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EDITORIAL

This issue of HTB features reports from the XV International Drug Resistance workshop, held from 13-17 June in Sitges, Spain.

We have focused on reports from this meeting that have clinical relevance together with implications of resistance in both developed and resource limited settings.

This month the FDA made several important new drug approvals. Darunavir (formerly TMC-114) is a protease inhibitor that is an essential addition to choice of treatments for patients with resistance to existing drugs. Atripla is the first once-daily, one pill combinations: a coformulation of efavirenz, tenofovir and FTC, and is the result of a collaborative between three companies.

Other FDA approvals include four new formulations of generic antiretrovirals manufactured by Indian companies for use in the world's poorest countries. We have included in this issue a table of more than 20 currently FDA approved generic ARVs.

Notably absent from the list are protease inhibitors or many other important drugs suitable for second-line treatments.

The issue of access to drugs for second-line therapy is highlighted in a press release from the International Treatment Preparedness Coalition (ITPC) relating to a meeting between community advocates and companies who have developed key drugs.

Finally, we apologise for the slightly later schedule of this summer double-issue of HTB. Our next issue in September will have much to report, both on treatment and access, following the International AIDS Conference being held in Toronto at the end of August.

TREATMENT ALERT

Dear Doctor letter issued in the U.S. relating to 14 reports of intracranial haemorrhage (ICH) events with tipranavir/r

On 30 June 30, 2006 Boehringer Ingelheim and FDA informed Healthcare Professionals in the US about important new findings related to tipranavir (Aptivus) capsules, co-administered with ritonavir, 500mg/200mg. Boehringer Ingelheim identified 14 reports of intracranial haemorrhage (ICH) events, including 8 fatalities, in 6,840 HIV-1 infected individuals receiving tipranavir capsules in combination antiretroviral therapy in clinical trials.

Many of the patients experiencing ICH in the tipranavir clinical development program had other medical conditions (CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse) or were receiving concomitant medications, including anticoagulants and antiplatelet agents, that may have caused or contributed to these events. An increased risk of ICH was previously observed in patients with advanced HIV-1 disease/AIDS.

Further investigations are ongoing to assess the role of tipranavir in ICH.

No pattern of abnormal coagulation parameters were observed in patients receiving tipranavir in general, or preceding the development of ICH. Routine measurement of coagulation parameters is not currently indicated in the management of patients on tipranavir. However, in *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving tipranavir/ritonavir.

According to the Dear Healthcare Provider letter, tipranavir/ritonavir should be used with caution in patients who may be at risk for increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents or anticoagulants.

Information on ICH risk and platelet aggregation inhibition findings will be included in the following sections of the Package Insert:

The new Black Box Warning reads:

“APTIVUS CO-ADMINISTERED WITH 200 MG RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF BOTH FATAL AND NON-FATAL INTRACRANIAL Haemorrhage. (SEE WARNINGS) APTIVUS CO-ADMINISTERED WITH 200 MG RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF CLINICAL HEPATITIS AND HEPATIC DECOMPENSATION INCLUDING SOME FATALITIES. EXTRA VIGILANCE IS WARRANTED IN PATIENTS WITH CHRONIC HEPATITIS B OR HEPATITIS C CO-INFECTION, AS THESE PATIENTS HAVE AN INCREASED RISK OF HEPATOTOXICITY. (SEE WARNINGS)”

INDICATIONS AND USAGE (new usage bullet)

• Use caution when prescribing tipranavir/ritonavir in patients who may be at risk of increased bleeding or who are receiving medications known to increase the risk of bleeding.

WARNINGS

Intracranial Haemorrhage

Tipranavir, co-administered with 200 mg of ritonavir, has been associated with reports of both fatal and non-fatal intracranial haemorrhage (ICH). Many of these patients had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events. No pattern of abnormal coagulation parameters has been observed in patients in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on tipranavir.

Platelet Aggregation Inhibition

In *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving tipranavir/ritonavir.

Tipranavir/ritonavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents or anticoagulants.

PRECAUTIONS, Information for Patients

Patients should be informed that tipranavir co-administered with 200 mg of ritonavir has been associated with reports of both fatal and non-fatal intracranial haemorrhage.

Patients should report any unusual or unexplained bleeding to their physician.

ADVERSE REACTIONS (added term to Nervous System Disorders)

Intracranial haemorrhage

ANIMAL PHARMACOLOGY AND TOXICOLOGY

In preclinical studies, tipranavir treatment induced changes in coagulation parameters (increased prothrombin and activated partial thromboplastin times) in rodents. At higher doses and in extreme cases, these changes led to bleeding in multiple organs and death. The mechanism for this effect is unknown. This effect was not seen in preclinical studies with dogs.

Source: FDA list serve

Pdf copy of the Dear Healthcare Provider letter:

http://www.fda.gov/medwatch/safety/2006/Aptivus-tipranavir_DHCP.pdf

The revised product labeling is available in pdf format at:

http://www.fda.gov/medwatch/safety/2006/Aptivus_PI.pdf

C O M M E N T

Intracranial haemorrhage (ICH) events are rare events and the rate reported in patients using tipranavir/r was similar to those previously reported in advanced patients with HIV.

The EMEA have not yet decided whether a similar Dear Doctor will be issued in Europe, and the timeline for this process means that any similar communication is unlikely within the next month.

CONFERENCE REPORTS

XV International Drug Resistance Workshop

13-17 June 2006, Sitges, Spain

Introduction

The annual resistance meeting is a closed workshop for around 200 delegates, nearly all of whom are presenting authors for research papers that are discussed at the meeting.

Although much of the meeting is focused on basic science, there are always studies with important implications for current clinical practice.

The following reports are included in this years review of the meeting.

- Ritonavir reduces virological failure and resistance in treatment naïve patients treated with atazanavir
- Resistance implications of monotherapy with lopinavir/r (Kaletra)
- Resistance to darunavir (TMC-114): predicting responses for treatment experienced patients
- Epidemiological studies and transmission of resistance
- K103N containing variants persist longer in women with subtype D and with higher viral loads in HIVNET 012 long term follow up
- No subtype-based differences in baseline levels of K103N-containing variants in women receiving single dose nevirapine
- Phenotypic NNRTI resistance and genetic diversity in antiretroviral naïve women
- High prevalence of the K65R mutation in Botswana patients treated with ddl/d4T-based regimens
- Selection of K65R mutation with tenofovir pressure in subtype C HIV-1 isolates
- Limitations in online tools to identify HIV-1 subtypes
- Categorisation of transmitted HIV drug resistance using the WHO/CDC HIV drug resistance threshold survey method may be useful in resource limited settings
- Resistance implications from PrEP and microbicide studies in macaques
- Low-level resistance linked to treatment failure: a role for more sensitive testing for naïve patients
- Testing for resistance after starting treatment

Abstracts from the workshop are published as a supplement to Antiviral Therapy (2006). Pdf files for abstracts from each section of the conference are available free online (click link to Antiviral Therapy, and scroll down to the bottom of the page):

<http://www.intmedpress.com>

Abstracts are also published online at the excellent conference database published by aegis.org where individual abstract pdf files can also be downloaded.

<http://www.aegis.org/conferences/hivdrw/>

Resistance implications of monotherapy with lopinavir/r (Kaletra)

Simon Collins, HIV i-Base

Resistance results were presented from two randomised studies of patients who failed on lopinavir/r (Kaletra) monotherapy.

The MONARK study randomised 136 treatment naïve patients with baseline viral load <100,000 copies/mL to either lopinavir/r monotherapy (n=83) or lopinavir/r+AZT+3TC (n=53), with follow-up for 96 weeks.

Mean duration of follow up for this analysis was 64 weeks (range 48-96 weeks). Resistance testing was performed following rebound >500 copies/mL after achieving <50 copies/mL, or >1 log from nadir of <400 copies/mL, or after study discontinuation.

A significantly greater percentage of patients receiving monotherapy had viral rebound or poor suppression, therefore qualifying for resistance testing: 21/83 vs 3/53 (25% vs 6%). In the monotherapy arm, two patients showed protease mutation changes from their baseline sequence: one showed M46I on viral rebound at week 40, and the second developed L10F/L and V82A/V mixtures at week 72 after extended duration of low-level viraemia (VL <500 copies/mL). One patient in the 3-drug arm developed M184V resistance to 3TC, but with no change in protease.

The authors emphasised that resistance to lopinavir/r when used in 3-drug regimens is very rare (ie no cases out of 654 patients in 4 registrational trials and only a single case report has been published), but that other case reports of development of PI resistance mutations have been reported from monotherapy studies. They concluded that the barrier for the selection of PI resistance with LPV/r monotherapy may be lower than with lopinavir/r-based 3-drug regimens.

Hackett and colleagues presented resistance data from a second 96-week monotherapy study, that randomised 155 antiretroviral-naïve patients 2:1 to either lopinavir/r 400/100mg twice daily (n=104) or efavirenz 600mg once daily (n=51), both with background AZT+3TC. At 24 weeks, and after 3 consecutive undetectable viral load tests <50 copies/mL, 92/104 (88%) of lopinavir/r patients discontinued AZT+3TC and continued on lopinavir/r monotherapy. Median follow-up in this interim analysis was median of 56 weeks (IQR 47-64 weeks).

9/92 (10%) patients on monotherapy had confirmed viral load rebound > 400 copies/mL. Of the 8 evaluable resistance test results, 2 patients developed PI mutations. One patient rebounded at week 40 (16 weeks after reducing to monotherapy) with L10F, M46L, L63P. Further mutations accumulated in this patient (V82A, and I54V were detected at week 48) after the investigator, contrary to the study protocol, continued the patient on monotherapy. The second patient rebounded with extensive PI and RTI resistance 4 weeks after reducing to monotherapy at week 40. Subsequent retesting of baseline and on-treatment samples, indicated re-establishment of pre-existing mutations, which should have been identified at baseline as exclusion criteria.

However, despite baseline resistance, both patients had successfully suppressed viral load <50 copies/mL while on triple therapy, but rebounded after reduction to lopinavir/r monotherapy.

This led the authors to caution that while the risk of resistance with lopinavir/r monotherapy was low, it was higher than with lopinavir/r based 3-drug combination. They also cautioned against the applicability of lopinavir/r monotherapy even after induction therapy in patients with previous ARV exposure, independently of whether resistance was detected at baseline, or in populations where the risk on infection with drug-resistant HIV is an issue.

C O M M E N T

Virological and clinical responses from several small ritonavir-boosted PI monotherapy studies generated hope for the potential of simplified treatment irrespective of previous or concomitant nucleoside use.

Of these, lopinavir/r has received most attention, as toxicity limited the use of indinavir/r monotherapy and potency is a concern for atazanavir/r monotherapy; but these studies were small (generally <20 patients), non-randomised and uncontrolled.

This is also the first significant data on resistance implications with this strategy. The results indicate that background nucleosides contribute something, and support a stronger caution against lopinavir/r monotherapy for treatment-experienced patients.

Final results will be important for both studies. Baseline resistance was only presented for treatment failures in the first study, and no comparative data was provided on the rate of failure for patients using efavirenz in the second study.

Also, although semantics are not the focus of the research, the use of the term 'deintensification' - used in both these presentations - probably isn't helpful when describing reduction therapy.

References:

1. Norton M et al Drug resistance outcomes in a trial comparing lopinavir/ritonavir (LPV/r) monotherapy to LPV/r + zidovudine/lamivudine (MONARK Trial). XV International Drug Resistance Workshop, 13-17 June 2006, Sitges, Spain. Abstract 74.
2. Hackett JR Jr et al. Selection of protease inhibitor (PI) resistance mutations during virological failure of lopinavir/ritonavir (LPV/r) monotherapy in an induction-maintenance study. XV International Drug Resistance Workshop, 13-17 June 2006, Sitges, Spain. Abstract 75.

