

The e-mailed (pdf version) of HTB is fully hyperlinked, including contents page and referenced websites

May 2005

CONTENTS

EDITORIAL	2
SPECIAL REPORT:	2
• Lymphogranuloma venereum – an overview: update on UK cases of LGV	
CONFERENCE REPORTS:	5
11th Annual BHIVA Conference, 22-25 April, Dublin	
CONFERENCE REPORTS:	5
Third European HIV Drug Resistance Workshop, 30 March – 1 April, 2005, Athens	
• Tenofovir, nucleosides, and non-nucleosides	
• Protease inhibitors	
• CCR5 antagonists	
CONFERENCE REPORTS:	12
Paediatric reports from 12th Conference on Retrovirus and Opportunistic Infections, 22-25 February 2005, Boston	
• Once-daily lopinavir/ritonavir for children may offer advantages	
• Lopinavir/ritonavir for young infants	
• Paediatric dose finding studies of atazanavir and atazanavir/ritonavir	
• Switching d4T to tenofovir and protease inhibitors to efavirenz in children	
CONFERENCE REPORTS:	15
40th Annual Meeting of the European Association for the Study of the Liver, 13-17 April, 2005, Paris	
TREATMENT ACCESS	15
• Millions in Global Fund grants go unused: Indian government bureaucracies kill off people living with AIDS	
ANTIRETROVIRALS	18
• Draft BHIVA treatment guidelines online for comment	
PAEDIATRIC CARE	19
• US guidelines on paediatric care updated	
HEPATITIS COINFECTION	20
• UK guidelines for liver transplantation in HIV-positive patients	
• Sexual HCV reinfection of HIV-positive gay man while receiving PEG-interferon plus ribavirin	
• First European recommendations for the treatment of patients co-infected with HIV and HBV/HCV	
OTHER NEWS	22
• Newly acquired HIV infections are key to transmission	
• Calls to i-Base phonenumber now free from Orange mobile networks	
• Request for overseas volunteers	
ON THE WEB	23
PUBLICATIONS AND SERVICES FROM i-BASE	25
DONATION FORM	28
FAX-BACK ORDER FORM	29

EDITORIAL

The lead article in this issue provides an overview of lymphogranuloma venereum (LGV) and an update of recent cases in the UK.

Although this is still a rare incidence of LGV in gay men and MSM, the symptoms are extremely debilitating if untreated, and yet respond promptly to a simple course of antibiotics.

LGV was the focus of presentations at the BHIVA Spring conference in Dublin that stressed the importance of treatment for similar symptoms, even if a diagnosis is not confirmed or available. Awareness of the additional information and the surveillance system that was established at the end of 2004 by the Health Protection Agency is clearly important for all GU treating physicians.

This issue of HTB also includes excellent reports by Mark Mascolini from the Third European Resistance Workshop, that include important new data on the resistance profile of tipranavir.

His additional articles on the NATAP.org website, from which these articles are selected are highly recommended additional reading.

Distributed with this issue of HTB are the new i-Base guides to HIV, Pregnancy and Women's Health; and Changing Treatment: what to do when your combination fails.

Both these guides are non-technical, easy-to-understand guides to treatment, written for HIV-positive people to be more informed about their treatment options.

All i-Base publications are free, please order them in bulk for your clients and patients using the fax-back order form on the back page, or easier still, directly from our new website:

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

SPECIAL REPORT

Lymphogranuloma venereum – an overview: update on UK cases of LGV

Leighton Davies MD for HIV i-Base

Lymphogranuloma venereum (LGV) is a sexually transmitted infection caused by the L1-L3 serovars of the obligate intracellular bacterium *Chlamydia trachomatis*. These particular strains of *chlamydia* are more virulent and tend to produce more invasive disease in humans. Chlamydial serovars A-K, which are largely confined to infecting columnar epithelial surfaces of the genital tract and the eye are far more prevalent than the LGV serovars which predominantly infect monocytes and macrophages, passing through epithelial surfaces to regional lymph nodes usually resulting in disseminated infection.

LGV, which was relatively common in industrialised countries until the advent of broad-spectrum antibiotics in the first half of the twentieth century, has become a rare disease, while remaining endemic in parts of Africa, Asia, South America and the Caribbean. Clinically it is difficult to distinguish from other causes of genital ulcer disease – especially those associated with “bubo” formation (large, swollen lymph nodes), such as chancroid. However, there has recently been a resurgence of its appearance in the western world, with subtle changes in its mode of presentation. It is estimated that LGV accounts for between 10 and 20% of genital ulcer disease in parts of the world where it is endemic, with chancroid, syphilis and herpes simplex infection being far more common. Indeed, 10% of patients presenting with buboes to a clinic in Bangkok were found to have LGV, with a large epidemic recently reported among crack cocaine users in the Bahamas. [1-3]

Clinical features

Classically the clinical course has been divided into three stages: The primary stage involves the site of inoculation, the secondary stage the regional lymph nodes and occasionally the anorectum, with the tertiary stage comprising late sequelae affecting the genitals or rectum.

