)	-7* (-15 to 2)	-4* (-12 to 5)	+19 (+8 to 30)
B/line TG	129	110	127	155	128
Change TG (95%CI)	+2 (-22 to 26)	-5* (-20 to 9)	-2* (-23 to 18)	-43* (-87 to 1)	+43 (-1 to 96)

* p<0.05 compared to EFV

Several interaction studies involving MK-0518 were also presented at ICAAC:

- Tipranavir/ritonavir slightly lowered Cmin of MK-0518 but didn't affect AUC or Cmax. [3]
- Tenofovir had no significant interactions with MK-0518. [4]
- Efavirenz Cmin, AUC and Cmax were all slightly reduced by MK-0518, but no dose adjustment was recommended. [5]

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Cell studies predict cross-resistance among integrase inhibitors

Mark Mascolini, natap.org

Serial passage studies involving the Japan Tobacco/Gilead integrase inhibitor GS-9137 identified several resistance-conferring mutations, one of which can render HIV resistant to the drug by itself [1]. The study also yielded evidence of cross-resistance between GS-9137 and two other integrase inhibitors no longer being developed.

Researchers from Japan Tobacco and Kyoto's Institute for Virus Research performed classic serial passage studies in which technicians propagated lab strains of HIV while subjecting cultures to slowly increasing doses of an antiretroviral. This exercise revealed an E92Q mutation in the integrase catalytic core domain after 30 passages. H51Y and S147G joined E92Q after 60 passages. E157Q arose during passage 70.

Studies testing the susceptibility of HIV-1 to GS-9137, to the earlier Merck integrase inhibitor candidate L-870,810 [2], and to AZT indicated that E92Q alone confers resistance to GS-9137 and cross-resistance to L-870,810. Susceptibility to both GS-9137 and L-870,810 dropped dramatically when the researchers engineered molecular clones to carry two or three of the identified mutations. Clusters of different mutations identified earlier in studies of two Merck integrase inhibitor candidates also rendered virus highly resistant to GS-9137.

The researchers also presented data showing that virus isolated from 4 people with antiretroviral experience remains highly susceptible to GS-9137, as one would expect.

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HIV may use different coreceptors in blood and brain

Mark Mascolini, natap.org

HIV circulating in blood and cerebrospinal fluid (CSF) showed evidence of homing to different cellular coreceptors in 10 of 28 people (36%) studied at Lund University in Sweden [1]. The findings raise questions about separate HIV evolution in the brain and how CCR5 antagonists—now in late stages of testing—may affect that evolution.

In earlier studies, these researchers engineered a set of chimeric receptors that combine parts of the CCR5 receptor and the CXCR4 receptor [2]. HIV that uses CCR5 ("R5-tropic" virus) typically predominates early in the course of infection. In later stages of infection HIV that prefers CXCR4 ("X4-tropic" virus) predominates in some people.

With colleagues from Sahlgrenska Academy in Goteborg, the Lund team analysed paired plasma and CSF virus sampled from 28 HIV-infected people at different stages of infection. They used virus stocks to infect cell lines transfected with CD4 and either CCR5, CXCR4, or their R5/X4 chimeras.

R5-tropic virus predominated in both plasma and CSF. But there were exceptions. Plasma HIV isolates from 7 people used X4 either alone (in 1 person) or with R5 (in 6). Four of these 7 people had only R5-tropic virus in CSF. Six of 21 people who had exclusive R5-tropic virus in plasma and CSF had major differences in chimeric coreceptor use. Thus, all told, 10 of 28 people had evidence of discordant coreceptor tropism in plasma and CSF.

The ability of plasma R5 virus to use the R5/X4 chimeric receptor labeled FC-2 strongly correlated with greater CD4 deficits but did not correlate significantly with higher viral load. Nine people with FC-2 use and exclusive R5 isolates in plasma had a median CD4 count of 49 versus 495 CD4s in 12 people with FC-2-negative virus ($P = 0.004$). As earlier studies show, X4 virus or mixed R5/X4 virus signaled advanced CD4 depletion (median 60 cells, $P = 0.005$ versus the FC-2-negative group).

The researchers suggest that evolution of different coreceptor tropism in blood and CSF "most likely reflects more efficient [viral] replication in abundant target [CSF] cells," such as macrophages and microglial cells. They conclude that "discordance of viral phenotype in plasma and CSF is frequent and needs to be considered in the context of emergent treatment" with CCR5 antagonists.

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Critical interactions between darunavir (TMC114), lopinavir, Viagra, and oral contraceptives

Mark Mascolini, natap.org

Three separate studies demonstrated important interactions between the protease inhibitor (PI) darunavir (TMC114) and (1) lopinavir/ritonavir, (2) sildenafil (Viagra), and (3) the oral contraceptive Ortho-Novum, which contains ethinyl estradiol and norethindrone.

Despite doubling the darunavir dose from 600 to 1200 mg twice daily, researchers could not keep levels of this new PI high enough when given with 400/100 mg of lopinavir/ritonavir or 533/133 mg of the boosted PI [1]. The Tibotec investigators concluded that darunavir should not be prescribed with lopinavir/ritonavir.

This study in 33 HIV-infected volunteers recorded a slightly raised lopinavir/ritonavir area under the concentration-time curve (AUC), minimum concentration, and predose concentration with either 400/100 or 533/133 mg of lopinavir/ritonavir twice daily and either 1200 mg of darunavir twice daily or 1200/100 mg of darunavir/ritonavir twice daily.

Despite the doubled dose of darunavir, the PI's AUC, maximum concentration, minimum concentration, and predose concentration were all considerably lower with lopinavir/ritonavir than without the boosted PI. Darunavir's AUC at a dose of 1200 mg twice daily plus lopinavir/ritonavir was about 40% of the AUC with darunavir/ritonavir at 600/100 mg twice daily without lopinavir.

The sildenafil study enrolled 16 healthy HIV-uninfected men who took 100 mg of sildenafil on day 1, then 400/100 mg of darunavir/ritonavir twice daily for 8 days, with a single 25-mg sildenafil dose on day 7 [2]. Despite the quartered sildenafil dose given with darunavir/ritonavir, sildenafil AUC was equivalent to the AUC of full-dose sildenafil given without the PIs. Sildenafil's maximum concentration was 38% lower with the 25 mg dose plus the PIs than with 100 mg without the PIs. The Tibotec researchers expect that results would be similar if 25 mg of sildenafil were given with the licensed darunavir/ritonavir dose of 600/100 mg twice daily.

The Tibotec team proposes that 25 mg of sildenafil over 48 hours can be recommended as a starting dose when sildenafil is taken with darunavir/ritonavir. They suggest that results of this study can be used to shape dosage recommendations for other CYP3A substrate PDE-5 inhibitors given with darunavir/ritonavir, including verdenafil (single dose not to exceed 2.5 mg in 72 hours) and tadalafil (single dose not to exceed 10 mg in 72 hours).

The oral contraceptive study involved 19 HIV-infected women, 8 of whom did not complete the study [3]. Five stopped because of side effects, 1 withdrew consent, and 2 stopped coming back for study visits. The study design called for women to stop treatment if they had a grade 2 cutaneous problem; 3 had drug eruptions, 1 had papular rash, and 1 had a hypersensitivity reaction.

Levels of both ethinyl estradiol and norethindrone fell when women took Ortho-Novum with 600/100 mg of darunavir/ritonavir twice daily. Average minimum concentration, maximum concentration, and AUC of norethindrone dropped by 30%, 10%, and 14% with the PIs. Ortho-Novum did not greatly affect concentrations of darunavir/ritonavir.

The Tibotec researchers recommend alternative or additional contraceptive measures when women take estrogen-based contraceptives similar to Ortho-Novum with darunavir/ritonavir.

C O M M E N T

Clearly darunavir and lopinavir/r should not be used in the same combination. The recommendation to use 25mg sildenafil (Viagra) when using darunavir is similar to other PIs. Oral contraceptives should not be relied on by patients using darunavir in their combination.

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NRTI elvucitabine active against HIV in a 7-day monotherapy study

Liz Highleyman, aidsmap.com

The investigational nucleoside reverse transcriptase inhibitor elvucitabine demonstrated potent and prolonged anti-HIV activity in a seven-day monotherapy study, according to late-breaking data presented on Friday at the 46th Interscience Conference on Antiretroviral Agents and Chemotherapy (ICAAC) in San Francisco.

Elvucitabine (also known as L-Fd4C) is an L-cytosine nucleoside analogue being developed by Achillion Pharmaceuticals of New Haven, Connecticut, in the U.S. A small study reported at last year's ICAAC showed that various doses of elvucitabine plus lopinavir/ritonavir (Kaletra) suppressed HIV RNA by as much 2 log₁₀ copies/mL over 21 days.

The previous trial demonstrated the short-term safety of elvucitabine, but was not able to determine how much of the observed antiviral effect was attributable to the new drug and how much to lopinavir/ritonavir. Accordingly, researchers then carried out a study of elvucitabine used as monotherapy.

The present Phase II double-blind study, described by Philippe Colucci of the University of Montreal, included 24 HIV-positive participants who were randomly assigned to receive 10 mg once-daily elvucitabine or placebo. After seven days on elvucitabine monotherapy, these patients were given lopinavir/ritonavir for an additional 21 days in order to reduce the risk of drug resistance, since elvucitabine remains in the body for a prolonged period.

All participants but one were men, and all but one were white; the average age was about 40 years. The presenter noted that future multicentre trials will aim to enrol a more diverse study population.

Baseline characteristics were generally similar in both arms, but participants randomised to the elvucitabine group had a slightly lower CD4 cell count than those in the placebo arm (mean 320 vs 403 cells/mm³). The mean HIV RNA level was about 4.75 log₁₀ copies/mL.