Ritonavir reduces virological failure and resistance in treatment naïve patients treated with atazanavir

Simon Collins, HIV i-Base

Atazanavir was licensed in the US in June 2003 as a treatment for naïve or experienced patients, and in Europe it was licensed in March 2004 for use in treatment-experienced patients only. In practice, especially when once-daily combinations are important, and when there is a caution against using efavirenz, atazanavir is becoming used off-label in the UK as first line treatment. It's lack of effect on lipids and good tolerability, also contributes to this use.

The licensing indication is further complicated by recommendations for ritonavir boosting. Although the US product specifications specify that a daily dose of 300mg ritonavir, boosted with 100mg ritonavir is the preferred dose, unboosted atazanavir (400mg once-daily) is still included in recommendations. In Europe atazanavir was approved as a boosted PI.

At the Resistance Workshop, Donna McGrath and colleagues from Bristol-Myers Squibb presented an evaluation of resistance in treatment naïve patients randomised to either boosted (ATV300/RTV100mg; n=95) or unboosted (ATV400; n=105) atazanavir, as part of first line therapy. Background nucleosides for both regimens were 3TC plus d4T extended release (once-daily).

Virological failure occurred in approximately 10% of patients using unboosted atazanavir compared to 3% in patients using ritonavir boosting, and is detailed in Table 1.

Tale 1: Virological response and resistance in patients receiving atazanavir +/- ritonavir

	ATV 400mg	ATV300mg/ RTV100mg
N	105	95
Virological failure	10 (10%)	3 (3%)
Never suppressed & on-study wk48	2/10	0/3
Viral rebound	6/10	3/3
D/c due to poor VL response	2/10	0/3
No. of isolates for Rx testing	8/10	2/3
New emergent mutations	4/8	0/2
PI: I50L, I50I/L	3/8	0/2
PI: 63A/P/S; 63P; 63P/S	1/8	0/2
RT: M184V at failure	7/8	1/2

New PI resistance was seen in 4/8 patients (3 with I50L or mixed I50I/L, with emergent E34E/Q, and one with G73G/S plus T74T/A substitutions, respectively) vs 0/2 patients in the unboosted vs boosted groups respectively. Baseline genotype showed 1 to 3 protease substitutions at L10, K20, M36, L63 and A71 in all patients who subsequently failed treatment. No data was provided for patients who successfully responded to treatment.

Only one of the failing patients (on unboosted atazanavir) showed phenotypic resistance (28-fold change) but retained phenotypic sensitivity to other PIs. The other 7 patients not using ritonavir, also retained phenotypic sensitivity to other PIs. The M184V substitution and phenotypic resistance to 3TC developed in 1/2 and 7/8 patients whose treatment failed in the ATV300mg/RTV100mg and ATV400mg groups respectively.

The study concluded that these data suggested a protective benefit from ritonavir boosting for naïve patients in both reduced risk of virological failure and that, if failure occurs, a reduced risk of resistant mutations.

Ref: McGrath D et al. Evaluation of resistance patterns in treatment-naïve subjects with virological failure on atazanavir- or atazanavir/ritonavir containing regimens. XV International Drug Resistance Workshop, 13-17 June 2006, Sitges, Spain Abstract 87.

Resistance to darunavir (TMC-114): predicting responses for treatment experienced patients

Simon Collins, HIV i-Base

As the drug closest to approval and the subject of much hope based on preliminary studies, it was appropriate that there were more individual posters relating to darunavir (TMC-114) than for other individual drugs (and mainly, but not all, were from Tibotec). With limited data from people who have failed on darunavir, several of the analyses reported below are preliminary, but also important. Darunavir was approved by the FDA on 23 June 2006.

The first study from de Bethune and colleagues, showed the difficulty of selecting for darunavir resistance during in vitro passaging. Earlier studies showed PI mutations at R41T and K70E after 75 passages (260 days) which resulted in approximately 10-fold phenotypic resistance. This was extended to 327 passages (1155 days) in which further resistance developed at H69Q and V77I, plus an additional eight mutations in the gag gene (both inside and outside the cleavage site) and resulting in greater phenotypic fold-changes. However, when these mutations were reproduced in recombinant form, they remained phenotypically sensitive.

Key mutations at R41T, K70E or 41T and 70E combined only resulted in fold-change phenotype of 0.3, 0.7 and 0.2 to darunavir, and ranged from 0.2 to 1-fold FC to ritonavir, nelfinavir, saquinavir, amprenavir, lopinavir, atazanavir or tipranavir. Darunavir resistance also occurred more slowly than a similar in vitro experiment with these other six other PIs. The results indicated that resistance develops differently against wild-type virus compared to PI-resistant virus and will be important if darunavir is used in treatment naïve studies.

Picchio and colleagues from Virco predicted phenotypic sensitivity to darunavir using over 56,000 sample genotypes with different levels of PI resistance, from their database from 2004-5. [2] Clinical and/or biological cut-offs using upper and lower levels for each PI were used (3.4 and 99.6 for darunavir) to determine the relative sensitivity to darunavir, defined as maximal, reduced and minimal sensitivity. The complicated methodology is difficult to summarise, but both darunavir and tipranavir

showed a low proportion of samples (<5%) with minimal and reduced responses. In a subgroup (n=371) with minimal and reduced response to all PIs except darunavir and tipranavir, ~70% had minimal or reduced response to both new PIs, ~20% had minimal or reduced response only to tipranavir with maximal response to darunavir; and 8% had minimal or reduced response to darunavir and maximal response to tipranavir.

They concluded that these data support a high genetic barrier to the development of resistance to darunavir and that isolates with high levels of PI resistance remain susceptible to this new PI.

Martin King from Abbott showed data from 18 treatment-experienced patients who demonstrated evolution of resistance to lopinavir/r. Median (IQR) FC susceptibility to LPV was 6.9 (4.4-18) at baseline and 63 (34-120) at virological rebound. Fold change for darunavir 1.4 (1.0-1.9) and 2.7 (1.2-9.2); and for tipranavir of 1.9 (1.1 – 3.2) and 1.8 (1.1-5.1) at the same timepoints respectively, suggested that phenotypic sensitivity to both darunavir and tipranavir was retained after high-level resistance to lopinavir/r. [3]

Important data on virological response to darunavir was presented by Tony Vangeneugden and colleagues who looked at phenotypic sensitivity score of background regimens from the three POWER studies, using vircoTYPE resistance assay. [4]

In combined analysis, shown in Table 1, they reported that PSS was predictive of virological responses to darunavir and control groups.

Table 1: Responses in POWER studies by baseline PSS score

PSS	<0.5	0.5-1.5	>1.5
Baseline	47%	43%	10%
VL <50 c/mL at 48 weeks:			
TMC/R 600/100	28%	60%	56%
control group	2%	11%	22%
Predicted mean VL drop at week 24 (log)	-1.50	-1.94	-2.57
Actual drop week 48	-0.98	-2.08	-2.00
Control group week 48	-0.12	-0.45	-0.46

Greater proportions of patients with a high PSS achieved viral load <50 copies/mL at weeks 24 and 48, although patients receiving darunavir had a consistently great response to treatment compared to control patients regardless of PSS score.

The numbers of PI mutations was not significant in the multivariate analysis (p=0.13). Most predictive were baseline CD4 and viral load, mean duration of HIV infection and baseline sensitivity to darunavir (p<0.0001) and baseline PSS score (p<0.0001).

Finally, Marie-Pierre de Béthune and colleagues presented an analysis of phenotypic and genotypic determinants of resistance related to virological response, summarised in Table 2. [5]

Table 2: Virological response and baseline sensitivity to darunavir

Fold change sensitivity	<10-fold	10-40-fold	>40-fold
Baseline %pts	70%	27%	13%
% > 1 log reduction	50%	25%	12%
VL reduction (log)	-2.0	-1.08	-0.78
Median no. PI mutations	<10	10-11	>12

Darunavir fold-change increased with number of resistance mutations. While darunavir fold change was the strongest predictor of response, mutations associated with a diminished response included V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V and L89V, which were mostly present with a high number of other PI mutations. When 0, 1 and 2 of these key mutations were present, 64%, 50% and 42% of patients respectively achieved <50 copies/mL at week 24; with response rates of only 20% of patients with 3 and <10% or patients with 4 of these mutations were present.

This group was a better predictor than the IAS PI mutation list (where around 30-50% patients responded with up to 10 IAS mutations, and <20% responded with 11 or more mutations).

References:

Unless stated otherwise, all references to abstracts relate to the Programme and Abstracts from the XV International Drug Resistance Workshop, 13-17 June 2006, Sitges, Spain. The abstract book is published as a supplement to Antiviral Therapy 2006, Volume 11.

1. de Béthune M-P et al. The pathway leading to TMC114 resistance is different for TMC114 compared with other protease inhibitors. Abstract 19.
2. Picchio G, Staes M et al. Analyses of susceptibility and cross-resistance between TMC114 and other protease inhibitors among >56,000 routine samples, using linear regression model-based fold change predictions. Abstract 28.
3. King M et al. Phenotypic susceptibility to TMC-114 and tipranavir before and after lopinavir/ritonavir-based treatment in subjects demonstrating evolution of lopinavir resistance. Abs 29.
4. Vangeneugden T et al. Impact of optimised background regimen on virological response to TMC114 with low-dose ritonavir in POWER 1, 2 and 3, as measured by the phenotypic susceptibility score. Abstract 31.
5. de Béthune MP, de Meyer S et al. Phenotypic and genotypic determinants of resistance to TMC114: pooled analysis of POWER 1, 2, and 3. Abstract 73.

Epidemiological studies and transmission of resistance: evidence for optimism – or issues with interpretation?

Simon Collins, HIV i-Base

Overview of epidemiology studies

Several epidemiological studies contributed to a generally optimistic atmosphere at the workshop, by suggesting that the potential for widespread multi drug resistance has generally been limited, and that rates of resistance to 2- or 3-classes of drugs may be still remain consistently low.

Trends in resistance, as expected, generally mirror changes in ARV use, with prevalence of PI-associated mutations dropping as NNRTI-based regimens became more widely used - and within class changes – generally reduction in TAMS and ddI-related mutations and an increase in K65R reflecting wider use of tenofovir. Similarly, D30N decreased and I50L increased reflecting lower use of nelfinavir and higher use of atazanavir. As usual, regional and national variations were reported among studies. [1, 2, 3]

However, lower prevalence in many of these cross-sectional studies, may miss the cumulative increase of resistance, that would be picked up from longitudinal studies. The importance of this methodology was raised at the 2004 Workshop by researchers from the UK-CHIC cohort. [4]

The importance of collecting longitudinal data tracked in individual patients, was addressed by Akash Shah from Yale University in a poster at this years meeting, which reported longitudinal retrospective data (every 6 months) from around 400 US patients enrolled in the two clinics in Connecticut. [5]

Although complete data from month 0, 6, 12, and 18 was only available for 396, 204, 153 and 84 patients respectively, the cumulative presence of resistance increased from around 32% to 46% in patients with 18 months data ($p=0.08$), and from 31% to 50% in patients with 12 months data ($p=0.001$). The study reported that genotypic resistance increased at approximately 5% per 6 months, but with current follow-up appeared to plateau at 50%.

Previous presentations from the UK CHIC group showed cumulative resistance to a single drug of approximately 10% occurring every two years, and importantly linked this to a similar increase in risk of virological failure over a similar period. While incidence of 3-drug resistance was ~1% the cumulative risk of 3-drug resistance increased to ~4% over 6 years. [4]

In looking at the results from the following studies that reported a generally stable incidence of resistance, including multi-drug resistance, it is important to bear these methodological differences in mind.