The primary stage occurs after an incubation period of 3-30 days with the formation of a small painless papule, which may ulcerate occurring at the site of inoculation. This primary lesion is virtually always self-limiting and may not always occur and in most cases passes unnoticed by the patient.

The secondary stage occurs some weeks after the primary lesion and can take one of two forms:

(1) **The inguinal form** – commoner in men since the lymphatic drainage of the vagina and cervix is to the retroperitoneal rather than the inguinal lymph nodes. Its cardinal feature is the presence of painful inguinal and/or femoral lymphadenopathy, which is

usually unilateral. Adenopathy above and below the inguinal ligament is termed the 'groove sign' and was once thought to be pathognomonic of LGV. The lymph nodes are usually firm and necrotic. The necrotic areas may enlarge and coalesce to form stellate abscesses, which eventually break down to form discharging sinuses, although this is relatively uncommon and more a feature of chancroid.

(2) **The ano-rectal form** – classically more common in women; and in men who have sex with men (MSM) who practise receptive anal intercourse. It usually presents as a haemorrhagic proctitis. Patients present with bleeding per rectum and pronounced proctalgia, often associated with systemic features – pyrexia, chills and weight loss. Proctoscopy reveals a granular or ulcerative proctitis (similar to ulcerative colitis), which is nearly always confined to the distal 10cm of the ano-rectal canal (4). Extragenital lymphadenopathy has also been described.

The tertiary stage occurs usually as the result of chronic untreated LGV: fibrosis leads to lymphatic obstruction causing elephantiasis of the genitals in either sex with rectal involvement leading to the formation of strictures and fistulae. This often leads to surgical correction of the problem, which can often be severe and debilitating. The tertiary stage occurs far more commonly in women giving rise to a syndrome known as esthiomene (Greek = "eating away"), with widespread destruction of the external genitalia.

Diagnosis

The differential diagnosis of sexually acquired genital ulceration includes chancroid, herpes simplex, syphilis and donovanosis (granuloma inguinale). Less commonly this may arise as a result of trauma, non-sexually transmissible infections e.g. cutaneous leishmaniasis and a fixed drug eruption. The differential diagnosis of inguinal adenopathy includes chancroid, herpes and syphilis although a genital ulcer usually precedes lymphadenopathy in these cases. More generalised lymphadenopathy has a wider differential including lymphoma and HIV.

Laboratory diagnosis of LGV largely depends on serological tests which are genus specific and do not distinguish between infection with other chlamydial species. However, since LGV is far more invasive than other members of the genus it usually leads to higher titres of serum immunoglobulins than uncomplicated infections of *C trachomatis* serovars D-K. A titre of > 1:256 strongly supports the diagnosis while a titre of <1:32 virtually rules it out except in the very early stages of infection. The microimmunofluorescence (MIF) test can distinguish between infection by different chlamydial species but is not widely used in clinical practice. However, a MIF IgG titre of > 1:128 strongly suggests LGV although invasive genital infection by serovars D-K (eg pelvic inflammatory disease) can also give rise to high titres of anti-chlamydial antibody.

Further identification of the organism can be achieved by aspirating bubo fluid or in ulcer material and isolating *C Trachomatis* in tissue culture. This technique is also not widely available. In contrast to diagnosing infection with serovars D-K by commercially available enzyme immuno-assays (EIAs), which are used extensively to diagnose urethral and cervical infection, this form of diagnosis has not been widely evaluated for LGV. Similarly, DNA amplification assays (PCR or LCR) which detect *Chlamydia* specific genomic or plasmid DNA have also not been widely evaluated for the detection of LGV - although PCR was used extensively to diagnose LGV in samples taken from ulcer samples in the Bahamas.

The detection of *C Trachomatis* in bubo material by any of these methods strongly supports the diagnosis of LGV while detection of the organism in ulcer material only supports the diagnosis if it can be shown to be an LGV strain by DNA sequencing or typing with a monoclonal antibody – methods which by and large are not routinely available in day to day practice.

Management

Recommended treatment for both bubonic and anogenital LGV is doxycycline 100mg twice daily for at least 21 days. In pregnant women or persons otherwise intolerant of tetracyclines a macrolide antibiotic such as erythromycin 500mg four times daily, also for 21 days should be employed. Azithromycin is also likely to be effective against LGV although the exact duration of treatment has not been correctly determined; one suggested course would be 1g daily for 10-14 days.

LGV in the 21st Century

Since December 2003 a worrying number of outbreaks of LGV have been reported in European and North American cities. These appear to be largely confined to HIV positive MSM and most appear to be caused by the L2 genotype. Most cases present with a haemorrhagic proctitis and are confined largely to men of white ethnicity. High levels of concurrent sexually transmitted infections (Gonorrhoea, syphilis, HSV and hepatitis B virus) were also seen. Transmission of Hepatitis C virus (HCV) has been associated with the LGV outbreak in Rotterdam in the Netherlands. Contact tracing has largely proven to be a futile exercise as most of the infected men reported numerous anonymous sexual encounters with high levels of unprotected anal intercourse and other high risk practices such as fisting (which itself is strongly associated with the sexual transmission of HCV) and sharing of sex toys.