Patients had minimal previous antiretroviral treatment experience, and genotypic testing showed that they did not have mutations associated with resistance to elvucitabine or lopinavir/ritonavir (M184V, M184I, D237E).

By Day 7, HIV viral load declined by an average of 0.85 log₁₀ copies/mL from baseline in patients taking elvucitabine, compared with essentially no change in the placebo group ($p < 0.001$). The mean CD4 cell count increases were 62 vs 9 cells/mm³, respectively. HIV RNA continued to decrease even after stopping the drug, but the decline became less pronounced as elvucitabine concentrations dropped. On Day 21 (14 days after the last elvucitabine dose), the maximal viral load decrease was 1.73 log₁₀ copies/mL, before rising again.

Pharmacokinetic analyses showed that the overall half-life of elvucitabine was about 100 hours, and there were still detectable concentrations in plasma and peripheral blood mononuclear cells at Day 21. Maximum concentrations and maximum trough levels of plasma elvucitabine were attained on the final day of dosing, but concentrations remained above the IC₅₀ (the level at which viral replication is reduced by 50%) for up to 14 days after discontinuation.

Overall, elvucitabine was well-tolerated. No major safety issues were identified, and the emergence of virus with resistance to elvucitabine or lopinavir/ritonavir was not observed.

The researchers concluded that, "These results confirm that elvucitabine monotherapy demonstrates significant antiviral activity over seven days of dosing." They added that the drug's long plasma and intracellular half-life and concentration-dependent efficacy "may provide a better barrier to resistance than antiviral agents with short half-lives."

Based on the results of this and previous studies, Achillion plans to proceed with larger clinical trials of elvucitabine in combination with other antiretroviral agents. If the drug proves safe and effective over longer periods in more patients, it offers the prospect of an antiviral medication that may be able to be administered less often than once daily.

Source: www.aidsmap.com

Ref: Colucci P et al. Efficacy and novel pharmacology of elvucitabine in a 7 day placebo controlled monotherapy study. 46th ICAAC, San Francisco, 2006. Abstract H-1670d.

Efavirenz/tenofovir fails as 2-drug maintenance regimen

Mark Mascolini, natap.org

Efavirenz plus tenofovir given as a simplified maintenance regimen did not control HIV as well as the same two drugs plus 3TC in a 48-week French trial [1]. Three people in the two-drug arm and none in the three-drug arm had to stop an antiretroviral because of treatment-related side effects.

Pierre-Marie Girard (St. Antoine Hospital, Paris) and colleagues across France recruited 143 people with a viral load below 50 copies/mL for at least 6 months on their current regimen, no history of virologic failure, and no significant lab or clinical abnormalities. Study participants were randomised to start efavirenz/tenofovir or those two drugs plus 3TC.

The group had a median age of 40 years (range 22 to 73) and a median CD4 count of 473 (range 78 to 1775); 35% had CDC stage C disease. They had taken antiretrovirals for a median of 3.7 years (range 0.5 to 7.7). While 45.5% were taking two nucleosides plus one protease inhibitor, 43.5% were taking a non-nucleoside with two nucleosides. Nearly three quarters (71%) were using AZT and 3TC as their nucleosides.

After 48 weeks, both intention-to-treat analysis and on-treatment analysis showed better virologic control in the three-drug

group (Table 1). The 95% confidence interval for both comparisons stretched beyond the range set to establish non-inferiority of the two-drug regimen (14%).

Table 1: Two- versus three-drug maintenance for 48 weeks

	EFV/TDF	EFV + 2RTIs	Difference (upper bound 95% CI)
n	72	71	
Intent-to-treat <50 c/mL	81.7%	97.2%	15.5% (23.7%)
On treatment <50 c/mL	90%	100%	10.0% (15.5%)

Three people in the two-drug group had NNRTI-related resistance mutations by week 48, while no NNRTI mutations emerged in the triple-drug group. Ten people in the two-drug arm stopped one or more study drugs, 3 of them because of treatment-related side effects (2 transaminase elevations and 1 case of vertigo). No one in the three-drug arm stopped an antiretroviral because of side effects, though two stopped coming back for follow-up visits.

Median CD4 counts climbed by 35 cells/mm³ in the three-drug group and 14 cells in the two-drug group, but this difference lacked statistical significance (p=0.94). Median hemoglobin rose 0.80 g/dL in the triple-therapy arm and 0.45 g/dL in the double-therapy arm, a difference that also fell short of significance (P = 0.14). Creatinine clearance fell 3.3 mL/min in the three-drug arm and rose 1.7 mL/min in the two-drug arm, again a non-significant difference (p=0.17).

In the group as a whole, triglycerides fell 0.25 mmol/L (p<0.001) and total cholesterol fell 0.3 mmol/L (p<0.001). Dangerous low-density lipoprotein cholesterol dropped 0.2 mmol/L in the triple-therapy group (p=0.015 versus baseline) but rose (non-significantly) by 0.15 mmol/L in the two-drug group (p=0.5). The treatment groups did not differ in lipid changes or fat distribution. Subcutaneous abdominal fat rose significantly in the whole study group (9 cm², p=0.017), while the visceral-to-subcutaneous adipose tissue ratio fell by 0.05 (p=0.06).

Reference

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Nucleoside inhibitor MK-0608 mediates suppression of HCV replication for >30 days in chronically infected chimpanzees

Jules Levin, natap.org

There are 3 HCV polymerase inhibitors in patient studies now: HCV-796; R1626; NM283. HCV-796 & R1626 showed 1.2 to 1.4 log viral load reductions in 10 day studies. And there are 2 HCV protease inhibitors in patients studies: VX-950, which showed 4.4 log reductions in 14 day study in viral load, and SCH503034 which showed about 1.8 logs viral load reduction in 14 day study.

David Olsen et al from Merck reported in a poster on this last day at ICAAC new study results of a study reporting the effect of a new HCV polymerase inhibitor MK-0608 in chimpanzees. The first presentation of MK-0608 was at the HIV Drug Resistance Workshop in the Summer of 2006 where a 5.7 log reduction was seen in chimps after 7 days, and with one dose three logs reduction was seen.

The results reported an average reduction of 4.7 logs HCV RNA for 4 chimps who were treated. Three of 4 chimps had undetectable HCV RNA with a sensitive assay. But the baseline viral loads were lower for these 3 chimps than the chimp that saw a 5.7 log viral load reduction reported at the Resistance Workshop. Of note, until now we have seen these types of deep HCV RNA reductions only in HCV protease inhibitors.

Once-daily dosing of MK-0608 for 37 days in HCV chronically infected resulted in a rapid decrease in plasma viral RNA to below the limit of quantification (20 IU/ml) in 3 of 4 animals in less than 10 days.

Continued administration for up to 37 days resulted in sustained suppression of viral load to levels below detection that remained undetectable throughout the dosing period.

Viral load in the fourth chimpanzee (starting titer >10⁶ IU/mL) decreased by 4.7 logs during dosing without the selection of resistant virus. All animals experienced a rebound in viral load upon cessation of dosing.

Author conclusions included that IV and oral dosing of MK-0608 to HCV infected chimpanzees resulted in significant reductions in viral load: >5 log reduction in viral load (mg/kg IV), no rebound during dosing and a delay in rebound after end of extended dosing. The resistance genotype included mutations at amino acid 282, with reversion back to wild-type sequence suggesting this mutation impacts on viral fitness.

Ref: Olsen DB, Davies M, Handt L et al. The nucleoside inhibitor MK-0608 mediates suppression of HCV replication for >30 days in chronically infected chimpanzees. 46th ICAAC, Toronto 2006. Abstract V-1914a.

CONFERENCE REPORTS

Report from the 10th Annual UK Resistance Meeting

21 September 2006, London

Svilen Konov, HIV i-Base

This year's Annual UK Resistance Meeting was held on 21 September in London. Faculty were Professor Jonathan Weber, FRCP Imperial College, London and Dr Anna Maria Geretti from Royal Free Hospital, London.

The meeting has been traditionally known for its high quality and opportunity to see the presentations of leading specialists in the field. This year was no exception. This report covers six of the oral presentations.

Garcia-Diaz and colleagues from the Royal Free Hospital and UCL Medical School in London genotyped 239 (169 male, 50% white) subjects with early infection (seroconversion within 4-5 months, shown by a detuned HIV antibody test) in order to characterise the resistance rates. [1]

The subtype distribution was 56%-B, 19%-C, 7%-A, and 12%-other non-B (CRF02, D, G, CRF01, CRF 06, CRF13, CRF16). Resistance mutations were detected in 17 subjects (7.1%), 15 UK born, 1 from South Africa, and 1 from Pakistan. The prevalence by drug class was: NRTI 10/239 (mainly TAMs), NNRTI 4/239 (exclusively K103N), PI 4/239 (M46L, V82L, L90M). One person had both NRTI and PI mutations. The researchers concluded that the prevalence of primary resistance was significant, in this group mainly restricted to people born in the UK.

Cozzi-Lepri from University College London and a team of international collaborators compared 9 existing rule-based genotype interpretation systems for abacavir (ANRS, CHL, Detroit, Stanford, QUEST, Rega, Retrogram, Sao Paolo, and TRUGENE). [2]

1306 patients with a viral load >500 copies/mL and who had a genotypic test at the time of starting an abacavir-containing regimen were included. The median number of abacavir-associated resistance mutations was 3 (range 0-7). The median week 8 viral load reduction was 1.61 log₁₀ copies/mL. Most of the interpretation systems, however, showed larger viral load reductions in patients classified as sensitive compared to intermediate or resistant. The team highlighted the issue that there is still a high degree of variability in predicting susceptibility to abacavir between different interpretation systems..