Lisa Ross and colleagues from GSK presented results from the largest US prevalence study at the meeting, with samples from 1795 treatment naïve patients from 33 states, who enrolled into clinical trials from 2000-2004. [6]

Incidence of IAS mutations for this cohort was around 10% (2000/2004: 5/13% - NRTI 3/4%, NNRTI 2/7%, PI 2/5%, by year). Geographical differences were reported for increases in the South (4/14%) and Northeast (8/16%) compared to more constant incidence in the Midwest (10/10%) and the West (6/6%). While multi-class resistance mutations didn't increase over time in this cohort the incidence of overall resistance doubled from 2000 to 2004 in the South and Northeast.

Viktor von Wyl and colleagues from the Swiss cohort presented data from just over 2,500 patients, followed for over 6,000 patient years, and with 1443 resistance tests linked to treatment failure. [7] They reported no increasing trend over time of resistance to one or more drug class, and that the prevalence of triple class resistance slightly fell over a five year period from 1999. However, a second Swiss study from the same research group, looking at around 10% of all recent infections from 1996 to 2005, while reporting a generally stable rate of transmission of resistant virus (NRTI being highest at 5.8%, and 2- and 3-class resistance present in 1.8% samples), did report a significant increase in NNRTI transmitted virus in 2005. [8]

Deenan Pillay and colleagues calculated the viral burden of drug resistance in a largely MSM clinic cohort of 1482 patients in follow-up from 1998 who had median of 9 viral load results, and a total of almost 500 resistance tests. [9]

Looking at common mutations (at 41, 103, 184 and 215 in RT; and at 90 in protease) they multiplied presence of each mutations by related viral load, accounting for differences over time, and calculated an overall burden of 6.8% resistant virus. This proportion reduced over the study period (2000-2003). The relative frequency of specific mutation burden in the cohort was T215any > M41L > K103N > M184V > L90M. Over the same period, resistance was transmitted to 24/150 acutely infected individuals, with frequency of K103N > 215any > M41L > L90M and no cases of M184V. The viral burden of resistant virus has fallen during this period, with greater viral control, and the researchers used this data to support an optimistic prediction that the transmission of resistance is likely to continue to fall.

Hong-Ha Truong and colleagues from San Francisco reported a reduction of drug resistant in just over 100 recently diagnosed individuals in 2004 (8-12% depending on site) compared with rates in 1996-2001 of between 18 and 27% depending on year. [10] Data from 2004 came from a primary HIV infection study and from patients seen at STD clinics, but showed no statistically significant differences between the two settings.

In Europe, Annemarie Wensing from Utrecht Medical Centre, and the EU-sponsored SPREAD programme, reported that prevalence of resistance in recent diagnoses was 9.1%, most of whom (71%) showed only single mutations (although acknowledging that viral reversion could underestimate these rates). [11]

These findings were from almost 1100 patients, recruited prospectively and diagnosed during 2002-3 in 17 European countries. The prevalence of NRTI, NNRTI and PI mutations was 5.4%, 2.6% and 3.0%. Interestingly, people from high prevalence countries had half the risk of transmission of drug resistant infection (OR=0.49; 0.24-0.99, p=0.046). 52% of resistant virus included a mutation or mixed virus at RT 215. 1.3% of patients were infected with three-class resistant virus.

Susan Little and colleagues from University of San Diego, California, reported an increasing in transmission of NNRTI resistance in North America and Australia in a cohort of 1535 patients who were largely male (94%), non-Hispanic white (70%) and who were diagnosed with recent infection following sexual exposure. [12]

Genotype and phenotype results were available for almost 1200 and 1000 patients respectively, with 650 patients having results from both tests. When comparing the periods 1995 to June 2000 and July 2000 to 2006, they found high level NNRTI resistance increased from 6 to 11% (p=0.014), although overall resistance did not (9 to 15%, p=0.096). The group reported higher NNRTI resistance in the Californian patients (compared to New York or other areas), and that a decrease in NRTI resistance was only significant in New York. MDR remained stable at 2-4%, by both genotype and phenotype, throughout the study.

Methamphetamine use linked to transmission of drug resistance

A second presentation from Susan Little's group, reported results from a preliminary study, that linked use of recreational drug methamphetamine (crystal meth) with acquiring drug-resistant HIV. [13]

Among 214 MSM diagnosed with recent infection between 2002 and 2006, and who completed self-assessed interviews on substance use, 12.6% had transmitted drug resistance. Among those with drug resistance, 19% reported use of methamphetamine and 9.5% did not, and this was statistically significant in a multivariate analysis (OR=4.29, p=0.01). Use of other substances was not significant, though annual income (>\$10k, or \$10-30k, compared to >50k or higher) had a similar impact.

Joe Eron from University of North Carolina, looked at prevalence of triple-class resistance (defined as at least one mutation to each of the NRTI, NNRTI and PI classes) in a cohort of just under 1600 treatment-experienced patients, half of whom (n=789) had been exposed to 3 classes. [14]

The first treatment for 50% of these patients had been 3-drug HAART, with 20% and 30% having started with either dual- or monotherapy respectively. In 609 patients with genotype results, the overall prevalence of triple-class resistance was 20%; but this was only 10% in HAART initiators (over median 4 years follow-up) compared to 26% in patients who first treatment was mono- or dual-therapy. Only the number of prior ARVs and non-HAART exposure were independent predictors of triple-class resistance.

Transmission of resistance to T-20

Bernard Masquelelier from Laboratoire de Virologie, CHU de Bordeaux, reported on 56 recently infected (seroconversion during 2004-2005) treatment-naïve French patients in the Aquitaine cohort, and reported an overall prevalence of 16% transmitted resistance. Importantly, they reported the first two cases of transmission of resistance to T-20 (enfuvirtide). [15]

The first case had N42D mutation in the HR region of gp-41, along with additional mutations in protease (D30N, M36I, N88D) and RT (M41L, L210W, T215D). Phylogenetic analysis from the sexual partner (who was also treatment naïve) showed the same genotype, suggesting consecutive MDR transmission. The second case had G36D mutation in the HR1 region, with no additional protease or RT changes.

The authors suggested that broadening the genotype range to include resistance to fusion inhibitors is important for surveillance studies, and that genotyping the gp-41 region should be considered before starting patients on T-20.

Finally, Mark Oette from University of Düsseldorf, prospectively tested 831 patients who started their first HAART regimen from 2001-2005. [16]

Pre-treatment samples with resistance increased from 4.8% in 2001, to 7.3%, 8.7%, 11.6% and 9.0% in each subsequent year to 2005, although this trend did not reach statistical significance. Importantly, the researchers concluded that further surveillance of primary drug resistance was essential, and that genotypic resistance testing prior to starting HAART should be regarded as standard of care for all patients.

Similarly, Davey Smith and colleagues, after reporting one of the highest prevalence of resistance in newly diagnosed individuals (24.5% in 106 new diagnoses), reported that modeling healthcare costs and showed that resistance testing was at least as cost-effective as other healthcare interventions, when resistance in treatment-naïve patients was 8-10% or higher. [17]

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Unless stated otherwise, all references to abstracts relate to the Programme and Abstracts from the XV International Drug Resistance Workshop, 13-17 June 2006, Sitges, Spain. The abstract book is published as a supplement to Antiviral Therapy 2006, Volume 11.

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K103N containing variants persist longer in women with subtype D and with higher viral loads

Polly Clayden, HIV i-Base

A group of women who had received single dose nevirapine in the HIVNET 012 trial were enrolled in a long-term (up to five years) follow-up study.

Tamara Flys and coworkers from John Hopkins, analysed plasma samples from 184 of these women. The group included 39 women who were re-exposed to single dose nevirapine in one or two subsequent pregnancies. The LigAmp sensitive and quantitative point mutation assay (cutoff: 0.5% K103N) was used to detect the K103N mutation.

The authors reported a cumulative percentage of women with undetectable K103N of 58.6% by 6-8 weeks, 85.2% by 2 years, 92.1% by 3 years, 99.1% by 4 years, and 99.1% by 5 years among women receiving only single dose nevirapine in one pregnancy.

They found that the rate of “fading” of detectable K103N containing variants was slower in women with subtype D than A.

In multivariate analysis, sub types (D versus. A, HR: 0.50, 95% CI: 0.33–0.76, $p=0.0005$) and pre-nevirapine viral load (per log increase, HR: 0.63, 95% CI: 0.48–0.83, $p=0.0007$), were independently associated with slower fading, while baseline CD4 cell count was not.

Of the 39 women who received single dose nevirapine for subsequent pregnancies during the follow-up study, most had undetectable K103N within a year of re-exposure.

They also found that when K103N was detected, it was present at low levels, and “faded” from detection within 1 year of additional follow-up.

The authors concluded that K103N was undetectable in plasma from most women within 6–8 weeks of receiving single dose nevirapine in pregnancy, and in plasma from all evaluable women within 4 years. This included women who were re-exposed to single dose nevirapine in a subsequent pregnancy during the follow-up period. They noted, “K103N-containing variants persisted longer in women with subtype D and in women with higher baseline viral loads.”

Ref: Flys TS, Mwatha A, Donnell D et al. Fading of K103N-containing HIV-1 variants after initial and repeated exposure to single dose nevirapine for prevention of HIV-1 mother-to-child transmission (HIVNET 012). XV International HIV Drug Resistance Workshop, Sitges, Spain, July 2006. Abstract 46.

No subtype-based differences in baseline levels of K103N-containing variants in women receiving single dose nevirapine

Polly Clayden, HIV i-Base

Previous research has found the frequency of nevirapine resistance after receiving single dose nevirapine is higher in women with HIV-1 subtype C (69%) than D (36%), and lowest in women with subtype A (19%). K103N is the most common nevirapine-associated resistance mutation, detected 6–8 weeks after nevirapine administration in all three subtypes.

In another poster from the same group, Jessica Church and coworkers presented findings from a study, in which they quantified the level of K103N-containing variants in baseline samples from antiretroviral drug naive women with subtypes A, C and D. All women were receiving single dose nevirapine, in the HIVNET 012 trial (Uganda, 1997-1999) or the NVAZ trial (Malawi, 2000–2003).

Samples were taken prior to the women receiving single dose nevirapine in the HIVNET 012 trial, and at delivery (within hours after receiving single dose nevirapine) in the NVAZ trial. Samples were available from 279 women (125 subtype A, 63 subtype C and 91 subtype D).

Using the ViroSeq HIV-1 Genotyping system HIV genotyping was successful for 254 (91.4%) women (120 subtype A, 47 subtype C, and 87 subtype D). None of the samples had K103N detected by Viroseq.

Five (2%) of the 254 women had polymorphisms at or near codon 103: 1 each with K101Q, K103R, K103Q, and 2 with V106I.

Samples were also analysed for K103N containing variants using the Ligamp point mutation assay. 236 (92.9%) of the 254 genotyped samples were successfully re-amplified (110/120 subtype A, 46/47 subtype C and 80/87 subtype D).

The investigators found the percentage of K103N was <0.5% in 231/236 (97.9%) samples. K103N was detected at $\geq 0.5\%$ in 5 samples: 4 samples had 0.5-1% K103N and 1 had 3.9% K103N (a sample with K103Q). They reported that this was likely to represent a false positive result, since K103N was not detected in any of 92 clones from that sample. Only 2 of the 5 women with K103N detected at baseline had K103 detected 6-8 weeks after single dose nevirapine.

The investigators noted that the lack of detection of K103N was unlikely to be due to low viral load. The median viral load was >20,000 copies/mL for all three subtypes, and >2,000 copies/mL (the minimum viral load required to detect 0.5% K103N) in 210(93%) of the 225 samples with viral load data.