In response to these outbreaks the Health Protection Agency for England initiated enhanced surveillance measures for LGV. These were established in October 2004 after several sexual health clinics (predominantly in London) reported increased

numbers of cases of bloody proctitis. Clusters of LGV have so far been identified in Rotterdam (>92 cases), Antwerp (27 cases), Paris (38 cases) and confirmed cases in Stockholm and Hamburg in addition to sporadic cases in New York, San Francisco and Atlanta in the USA. These outbreaks appear to be concentrated in sexual networks of gay men and appear to be associated with sex parties that have attracted men from across Europe.

The HPA sent out an alert to GUM clinics in England and established a case definition, reference service and reporting system for LGV. [5] The case definition used by the HPA is confirmation of *C Trachomatis* and presence of LGV serovars - L1, L2 or L3 by genotyping. The HPA reference service tests rectal specimens from patients with ano-rectal symptoms (bloody proctitis, rectal discharge) or urethral specimens from patients with inguinal lymphadenopathy known to be positive for *C Trachomatis*.

In January 2005, the first 24 cases of LGV were reported in the UK – most from London clinics. Enhanced surveillance data were available for 19 cases and confirmed characteristics similar to other European cities: all were MSM, 17 HIV positive, 4 were also HCV positive and most had symptoms suggestive of LGV.

Up to the middle of February 2005, a total of 34 cases of LGV have been reported in the UK. [6] In addition other anecdotal cases have been reported from other centres in the UK which were not subject to the HPA's enhanced surveillance (eg in Swansea an HIV positive MSM presented with a haemorrhagic proctitis and high levels of anti-chlamydial antibodies, (>1:256), genotyping was not available but the diagnosis of LGV was made presumptively and he responded to 21 days treatment with doxycycline 100mg bd). [7]

Noteworthy features of the recent outbreaks are that they tend to occur in white MSM, although some patients have reported sexual encounters with men from Africa or Latin America. Furthermore, very few cases of urethral infection have been reported alongside rectal infections, which further confounds the epidemiology of the outbreaks.

Conclusions

The implications are quite clear: All clinicians who deal with HIV positive gay men's sexual health should be vigilant to the possible presenting symptoms of LGV and wherever possible enrol the assistance of the HPA in establishing a diagnosis. Adequate treatment should be initiated as soon as possible thereby avoiding the potentially serious sequelae of untreated LGV. Ultimately it should not be forgotten that infection with LGV is usually associated with concomitant infection with another STI – this is especially true for HIV, which is propagated far more easily in the presence of genital ulcer disease.

C O M M E N T

LGV was the focus of presentations at the BHIVA Spring conference in Dublin that stressed the importance of treatment for similar symptoms, even if a diagnosis is not confirmed or available.

Awareness of the additional information and the surveillance system that was established at the end of 2004 by the Health Protection Agency is clearly important for all GU treating physicians.

http://www.hpa.org.uk/infections/topics_az/hiv_and_sti/LGV/lgv.htm

References:

1. Hitun Y et al. Comparison of clinically directed, disease specific and syndromic protocols for the management of genital ulcer disease in Lesotho. *Sex Transm Inf* 1998 74 (suppl 1) S23-28.
2. Viravan C et al. A prospective clinical and bacteriologic study of inguinal buboes in Thai men. *Clin Infect Dis* 1996 22, 233-239.
3. Bouwens JE et al. Epidemic LGV during epidemics of crack cocaine use and HIV infection in the Bahamas (in press)
4. Quinn TC et al. Chlamydia trachomatis proctitis *N Engl J Med* 1984 311 1543-1546.
5. Health Protection Agency. Enhanced surveillance of LGV in England. *Commun Dis Rep CDR Wkly* [serial online] 2004. 14 (41). News – available at:
<http://www.hpa.org.uk/cdr/PDFfiles/2004/cdr4104.pdf>
6. Macdonald N et al. Initial results of enhanced surveillance for LGV in England. *Eurosurveillance* 2005 10 20. January 2005 (available at:
<http://www.eurosurveillance.org/ew/2005/050127.asp>
7. Personal communication with Dr K. Yoganathan, Consultant GU Physician, Singleton Hospital, Swansea, UK.

CONFERENCE REPORT

11th Annual BHIVA Conference

22-25 April, Dublin

This joint meeting – the British HIV Association (BHIVA) jointly organised the meeting with British Association for Sexual Health and HIV (BASHH) - drew over 800 delegates to hear a wide range of excellent presentations, was held just as this issue of HTB went to press.

Reports from the meeting will follow in the June issue of HTB.

Abstracts are posted to the online conference database resource at AEGiS.org.