Winters and colleagues from Virco and Tibotec presented clinical cut-offs for darunavir (TMC114). [3]

They used a multiple linear regression model to predict the darunavir fold change from the viral genotype and a linear regression model that used the data from the POWER 1, 2, and 3 studies to predict the 8-week change in viral load on regimens containing ritonavir-boosted darunavir. This model was used to define two clinical cut-offs linked to predicted darunavir fold-change values, associated with 20 or 80% loss of the darunavir/r response, for subjects infected with wild type strains. The 20% and 80% loss of wildtype darunavir response were predicted at 3.4 and 97 fold change respectively. Detailed reports on resistance and sensitivity to darunavir were included in reports from this years International Resistance Workshop in the July/August issue of HTB. [4]

Booth CL and researchers from Royal Free Hospital and UCL Medical School together with people from Virco looked into the inter-laboratory reproducibility of the identification of resistance-associated mutations and pol-derived HIV-1 subtyping. [5]

The team tested 65 samples by ViroSeq and by Virco's in-house assay. As some samples did not yield a sequence the total number of paired genotypes achieved was 57. Among them 1 (2%) showed no resistance mutations, 9 (16%) showed a resistance mutation by one assay and a mixture of the same mutant with wild-type by the other. In general, concordance was good, but not perfect.

As abacavir/3TC is a commonly used as a backbone nowadays, Reddy HV and colleagues from Hull York Medical School and the Virology Department of the Leeds teaching hospitals, investigated retrospectively the frequent early failures of regimens containing this dual-nucleoside backbone. [6]

They reviewed the case notes of 8 patients who started on abacavir/3TC, four of whom achieved durable complete viral suppression. Three patients had a virological relapse within 2-4 months despite good adherence, and lack of serious adverse events and resistance at baseline. The three patients were male, two with a subtype C and one with a subtype B. Two of them used efavirenz and one used nevirapine. The resistance tests at rebound showed K65R (in all three), L74V (in one), Y181C (in one), and G190E (in two). Even though a large prospective randomised trial demonstrated that abacavir/3TC plus an NNRTI is an efficient treatment, there are instances when the clinical practice is at odds with the conclusions of that study and those call for further exploration.

Another study from Royal Free Hospital (Booth and colleagues) looked into the prevalence of drug resistance in patients with viral load above 50 and below 5000 copies. [7]

Among the 2000 people who were followed in the study, 100 were within the above-mentioned virological range. The most common mutations discovered were:

RT: M184V (in 30%), K103N (in 21%), D67N (in 16%), T215Y (in 16%), M41L (in 15%), K70R (in 15%), K219Q/E (in 15%), L210W (in 6%), and Y181C (in 5%)

PR: L90M (in 10%), I84V (in 7%), M46I (in 5%), and I54V (in 5%)

The study shows that even if the prevalence of resistance is high, it is not universal in patients failing HAART with a viral load of <5000 copies/mL.

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Unless stated otherwise, all references are to the programme and abstracts for the 10th Annual Resistance Meeting, 21 September 2006, London.

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4. Resistance to darunavir (TMC-114): predicting responses for treatment experienced patients. HIV Treatment Bulletin July/August 2006. <http://www.i-base.info/htb/v7/htb7-7-8/darunavir.html>
5. Booth CL, Ramaswamy M et al. Inter-laboratory reproducibility of the identification of resistance-associated mutations and pol-derived HIV-1 subtyping. Abstract 4.
6. Reddy HV, Hale A et al. Frequent early failure of KivexaÆ-containing regimes associated with emergence of K65R. Abstract 5.
7. Booth CL, Garcia-Diaz A et al. Prevalence of antiretroviral drug resistance mutations in patients with viral load above 50 and below 5000 copies/mL while on HAART. Abstract 6.

CONFERENCE REPORTS

Further reports from XVI International AIDS Conference

13-18 August 2006, Toronto, Canada

Introduction

In the September issue of HIV Treatment Bulletin, we included first reports from this important meeting, including studies relating to treatment access, new antiretrovirals, treatment strategies including boosted PI-monotherapy, malignancies, basic science, some paediatric care and a range of other studies.

In this issue, we conclude our coverage with reports on women's health, prevention of mother to child transmission (PMTCT) and additional paediatric studies.

These reports include:

- Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV positive women in Lusaka, Zambia
- Effect of herpes simplex therapy on genital and plasma viral load
- Maternal health and prevention of mother to child transmission
- 18-month effectiveness of short-course perinatal antiretroviral regimens combined to infant-feeding interventions for PMTCT in DITRAME PLUS ANRS 1201/1202 2001-2005
- HIV prevalence rates amongst 6 week old infants in South Africa: the case for universal screening at immunisation clinics
- Maternal illness during pregnancy is associated with *in utero* mother to child transmission
- Extensively drug resistant TB (XTB) in South Africa

Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV positive women in Lusaka, Zambia

Polly Clayden, HIV i-Base

Cervical cancer is the second most common cancer among women worldwide and the most common cancer among women in resource limited settings. Each year there are an estimated 500,000 new cases and approximately 275,000 deaths and 20% of these deaths occur in sub-Saharan Africa.

HIV positive women are at higher risk for the development of HPV-induced squamous intraepithelial lesions (SIL) of the cervix. Additionally they have lower spontaneous regression rates of SIL higher progression rates of low grade SIL and higher recurrence rates after treatment.

In industrialised countries, where screening is routine, HIV-positive women are not at higher risk of invasive cervical cancer than HIV-negative women if it is detected and treated at an early enough stage. HIV-positive women living in resource-limited settings who are accessing antiretroviral therapy have the potential to live long enough for cervical cancer to manifest and progress.

Groesbeck Parham from the University of Alabama and the Centre for Infectious Disease Research in Zambia presented findings from a study evaluating the prevalence and predictors of cervical cytological abnormalities in 150 eligible, non-pregnant, HIV-infected women accessing HIV care and treatment services in Lusaka, Zambia. The women received a pelvic examination and cervical specimens were analysed with liquid-based monolayer cytology and tested for HPV.

In this cross-sectional screening study, the median age of the women was 36 years (range 20-49 years) and their mean CD4 count was 161 cells/mm³ (range 7-942 cells/mm³).

The authors reported that 77% of women were receiving antiretrovirals, but they noted that the majority had initiated treatment within the previous six months. A small number (2%) of the women were smokers. The median age of first sexual intercourse was 18 years (range 12-29 years); the median age of first pregnancy was 20 years (range 14-31 years) and the median number of pregnancies was 3 (range 0-10); 17.2% had six or more lifetime sexual partners and only 25.2% reported consistent condom use.

The cytology results showed only 6.21% of the women had normal cell samples, 17.22% atypical squamous cells of undetermined significance (ASCUS); 23.42% low grade SIL; 33.83% high grade SIL and 19.32% had lesions suspicious for squamous cell carcinoma (SCC).

Univariate analysis revealed low CD4 count (OR: 1.25 [95% CI 1.03-1.54], p=0.027) and presence of high risk HPV (OR:9.25 [2.60-32.88], p=0.001) to be significantly associated with severe cytological abnormalities. Multivariate analysis found presence of high risk HPV (Adj. OR: 12.4 [2.62-58.1], p=0.02) to be a significant predictor.

The authors concluded that this Zambian study found one of the highest prevalence rates of high-grade cervical cytology (>=HSIL), which they attributed to severe immune suppression. They also reported a significant diversity and multiplicity of HPV types.

At the beginning of the presentation, Dr Parham reminded us that death from cervical cancer is a "direct result of absence or failure of screening programmes". In Zambia and throughout sub-Saharan Africa very few women with HIV/AIDS are ever screened for cervical cancer and he described an "enormous need."

C O M M E N T

These results are shockingly high ("among the highest ever reported") and, as emphasised in the report, largely preventable with proper cervical cancer screening and early and effective treatment.

The authors also highlighted several questions that need to be addressed within this setting:

- **Are nutritional deficiencies significant?**
- **Does the prevalence of different HPV types vary with different degrees of immunosuppression?**
- **Are differential attributable cervical cancer risks associated with each high risk HPV type?**
- **Would the HPV vaccine be effective in this population/environment?**
- **What is the natural history of HPV-induced cervical neoplastic disease in the era of HAART?**
- **Can treatment of cervical neoplasia lower the risk of transmission and acquisition of HIV?**

Ref: Parham G, Sahasrabudde V, Vermund S et al. Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV-infected women in Lusaka, Zambia. XVI International AIDS Conference, Toronto, Canada. 13-18 August 2006. Oral Abstract TUAB0303.

Effect of herpes simplex therapy on genital and plasma HIV viral load

Polly Clayden, HIV i-Base

There is strong evidence associating infection with herpes simplex virus type 2 (HSV-2) with HIV transmission. More than 80% of people with HIV are co-infected with HIV-2 in Africa.

In an oral presentation, Phillippe Mayaud reported findings from the ANRS 1285 trials. These are two proof-of-concept, randomised, placebo-controlled trials measuring the impact of valacyclovir on plasma and genital viral load among HSV/HIV-infected women either receiving HAART (ANRS 1285b), or not needing HAART (ANRS 1285a), in Burkina Faso. [1, 2]

In ANRS 1285a, 140 women were randomised to receive valacyclovir (lg daily) or placebo. Plasma and genital viral load were measured twice-weekly and data were available for analysis from 136 women. The investigators reported a -0.41 and -0.58 log¹⁰ copies/mL reduction in quantity of genital and plasma HIV-1 RNA respectively over three months, in the women receiving valacyclovir. They also found a 65% reduction in HSV-2 genital shedding and an 84% reduction of occurrence of ulcers.

In ANRS 1285b, 60 women receiving HAART were randomised to valacyclovir or placebo (mean CD4 count: 266 and 295 cells/mm³ respectively).