They concluded that nevirapine resistance mutations are uncommonly detected in antiretroviral naïve African women with subtypes A, C and D. They wrote: “We did not find any differences in the baseline levels of K103N containing variants that could explain the subtype-based differences in the frequencies of nevirapine resistance seen in these women after single dose nevirapine exposure.”

Ref: Church JD, Gaa yLA, Taha TE et al. Analysis of levels of K103N-containing HIV-1 variants in antiretroviral drug naive African women with HIV-1 subtypes A, C and D who subsequently received single dose nevirapine for prevention of HIV-1 mother-infant transmission. XV International HIV Drug Resistance Workshop, Sitges, Spain, July 2006. Abstract 96.

Phenotypic NNRTI resistance and genetic diversity in antiretroviral naïve women

Polly Clayden, HIV i-Base

In a further poster from this group Susan Eshleman and coworkers presented findings from a study in which they used a sensitive phenotypic assay to determine the frequency of antiretroviral resistance in drug naïve Ugandan women who subsequently received single dose nevirapine for prevention of HIV-1 mother to child transmission in the HIVNET 012 trial.

The investigators tested 24 subtype A and 25 subtype C samples for nevirapine and efavirenz resistance and found 38 samples (78%) to have phenotypic NNRTI resistance. They found the frequency of resistant variants ranged from 0.3–1.9%.

Twenty-one of the samples (half of those with phenotypic resistance) had known NNRTI resistance mutations at frequencies of 0.15–1.1%. Among the 13,870 RT isolates, the NNRTI-resistant mutations K101E (2), K103N (1), V106A (12), V108I (2), Y181C (6), Y188C (6), Y188H (3), Y188C (5), M230L (2), P236L (1) and L283I (1) were present.

Some isolates with phenotypic NNRTI resistance that lacked known NNRTI resistance mutations had unusual variants not present in the majority species. These variants that confer phenotypic resistance include: L100V, K102R, K103E/R, K104R, I132L/M/T/V, Y188N, M230I/R/V and L283C.

The investigators summarised their findings:

- NNRTI-resistant viruses are present at low levels in most ARV drug naïve Ugandan women.
- In 35% of these samples, phenotypic NNRTI resistance was not explained by IAS-defined NNRTI resistance mutations.
- Combinations of “polymorphisms” result in decreased NNRTI susceptibility.
- The frequency of drug resistance varies among individuals suggesting that discrete viral populations have different levels of genetic diversity.
- A coupled reverse transcription/mutation assay identifies patient-derived RT variants that may replicate with different levels of fidelity.

Ref: Nissley DV, Church JD, LA Guay et al. Phenotypic NNRTI resistance and genetic diversity in drug-naïve individuals. XV International HIV Drug Resistance Workshop, Sitges, Spain, July 2006. Abstract 138.

High prevalence of the K65R mutation in Botswana patients treated with ddl/d4T-based regimens

Polly Clayden, HIV i-Base

Although the K65R substitution can cause extensive cross-resistance among currently prescribed NRTIs, this mutation has been found relatively rarely among HIV positive people with subtype B using antiretroviral drugs. An increase in the frequency of K65R mutations among people treated in industrialised countries, is associated with extensive use of tenofovir (TDF) over the past few years.

Investigators from Botswana-Harvard School of Public Health AIDS Initiative, Botswana; McGill University AIDS Centre, Canada; Princess Marina Hospital, Botswana and Harvard School of Public Health, USA had previously found, using cell culture TDF selections, that the time to emergence of K65N varies among subtypes with the most rapid development found for HIV-1 subtype C virus. Additionally they had found emergence of the K65R in 3/8 Botswana patients treated with ddl-containing regimens.

Following these observations, Florence Doualla-Bell and coworkers from the group, performed a study evaluating the incidence of K65R in patients who received antiretroviral therapy, both in first and second line regimens, through the Botswana National Antiretroviral Treatment Programme.

They analysed the reverse transcriptase (RT) genotypes of subtype C isolates from 23 patients from Botswana who had treatment failure, while on combination regimens that included ddl and d4T.

Ten of these patients had initiated treatment with ddl/d4T-based regimens while 13 had started therapy with AZT/3TC/NVP or AZT/3TC/EFV before switching to ddl and/or d4T containing regimens.

The investigators found that 7/23 patients with virological failure had the K65R substitution, after a median exposure to combination ddl/d4T of only 8 months (range 4–18 months). Four of these individuals developed K65R while still receiving ddl/d4T at the time of genotyping; 3/7 patients developed only K65R, while 4 others also developed Q151M, F116Y, and S68G.

The association of K65R/M184V was seen in 2 patients who had received both ddl/d4T and AZT/3TC-based regimens. In contrast, 8/13 patients who received 3TC/AZT in their initial regimen mostly developed thymidine-associated mutations

(TAMs) eg M41L, D67N, K70R, T215Y/F and 219E/Q, while 5/13 had no NRTI resistance.

The investigators suggested that the presence of TAMs in patients who first received AZT/3TC may explain the non-emergence of K65R while subsequently receiving ddI/d4T, "due to presumed antagonism among these mutations".

They concluded that the K65R substitution may emerge at a higher frequency in people with subtype C viruses who receive treatment with ddI/d4T. This high rate was strongly associated with the absence of TAMs at baseline.

The investigators wrote: "In view of widespread ARV access in sub-Saharan countries, these findings establish a degree of concern in regard to the possibility that certain mutations, such as K65R, may emerge more rapidly in viruses of subtype C." They also noted that the first line regimen currently recommended by the Botswana guidelines is AZT/3TC/EFV or NVP "which may explain why the incidence of the K65R mutation is not elevated in currently treated individuals."

Ref: Doualla-Bell F, Avalos A, Brenner B et al. Ref: High prevalence of the K65R mutation in human immunodeficiency virus-infected Botswana patients treated with ddI/d4T-based regimens. XV International HIV Drug Resistance Workshop, Sitges, Spain, July 2006. Abstract 46.

Potential for easier selection of K65R mutation with tenofovir pressure in subtype C HIV-1 isolates

Polly Clayden, HIV i-Base

In second poster, authored by Mark Wainberg and coworkers, the same group presented findings from a study using a tissue culture based strategy to evaluate differences related to subtype and circulating recombinant forms (CRF) in the development of resistance in to TDF. [1]

Representative subtype B (n=4), C (n=6), A/CRF1 (n=3), CRF2 (n=3), G (n=1), and HIV-2 (n=3) isolates were selected for resistance to TDF, 3TC and ddI in cell culture. The investigators determined sequence diversity among subtypes and time to development of TDF resistance by genotype. Cell-based phenotypic and reverse transcriptase assays were used to determine the effects of the K65R substitution on drug susceptibility and viral replicative capacity.

The investigators reported that the K65R mutation confers resistance to TDF. They reported that subtype C viruses possess unique polymorphisms in RT codons 64 (AAG_AAA), 65 (AAA_AAG), and 66 (AAA_AAG), and that these are absent in other viral subtypes.

The K65R mutation (AAG_AGG) was found at 12 weeks in four subtype C viruses with TDF pressure. No mutations conferring resistance to TDF were found in four subtype B (>52–74 weeks), one of each of A, AG and G (>30–33 weeks) and three HIV-2 (>27–29 weeks) selections. K65R appeared by weeks 55 and 73 weeks in two subtype AE (CRF1) selections.

In contrast, there was no variation in time to emergence of M184V with 3TC pressure (weeks 8–14) among subtypes. The time to emergence of K65R was attenuated in M184V-containing subtype C isolates.

The K65R transitions in subtype C, B and AE conferred similar 4–10 fold resistance to TDF and 5–40 fold cross-resistance to each of abacavir, 3TC, and ddI, while not affecting AZT susceptibility.

There were no significant differences in the relative replicative capacities of subtype C, B and AE viruses containing K65R as compared to wild type.

The investigators wrote: "TDF-based regimens will need to be carefully monitored in subtype C infections for possible facilitated selection of K65R. In addition, these data establish concern in regard to the use of TFV in HIV prevention studies in areas of the world in which subtype C viruses are predominant."

C O M M E N T

While unique characteristics (ie enhanced pathogenicity) have been erroneously ascribed to subtype C by some of the scientists on these studies, the potential clinical ramifications of these findings need to be reproduced in larger numbers by additional research groups.

We know from larger studies that most of the protease and RT positions associated with drug resistance in subtype B viruses are selected by antiretroviral therapy in one or more non-B subtypes as well and there is no evidence that non-B viruses develop resistance by mutations at positions that are not associated with resistance in subtype B viruses [2], although the pathway to the development of mutations in non-B subtypes is not well-established.

What is well established is that adherence to antiretroviral therapy is the key to preventing the emergence of drug resistance. The latest reports from Botswana are that adherence rates are high and that at the Infectious Diseases Care Clinic (IDCC) at Princess Marina Hospital in Gaborone, which monitors and manages patients with treatment failure, only 4% of the clinic's 14,000 patients have had to be switched to second or third line regimens. As the African continent's first national ART programme, Botswana's efforts will be closely watched by its neighbours and by the world.

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Limitations in online tools to identify HIV-1 subtypes

Simon Collins, HIV i-Base

Clive Loveday from ICVC collaborative research group, who lead much of the early interest in research into the relevance of sub-type on treatment response in the UK, reported a significant discordance between different online resources used to define HIV sub-type. [1]

This study submitted 1002 consecutive clinical *pol* samples to five popular online interpretation tools: Stanford, NCIB, REGA, STAR and Los Alamos RIP 2.0.*

100% of samples were assigned a sub-type in the Stanford, NCIB and Los Alamos databases, with approximately 23% and 13% of the REGA and STAR resources unable to identify sub-type. However, concordant results from all five systems were only produced for 58% of samples with the remaining 42% (417 samples) resulting in 40 combinations of patterns of concordance/discordance: ~16% were concordant across four resources and 13% concordant across three resources. 5% samples produced discordant results between all five resources.

The authors concluded that use of any one tool alone, compared with any of the other tools, will result in misclassification of 20% or more patients' sub-type, and that unassigned samples from REGA and STAR probably reflected the higher stringency of those tools. Also, that discordance reflected the difficulty of keeping resources updated, particularly with the evolution of new and recombinant viruses.

Implications for epidemiological studies are important: several posters at the workshop highlighted a broadening in European populations from traditionally defined geographically defined populations and HIV sub-type. For example, Ana Garcia-Diaz reported that 46% of new infections at the Royal Free Hospital (105/239) from 2004-2006 were non-B sub-types and that only 80% of these were reported in heterosexuals [2], and Marie-Laure Chaix reported that non-B sub-types were reported in ~11% of newly diagnosed gay and bisexual men in France [3].

* weblinks:

Stanford ([//hivdb.Stanford.edu/](http://hivdb.Stanford.edu/));

NCBI ([//www.ncbi.nlm.nih.gov/](http://www.ncbi.nlm.nih.gov/));

REGA ([//dbpartners.stanford.edu/RegaSubtyping/](http://dbpartners.stanford.edu/RegaSubtyping/));

STAR ([//www.vgb.ucl.ac.uk/starn.shtml/](http://www.vgb.ucl.ac.uk/starn.shtml/));

LosAlamos RIP 2.0 ([//hiv-web.lanl.gov/content/hiv-db/RIPPER/RIP.html/](http://hiv-web.lanl.gov/content/hiv-db/RIPPER/RIP.html/))

C O M M E N T

This is a high rate of non-concordance and it is unlikely that clinics in the UK testing for HIV sub-type, receive results from more than one database.