<http://www.aegis.org>

They are also posted to the BHIVA conference website in various pdf formats:

<http://www.bhiva.org>

CONFERENCE REPORT

Third European HIV Drug Resistance Workshop

30 March – 1 April, 2005, Athens

The following selected articles are from Mark Mascolini's reports for NATAP.org from the Third European Drug Resistance Workshop, 30 March-1 April, Athens.

To view slides from oral presentations, abstract (as pdf files) and some posters from the Third European HIV Drug Resistance Workshop, go to:

<http://www.hivpresentation.com>

Further reports from the meeting are also available online:

<http://www.natap.org>

Mark Mascolini writes about HIV infection (markmascolini@earthlink.net).

Tenofovir, nucleosides, and non-nucleosides

Mark Mascolini for NATAP.org

Despite a grand and growing panoply of antiretrovirals, how little we know about HIV can be humbling. For example, noted Hans-Georg Kraeusslich (University Clinic, Heidelberg), several schematic slides at the Third European HIV Drug Resistance Workshop portrayed HIV as a crisply uniform icosahedron-a 20-sided globe [1]. His own immaculate slides of ice-coated virions showed snowball-smooth spheres of discrepant size.

But even Kraeusslich's slides lie, he freely admitted. A trick-animation look at viral budding and maturation-pasted together from a series of still photos-suggested that HIV's core protein condenses from airy nothingness inside the viral shell, just as Marley's ghost materialises to haunt Scrooge. But Kraeusslich's research shows that the core builds up bit by bit from one end to the other.

Questions of more clinical urgency haunt all HIV clinicians trying to treat people with drug-resistant virus:

- Will zidovudine (AZT) heed recent theory and constrain the K65R mutants oft provoked by tenofovir disoproxil fumarate (TDF)?
- Do proliferating reports of rapid resistance to enfuvirtide (T-20) point to limits with this fusion inhibitor - or only to limited skill in its use?
- Will transmission of resistant virus rise unabated, as in some European countries, or settle onto a plateau, as in others?
- Will tipranavir emerge as a muscular alternative for people with protease inhibitor-resistant virus, or simply as another stopgap after multiple regimen failures?

- Will the next likely antiretroviral class, the CCR5 antagonists, prove a powerful new weapon - or will they spur HIV to fashion faster routes to progression?

This installment covers studies on resistance to nucleotides, nucleosides, and nonnucleosides. Subsequent segments explore workshop reports on resistance to protease inhibitors, resistance to entry inhibitors, evolution of resistance during multiregimen failure, pharmacokinetics and resistance, transmission of resistant virus, and resistance among HIV-1 subtypes.

Tenofovir resistance and rescue: more on K65R

K65R can be bad news. Its emergence, often linked to tenofovir disoproxil fumarate (TDF), can compromise viral susceptibility to all marketed (and many experimental) nucleosides-with one intriguing exception: AZT [2]. A possible explanation for this variance emerged in work by Urvi Parikh in the University of Pittsburgh lab of John Mellors [3]. K65R apparently remodels reverse transcriptase in a way that prevents excision of AZT - and so stops resistance to this drug through emergence of thymidine analogue mutations (TAMs, M41L, D67N, K70R, L210W, T215Y/F, K219Q/E).

Mellors and Parikh theorise that giving AZT with other nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) can stifle evolution of K65R, [2] and they cite work buttressing this theory [4-6]. But can AZT beat back virus already tagged with K65R?

Yes, at least in three cases with K65R and no TAMs reported at the European Resistance Workshop by Schlomo Staszewski (J.W. Goethe University Hospital, Frankfurt). [7] All three people added AZT to failing regimens without switching the other drugs and enjoyed speedy and prolonged visits to sub-50-copy territory. The three shared two key traits-a detectable viral load while taking a regimen that provoked K65R, and no TAMs (Table 1.1).

Table 1.1 Three people who added AZT to a failing regimen

PR = protease; RT = reverse transcriptase.

	Case 1	Case 2	Case 3
Current regimen	ddl, 3TC, abacavir	ddl, TDF, abacavir	3TC, TDF, nevirapine
Past regimens	None	-Indinavir, efavirenz, nevirapine -Saquinavir, lopinavir/ritonavir	None
Current (and archived) mutations	RT: K65R , L74V, Y115F, M184V PR: L63P, V77I	RT: K65R , L74V, Y115F, M184V PR: L10V, M36I Archived RT: K103N Archived PR: L101/V, M36I, I54V	RT: K65R , Y181C PR: L63P, G190S
Viral load when adding AZT	5300 copies/mL	48000 copies/mL	1130 copies/mL
Duration <50 c/mL after adding AZT (m)	8	15	6

Baseline mutation patterns suggested resistance to all three drugs in the failing regimen. Yet in all three people the viral load plunged immediately after they added AZT and has remained undetectable for 6 to 15 months. CD4 counts stayed stable (in cases 1 and 3) or climbed (in Case 2).