The investigators reported that in this trial there was some evidence of a reduction in plasma HIV-1 RNA among the women on valacyclovir, but it did not reach statistical significance (p=0.06). They found very little HSV-2 shedding but a further reduction of 70% in the valacyclovir arm, and no occurrence of ulcers in both arms.

They explained that this was the “First randomized clinical trial to demonstrate casual relationship between HSV-2 and HIV-1 replication” and that the effect persists amongst the small subset of women on HAART who are baseline shedders.

They wrote “Results of both trials suggest that effect on genital HIV-1 RNA is driven partly by concomitant reduction in plasma HIV-1 RNA, and partly by the facilitating role of HSV-2 on HIV-1 genital replication, although this effect was limited in women taking HAART. Plausible explanations for impact on plasma HIV-1 include immunological mechanisms, circulating soluble factors and/or HIV-infected cells, or effect on other herpes-related viruses.”

Dr Mayaud questioned whether these findings would have sufficient impact to reduce HIV transmission, and suggested that we await the results of ongoing trials among serodiscordant couples from Celum et al. He also explained that specific trials were needed to determine whether virological impact at systemic level be translated into impact on CD4.

References

1. Mayaud P, Ouedraogo A, Nagot N et al. Herpes simplex virus type 2 (HSV-suppressive therapy to reduce genital and plasma HIV-1 RNA: overview of ANRS 1285 trials, potential mechanisms and future interventions. XVI International AIDS Conference, August 2006, Toronto. Oral abstract TUAC0501.
2. Nagot N, Ouedraogo A, Konate I et al. Impact of valacyclovir on genital and plasma HIV-1 RNA: a randomised controlled trial among women taking HAART (ANRS 1285b). XVI International AIDS Conference August 2006, Toronto. Poster abstract TUPE0402.
http://www.iasociety.org/abstract/show.asp?abstract_id=2189180

IAS: MATERNAL HEALTH AND PMTCT

Maternal health and prevention of mother to child transmission

Polly Clayden, HIV i-Base

There was a noticeable lack of new data on prevention of mother to child transmission at this conference, and despite some strong statements about “women and girls” throughout the week, most studies placed little emphasis on the mothers’ health.

“We have the tools and we have to move forward”, Elaine Abrams insisted in her presentation. Presenting a convincing case for the substantial benefits of linking prevention of mother to child transmission (PMTCT) with HIV care and treatment programmes. She highlighted that this would not only strengthen PMTCT interventions - for example with use of HAART where appropriate - but also enhance women’s and children’s health, “In keeping mothers healthy and alive we are also likely to keep their babies healthy”. The opportunity provided by PMTCT for identifying HIV positive women must not be lost, with regard to linking these women with the treatment and care services they need. Although the experience to date of linkage programmes is limited, there are innovative models to guide us, including the MTCT-Plus initiatives.

We have failed to reach more than 90% of pregnant women needing PMTCT, predominantly those living in resource-limited settings. We have failed to focus on maternal health. In addition to increasing coverage, we need to improve the follow-up of HIV-positive mothers and their babies and to obtain outcome data for the evaluation of programmes in “real-life” settings.

18-month effectiveness of short-course perinatal antiretroviral regimens combined to infant-feeding interventions for PMTCT in DITRAME PLUS ANRS 1201/1202 2001-2005

Polly Clayden, HIV i-Base

Valeriane Leroy presented findings from a recent analysis of the ANRS 1201/1202 DITRAME PLUS study - that has looked at pre-, peri- and post-natal antiretroviral regimens for prevention of mother to child transmission (PMTCT) of HIV in Abidjan, CÔte d'Ivoire - to assess the 18-month effectiveness of two short-course antiretroviral regimens combined with infant-feeding options. [1]

This sub study included women/infant pairs enrolled in DITRAME PLUS 1201, conducted between 2001-2002, (n=375) and DITRAME PLUS 1202 between 2002-2003 (n=336). In the 1201 study, women received AZT from 36 weeks gestation and single dose nevirapine (SD NVP) at delivery, and the infants SD NVP and AZT for 7 days. In the 1202 study, women received AZT+3TC from 32 weeks, SD NVP and AZT+3TC for three days post partum and the infants received SD NVP and AZT for 7 days.

Women were given the choice between formula feeding, with formula and equipment provided free of charge for 9 months (n=195 and n=126 in DITRAME PLUS 1201 and 1202 respectively), or exclusive short-term breastfeeding with early cessation from four months (n=169 and n=198 in DITRAME PLUS 1201 and 1202 respectively).

Follow up of mother infant pairs was over two years in two clinics. Blood samples for HIV diagnosis were taken at day 2, week 4-6, month 3 and then quarterly until 18 months or two months after breastfeeding cessation.

The investigators defined paediatric HIV infection as a positive PCR at any age, or if aged >18 months, a positive HIV serology. Postnatal transmission (PT) was defined as a child with a negative PCR from a sample obtained at >4weeks who later became infected. Cumulative transmission risks (CTRs) of infection were estimated using Turnbull method in each infant-feeding group defined at day 2.

The ANRS 049a DITRAME study conducted between 1995 and 1999 - in which women received short course AZT from 36 weeks gestation until delivery, followed by unrestricted breastfeeding - was used as the reference cohort (n=238).

Overall, the study population was broadly similar across the regimen and feeding option groups, but 15.5% of women were eligible for HAART in the reference group vs 24.6%, 31.8 (in 1201), 20.3 and 20.6 (in 1202) in the breast feeding and formula feeding groups respectively.

The investigators found that 107/926 infants (for whom 18 months CTR data were available) were HIV infected, of whom 27 were PT cases. There were 15 (22%, 95% CI: 16-30%) in the reference group, 10 (16%. 95% CI: 10-27%) in the 1201 breast fed group, 1 (9%. 95% CI: 6-14%) in the 1201 formula fed group, 1 (7%, 95%CI: 4-11%) in the 1202 breast fed group and 0 (6%. 95%CI: 2-10%).

In a multivariate model adjusted for maternal HAART eligibility, home delivery and low birth weight (2.5kg), the investigators found that both 1201 and 1202 groups had lower CTR than the reference cohort.

Table 1: Correlates of 18 month infection with DITRAME Plus – Multivariate model

	N=688	CTR (%)	AHR	95% CI
Cohort				
AZT/SDNVP(ref)	364	11.6	1	-
AZT/3TC/SDNVP	324	6.3	0.38	0.20-0.70
Infant feeding				
Short term BF	367	10.3	1	-
FF	321	7.9	0.60	0.35-1.04
Maternal VL (for 1 log increase)			1.88	1.61-2.19
Prepartum prophylaxis (for 10 days increase)			0.98	0.97-0.99

Only treatment regimen, length of prophylaxis and maternal viral load were predictive of infant infection (see Table 1).

Dr Leroy concluded that peripartum short course regimens, combined with infant feeding interventions, significantly reduce MTCT compared to short course AZT in a long-term breastfeeding population. Both formula feeding and short-term breastfeeding

were protective, but there was no significant protective effect of formula feeding compared to short term breast feeding. She noted that the most effective of these strategies could result in 18 month TR as low as 6%.

C O M M E N T

These results are similar to the French cohort experience of adding 3TC at 32 weeks gestation to AZT. This was also very effective at reducing MTCT but associated with high rates of 3TC resistance. [2]

Although just failing to reach statistical significance (95% CI crossing 1 [0.35-1.04]) formula-feeding was associated with a biologically significant reduction in the risk of transmission (adjusted hazard ratio 0.6) compared with weaning at 4 months.

References

1. Leroy V, Ekouévi D.K., Dequae-Merchadou L et al. 18-month effectiveness of short-course perinatal antiretroviral regimens combined to infant-feeding interventions for PMTCT in Abidjan, Côte d'Ivoire. DITRAME PLUS ANRS 1201/1202 2001-2005. XVI International AIDS Conference, Toronto, Canada. 13 - 18 August 2006. Oral abstract THAC0101.
2. Mandelbrot L. et al. Lamivudine-Zidovudine combination for prevention of maternal-infant transmission of HIV-1. JAMA 2001;285:2083-93.

HIV prevalence rates amongst 6 week old infants in South Africa: the case for universal screening at immunisation clinics

Polly Clayden, HIV i-Base

Standard PMTCT surveillance methods have failed to assess the number of vertical infections being prevented in infants. Although rates of 11.9% with single dose nevirapine in the HIVNET 012 study are quoted liberally in discussion around the success of this strategy, field data can show considerably higher rates of transmission.

"We are spending millions of dollars and we don't know how well we are doing" said Nigel Rollins of the University of KwaZulu-Natal (KZN) presenting data from a pilot surveillance study to determine mother to child transmission (MTCT) rates in KwaZulu-Natal.

In this programme, routine, anonymous, unlinked, HIV prevalence testing was performed on infants with consenting parents or guardians, attending 6-week immunisation clinics at seven primary health care clinics offering PMTCT services.

Dried blood spot (DBS) samples were collected on filter paper and tested for HIV antibodies (maternal) using a commercial ELISA. DBS samples of infants that were antibody positive were then tested for HIV RNA by PCR. The mothers were also asked about any previous pregnancies and whether the child was alive or dead.

Dr Rollins explained that trained lay people from local communities collected the DBS and conducted the interviews.

DBS samples were collected from 2,439 infants aged 4-8 weeks of age who were brought for their first DTP immunisation. The investigators reported HIV antibodies in 914 infants representing the maternal seroprevalence rate of 37.6% (CI: 35.7-39.6%); amongst mothers aged 20-29 years this was 46.9% (CI: 42.9% - 50.9%). This concurs with previously reported prevalence rates for KZN.

189 children born to these positive mothers tested HIV positive by PCR on the DBS (7.6%) giving a transmission rate of 20.8% (CI: 18.2 - 23.6%). Amongst mothers who reported that they were HIV-positive who had taken single dose nevirapine, transmission rate was 15.3%.