While sub-type appeared to have relatively small implications for initial response to treatment, as the studies above indicate, the implications for resistance may be more significant.

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Unless stated otherwise, all references to abstracts relate to the Programme and Abstracts from the XV International Drug Resistance Workshop, 13-17 June 2006, Sitges, Spain. The abstract book is published as a supplement to Antiviral Therapy 2006, Volume 11.

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Categorisation of transmitted HIV drug resistance using the WHO/CDC HIV drug resistance threshold survey method may be useful in resource limited settings

Polly Clayden, HIV i-Base

Widespread HIV drug resistance is of great concern in settings where antiretroviral treatment is being rapidly scaled up, particularly when access to regimens is limited.

In order to evaluate transmitted HIV drug resistance (HIVDR) in resource-limited settings, the World Health Organisation (WHO) and the Centers for Disease Control and Prevention have developed a low resource strategy, the HIVDR threshold survey (TS), based on a sequential sampling method.

This method was developed for use in specific geographical areas of resource-limited countries where transmitted HIVDR is likely to be seen first. It categorises the prevalence of transmitted HIVDR for each relevant antiretroviral drug and class of drug as <5%, 5–15%, or >15%, based on 47 specimens from people recently diagnosed with HIV. It was developed using computer simulations based on a million HIVDR results generated from expected distributions and 1797 actual HIVDR results from 28 clinical centres.

The investigators compared TS categorisations with HIVDR prevalence estimates from surveys of recently infected individuals in two areas where previous studies showed >20% transmitted HIVDR. Genotyping was performed on samples from 367 people with diagnosed with HIV between 2003 and 2005 at 27 sites in Los Angeles and 268 people at 23 sites in Chicago. All were subtype B. Prevalence was estimated based on results from all recently infected participants identified by a less-sensitive enzyme immunoassay (LS-EIA). For the TS categorisations, analyses were restricted to the first 47 HIV-positive eligible samples from each area.

Based on the LS-EIA, 73 samples were eligible from Chicago and 66 from LA. The prevalence of transmitted HIVDR to one or more drug in any class in Chicago was 24.7% (NRTIs: 15.1%; NNRTIs: 12.3%; PIs: 2.7%); and 19.7% in LA (NRTIs: 13.6%, NNRTIs: 10.6%, PIs: 1.5%). The TS categorisations for Chicago were: overall HIVDR: >15%, NRTIs: >15%, NNRTIs: 5–15%, PIs: <5%. And for LA, the TS categorisations were: overall HIVDR: >15%, NRTIs: 5–15%, NNRTIs: 5–15%, PIs: <5%.

They reported that in these two areas of high prevalence of transmitted HIVDR, the analysis based on the first 47 samples correctly categorised the prevalence estimates based on the larger number of samples. They suggested that the TS method may make HIVDR surveillance feasible in resource limited settings, where people are rarely diagnosed in recent infection.

As this method focuses on areas where HIV drug resistance is most likely to be transmitted first, it could support plans for appropriate public health interventions. They wrote, "Separately categorising transmitted HIVDR prevalence in specific geographic areas also avoids basing conclusions about a 'national' prevalence of transmitted HIVDR on results from a few sites."

Ref: Bennett DE, Smith A, McCormick L et al. Categorisation of transmitted HIV drug resistance using the WHO/CDC HIV drug resistance threshold survey method. XV International HIV Drug Resistance Workshop, Sitges, Spain, July 2006. Abstract 103.

Resistance implications from PrEP and microbicide studies in macaques

Simon Collins, HIV i-Base

Several studies looking at pre-exposure prophylaxis (PrEP) were included in the meeting.

Garcia-Lerme and colleagues presented data from a study that exposed 12 macaques rectally to SHIV each week for 14 weeks, with 6 animals each receiving either tenofovir/FTC or FTC alone, and a comparator group of 15 animals who received no ARV treatment. [1]

14/15 of the control animals became infected after a median of two challenges (range 1-10), with 4/6 animals in the FTC group becoming infected after a median of 11 exposures, at 5, 6, 12 and 13 weeks. All six macaques receiving tenofovir/FTC were protected from infection.

A second abstract from the same study, reported that peak viremia was –2.2-fold lower in the animals receiving FTC vs the control group (4.5 +/- 0.4 log versus 6.7 +/- 0.3 log), and remained lower over the 14 week follow-up period. Resistance to FTC occurred in only 2/4 animals at weeks 6 and 7, which was longer than has been seen previously in monotherapy studies. This study was first presented at the Retrovirus conference in February 2006, and was reported in the May issue of HTB. [3]

Previous studies have shown the potentially high risk of resistance to tenofovir occurring in monotherapy after 1-6 weeks. [4] Koen Van Rompay from California National Primate Research Centre, presented results from a study in which 12 SHIV-infected rhesus macaques were treated with tenofovir monotherapy at week 20, and had the development of resistance monitored by PCR 5 months later. All animals had an approximate –1.0 log drop in viral load, that remained stable for 20 weeks. All animals developed K70E at median 2 weeks, which tended to be replaced by K65R after a median of 4 weeks

(K65R was present in 80% animals after 12 weeks). Each of these mutations developed on different genomes.

Dawn Moore, from Case Western Reserve University, presented results from another rhesus monkey study, looking at whether resistance developed following a single dose of the microbicide PSC-RANTES (PSC). [6] While high concentrations of PSC (1mM) have been shown to inhibit SHIV infection, at lower concentrations this protection is lost, and this has been difficult to explain given a low IC50 of <1-10nM.

In this study, although stable sequences were seen post-exposure in nearly all animals, discreet mutations developed in the V3 crown and in gp41 of *env* in a number of PSC-treated animals. These included K311R (V3) and N631D (HR2 gp41), and this conferred 18-fold resistance to PSC compared to wild-type SHIV virus.

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Low-level resistance linked to treatment failure: a role for more sensitive testing for naïve patients

Simon Collins, HIV i-Base

Several studies have already shown that low level NNRTI resistance is linked to clinical failure and that both the low genetic barrier to NNRTI resistance and the limits of sensitivity of standard genotype tests pose a challenge for detecting mutations in treatment naïve patients who may have been infected with NNRTI-resistant virus.

A study from Johnson and colleagues investigated the impact of low-frequency drug-resistant viruses on antiretroviral treatment success, and any association existed between minority variants with resistance-associated mutations at baseline and poor virological suppression.

The group performed baseline resistance testing on treatment-naïve patients who participated in GSK trial four years ago using abacavir/3TC/efavirenz. They looked for K103N, Y181C, and M184V using real time PCR-based assays sensitive to mutations present at ~0.5% (compared to ~20% with standard tests) in 69/70 subjects who had virological failure (>50 RNA copies/ml) by 48 weeks) and a control group of 69 patients with fully suppressed virus.

Standard virus population genotyping only identified K103N or M184V at baseline in 3 people. Real time PCR testing detected these mutations, plus previously unidentified resistance-associated mutations at low frequencies (~0.6–16%) in 7 other individuals.

All 10 people with detectable K103N, Y181C, or M184V at baseline were virological failures, and none were detected in the control group. The correlation between low-frequency resistance and virological failure was significant (P=0.005).

Of those with detectable treatment-relevant mutations at baseline, 2/10 never suppressed, 4/10 failed within 2 months, 2/10 failed by month 4, and the remaining two failed by month 6 of treatment. Three of four persons with available genotypes at failure had the same mutations as low-frequency variants at baseline.

The authors concluded that the clinical significance of drug-resistant viruses at frequencies <20% was demonstrated by this strong association with virological failure, and was independent of baseline viral load.

C O M M E N T

Current prevalence of transmitted resistance, and the high subsequent cost of first-line treatment failure, have lead to recommendations in both the UK and US management guidelines, for resistance testing prior to starting treatment in naïve patients.

In practice this means including resistance testing on diagnosis, or storing a sample for later use, in order to have an optimum chance of not missing mutations that revert to wild type, between diagnosis and the date that treatment is eventually started.

Other studies have shown limitations of standard genotyping in detecting NNRTI resistance in treatment experienced patients [2], but this study is particularly important for its implications for naïve patients.

References

1. Johnson JA, Li J-F, Wei X, et al. Baseline detection of low-frequency drug resistance-associated mutations is strongly associated with virological failure in previously antiretroviral-naïve HIV-1-infected persons. XV International HIV Drug Resistance Workshop, Sitges, Spain, July 2006. Abstract 46.
2. Mellors J et al - Low frequency non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant variants contribute to failure of efavirenz-containing regimens in NNRTI-experienced patients with negative standard genotypes for NNRTI mutations. XII International HIV Drug Resistance Workshop, Los Cabos, Mexico, 10-14 June 2003. Abstract 134. See report in HTB August/September 2003.
<http://www.i-base.info/pub/htb/v4/htb4-7/Low.html>

Testing for resistance after starting treatment

Simon Collins, HIV i-Base

Standard genotype assays generally are unable to detect mutations unless they are present in over 10-20% of the virus population, and provide optimum results while the virus remains under selective pressure of the resistant drug.

Transmitted drug resistance that impacts on viral fitness generally reverts to wild-type during the months and years after infection which will often limit the chance of detection with routine genotype tests. However, selective pressure from treatment that include resistant drugs, is likely to force resistant mutations to return to detectable levels within a few weeks of starting treatment.

Shealey and colleagues from Vanderbilt University Medical Center compared the results of pre-treatment testing compared to genotype tests after starting treatment in 24 chronically infected adults who had stored samples prior to starting treatment, and 3 months afterwards.

3/24 patient samples detected resistant mutations prior to treatment, with three additional patients showing resistance during initial drug pressure after a median 43 days (range 7-114).

The authors concluded that using resistance tests after starting treatment doubled the detection of resistance in chronically infected individuals from 12.5 to 25%, but that larger studies were required, and these studies could look at whether specific mutations are better detected post therapy than pre-therapy.

C O M M E N T

This is an interesting study and some clinicians may already use resistance testing 4 weeks after starting therapy in patients with suspected resistance that is unlikely to still be detected at baseline.

However this is probably only appropriate in a limited group and delaying resistance testing for all patients would subject those patients with detectable mutations to an unnecessary period of suboptimal treatment.

Current UK guidelines already recommend resistance testing after 4-12 weeks in patients with sub-optimal viral responses.

Ref: Shealey W, Shepard B, Sutton L et al. An alternative timing strategy for resistance genotyping. XV International HIV Drug Resistance Workshop, Sitges, Spain, July 2006. Abstract 166.

ANTIRETROVIRALS

New formulation of lopinavir/r approved in Europe (Kaletra) and new tradename for access countries (Aluvia)

On 3 July 2006 Abbott announced that it has received marketing authorisation from the European Commission for the Meltrex tablet formulation of lopinavir/ritonavir (Kaletra).

The tablet reduces the daily pill count to 2 tablets, twice daily compared to 3 capsules twice daily, for standard dosing.

The new tablets do not require refrigeration (can be stored at room temperature up to 30 degrees C) and can be taken with or without food.

A single Kaletra tablet will now be composed of 200 mg lopinavir and 50 mg ritonavir, as compared to 133.3mg lopinavir and 33.3mg ritonavir in the previously introduced soft capsule.

With the approval of Kaletra tablets in the EU, the vast majority of patients will convert to the tablet formulation. Patients should finish taking their current supply before starting a new prescription and should never take Kaletra tablets and capsules together.

The formulation for resource poor countries is being produced with a different coloured finishing dye: the tablet will be yellow in Europe and the US, and terracotta for access countries, where it will be marketed with a different tradename, Aluvia (rather than Kaletra).

Capsules will remain available in special cases where they are needed, including paediatrics.