What can one make of three case reports? Not a universal intensification strategy, to be sure. The reports do endorse the idea that K65R-tainted virus remains susceptible - perhaps highly susceptible - to AZT. And they may provide tinder for controlled trials.

But the oblique interface between K65R and TAMs needs more study. Recent work by Pittsburgh's Parikh determined that K65R and the keystone TAM T215Y/F/I never sit on the same genome, even when population sequencing detects both in plasma samples [8]. But clonal analysis by a French team found that the same viral clone can bear K65R and an array of TAMs [9].

A chart review by clinicians at two Spanish hospitals, Ramón y Cajal in Madrid and Germans Trias i Pujol in Badalona, confirmed Staszewski's finding that K65R mutants can respond to regimens that still include TDF, didanosine (ddl), or abacavir [10]. In a separate, larger study, Carolina Gutiérrez (Ramón y Cajal Hospital) rated K65R much more likely after failure with TDF than with ddl or abacavir [11].

The two-hospital enquiry analysed K65R trends in 33 people treated from 1996 to 2004. The mutation arose more often with TDF ($n = 21$) than with ddl ($n = 17$) or abacavir ($n = 11$). A lamivudine (3TC)-linked M184V mutation popped up in 11 people taking TDF (52%), 9 taking ddl (54%), and 7 taking abacavir (54%).

After K65R emerged, 16 people started a regimen containing ddl, 12 a combination including TDF, and 8 an abacavir regimen. Virologic response after a median 12 weeks of follow-up (range 2 to 60 weeks) did not differ between those starting ddl (-1.1 log), TDF (-1.0 log), or abacavir (-1.3 log). And the RNA decline rate proved similar with or without M184V. Gutiérrez did not report how many people took AZT after K65R appeared, so the impact of that nucleoside cannot be assessed here.

In the single-hospital study, Gutiérrez sequenced 981 viral isolates and found K65R in 21 (2%). That rate vaulted from 0.2% in 842 isolates collected in 1996-2002 to 13.7% in 139 isolates from 2003-2004 ($P < 0.001$). K65R arose with 13 of 97 TDF regimen failures (13%) compared with 9 of 153 abacavir failures (6%) and 9 of 344 ddl failures (3%) ($P < 0.001$). Regardless of which of these three NRTIs people took, K65R emerged significantly more often with triple-NRTI regimens than with NRTIs plus a nonnucleoside or protease inhibitor ($P = 0.001$).

Another look at ddl/TDF/efavirenz failure

High rates of early virologic failure with regimens combining ddl and TDF with an NNRTI - usually efavirenz - [12-14] prompted a letter from Gilead and Bristol warning European clinicians to avoid this NRTI doubling, especially in people starting treatment with a high viral load [15]. An Italian trial that randomised treatment-naïve people to ddl/TDF/efavirenz, 3TC/TDF/efavirenz, or AZT/3TC/lopinavir/ritonavir shed more light on viral vicissitudes with ddl/TDF [16].

Despite the small size of this 30-person pilot by Carlo Torti (Institute for Infectious and Tropical Diseases, Brescia), it does merit interest because of the once-daily comparison of ddl versus 3TC with TDF/efavirenz and because of an intriguing pharmacokinetic hint. Although pretreatment traits did not differ significantly between study arms, the ddl/TDF group began with the lowest median CD4 count (113 cells/ μ L, IQR 42 to 231 cells/ μ L) and the highest median load (4.78 logs-about 60,250 copies/mL-IQR 4.36 to 5.25 logs).

After 14 weeks of treatment 6 of 9 people (67%) taking AZT/3TC/lopinavir, 9 of 10 (90%) taking 3TC/TDF/efavirenz, and 5 of 11 (45%) taking ddl/TDF/efavirenz had fewer than 50 copies/mL. After 28 weeks of therapy 7 of 8 (87.5%) on AZT/3TC/lopinavir, all 10 on 3TC/TDF/efavirenz, and 6 of 10 on ddl/TDF/efavirenz were under the 50-copy mark. Plasma loads dropped significantly faster with the 3TC/TDF combo than with ddl/TDF ($P = 0.0001$).

In 3 people who failed to lower their viral load at least 10-fold by week 4 with ddl/TDF/efavirenz, the NNRTI mutations K103N, Y188L, and G190E emerged first, followed by K65R. The nucleoside-educed D67N and K219Q substitutions arose in one person and L210F plus T215D in another.

Efavirenz levels measured over 24 hours on day 7 proved substantially lower with early failure of ddl/TDF/efavirenz (22.29 h x mg/L) than in people who responded to that regimen (49.10 h x mg/L).

Resistance to TMC278, a new nonnucleoside

Tibotec grooms two novel nonnucleosides in its stable of antiretroviral hopefuls, TMC125 and TMC278. Though TMC125 has seniority, recent reports fattened the resume of TMC278. A dose-finding study unveiled at this year's Conference on Retroviruses charted a 1.2-log viral load drop in 7 days with TMC278, regardless of the dose used [17]. At the European Resistance Workshop, Tibotec's Marie-Pierre de Béthune offered a resistance analysis of the drug [18].