A group of 7.6% women reported having tested HIV-negative during the antenatal period but HIV antibodies were identified in the DBS of their infant and 31.2% of these infants were infected. Dr Rollins suggested that these women may have been in the window period at the time of their HIV tests or they may have been infected during pregnancy. High maternal viral load following seroconversion is likely to have caused this high transmission rate.

He concluded that screening of all infants at immunisation clinics using this method effective is feasible for monitoring the overall impact of PMTCT programmes.

He then went on to discuss factors that could contribute the poor performance of these programmes. Although there is a group of women for whom testing and nevirapine are effective for PMTCT, he reminded us that women may become infected in the antenatal period, or be in the window period during routine screening. Additionally a number of women have no access to services and therefore receive no intervention.

Child mortality rates - which had reduced considerably from 48 per 1000 before 1990 to 31 per 1000 between 1990 and 1994 - has increased dramatically in the last five years to 99 per 1000. Dr Rollins attributes this to HIV infection of the children and greater mortality among children whose mothers die of AIDS.

C O M M E N T

Outcomes in clinical trials can be expected to be better than in the field, but, nevertheless, these results are disappointing, as even by age 6 weeks the HIV infection rate among those infants exposed to NVP in labour was 15.3%.

The high rate of primary infection during pregnancy among these mothers is a major cause for concern. The 7.6% HIV positive women not identified in pregnancy is higher than has been reported for seroconversion rates elsewhere. One large study in progress in KZN found a rate of about 5% - reported in a conference abstract - and a lower rate was reported in an article looking at patients from Western Cape.

It is unclear what the uptake of testing was in pregnant women in this programme, and it could be that women who knew they were positive did not agree to be tested. The 15% transmission rate in women who took NVP is similar to the Kampala data presented at CROI, but higher than reported rates with NVP in urban Johannesburg settings (Bara and Coronation reported around 9%) and probably reflects the predominantly breastfeeding environment.

Although these data are depressing, they make a strong argument for opt-out testing in pregnancy, and repeat tests in late pregnancy or at delivery in high prevalence areas, and the implementation of the best possible regimen available, with an emphasis on antenatal and maternal care.

Dr Rollins made "the case for universal screening at immunisation clinics". This would offer another opportunity for a woman to learn about her status and look after her own health as well as her child's, and an opportunity to identify positive children and get them into early HIV care and follow up.

Single dose nevirapine still remains the mainstay of many PMTCT programmes, and represents the minimum intervention where other interventions are not available. But once again these data highlight a massive variation in this strategy's efficacy. Even with this minimum intervention, there is room for improvement of services. The latest version of the WHO guidelines clearly advocate for the use of more complex interventions such as HAART, or short course AZT plus single dose nevirapine where possible. To a question about adding short course AZT to the single dose nevirapine, Dr Rollins argued that not only the regimen, but also the quality of the programmes and services need to be addressed and the health system supported.

Ref: Rollins N, Mzolo S, Little K et al. HIV prevalence rates amongst 6 week old infants in South Africa: the case for universal screening at immunization clinics. XVI International AIDS Conference, Toronto, Canada. 13-18 August 2006. Oral abstract THAC0104.

Maternal illness during pregnancy is associated with *in utero* mother to child transmission

Polly Clayden, HIV i-Base

In utero transmission accounts for 20-30% of mother to child transmissions among breastfeeding populations. As interventions to reduce intrapartum transmission risk become more accessible in sub-Saharan Africa, *in utero* transmission will account for a greater proportion of paediatric HIV infections.

Carey Farquar from the University of Washington and University of Nairobi Collaborative Research Group presented findings from a prospective cohort study to determine correlates of *in utero* HIV transmission.

In this study of 463 infants born to HIV positive mothers, women were enrolled before 32 weeks gestation and received AZT from week 34. At 32 weeks, mothers were interviewed for medical history during pregnancy, and tested for STIs (syphilis, gonorrhoea, chlamydia and trichomonas), bacterial vaginosis, CD4 count and viral load in plasma and cervical secretions.

Study visits were every two weeks and then weekly after starting AZT. Mother and infant visits were then monthly for one year. Infants were tested at birth for HIV-1 DNA (filter paper) and RNA (plasma) within 48 hours of delivery. Infant HIV status was then assessed every 3 months. Seventy seven infants died and 48 were lost to follow up.

Of the 88 infants infected during the study period, the investigators found that 29 infants (6%) had detectable HIV-1 DNA or RNA within 48 hours of birth and were defined as infected *in utero* (33% of the HIV infected infants). Additionally, 37 infants (42%) were negative at birth and positive at month 1; 12 (14%) had no sample at birth and were positive at month 1; and 10 were HIV-negative at month 1 and positive at a later time point. The infected *in utero* infants were compared to those uninfected or infected at a later time point (n=422).

In multivariate analysis, higher maternal plasma HIV-1 RNA (log 10 copies/mL) OR 1.9 (95% CI: 1.1-3.1, p=0.02); maternal AZT \geq 3 weeks, OR 0.4 (95% CI: 0.2-1.0, p=0.04); history of cough, fever or diarrhoea during pregnancy, OR 2.6 (95% CI: 1.2-5.8, p=0.02) and bacterial vaginosis at 32 weeks were significantly associated with *in utero* transmission.

Speculating on the mechanism Professor Faquar suggested that illness during pregnancy could cause a transient increase in viral load or immune activation, or that *in utero* transmitting women were infected with HIV during pregnancy.

She stressed that "interventions must also emphasise maternal health".

C O M M E N T

Various studies have suggested that most transmission occurs at the time of delivery and that *in utero* transmission probably occurs late in pregnancy.

Interventions which effectively reduce transmission to < 1- 2% have generally been initiated late in the second trimester which supports the presumption that *in utero* transmission is a late event. This study importantly identifies non-specific markers of infection during pregnancy with risk of *in utero* transmission.

More information is required to know whether these represent preventable events and whether short course AZT commenced at 28-32 weeks is protective. Also, particularly given the data from CROI on cotrimoxazole reducing chorioamnionitis etc (Walker et al), this also may well be a valuable intervention.

Ref: Farquhar C., Mbori-Ngacha D, Harris J et al. Illness during pregnancy is associated with in utero human immunodeficiency virus type-1 (HIV-1) transmission. XVI International AIDS Conference, Toronto, Canada. 13-18 August 2006. Oral abstract THACO102.

IAC: TB COINFECTION

Extensively drug resistant TB (XTB) in South Africa

Polly Clayden, HIV i-Base

Tuberculosis has long been neglected because it is treatable and predominantly affects the poor. Very concerning data on extensively drug resistant TB was presented in a study from South Africa.

In an oral late breaker, Neel Ghandi presented results from a study to determine the extent of multi drug resistant (MDR) and extensively drug resistant (XDR) among patients presenting with TB in in KwaZulu Natal. [1]

MDR TB is defined as having resistance to isoniazid and rifampicin. XDR TB is defined as having resistance to all first and second line TB drugs (isoniazid, rifampicin, ethambutol, streptomycin, kanamycin and ciprofloxacin) and was described in a recent CDC and WHO report (see articles later in this issue of HTB). Only 347 XDR TB isolates have been found worldwide. [2]

This was a cross-sectional study of patients suspected to have active TB at a rural district hospital. Isolates were collected for mycobacterial culture from January 2005 to March 2006.

The investigators found that out of a group of 1539 patients, 995 (68%) were culture negative and 544 (35%) patients were culture positive for TB. Of these, 323 (69%) were not resistant to both isoniazid and rifampicin and 221 (41%) were resistant (ie had MDR TB). Of these 53 (24% of MDR isolates, 10% of all positive cultures) had resistance to all first and second line drugs tested (ie had XDR TB).

The XDR TB patients were a median of 35 years (range 20-75 years), 25 (49%) were women; 42 (79%) were sputum smear positive and 11 (21%) were sputum smear negative. Of the group, 26 (51%) had no prior TB treatment; 14 (28%) had cured or completed treatment and 7 (14%) had defaulted or failed treatment.

The investigators suggested that the majority of these patients were newly infected with drug resistant TB strains, and had not developed drug resistance on treatment. They reported that 64% had been hospitalised for any cause prior to the onset of XDR TB. The group of patients included two healthcare workers who died with confirmed XDR TB (and four others with suspected XDR TB). "Nonsocomial transmission in hospitals is probable" Dr Ghandi said, but transmission in the community is also possible as 36% of XDR TB patients had no prior hospitalisations.

They also reported 26/30 (87%) XDR TB patients were infected with a genetically similar strain. 52 of 53 (98%) XDR TB patients have died; the median survival after sputum collection was 16 days (range: 2-210).

All 44 (88%) XDR TB patients who had been tested for HIV, were HIV positive and 15(34%) were on antiretroviral therapy.

The investigators wrote: "The convergence of the TB/HIV epidemic with MDR and XDR TB in resource poor settings is a deadly threat to gains in survival achieved by TB DOTS and ARV therapy."

C O M M E N T

See also the articles later in this issue of HTB.

Ref: Gandhi NR, Moll A, Pawinski R et al. High prevalence and mortality from extensively-drug resistant (XDR) TB in TB/HIV coinfecting patients in rural South Africa. XVI International AIDS Conference, Toronto, Canada. 13 - 18 August 2006. Abstract THLB0210.

ANTIRETROVIRALS

Early access programme for MK-0518 integrase inhibitor

As this issue of HTB went to press, a named patient programme (NPP) for MK-0518, an integrase inhibitor currently in Phase 3 development by Merck, was due to be launched in the UK, with expected availability in the UK from late October. The programme is also called EARMRK and started in the US on 11 September 2006.