C O M M E N T

The lack of diet restrictions and need for refrigeration, together with the lower pill count should improve quality of life and is likely to be popular. Costs are not expected to rise in Europe for the new formulation.

The heat stability of this formulation makes lopinavir/r no a more realistic option for people in hot climates. The price announced by Abbott for resource limited settings is \$500 year.

U.S. approval for darunavir (TMC-114, Prezista)

On 23 June 2006, the Food and Drug Administration (FDA), granted accelerated approval in the U.S. for darunavir (formerly TMC-114, tradename Prezista), for treatment experienced adults who are not responding to treatment with other antiretroviral drugs.

Darunavir is a protease inhibitor and needs to be boosted with a low-dose of ritonavir to increase plasma concentrations. The recommended oral dose of darunavir tablets is 600 mg (two 300 mg tablets) twice daily taken with ritonavir 100 mg twice daily.

Darunavir/r needs to be taken with food, although the type of food does not affect exposure to darunavir.

The accelerated approval is based on two randomised, controlled studies comparing the safety and effectiveness of a darunavir/r combination with other ritonavir-boosted protease inhibitor combinations. Patients in both arms of these trials also used other anti-HIV drugs, with or without T-20 (enfuvirtide).

Seventy percent of treatment-experienced patients achieved a virologic response with darunavir/r in combination therapy compared to 21 percent in comparator-PI control group at week 24.

The most common side effects reported by patients on the darunavir/r regimen included diarrhea, nausea, and headache. About seven percent of patients on this combination therapy experienced skin rashes ranging from mild to serious.

The risks and benefits of darunavir have not been established for treatment naïve adults or for children.

Darunavir is manufactured for Tibotec, and distributed by Janssen Cilag, part of the Johnson & Johnson group.

C O M M E N T

The UK currently has a named-patient programme for patients requiring darunavir prior to European approval.

The average wholesale price announced for darunavir in the US was \$25.00 a day (excluding cost of boosting ritonavir, and other ARVs used in the combination), which is very close to atazanavir.

In the weeks prior to approval a wide networks of community advocates and organisations in the US petitioned Tibotec over pricing of darunavir. Historically, it has been the rule, rather than the exception (ie probably all ARVs except indinavir and nevirapine) for companies to price new compounds significantly higher than existing antiretrovirals.

The prices of the last two protease inhibitors, atazanavir (Reyataz) from Bristol Myers Squibb and tipranavir (Aptivus) from Boehringer Ingelheim, each in turn set new record high prices for drugs in their class, bringing the US price of protease inhibitors alone to well over \$10,000 and the cost of a typical regimen in excess of \$16,000.

While the cost of treatment at the current levels is prohibitive for many, and burdens US assistance programmes like ADAP, where many states already have waiting lists for ARV therapy, the response from some activist groups recognised the positive effect from pricing darunavir at the same level as atazanavir. Reading between the lines - 'it could have been worse'.

AIDS Treatment News commented that 'the lower price could well be in the company's financial interest, by allowing first-line use if

the drug proves suitable - especially important now that its rival tipranavir does not seem to be working well as a first-line treatment, because of performance that appears slightly inferior to a good standard treatment based on Kaletra'... and that 'there is much hope for darunavir as first-line therapy, but we do not have the data yet'.

Sources:

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>

A pdf version of the approved label is available as a pdf download:

<http://www.fda.gov/cder/foi/label/2006/021976lbl.pdf>

AIDS Treatment News:

<http://www.aidsnews.org/2006/06/prezista-approved.html>

Boehringer stops tipranavir trial in treatment-naïve patients

On 13 June 2006, Boehringer Ingelheim announced that it was closing a clinical trial of HIV drug tipranavir (Aptivus) in treatment-naïve patients due to insufficient effectiveness at 60 weeks.

Tipranavir was approved in Europe in October 2005 and is currently only indicated in combination with ritonavir in treatment-experienced patients who are resistant to other PIs.

The study that has now been closed, BI 1182.33, recruited 558 treatment-naïve patients in 15 countries including France, Germany and the UK, and was a non-inferiority trial against lopinavir/r (Kaletra), whose primary endpoint was the proportion of patients with an undetectable viral load (< 50 copies/mL).

Patients in both tipranavir arms received 500 mg tipranavir twice daily. Only the ritonavir dose varied, at 200 mg or 100 mg twice daily.

For both doses of ritonavir, tipranavir's non-inferiority was proved at 48 weeks.

However, following this, the 200 mg ritonavir arm was closed due to an asymptomatic elevation of liver enzyme levels. This phenomenon had already been observed in the RESIST treatment-experienced trials.

A subsequent 60-week analysis, showed that the effect of tipranavir/ritonavir (500 mg/100 mg twice daily) had declined and that this therapy was now inferior to Kaletra in terms of virologic success.

The press release does not specify the proportion of patients with undetectable viral loads, but says that there was a 15.03% difference between the lopinavir/r and tipranavir arms, 0.3% above the limit fixed in the trial protocol.

Boehringer Ingelheim decided at this point to halt the whole trial, specifying that this "does not change the positive benefit-risk profile of tipranavir/ritonavir (500 mg/200 mg) for the highly treatment-experienced patient population for which it is currently indicated."

Source: Boehringer Ingelheim Press Release (13 June 2006)

FDA approves fixed-dose combination of efavirenz/tenofovir/FTC (Atripla): joint company collaboration produces once-daily one pill combination

On 12 July 2006, the Food and Drug Administration (FDA) today approved Atripla, a new fixed-dose combination of three widely used antiretroviral drugs, to be taken in a single tablet once a day, alone or in combination with other ARVs. Atripla is the first fixed dose combination available in the United States to combine two different classes of antiviral drugs in a single pill. This "one-pill-once-a-day" product to treat HIV/AIDS combines the active ingredients of efavirenz (an NNRTI), with FTC (emtricitabine) and tenofovir DF (NRTIs). FTC and tenofovir are also available in a fixed dose combination (Truvada).

Atripla is the result of an inter-company cooperative effort between Gilead Sciences, the manufacturer of FTC and tenofovir, with Bristol-Myers Squibb, the manufacturer of efavirenz. Merck controls the marketing of Sustiva outside the United States.

Atripla was approved in less than 3 months under FDA's fast track program. Achieving a bioequivalent formulation was a significant challenge, and at least four earlier formulations failed to produce bioequivalence within the required range for all three drugs. The approval is the result of an expedited review process outlined in guidance for industry from the FDA in May 2004 that encourages manufacturers to develop fixed dose combination and co-packaged products consisting of previously approved antiretroviral therapies for the treatment of HIV infection. (<http://www.fda.gov/oc/initiatives/hiv/hivguidance.html>)

The labeling of Atripla includes a boxed warning that the drug's use can cause lactic acidosis. In patients with chronic Hepatitis B infection, the discontinuation of the treatment with Atripla (which is not indicated for this use) can result in severe flare-ups of Hepatitis B infection. Other potential serious adverse events reported for the use of Atripla include serious liver toxicity, renal impairment and severe depression. The most common adverse events experienced by participants in the combination trial included headache, dizziness, abdominal pain, nausea, vomiting, and rash.

FDA approved efavirenz (Sustiva) in 1998, tenofovir DF (Viread) in 2001 and FTC (Emtriva) in 2003. Truvada, which combined tenofovir and FTC in a fixed dose combination, was approved in 2004.

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>

Evidence that CCR5 is protective against West Nile virus: implications for CCR5 inhibitors

Simon Collins, HIV i-Base

Much of the excitement around development of CCR5 inhibitors, despite set backs for two of the three current lead compounds in development, was related to the lack of evidence for a biological role for CCR5.

However, in a short article in the 12 May edition of AIDS [1], Charlene Crabb highlighted a recent paper in Journal of Experimental Medicine that linked CCR5 receptor usage to a protection against West Nile virus (WNV). [2]

WNV is a mosquito-borne virus that can infect birds, horses and other animals, and humans, and has spread across the US since 1999, where it is now considered endemic. Although 80% cases in the US of WNV remain subclinical, approximately 1% result in more serious illness including neuroinvasive disease, including meningitis, encephalitis which is often fatal, and/or flaccid paralysis.

After finding that WNV was fatal in mice with CCR5-delta32 deletion, William Glass and colleagues from NIAID then looked at whether this related to risk of human WNV infection. They found around 4% individuals in two cohorts of patients infected with symptomatic WNV were homozygous for CCR5 delta-32, compared to <1% of the general population. The magnitude of increased risk was statistically significant, with approximately 30% higher rates when looking at Caucasian patients only, and was linked to more severe progression of WNV irrespective of race (25-30% fatality vs <5% in overall population).

The authors concluded that this identified the first genetic susceptibility factor for WNV infection and also the first association of the CCR532 allele with susceptibility to an infectious disease. They cautioned that this may have implications for using CCR5 inhibitors in HIV-infected patients in areas endemic for WNV.

C O M M E N T

The proposed mechanism of action in mice is related to WNV inducing expression of CCR5 ligands in the WNV-infected mouse brain; and survival from WNV encephalitis through trafficking of leukocytes into the infected brain.

From 2001-2004 in the US, there were over 16,500 laboratory confirmed cases of WNV reported to the CDC of which 648 were fatal (3.9%). [3]

Any risk from HIV-positive people using CCR5 inhibitors will be dependent on geographical risk of WNV – which has not been reported in the UK. However, much of the interest generated by these findings, relates to identifying a role for CCR5, which may not now be as innocuous as was originally hoped.

References:

1. Crabb C. Testing a CCR5 drug? Avoid mosquito bites. AIDS :Volume 20(8) 12 May 2006 p N3-N4.
2. Glass WG, McDermott DH, Lim JK et al, CCR5 deficiency increases risk of symptomatic West Nile virus infection. J. Exp. Med. 2006 203: 35-40.
3. The CDC website includes a mosquito map showing prevalence of WNV across the US.
http://westnilemaps.usgs.gov/us_mosquito.html

TREATMENT ACCESS

Activists meet with Gilead and Abbott over access to second-line therapy

On 13-14 July, 25 activists from Africa, Asia, Latin America, the Caribbean, Eastern and Western Europe and the United States, met in London with two companies whose AIDS drugs are crucial in second-line regimens. Currently, patients in most developing countries and in many middle income countries have no treatment options if their first regimen fails due to resistance or side effects, because of the cost of second-line medicines.

Gilead Sciences of Foster City, California manufactures tenofovir, which works against strains of the virus resistant to first-generation nucleoside reverse transcriptase inhibitors like AZT and 3TC. Abbott Laboratories of Abbott Park, Illinois, makes two drugs, ritonavir and lopinavir, which are sold in combination under the trade name Kaletra. Ritonavir alone also has a crucial role in boosting the effectiveness of other protease inhibitors made by other manufacturers. Both drugs have been available for several years to HIV-positive people in Western Europe, North America and elsewhere in the developed world.

However, while approximately 1.3-1.5 million people in developing countries are now on first-line antiretroviral treatment, which costs from approximately \$135 a year upwards, the least expensive second-line regimen costs upwards of \$500 a year. Most countries are struggling to scale-up access to first line regimens for those who need them and the cost of second-line regimens will make these agents simply out-of-reach for most public sector programs, threatening the survival of those people who are resistant to, or who cannot tolerate, first-line treatment.

Key issues raised with both companies included:

- The patent status of their drugs in developing countries with capacity to manufacturer for domestic use or for export and the vital importance of generic competition in ensuring affordable medicines;
- The importance of voluntary licenses that enable generic companies to manufacture their drugs. While Gilead is in negotiation with 5-7 generic companies in India to produce tenofovir, Abbott refuses to grant any voluntary licenses to generic producers to make Kaletra;
- Pricing of drugs from the brand-name companies in lower and upper middle-income countries that are not able to benefit from lowest prices offered to least-developed countries (LDCs). Prices in many middle-income countries are currently unaffordable;
- Importance of affordable second-line therapy – at or near the cost of first-line treatment;
- The need for research and development on lower cost options for second-line therapy;
- Coordination of industry policies on pricing for low, low middle and upper middle income countries (e.g. Abbott offers preferential pricing to 67 “low” income countries while Gilead offers this discount to 97 countries).