Tested against 10 strains bearing one or two nonnucleoside mutations, TMC278 retained a 50% effective concentration (EC₅₀) below 1 nM against five of them (L100I, K103N, V106A, G190A, G190S) and below 2.8 nM for the others (K101E, Y181C, Y188L, L100I/K103N, K103N/Y181C). Efavirenz, on the other hand, had an EC₅₀ above 10 nM against eight of these 10.

In a test against more than 1500 recombinant nonnucleoside-resistant clinical isolates, TMC278 retained full activity (EC₅₀ below 1 nM) against nearly 60% and some activity (EC₅₀ below 10 nM) against most of the rest. Nearly every recombinant virus in this panel proved resistant to nevirapine, and about 40% were highly resistant to efavirenz.

Whereas 1 nM of nevirapine or efavirenz promptly selected resistant virus in high-multiplicity-of-infection experiments, neither 1 nor 40 nM of TMC278 selected resistant virus through 32 days of study. While only one mutation can render nevirapine or efavirenz impotent, eight mutations (including L100I, V106I, Y181C, and M230I) piled up before virus lost susceptibility to TMC278.

Though Béthune vowed that Tibotec has not dropped development of TMC125, TMC278 may have a pharmacologic edge

– one-pill, once-daily dosing seems likely. Clinical trials of TMC125 used twice-a-day dosing.

Resistance after single-dose nevirapine

Single doses of nevirapine for a woman in labour and her newborn child are the simplest way to lower the risk of HIV transmission. But the strategy almost always evokes resistant virus, even when standard assays can't spot it. Laurence Vergne (Centre Muraz Unité VIH, Bobo Dioulasso, Burkina Faso) added another chapter to this sad chronicle with a study of 44 women in Burkina Faso and 37 in Cameroon [19].

The women carried a wide array of HIV-1 subtypes and circulating recombinant forms (CRFs), including 54% with CRF02, 24% with CRF06, 7% with subtype A, 4% with subtype G, and 3% each with CRF01 or CRF13. Vergne amplified reverse transcriptase in virus from all of the women in Cameroon and 79.5% of those in Burkina Faso.

The median time from nevirapine dosing to resistance testing measured 18 days in Burkina Faso and 24 days in Cameroon. Probably because of faster testing in Burkina Faso, Vergne recorded more resistant virus there-in 8 of 44 women (18%) versus 3 of 37 (8%) in Cameroon.

Two recent studies using assays that can see smaller traces of mutant virus charted resistance rates approaching 70% in South African women [20,21]. Both studies confirmed that highly sensitive PCR assays pick up mutations missed by standard population sequencing. Speaking at February's Conference on Retroviruses, resistance deans Douglas Richman and François Clavel voiced their belief that virtually *everyone* who takes single-dose nevirapine walks away with resistant virus. Even supersensitive techniques hunt for mutations only in plasma, whereas most resistant virus settles down in cells harder to assay.

Do these covert resistant strains pose a clinical threat? Yes, suggested two case studies detailed at the workshop by Marcelo Soares (Federal University of Rio de Janeiro, Brazil) [22]. He documented the K103N mutation in one child and K101E in another, although neither child had been exposed to nonnucleosides and standard genotyping did not spot the mutants in their mothers.

Analysis of 25 clones generated from the second mother's virus did turn up K101E in one clone. Twenty clones from the first mother showed no K103N, but standard genotyping saw that mutation in the father. Soares figured the father transmitted the virus to his wife, who still harbours the mutant even though clonal analysis missed it. Another possibility is that K103N arose spontaneously in the child.

C O M M E N T

A recent publication in AIDS in patients identified by chart review also showed a surprising response to AZT+TDF+3TC. In failing patients 215 and K65R did not show up together. [Mauss S et al. Low rate of treatment failure on antiretroviral therapy with tenofovir, lamivudine and zidovudine. AIDS. 2005 Jan 3;19(1):101-2].

References

To view slides, abstracts and posters from the Third European HIV Drug Resistance Workshop, go to:

<http://www.hivpresentation.com>

1. Kraeusslich HG. HIV protease understanding - understanding protease resistance. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Invited lecture.
2. Parikh UM, Koontz DL, Chu CK, et al. In vitro activity of structurally diverse nucleoside analogues against human immunodeficiency virus type 1 with the K65R mutation in reverse transcriptase. *Antimicrob Agents Chemother* 2005;49:1139-1144.
3. Parikh U, Koontz U, Sluis-Cremer N, et al. K65R: a multinucleoside resistance mutation of increasing prevalence exhibits bi-directional phenotypic antagonism with TAM. 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004. San Francisco. Abstract 54.
4. Gulick RM, Ribaldo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004;350:1850-1861.
5. Winston A, Mandalia S, Pillay D, et al. The prevalence and determinants of the K65R mutation in HIV-1 reverse transcriptase in tenofovir-naive patients. *AIDS* 2002;16:2087-2089.
6. Winston A, Pozniak A, Mandalia S, et al. Which nucleoside and nucleotide backbone combinations select for the K65R mutation in HIV-1 reverse transcriptase. *AIDS* 2004;18:949-957.
7. Staszewski S, Dauer B, Stuermer M, et al. Intensification of a failing regimen with AZT may cause sustained virologic suppression in the presence of the K65R mutation. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Abstract 89. Poster 9.34.
8. Parikh U, Barnas D, Bixby C, et al. K65R and T215Y are not present on the same viral genome in plasma samples with both mutations detected by population sequencing. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. Abstract 98.
9. Wirlden M, Malet I, Derache A, et al. Clonal analyses of HIV quasiespecies in patients harbouring plasma genotype with K65R mutation associated with thymidine analogue mutations or L74V substitution. *AIDS* 2005;19:630-632.

10. Gutiérrez C, Pérez-Elias MJ, Page C, et al. Virological response in HIV-1 infected patients with K65R mutation in the reverse transcriptase gene. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Abstract 87. Poster 9.32.
11. Gutiérrez C, Moreno S, Pérez-Elias MJ, et al. Selection of the K65R mutation in HIV-1 patients under different antiretroviral regimens. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Abstract 88. Poster 9.33.
12. Moyle G, Maitland D, Hand J, et al. Early virological failure in persons with viral loads >10,000 copies/ml and CD4 count <200 cells/mm³ receiving didanosine/tenofovir/efavirenz as initial therapy: 12 weeks results from a randomised controlled trial. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 30-November 2, 2004. Washington, DC. Abstract H-566.
13. Podzamczar D, Ferrer E, Gatell JM, et al. Early virologic failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther* 2005;10:171-177.
14. Leon A, Martínez E, Mallolas J, et al. Early virological failure in treatment-naïve HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS* 2005;19:213-215.
15. Carter M. 'Dear Dr' letter issued about risks of using tenofovir and ddI together. [aidsmap.com](http://www.aidsmap.com/en/news/32A4DCAC-1FFD-4563-8919-81C5F25B455D.asp). March 4, 2005. <http://www.aidsmap.com/en/news/32A4DCAC-1FFD-4563-8919-81C5F25B455D.asp>.
16. Torti C, Quiros-Roldan E, Regazzi M, et al. Factors associated with early virological failure after tenofovir + didanosine + efavirenz combination in naïve patients: the KARINA-SISTHER group of the MASTER cohort. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Abstract 58. Poster 9.3.
17. Goebel F, Yakovlev A, Pozniak A, et al. TMC278: potent anti-HIV activity in antiretroviral therapy-naïve patients. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. Abstract 160.
18. de Béthune MP, Azijn H, Guillemont J, et al. In vitro characterisation of TMC278, a novel potent NNRTI with an increased genetic barrier to the development of resistance. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Abstract 93. Poster 10.3
19. Vergne L, Kouankack C, Diabougba S, et al. Selection of resistance mutations under nevirapine prophylaxis to prevent HIV-1 mother-to-child transmission in Africa. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Abstract 26. Poster 2.2.
20. Johnson J, Li JF, Morris L, et al. Resistance emerges in the majority of women provided intrapartum single-dose nevirapine. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. Abstract 100.
21. Palmer S, Boltz V, Maldarelli F, et al. Persistence of NNRTI-resistant variants after single-dose nevirapine in HIV-1 subtype-C-infected women. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. Abstract 101.
22. Afonso AO, Machado ES, Lambert JS, et al. Mother-to-child transmission of minority HIV-1 drug resistant strains. Third European HIV Drug Resistance Workshop. 30 March - 1 April, 2005. Athens. Abstract 25. Poster 2.1.

Protease inhibitors

Mark Mascolini for NATAP.org

With tipranavir coming before the FDA's Antiviral Drugs Advisory Panel in May, Boehringer Ingelheim's Douglas Mayers made a timely appearance at the Third European HIV Drug Resistance Workshop to update attendees on the potential of this protease inhibitor (PI) against resistant virus.

But his was hardly the only useful survey of PI prowess against resistant virus at the March 30-April 1 workshop. Other investigators compared ritonavir-boosted regimens, with a special fix on atazanavir and lopinavir. Two studies explored the impact of mutations not in protease, but in the gene that encodes HIV's Gag enzyme.

What will you get from tipranavir?

After years of development, tipranavir seems set to fulfill its early in vitro promise as a PI that reins in resistant virus better than current ritonavir-boosted options. Boehringer bosses are confident enough that they have already assigned the agent a brand name, Aptivus, in advance of a May 19 FDA review.

How apt that name may prove will be clear only when thousands of people with PI-resistant virus start taking this drug. At the 2005 Conference on Retroviruses, a 6-month comparison of 1100 PI-experienced people randomised to tipranavir/ritonavir or lopinavir/ritonavir found a significantly better response rate with tipranavir in a non-completer-equals-failure analysis—39.6% versus 21.4% ($P < 0.0001$) [1]. When statisticians confined the analysis to lopinavir-naïve people, tipranavir still yielded a better 6-month response (45.3% versus 36.1%), but the difference between arms was no longer significant.