Entry criteria for the programme include patients on a currently failing regimen with resistance to at least one drug in each of the three classes of oral antiretrovirals (RTI, NNRTI and PI) and who are at risk of clinical or immunologic progression. It is the responsibility of the clinician 'to determine that they need such an investigational medication to construct a potentially viable regimen'.

Currently, the medical affairs department at Merck UK are directing doctors to Parexel, the contract research organisation responsible for conducting the programme, and to register patients in the US through these websites:

<http://www.earmrk.com>

<http://www.benchmrk.com>

Merck in the UK can be contacted on 01992-467272 (main switchboard, ask for external affairs or medical information departments).

C O M M E N T

Data presented at the IAC conference and reported in the September issue of HTB, together with further data from ICAAC reported in this issue, show MK-0518 to be potentially one of the most important new options for patients with drug resistance. [1]

Data in treatment naive patients was presented at the 13th Conference on Retroviruses and OIs (CROI) earlier this year. [2]

MK-0518 needs to be used in combination with other drugs that are active. Currently, the only potential drug interaction with other ARVs is the investigational NNRTI etravirine (TMC-125).

Source: MSD press release

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. See HTB September 2006
<http://www.i-base.info/htb/v7/htb7-9/Integrase.html>
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>

Etravirine (TMC-125) available on named patient programme in the UK

A named patient programme (NPP) will be available in the UK from 16 October 2006, for access to etravirine (TMC-125), a second-generation NNRTI currently in Phase 3 development by Tibotec.

The program will provide access for HIV-1 infected patients who need the compound to construct a viable treatment regimen. TMC125 is a next-generation NNRTI active against NNRTI-resistant strains of HIV. The phase 3 clinical trials (DUET 1 and 2) in treatment-experienced HIV-1 infected patients are ongoing and have recently completed enrollment. The safety and efficacy of TMC125 in combination with other antiretroviral agents have not been established.

The TMC125 EAP is available to HIV-1 infected adults, at least 18 years old, who have limited treatment options either due to virological failure or intolerance to multiple ARV regimens. Patients must be three-class experienced, having received licensed treatment from each of the 3 major oral classes of anti-HIV drugs (NRTIs, NNRTIs, and PIs), and must have received at least two PI-based regimens.

Although TMC-125 is active against some strains on NNRTI-resistant virus, as with other new drugs, it has to be used in combination with other drugs to which the patient is sensitive. TMC125 is dosed at 200mg twice daily, (2 tablets twice daily) with food.

Named patient programmes are developed for patients who are in need of investigational treatments that show promise in early studies, prior to receiving a regulatory decision.

Doctors who are interested in access for their patients should make an unsolicited request to the Medical Information at Tibotec on:

01494 567444. Although the UK access is outside of a formal trial, entry criteria and related information are similar to the international access programme, details of which are listed at:

<http://www.clinicaltrials.gov/ct/show/NCT00354627?order=2>

C O M M E N T

Results from a Phase 2 study of etravirine in 199 treatment experienced patients were presented in Toronto and reported in the last issue of HTB, showing approximate reductions in viral load of -1 log at week 48 when added to optimum background regimen (OBR) compared to an OBR control arm.

There are several new agents that are likely to support combination for multidrug resistant patients. This choice now includes the protease inhibitor darunavir (TMC-114, already available on NPP), MK-0518, the integrase inhibitor available on NPP from late October, and T-20 for patients who still haven't used this entry inhibitor.

MK-0518 should not be used with TMC-125 until results of an interaction study have been completed. Both drugs are metabolised through a glucuronidation pathway that may make them contraindicated.

Source: Press release: Tibotec announces Expanded Access Program for its investigational agent TMC125 (25 September 2006).

Fixed dose combination (FDC) of tenofovir/FTC/efavirenz (Atripla) filed in EU

On 9 October 2006, filing for the fixed-dose combination of tenofovir/FTC/efavirenz (Atripla) was submitted to the European regulatory authorities (Committee for Medicinal Products for Human Use (CHMP), subject to validation by the EMEA). It usually takes approximately 6 months from filing for the EMEA to approve a Marketing Authorisation Application, and for the drug to become commercially available.

This one-pill, once-daily formulation is the result of a collaboration between Gilead Sciences (manufacturers of tenofovir and FTC), Bristol-Myers Squibb, and Merck Sharp & Dohme (who hold marketing rights for efavirenz in different European countries).

The product contains 600 mg of efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate, both nucleoside reverse transcriptase inhibitors (NRTIs).

This FDC was approved in the US on 12 July 2006.

Source: Gilead press release

Tipranavir available in Scotland - almost one year after EU approval

Simon Collins, HIV i-Base

A press release from Boehringer Ingelheim on 11 September highlighted acceptance by the Scottish Medicines Consortium (SMC) for tipranavir/ritonavir in treatment experienced patients.

The SMC statement included recommendations that:

- Tipranavir/r is accepted for restricted use within NHS Scotland for the treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.
- At 48 weeks, tipranavir, in combination with low dose ritonavir, showed a significant improvement in the reduction of viral load compared with other protease inhibitor plus ritonavir regimens. Although the overall rate and type of adverse events were similar, tipranavir had a higher incidence of hepatotoxicity, hyperlipidaemia, bleeding events and rash.
- Tipranavir is more expensive than other protease inhibitors and it is restricted to patients with a tipranavir mutation score of less than 4.

The press release stated: "The SMC reached their decision to approve tipranavir/r for these patients after a thorough analysis of the clinical data. The assessment considered the positive outcomes from 48 week analyses of two pivotal, open-label, randomized, phase III trials, RESIST 1 and RESIST 2. Patients enrolled in these trials had been treated previously with all three classes of antiretroviral drugs (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors), had received at least two protease inhibitor-based regimens for at least 3 months, had a viral load of at least 1000 copies/mL and had documented multiple resistance to protease inhibitors. The 48-week data from the RESIST studies, which were presented this year at the 13th Conference on Retroviruses and Opportunistic Infections (CROI), and which were recently published in the medical journal *The Lancet* (Vol 368, August 5, 2006), showed that tipranavir demonstrated durable response that was superior to that of the comparator boosted protease inhibitor regimens."

C O M M E N T

It is disturbing that such a delay after approval occurs in any EU country, especially for treatments specifically developed as life-saving treatments for patients with resistance to existing drugs. Tipranavir was approved in the US in June 2005 and in Europe in October 2005, and was available on EAP in the UK for 6 months prior to approval.

Scottish patients, doctors and advocates hope that a similar delay does not occur for the next drugs likely to be given EU approval: darunavir, etravirine and MK-0518.

Source: Press release, Boehringer Ingelheim, 11 September 2006.

FDA decision delayed on Biojector for administering T-20 pending additional safety information

Simon Collins, HIV i-Base

On 12 October, Roche issued a press release relating to the timeline for the FDA decision on the Biojector 2000 system that is currently being studied in an open label expanded access trial in the US.

Several small studies reported that many patients found this needle-free device, which fires T-20 through the skin under pressure, reduced the severity of injection site reactions, and improved quality of life.

In the larger safety study, a small proportion of patients have experienced haemotoma and nerve damage, largely relating to when the device has been used in site with earlier scar tissue or near bone - both of which are not recommended as injection sites in the prescribing information for T-20.

Collecting additional data on these events will probably delay the FDA decision until early 2007.

It is expected that this will have a similar effect on regulatory decisions in Europe. Currently, unless they have been able to purchase this privately in the US, UK patients do not have access to the Biojector.

Source: Roche press release (12 October, 2006)

TREATMENT ACCESS

Gilead licenses tenofovir to Indian generic manufacturers

On 22 September 2006, Gilead Sciences announced that it had signed new non-exclusive agreements with generic manufacturers in India, to produce and distribute generic versions of tenofovir disoproxil fumarate (tenofovir DF) to 95 low-income countries around the world, including India.

Affordable tenofovir is one of the treatments most in demand both for second-line therapy, and more tolerable first-line treatment.

The generic companies are Alkem Laboratories, Aurobindo Pharma, J.B. Chemicals & Pharmaceuticals, Matrix Laboratories, Medchem International, Ranbaxy Laboratories and Shasun Chemicals & Drugs. In August, Gilead announced similar agreements with India-based Emcure Pharmaceuticals, Hetero Drugs and Strides Arcolab.

The license agreements require that the generic companies meet certain national and international regulatory standards and include a technology transfer to enable expeditious production of large volumes of high-quality generic versions of tenofovir DF. In addition, these agreements allow the manufacture of commercial quantities of both active pharmaceutical ingredient (API) and finished product.

Source: Gilead press release

FDA tentative approvals of generic ARVs

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
ddI 10mg/mL oral solution (paediatric)	Aurobindo, India	5 October 2006
3TC/AZT 150 mg/300 mg FDC	Cipla, India	13 September 2006

“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 26 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:

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

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

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

Funding prospects improve for Round 6 Global Fund

Global Fund Observer

At least \$270 million will be available to finance Round 6 grants, and possibly as much as \$620 million, according to recent estimates by the Global Fund.

The cost of the first two years of Rounds 1 through 5 ranged between \$578 and \$1,014 million. By definition, the cost of Round 6 will not be known until the Technical Review Panel has reviewed applications and the board has decided which ones to approve. The deadline for submitting Round 6 proposals was August 3; the board decision will be made on November 3.

In Rounds 1 through 5, the Fund was able to finance all grants that the board deemed worthy of approval, though in the case of Rounds 4 and 5, formal approval of some of the grants had to be slightly delayed in order to make this possible.

When Round 6 was launched in early May there was no money at all for Round 6. This was because all commitments to the Fund at that time were required to cover Phase 2 renewals of grants that had been approved in earlier rounds. Thus, the amount of money that will be available for Round 6 will depend entirely upon the extent to which new pledges for 2006 and the first part of 2007 are received from donors to the Fund between May (when Round 6 was launched) and November (when grants are approved).