Activists will continue to push their concerns with Gilead and Abbott and other drug companies and raise these issues with UN agencies and their own ministries of health and make it a central issue for advocacy at the upcoming International AIDS Conference in Toronto in August 2006.

World CAB is a project of the International Treatment Preparedness Coalition, a network of over 700 people from over 100 countries around the world. There have been three World CAB meetings - the first with Roche, BI, and GSK in 2004 in San Francisco; the second with generic ART producers in 2005 in Mumbai, and this meeting Gilead and Abbott in July 2006. ITPC has an international steering group of about 30 people from around the world and each region has its own leadership structure, which selects advocates to attend the World CAB meetings. Delegates from this meeting came from Peru, Paraguay, El Salvador, Estonia, Croatia, Ukraine, Russia, Moldova, Zambia, Uganda, South Africa, Cameroon, Morocco, China, India, Suriname.

Source: ITPC press release

Reports from World CAB meetings and other ITPC documents are available at the following link:

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

FDA approves four new generic products for use in PEPFAR

In June 2006, the Food and Drug Administration (FDA) granted tentative approval for the following Indian generic products:

- Lamivudine - oral solution, 10 mg/mL (Cipla Ltd)
- Stavudine 15 and 20 mg capsules (Aurobindo)
- Abacavir Sulfate Oral Solution, 20 mg/mL (Aurobindo)
- 3TC/AZT/nevirapine fixed dose combination (Aurobindo)

The FDA's tentative approval of these products means that although existing patents and/or exclusivity prevent marketing of this product in the United States, the product meets all of FDA's safety, efficacy, and manufacturing quality standards required for marketing in the U.S. It will now be available for consideration for purchase under the President's Emergency Plan for AIDS Relief (PEPFAR).

Source: FDA list serve

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

List of current FDA approved generic formulations and products

Simon Collins, HIV i-Base

The list of approved drugs tracked in HTB over the last year is shown in Table 1 below.

This brings the total of FDA approved generic drugs and formulations to over 20 since the programme was launched.

Although the tentative approval process was developed so that more patients should be treated with less expensive formulations in PEPFAR programmes, it is unclear whether these US programmes are universally switching to the generic drugs.

An updated list of generic tentative approvals is included as a table in the article below. This will be updated as new approvals are announced and is accessible at:

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

While 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.

Table 1: FDA tentative approvals of generic ARVs

Date	Drug	Company
June 22, 2006	lamivudine oral solution, 10 mg/mL	Cipla Ltd, India
June 27, 2006	stavudine 15 and 20 mg capsules	Aurobindo Pharma, India
June 27, 2006	abacavir oral solution, 20 mg/mL	Aurobindo Pharma, India
June 27, 2006	3TC/AZT/nevirapine fixed dose combination (FDC)	Aurobindo Pharma, India
May 18, 2006	abacavir sulfate tablets, 300 mg	Aurobindo Pharma, India
March 27, 2006	zidovudine 100mg capsules	Aurobindo Pharma, India.
March 6, 2006	copackaged AZT/3TC + efavirenz	Aurobindo Pharma, India.
December 27, 2005	nevirapine oral suspension, 50 mg/5 mL	Aurobindo Pharma, India.
December 21, 2005	stavudine oral solution, 1 mg/mL	Aurobindo Pharma, India.
November 4, 2005	lamivudine oral solution, 10 mg/mL	Aurobindo Pharma, India.
September 7, 2005	zidovudine oral solution	Aurobindo Pharma, India.
August 25, 2005	zidovudine 300mg tablets	Aurobindo Pharma, India.
July 13, 2005	zidovudine 300mg tablets	Ranbaxy Laboratories, India
July 7, 2005	lamivudine + zidovudine fixed dose combination (FDC)	Aurobindo Pharma, India.
July 1, 2005	stavudine capsules	Aurobindo Pharma, India.
June 24 2005	efavirenz	Aurobindo Pharma, India.
June 20, 2005	nevirapine tablets	Ranbaxy Laboratories, India
June 20, 2005	nevirapine tablets	Aurobindo Pharma, India.
June 15, 2005	lamivudine tablets, 150 and 300 mg	Aurobindo Pharma India.
May 27, 2005	lamivudine tablets, 150mg	Ranbaxy Laboratories, India
January 26 2005	copackaged AZT/3TC + nevirapine	Aspen Pharmacare, South Africa.
December 3, 2004	didanosine (ddI) ER capsules, 200, 250, 400mg	Barr Laboratories, USA
May 17, 2004	FDA issue guidance document that describes the new process to expedite approval of low cost, safe and effective co-packaged and fixed dose combination (FDC) HIV therapies so that high quality drugs can be made available in Africa and developing countries around the world under the President's Emergency Plan for AIDS Relief (PEPFAR).	

Source for Table: FDA list serve

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

Data exclusivity: a new threat to affordable generic medicines

Leena Menghaney, MSF

The following information relates to the decision by the Indian government to amend the Drugs and Cosmetic Act, 1950. This is the act that protected the process a company invented to make a drug, but not the actual drug formulation itself, and which enabled some Indian generic manufacturers to produce chemically equivalent generic medicines at prices affordable to the developing world.

The Indian government are seriously contemplating inserting provisions in the Act, which will provide pharmaceutical companies exclusive rights over pharmaceutical data submitted by them to the Drug Controller of India for marketing approval i.e. *data exclusivity*.

What is data exclusivity?

- A new type of intellectual property right in the name of data protection, intended to provide exclusive monopoly rights to pharmaceutical companies where patents would not. Unlike what is being portrayed to the people and the media, Data Exclusivity, measures imply much more than non-disclosure of test data by the drug regulatory authority to rival pharmaceutical companies.
- Changes the current system of approval for generic medicines.
- How does it impact access to generic drugs: Provides pharmaceutical companies exclusive rights on pharmaceutical data so that they can effectively prevent the drug regulatory authorities (DRA) themselves from relying on test data already in their possession for subsequent approval of generic versions of the medicine.
- Practically, prevents DRAs from registering generic versions of a medicine for a period ranging from 5 to 10 years, unless the generic manufacturer independently carries out its own tests showing the safety and efficacy of the medicine.
- Even when a medicine is not protected by any patent, pharmaceutical companies are assured a minimum period of monopoly because of data exclusivity.
- It is the regulatory authorities that enforce data exclusivity rights. Unlike patents, the rights holder is spared the expense and embarrassment of being seen to enforce their rights in public. *Public health agencies reduced to enforcing private commercial rights!*

What is the current practice for approval of generic drugs?

As of now there are no data exclusivity provisions in Indian law. According to current practice in India, generic manufacturers have to apply for marketing approval of the generic version of a medicine to the DCGI. They are off-course required to provide bio-equivalence studies to prove that their generic version of the medicine is the therapeutic equivalent to the original and do not have to again submit test data regarding safety and efficacy which is already with the DCGI. For this the DCGI is entitled to rely on test data submitted by the pharmaceutical company who first sought marketing approval for the medicine.

Why are public interest groups concerned?

- Data exclusivity, measures have the effect of limiting generic competition. Generic production of drugs has been one of the most important, reliable, and powerful forces to reduce drug prices systematically in India and other developing regions, making essential, life-saving medicines such as antiretrovirals (ARVs) for the treatment of HIV/AIDS more affordable for individuals and the health systems that serve them.
- If such data exclusivity provisions are introduced in India the Drug Controller of India (DCGI) will be barred from relying on test data, which is already in its possession in granting marketing approval to generic medicines. Instead it will be forced to ask the Indian generic manufacturer to carry out its own clinical trials showing efficacy and safety of the medicine. Theoretically data exclusivity provisions do not legally prevent generic manufacturers from generating their own test data for marketing approval. However in reality the financial resources and the time needed for conducting clinical trials for generating test data already available with the Drug Controller creates a market barrier that is difficult for generic manufacturers to overcome and delays the introduction of the generic drug by a number of years.
- Data exclusivity measures in other countries is already preventing drug regulatory authorities from granting approval to generic medicines up to five to ten years, seriously delaying access to affordable generic versions of medicines. In Guatemala in February 2004, Atazanavir a drug used in HIV treatment (priced at US\$ 10, 000 per person per year) received data exclusivity protection for five years under the law passed by the government. However a more affordable generic version of Atazanavir cannot enter the Guatemalan market until 2009 as drug regulatory authorities have to provide data exclusivity protection to test data related to Atazanavir. As a consequence drug Regulatory authorities in Guatemala are themselves barred from relying on it to approve of subsequent generic versions.

- Coupled with the new patent law this can easily result in an absolute monopoly regime in pharmaceuticals, seriously affecting the manufacture and availability of affordable generic drugs. Can also seriously limit the ability of the government to make use of safeguards in their patent laws to protect public health.
- Unnecessary and possible human injury associated with duplicative testing.

What can organisations and individuals do?

The government is considering amendments to the Drugs and Cosmetics Act as it is under pressure from US, and multinational pharmaceutical companies to amend the Act to include data exclusivity protection provisions (see pg 103 of 2005 PhRMA “Special 301” Submission to United States Trade Representative).

- Write to the government of India to ask for more information on the issue and also to convey your concern on its possible decision on amending the Drugs and Cosmetic Act to include such provisions.
- Brief the parliamentarians and policy makers on the implications of data exclusivity
- Mobilise public opinion against such move

Source: Leena Menghaney, Campaign for Access to Essential Medicines, Medecins Sans Frontieres, Holland (in India)

TREATMENT GUIDELINES

Updated US perinatal guidelines

The Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States has been revised to include an update of the “Antiretroviral Drug Resistance and Resistance Testing in Pregnancy” section to reflect new recommendations for resistance testing for HIV-infected pregnant women.

The Perinatal Working Group now recommends resistance testing for 1) all pregnant women not currently receiving antiretrovirals, before starting treatment or Mother To Child Transmission (MTCT) prophylaxis, and 2) all pregnant women receiving antenatal antiretroviral therapy who have virologic failure or who have sub-optimal viral suppression after initiation of antiretroviral therapy.

The Working Group also counsels against adding single-dose maternal/infant NVP to an ongoing highly active antiretroviral regimen, as this does not provide additional efficacy in reducing perinatal transmission and may result in NVP drug resistance in the mother.

Information in Table 6 from the November 17, 2005 document has been updated and replaced with a recommendation box at the beginning of the “Antiretroviral Drug Resistance and Resistance Testing in Pregnancy” section; the old Table 6 has been removed and the remaining tables have been renumbered accordingly.

The updated section and new references are highlighted in the document.

The document is available in the “Guidelines” section of the AIDSinfo Web site under “Perinatal Guidelines”:
<http://www.aidsinfo.nih.gov/>

Updated slide sets to accompany the revised guidelines are also available:
http://aidsetc.org/ppt/p02-et/et-01-00/nrc_perinatal_07-06.ppt

Excellent website with supporting documents and links to guidelines:
<http://www.womenchildrenhiv.org>

HEPATITIS COINFECTION

Efficacy of treatment of acute hepatitis C in patients with HIV-infection

Simon Collins, HIV i-Base

In a paper in the 13 May edition of AIDS, Stephanie Dominguez and colleagues reported impressive responses to treatment of hepatitis C in a prospective pilot study of 25 consecutive HIV-positive men from two clinic in Paris, with acute HCV infection (documented seroconversion to HCV antibody or positive HCV RNA with negative PCR in previous 6 months). [1]

HCV was diagnosed due to clinical symptoms in 7 patients and following a rise in liver enzyme activity during routine HIV monitoring in 18 men.