Estimates presented by the Secretariat at the April board meeting showed a range of assumptions for new pledges that could lead to between \$200 million and a little less than \$600 million being available for the first two years of Round 6 grants.

At the end of June, the Fund updated its April estimate, saying that it was now certain of having at least \$270 m. for Round 6, and hopeful of as much as \$620 m. Since then, Russia has announced a major new pledge (see next article), with an unknown portion of that pledge coming in time to cover Round 6. And an even larger multi-year pledge is expected to be announced by another donor during the International AIDS Conference in Toronto next week.

Russia Announces Major Pledge to Global Fund

Russia has announced a pledge of \$270 million through 2010, sufficient to reimburse the cost of all Global Fund projects in Russia to date. This will be, by far, the largest pledge to the Global Fund from a country that also receives grants from the Fund.

Source: Global Fund Observer no.62, August 2006

GUIDELINES

BHIVA draft report on UK standards for HIV care

In preparing this report, now available for comment online, BHIVA has sought to produce a limited set of focused, auditable standards, which address key aspects of the organisation of NHS clinical care for adults with HIV infection. As such, this report is not intended as a comprehensive guide to good practice in HIV medicine. It should be read alongside BHIVA's clinical guidelines and other relevant standards, recommendations and guidelines, including earlier standards developed by the Medical Foundation for AIDS and Sexual Health, which give a broader perspective on good practice.

The clinical guidelines make recommendations about what treatments/interventions patients should receive, whereas this document focuses on where and by whom care should be provided. Although this document mentions PCTs and other NHS organisations that exist only in England and Wales, BHIVA believes that the principles and approach it sets out are broadly applicable across the UK as a whole.

An initial draft was prepared based on consultation with a limited number of selected individuals and then opened to wider consultation at a stakeholder workshop held at the Royal College of Physicians in July 2006. The document was substantially revised in the light of discussion at the workshop and other input from interested parties, and has now been opened for general public consultation.

BHIVA's draft report is open for consultation until 7 November 2006 at:
<http://www.bhiva.org>

Please forward your comments by 7 November 2006 online:
<http://www.bhiva-clinical-audit.org.uk>

or email to Hilary Curtis at:
hilary@regordane.net

US adult treatment guidelines updated

On October 10, 2006, the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents released a new revision of the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Most of the changes to the previous edition (highlighted in yellow in the pdf file) relate to recommendations for preferred and alternative antiretroviral components in treatment-naïve patients and on safety data that have emerged since the last revision.

Two boosted PI-regimens have been added to recommended first-line regimens: atazanavir/ritonavir (once daily) and fosamprenavir/ritonavir (twice-daily), both plus 2 RTIs. Previous recommendations only included efavirenz plus 2 RTIs or lopinaiv/ritonavir plus 2 RTIs.

The recommendations for choice of nucleosides are fixed dose combinations of either tenofovir/FTC or AZT/3TC. Alternative options are abacavir/3TC or ddl with either 3TC or FTC.

Tables 28 and 29 have been revised according to updates in the Perinatal Guidelines to incorporate preclinical and clinical data relevant to the use of darunavir during pregnancy and new recommendations on antiretroviral use during pregnancy.

Table 30 has been updated to include information on expanded access programs for two investigational agents, TMC125 and MK-0518.

The complete October 10, 2006, version of the adult treatment guidelines is available on the AIDSinfo web site at:
<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

C O M M E N T

It is noticeable that AZT remains a first-line preferred nucleoside and that no reference is made to the evidence linking AZT to lipotrophy, which led to UK guidelines in July 2005 downgrading the use of AZT to that of an alternative option.

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>

TB COINFECTION

Extensively drug resistant tuberculosis: A serious wake-up call for global health

Editorial, BMJ

Tuberculosis outbreaks in the developed world are newsworthy. [1] However, in the developing world, where deaths from tuberculosis are common, it takes something exceptional for an outbreak to attract much attention. In response to a recent report at the 16th international AIDS conference [2] and to increasing South African media reports, the World Health Organization last week expressed concern about extensively drug resistant tuberculosis (also referred to as "XDR tuberculosis"). [3]

Among 536 culture confirmed cases of tuberculosis at a rural hospital in South Africa, 41% were multidrug resistant, [2] defined as resistance to rifampicin and isoniazid (two key first line drugs). This is cause enough for concern as multidrug resistant tuberculosis has a worse outcome and its management is very difficult even in high resource settings. [4] Even more alarming was that 53 (24%) of the isolates from multidrug resistant tuberculosis fulfilled the definition of extensively drug resistant tuberculosis—namely, multidrug resistant tuberculosis that is also resistant to at least three of the six classes of second line agents. Such tuberculosis is virtually untreatable.

All patients in this outbreak who were tested were HIV infected, and 52 of the 53 died after a median of just 25 days. In 90% of the isolates the same genetic fingerprint was present, indicating extensive recent transmission. Fifty six per cent of patients had previously been admitted to hospital, raising the likelihood of nosocomial transmission.

Outbreaks of infectious diseases are always more newsworthy if their implications extend beyond the local context, which is the case with extensively drug resistant tuberculosis. For some years, such strains have been known to exist in Asia, North and South America, and Europe. In March this year, the Centers for Disease Control and Prevention and WHO reported a survey of over 17 000 tuberculosis isolates collected from around the world between 2000 and 2004.5 Overall, 2% of multidrug resistant strains were also extensively drug resistant, being most frequently found in eastern Europe, western Asia, and South Korea. Population based data from the United States, Latvia, and South Korea showed that 4%, 19%, and 15% respectively of multidrug resistant strains could be defined as extensively drug resistant.

The epidemiology and the limited genotypic data currently available [2, 6] indicate that this is not a single strain, but that extensively drug resistant strains are likely to have emerged in many different places and on multiple occasions. Paradoxically, this is both reassuring and alarming. It is reassuring in that the emergence of extensively drug resistant tuberculosis in more than one strain suggests that the mutations responsible are specific for drug resistance rather than reflecting a fundamental change in behaviour of the organism. This is nevertheless alarming because it also suggests that extensively drug resistant tuberculosis probably arises fairly regularly and is already disseminated.

Drug resistance to tuberculosis results largely from poorly managed care and control of the disease. Poor prescribing practices, low drug quality (or erratic supply), and suboptimal adherence can all contribute to this. Bacilli are subject to intense drug selection, and exposure to mono-therapy predisposes to an accumulation of mutations that confer resistance. Hence optimal treatment includes four drugs to which the organism is sensitive, and a single drug should never be added to a failing regimen. In much of the world, routine culture and sensitivity testing is not available. Thus, where multidrug resistant tuberculosis emerges, inappropriate treatment regimens may lead to serial acquisition of resistance mutations, with potential for emergence of extensively drug resistant tuberculosis. Widespread use of second line tuberculosis drugs (such as quinolones for respiratory tract infections) may also contribute to the development of resistance. Thus, the emergence of extensively drug resistant tuberculosis should come as no surprise—it was entirely predictable in the context of poor control practices.

The havoc that institutional transmission of multidrug resistant tuberculosis can wreak amongst HIV infected people was evident in the US in the early 1990s. [7] The very modest actual rise in the incidence of tuberculosis that coincided with these outbreaks has now been reversed, [8] albeit with extraordinary effort and cost. However, the huge potential for extensively drug resistant tuberculosis to further undermine control practices in communities in South Africa and elsewhere in the region is self evident and would be much more difficult to control. In some communities with an antenatal prevalence of HIV of 30%, annual notification rates for tuberculosis have already increased uncontrollably over the past 10 years, reaching 1500/100 000—a rate more than 250 times higher than rates in the US. [9] Extensively drug resistant tuberculosis must now serve as a serious wake-up call. Although the potential consequences may be most grave in settings with a high prevalence of tuberculosis and HIV, extensively drug resistant tuberculosis is nevertheless already a very serious development in many other parts of the world too. [5]

What response is needed? The global scale and molecular epidemiology of extensively drug resistant tuberculosis require urgent assessment, and laboratory capacity needs to be greatly increased within a network of sentinel sites. Control practices must be rigorously and effectively implemented. Increasing cure rates for tuberculosis through directly observed treatment short course (DOTS) is crucial. Detection rates for cases of tuberculosis need to be improved, highlighting the need for a new diagnostic test. Technologies that can determine the presence of drug resistance at the point of care are needed, as

are new drug treatments. The DOTS-Plus strategy [10] for treatment of multidrug resistant tuberculosis needs to be further developed for areas where the disease is established. Nosocomial transmission of tuberculosis is probably commonplace in the developing world, and simple, effective strategies to reduce such transmission need to be urgently implemented. More fundamentally, the emergence of extensively drug resistant tuberculosis is a reminder that tuberculosis needs massive broader commitment: the incompletely funded Global Plan to Stop TB [11] demands political will and financial action.

C O M M E N T

This recent BMJ editorial relates to the IAC Toronto study reported earlier in this issue of HTB. The references are useful for important related documents.

Source: www.bmj.com

Lawn SD. Extensively drug resistant tuberculosis: A serious wake-up call for global health. Editorial BMJ 2006;333:559-560 (16 September), doi:10.1136/bmj.38971.587222.AB

<http://bmj.bmjournals.com/cgi/content/full/333/7568/559>

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Global report on TB and HIV: new Analysis of TB/HIV epidemics in Bangladesh, Brazil, Nigeria, Tanzania, and Thailand

A new report from the Public Health Watch project of the Open Society Institute (OSI), looks at the preventable but growing global TB epidemic, its interaction with HIV/AIDS, and the inadequate response to the two diseases in Bangladesh, Brazil, Nigeria, Tanzania, and Thailand. The study, Civil Society Perspectives on TB/HIV Policy, was released in August and is available online.

"The need for early identification and treatment of TB is desperately urgent," says the UN Secretary-General's Special Envoy for AIDS in Africa, Stephen Lewis, in the foreword to the report. "We must never forget that in many countries, the majority of people who die of AIDS succumb to tuberculosis. TB and HIV act on each other with fatal force—a combination made in hell, which must be expunged from the catalogue of communicable disease."

Through a review of TB and TB/HIV policy, and extensive consultation with policymakers, activists, and patients, the report reveals that the interaction between TB and HIV/AIDS is particularly deadly in many sub-Saharan African countries due to widespread stigma, low levels of awareness, poorly coordinated services, and a lack of mobilization at the local, national and international levels.

In Tanzania, for example, the number of TB cases increased by almost six-fold between 1983 and 2003, from approximately 12,000 cases to 64,500, with 60 percent of the increase in TB incidence attributable to HIV.

HIV/AIDS is also fuelling the TB epidemic in Nigeria, the nation with the largest number of new TB cases in Africa, with a 6 percent annual increase in TB prevalence, and a four-fold increase in HIV rates among people living with TB between 1991 and 2001.

While Bangladesh, Brazil, Nigeria, Tanzania, and Thailand face varying rates of TB/HIV coinfection, the report points to the need for decisive governmental action to coordinate TB and HIV/AIDS policies and programs, both in countries with high coinfection rates such as Tanzania, as well as in countries at high risk for a burgeoning coepidemic such as Bangladesh.

In all five countries examined, people living with HIV/AIDS face serious obstacles to receiving prompt, effective treatment for TB, including lack of proper diagnostic tools.

Brazilian Public Health Watch researcher Ezio T-vora dos Santos Filho, who is living with HIV and has survived TB twice, asserts that even in middle-income Brazil, "only an individual with good connections and access to top-quality medical assistance (including rapid TB diagnostic tests) can survive a complex TB/HIV coinfection.

While the report emphasises that community mobilisation has proven essential in advocating for research, development of new tools, and increased resources for the fight against HIV/AIDS, the people and communities most affected by TB often lack resources and opportunities to engage in policy processes. TB-associated stigma also reduces advocacy on the disease.

Greater social mobilisation around TB and TB/HIV will be essential to reduce TB and TB-related deaths among people living with HIV/AIDS. According to the report, this will not occur without a concerted and sustained effort on the part of donors, policymakers and community activists to engage TB and HIV patients as partners.

This report - which focuses specifically on TB/HIV policy and the effects of the HIV/AIDS epidemic on TB control efforts - is a preview of a series of in-depth studies of the five countries that will be launched on Nov. 1, 2006, at the annual International Union Against Lung Disease Conference in Paris.

Source: Press release, Public Health Watch

A copy of the study is available at:

<http://www.publichealthwatch.info>

IMMUNOLOGY

Viral load is a poor predictor of CD4 decline at the individual level

Richard Jefferys, Treatment Action Group

One of the more notorious quotes in the history of HIV research came from David Ho at an International AIDS Conference in 1994. During a presentation on the factors driving HIV pathogenesis, Ho put up a slide with the line "it's the virus, stupid!" A study published in the journal *Science* in 1996 showing that viral load levels are a strong predictor of disease progression further solidified the view that there is a very direct connection between viral replication (as inferred by counting copies of HIV's genetic material using viral load assays) and the development of immunodeficiency. [1]

However, a number researchers - particularly the late Janis Giorgi from UCLA - continued to investigate the effects of HIV on the immune system and published papers showing that the degree of immune activation associated with HIV infection is also a very strong predictor of immune system decline. [2] Over recent years, researchers focused on studying HIV pathogenesis have reached a consensus that Giorgi was on the right track; the accumulated evidence strongly suggests that immune activation is a (perhaps the) major driver of HIV pathogenesis.

On Sept 27, a new study was published in *JAMA* that offers additional support for this viewpoint. The authors, led by Benigno Rodriguez from Mike Lederman's immunology research group at Case Western Reserve in Cleveland, looked at the ability of viral load measurements to predict future CD4 declines in individuals with HIV infection (the data were obtained from three large cohorts over a 12 year period). [3]

The researchers first confirmed that, on average, people with higher viral loads lose CD4 T cells from the peripheral blood faster than people with lower viral loads. For example, people with viral loads less than 500 copies/mL had an average loss of CD4 cells of -20 cells/mm³ per year whereas those with viral loads over 40,000 copies/mL had an average loss of -78 cells/mm³ a year). These data were completely consistent with the *Science* study from 1996.

However, the researchers also conducted a complex statistical analysis to try and unearth how much of an individual's CD4 T cell decline over a six month period could be accounted for by their initial viral load measurement. This analysis showed that only 5-6% of the inter-individual variation in CD4 T cell decline could be explained by the initial viral load level. So while it held true that higher viral loads are associated with faster CD4 decline and vice versa, the data showed that you cannot use the viral load to accurately predict the actual specific number of CD4 T cells that will be lost from the peripheral blood in a given individual over a six month period.

In the discussion section of the *JAMA* paper, the authors note that immune activation may be a key factor explaining the observed variation in CD4 T cell decline between individuals. As a hypothetical example, if two individuals have the same viral load but one loses CD4 T cells faster (as the *JAMA* study suggests can often happen), it's possible that differences in the levels of immune activation would explain - at least in part - the divergent outcomes. This would be consistent with

previous studies that have reported stronger associations between immune activation and disease progression than those seen between viral load levels and disease progression. There are also a number of complex factors that might impact how much immune activation occurs in the setting of HIV infection (e.g. co-infections, the functionality of the HIV-specific memory T cell response, the genetic make-up - particularly the HLA genes - of the individual, antigen-presenting cell function & turnover, the genetic make-up of the virus, etc.). There may also be additional factors that have yet to be uncovered. The authors close their discussion by noting:

“In humans, the predictive value of immune activation level on HIV disease course, independent of plasma HIV RNA levels, can be demonstrated even when measured during early infection or before actual seroconversion. [5, 6] Thus, immune activation may be a major determinant of T-cell turnover and CD4 cell depletion in chronic HIV infection both in human and animal hosts. Our results provide further support for additional studies exploring the relative contribution of immune activation to the pathogenesis of immune deterioration in treatment naive, HIV-infected persons.”

A couple of news articles have also reported on these findings. Erika Check profiled the immunology researchers behind the JAMA paper in Nature News and Jon Cohen wrote a piece in Science which interviewed John Mellors (author of the 1996 Science paper on viral load); [7] Mellors simply refuses to accept that that the JAMA paper is accurate. David Ho offers an uninterpretable defense of his view of the primacy of viral replication. Conversely, leading immunologists note that these data fit perfectly with understanding of HIV pathogenesis that has emerged over recent years based on studies of T cell turnover and immune activation markers. Key goals for future research will include analyzing the predictive value of immune activation markers in more detail, delineating the precise mechanisms by which HIV causes immune activation and investigating whether it's possible to develop novel & safe approaches to diminishing activation (potentially ameliorating its apparently harmful immunological consequences) in people with HIV.

Source: Treatment Action Group

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/

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FUTURE MEETINGS

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.

The CROI 2007 website, will be updated this summer to include information including details and deadlines for international scholarships and community educator programme. Deadline for abstract submission is 3 October 2006.

<http://www.retroconference.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

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

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

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

To coincide with the new publicity material for the treatment phoneline, we are also launching 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. For those who understand these matters, all pages conform 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 at our website, including editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Boards (UK-CABs), 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 3000 pages are served from the site each day.

Treatment training for advocates

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

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

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

<http://www.nkplus.org>

UK CAB: reports and presentations

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

Reading material, reports and presentations from these meetings (the 18th meeting was on 1 September 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 that are now 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 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 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.

New Italian translation of Introduction to Combination Therapy

A new translation of the Introduction to Combination Therapy has just been produced by the HIV-organisation Nadir.

It is available as a pdf file on the i-Base website (see below).

Translations of i-Base guides

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

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

In addition, pdf files of some of the translated publications are available on the i-Base site. Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on all information.

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

!

Chinese

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

Bulgarian

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

French

- HIV, pregnancy & women's health [1 MB] April 06
- Avoiding & managing side effects [344 Kb]
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- Changing treatment PDF [1 Mb]
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- Introduction to combination therapy [1 Mb] June 06

Portuguese

- Introduction to combination therapy [696 Kb] Sep 05

Russian

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

Serbian

- Introduction to combination therapy [227 Kb]

Spanish

- Avoiding & managing side effects [210 Kb]
- Introduction to combination therapy [192 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:

- Should I test? Will treatment work?
- What is the difference between HIV-1 and HIV-2?
- Why does my CD4 count change so much?

Find HTB on AEGiS

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

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

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

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

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

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website: <http://www.i-base.info>; by fax or post using the form on the back page by sending an email to: subscriptions@i-base.org.uk

Editor: Simon Collins

Commissioning Editor: Polly Clayden

Medical Consultants:

Dr Karen Beckerman, New York.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Paul Blanchard, British School of Osteopathy, London.

Dr Martin Fisher, Brighton & Sussex University Hospitals.

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

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

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Third Floor East, Thrale House, 44-46 Southwark Street, London SE1 1UN
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1 5 10 25 50 100 Other _____

Introduction to Combination Therapy (June 2006)

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Earlier versions are available in FRENCH, ITALIAN, SPANISH, PORTUGUESE, CHINESE, and GREEK as pdf files on the i-Base website

Changing Treatment - Guide to Second-line and Salvage Therapy (April 2005)

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Guide To Avoiding and Managing Side Effects (February 2005)

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Earlier versions are available in SPANISH (as a print version) and in FRENCH, SPANISH, ITALIAN, and CHINESE as pdf files on the i-Base website

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