At baseline, 23/25 patients were on HAART, with viral load <200 copies/mL: median CD4 count was 345 cells/mm³. Only

one patient, with HCV genotype 3, spontaneously cleared HCV by week 12, with all other patients maintaining HCV RNA >50 copies/mL. Median time between acute HCV diagnosis and start of study was 14 weeks.

As four patients declined treatment and one patient was contraindicated for ribavirin therapy, 19/25 were treated with PEN interferon alpha-2a (180ug/week plus 800mg RBV/day) for 6 months, followed by 6 month follow-up.

The study reported sustained virological response (SVR) rates in 10/14 (71%) patients with evaluable data at 24 weeks after the end of HCV treatment. The authors reported that study treatment was well tolerated, with no change in CD4 cell count and concluded "early treatment of acute HCV infection with PegIFN alpha-2a and ribavirin for 24 weeks yields a high sustained virological response rate in HIV-infected patients".

C O M M E N T

In general, the cohort data for treatment of acute HCV infection in coinfecting patients, are still evolving. Data from London (SVR) and Germany (EOT) indicate lower response rates 50-60% SVR, but these are still better than in chronic infection. As in HCV-monoinfection the optimal treatment strategy of PegIFN-monotherapy or PegIFN + RBV (800 mg or 1000-1200 mg) remains an open question.

Given the lower response rate in coinfecting patients the role of RBV 1000 – 1200 mg/d should be assessed. Given the general low number of patients a cooperation of the cohorts for analysing and collecting the data would be a major advantage.

This paper was submitted for publication in November and accepted in January 2006, therefore the results from the full cohort should already be available and will hopefully be presented in Toronto. Nevertheless, these data support the recommendation for early treatment of acute HCV infection from the European Consensus Conference for coinfection last year. [2]

This highlights the clinical importance of diagnosing acute HCV - particularly in the UK where approximately 200 cases of sexual HCV infection has been reported in HIV-positive gay men in London and Brighton over the last few years. Routine HCV testing of gay men associated with higher risk for HCV infection (group sex, shared toys, recreational drug use, fisting, UAI, recent STI) is clearly important.

References

1. Dominguez S, Ghosn J, Valantin M-A et al. Efficacy of early treatment of acute hepatitis C infection with pegylated interferon and ribavirin in HIV-infected patients. *AIDS* 20(8), 1157-1161 (12 May 2006)
2. Alberti A, Clumeck N, Collins S et al. Short Statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV coinfecting patients. *J Hepatol* 2005; 42:615-624.

HIV TRANSMISSION AND THE LAW

HIV transmission, the law and the work of the clinical team: draft recommendations for comment

This document has been written to provide information and guidance to health care professionals in their work, and has been uploaded to the BHIVA website for consultation until Friday 21 July 2006.

Recent legal cases concerning HIV transmission have raised complex questions for both clinicians and service users about rights, responsibilities and legal obligations to disclose information to others.

Clinicians working with people living with HIV are faced with situations that can bring various social values, including civil liberties, public health concerns, confidentiality, autonomy, and discrimination, into conflict. Although established generic ethical and professional principles continue to apply, certain features of the HIV epidemic have required special consideration.

For an effective therapeutic relationship to be established and maintained people living with HIV and their clinical carers must be able to discuss any relevant matter openly. An underlying principle in the provision of clinical care for people with HIV is the need for a secure and confidential environment in which extremely sensitive matters can be frankly and fully discussed.

The importance of ensuring that full trust is maintained by people with HIV in their clinical services in the light of the introduction of the criminal law into the HIV arena is fundamental, not only for the health of people living with HIV but also for people who may wish to seek information or testing and thus for the wider public health.

This paper focuses on the responsibilities and duties of health care staff in the knowledge that other sources of information on this matter exist for other audiences, including people living with HIV (see appendices for references and for additional sources of information).

Please access the website to download the draft recommendation document:
<http://www.bhiva.org>

OTHER NEWS

FDA adds last minute clause into package of patient reforms that protects pharmaceutical industry from litigation in cases of side effects

Simon Collins, HIV i-Base

An article in the 8 June edition of New England Journal of Medicine has drawn attention to important recent changes in the US regulatory requirements.

From 30 June the FDA requires new rules on information that have been publicised as measures to increase patient safety. These include label changes to reorganise information including highlighting most common safety concerns and adding a table of contents.

The urgency of these small changes are perhaps highlighted by the timetable for changes. Drugs already licensed will have 3-7 years to implement similar label changes, and drugs approved prior to 2001 are excluded altogether.

All these changes were open to an extended period of consultation, but after this closed, a new section was added that protects companies from legislation for purposes of litigation. The wording is such that it virtually preempts any litigation by patients who are injured from using a drug, even if the company failed to adequately warn patients of a known risk, unless they can prove that the company intentionally committed fraud.

The article also negatively compares the professional reference manual for drug listings in the US (the pharma-sponsored Physician's Desk Manual) with the British National Formulary (www.bnf.org), for grouping drugs by manufacturer rather than by class (preventing easy comparisons within a drug class) and for financial links with industry.

Additionally, for an organisation that is apparently interested in increasing patient safety and risk awareness, the article highlights how difficult the FDA website is to when trying to access information.

C O M M E N T

The US pharmaceutical lobby have been trying to reduce options for legal liability for several years. It is difficult to see how challenges to this legislation could be effective in the current US political climate.

Ref: Avorn J, Shrank W. Highlights and a hidden hazard - the FDA's new labelling regulations. NEJM 8 June 2006. 354 (23):2409-2411.

ON THE WEB

Full journal articles with free access:

PLoS Clinical Trials, 30 June 2006

<http://clinicaltrials.plosjournals.org/perlserv/?request=get-static&name=browse>

The clinical trials directive: how is it affecting Europe's noncommercial research?

Hartmann M, Hartmann-Vareilles F

<http://clinicaltrials.plosjournals.org/perlserv/?request=getdocument&doi=10.1371/journal.pctr.0010013>

Online Medical resources:

HIV inSite Knowledge Base

New and updated chapter from May and June 2006 include:

Syphilis and HIV

<http://hivinsite.ucsf.edu/InSite?page=kb-05-01-04>

Changing antiretroviral therapy: why, when, and how

<http://hivinsite.ucsf.edu/InSite?page=kb-03-02-06>

Nucleic acid-based HIV-1 viral load assays

<http://hivinsite.ucsf.edu/InSite?page=kb-02-02-02-01>

Metabolic complications of HIV therapy

<http://hivinsite.ucsf.edu/InSite?page=kb-03-02-10>

Clinical management of lower genital tract neoplasia among women with HIV

<http://hivinsite.ucsf.edu/InSite?page=kb-06-04-01>

Malaria and HIV

<http://hivinsite.ucsf.edu/InSite?page=kb-05-04-04>

Advocacy campaign tools online

The Community HIV/AIDS Mobilization Project (CHAMP) has created a new line of advocacy campaign tools.

Campaign tools include: Tracking Ally Recruitment, Tracking Target Research, How To Use a Sign-On Letter, Facilitating Conference Calls, Building a Rap for Outreach.

These tools are used in CHAMP Academy trainings and were specifically developed for Prevention Justice Partnerships.

CHAMP's Prevention Justice Partners are local or statewide community groups or service organisations in the United States that commit to a year-long project to fight for a specific, locally-relevant campaign for HIV prevention policy change.

<http://www.champnetwork.org/index.php?name=academy>

FUTURE MEETINGS

XVI International AIDS Conference

13-18 August 2006

The final conference programme is now available online, with over 400 sessions, meetings and workshops.

Reports based on abstracts selected from a record number of submissions will shape a particularly strong scientific programme. Other sessions will highlight lessons learned and engage delegates in discussions of how best to strengthen the global response to HIV/AIDS.

As we are now close to reaching the maximum delegate capacity, registration will be closed shortly. If the maximum delegate capacity is reached, the AIDS 2006 Registration Department reserves the right to refuse any registration.

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

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

24 – 26 September 2006, San Francisco

This workshop has established itself as the ideal setting for the presentation of new scientific data in the field of metabolic complications, lipodystrophy, drug toxicities and related topics in HIV. The 2006 congress will continue to act as a lively discussion forum for treating physicians and researchers to exchange information, while increasing understanding of the underlying mechanisms and approaches to the management of lipodystrophy and the many and varied adverse events associated with antiretroviral therapy.

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

IAPAC European Sessions 2006

12-13 October 2006, Budapest

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

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

This meeting empowers attendees to benefit from the collective knowledge and experience of their peers. After short presentations on critical treatment issues, the floor is opened to debate and discussion. This interactive symposium work

is crucial given that year's after the development of highly active antiretroviral therapy (HAART) there remain contentious and mystifying problems in the medical treatment of patients with HIV/AIDS.

This year's meeting includes:

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

To see the full program and faculty presenters, visit the iapac web site:

<http://www.iapac.org>

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 designed to be faster, easier to use, and simpler to navigate.

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

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

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

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

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

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

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

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

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

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

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

Treatment training for advocates

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

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

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

<http://www.nkplus.org>

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting every three months since May 2002. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

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

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

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

World CAB - reports on international drug pricing

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

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

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

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

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

Introduction to combination therapy

June 2006 edition

This non-technical patient guide to treatment is available in 12 languages. It explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance.

Printed and/or PDF versions of earlier versions of this booklet are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. Please see the 'translations' page or the website for more details.

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

April 2005 edition

Also updated and revised in April 2005, this is a non-technical patient guide to changing treatment and what to do if treatment fails.

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

Guide to avoiding & managing side effects

February 2005 edition

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

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

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

Guide to HIV, pregnancy & women's health

Spring 2005 edition

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

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

Spanish translation of pregnancy guide

A new spanish translation of the i-Base guide to pregnancy and women's health is available to download as a PDF file from the 'downloads' page of our website:

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

Translations of i-Base guides

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

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

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

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

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

Chinese

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

Bulgarian

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

French

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

Greek

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

Italian

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

Portuguese

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

Russian

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

Serbian

- Introduction to combination therapy PDF [227 Kb]

Spanish

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

Treatment 'Passports'

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

HIV Treatment Bulletin (HTB)

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

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

Treatment information request service – 0808 800 6013

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

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

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

New online Q&A service

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

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

Recent questions include:

- Have I been blessed to have been HIV+ for 20 years and still be alive?
- Do I need an HIV test after sex with a condom?
- Where can I get an HIV test?
- I need information on vaccines for hepatitis A and B
- How do I deal with recurrent shingles?
- I have many things to ask but I don't know how to explain in English.
- Why is the CD4 count different in everyone?
- How do I explain my hallucinations to my family when I have not disclosed HIV?
- I would like to know more about salvage therapy.
- Can you say something about the ability to speak out openly with my doctors?
- Is there a difference between HIV and AIDS?
- I want to know how worse it can get?
- I want to know more about side effects?

- Is there any difference in the way white and black people respond to treatment? What are the differences?
- Why has no cure been found? will there be one?
- Do I need to worry if I am late with my meds?
- What are polyps? And am I right in thinking they can be pre-cancerous growths?
- Is treatment the same for people starting with a low or high viral load?
- How can I find a clinic in the UK?

Find HTB on AEGiS

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

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

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

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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:

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HIV i-Base

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REFUNDS FROM THE TAX MAN

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

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

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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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Phoneline support material (pls specify required number of each)

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

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

1 Sheet 1 pad 5 pads 10 pads Other

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