Comparing tipranavir/ritonavir with four other boosted PIs, these researchers charted steeper viral load drops with tipranavir regardless of the mutation set studied – all changes from the protease consensus sequence; primary mutations at codons 30, 46, 48, 50, 82, 84, and 90; or substitutions at codons 33, 82, 84, or 90 [2].

But tipranavir may have one drawback for people with the most highly resistant virus: A study combining it with boosted lopinavir, amprenavir, or saquinavir charted 45%, 50%, and 80% lower trough concentrations of those PIs after people added tipranavir [3]. The CYP3A4-inducing effect of tipranavir appears to offset the inhibiting effect of ritonavir.

When will tipranavir work best? It's still not easy to say, although Douglas Mayers and Boehringer scientists may be closing in on an answer. Ongoing work failed to confirm early hints that mutations at protease positions 33, 82, 84, and 90 form a compact set of danger signals for tipranavir.

Resistance to tipranavir turned out to be more complicated than that. Analysing the impact of changes at all 99 protease positions on response to tipranavir in phase 2 and 3 trials, researchers compiled a list of 21 mutations at 16 positions that

hobble tipranavir. For the record, Table 2.1 spells them out.

Table 2.1. Mutations in the tipranavir resistance score

10V	13V	20M/R/V	33F
35G	36I	43T	46L
47V	54A/M/V	58E	69K
74P	82L/T	83D	84V

Some of these changes, Mayers observed at the workshop, don't appear in mutation scores for any other PI—the unfamiliar wrinkles at positions 13, 35, 43, 58, 74, and 83. On the other hand, tipranavir apparently owes some of its muscle against more common resistant strains to the absence of D30N, G48V, N88D/S, and L90M from the resistance score.

L90M? Wasn't that one of the fearsome foursome Boehringer once billboarded as potential tipranavir threats? That designation, Mayers explained, arose from an early Virco study that linked L90M to lowered viral susceptibility when combined with the keystone protease mutations V82T and I84V [4]. Other research spied L90M in clusters of critical mutations that robbed tipranavir of brawn. But Boehringer ultimately decided not to include it in tipranavir's 21-item mutation score for three reasons:

- Tipranavir does not select L90M in vitro or in clinical isolates.
- Multivariate analysis of lowered susceptibility to tipranavir did not implicate L90M.
- Multivariate analysis of clinical responses to tipranavir did not tar L90M.

Mayers and colleagues concluded that L90M – combined with critical changes at codons 82 and 84 – is merely a marker of highly mutated virus that bears a bevy of mutations from the tipranavir resistance score.

And what about that 21-item mutation score? Will genotypers and VircoTYPEs (VircoTYPE is the new name for VirtualPhenotype) have to revamp their reports to weigh the import of K20M, L33F, and I47V, for example, versus L10V, K20R, and I54A? Will clinicians have to memorise this sesquipedalian substitution chart, or at least keep it at their fingertips?

Probably not. Boehringer has already expended much effort reckoning simpler ways to gauge tipranavir's potential in people with PI-resistant virus. First, one can measure the fold-change in susceptibility to tipranavir before starting the drug. Anything below 1 is splendid. A fold-change below 4 foretells more than a half-log drop in viral load after 24 weeks in most people. But a baseline fold change above 4 means many people won't respond (Table 2.2).

Table 2.2. Response to tipranavir based on baseline susceptibility to the PI

Fold change	Change in viral load at 2 weeks*			Change in viral load at 24 weeks†		
	Log10	N	IQR	Log10	N	IQR
<1	-1.53	115	-0.97 to -1.92	-1.82	122	-0.35 to -2.88
1 to 4	-1.44	190	-0.68 to -1.86	-0.64	199	-0.17 to -2.34
>4	-0.66	89	-0.15 to -1.66	-0.32	91	+0.11 to -1.27

*On-treatment analysis.

†Last-observation-carried-forward analysis.

IQR = interquartile range.

This analysis is not cut-and-dried, Mayers noted, because most people with low susceptibility to tipranavir at baseline (more than a 4-fold change) had few active drugs to add to their new tipranavir regimen. So these people got less help from tipranavir than others – and little help from other antiretrovirals. Even so, the interquartile range shows that 25% of this group garnered more than a 1.27-log drop in viral load after 24 weeks.

A multiple regression model of virologic response to tipranavir salvage at 24 weeks picked out four independently predictive factors: use of tipranavir itself, use of enfuvirtide (T-20), more active drugs in the background regimen, and, yes, the tipranavir resistance score ($P < 0.01$ for all).

The 21-mutation tipranavir score did much better than the IAS-USA list of primary protease mutations in foretelling the response to tipranavir at 2 weeks. People whose virus carried up to seven of the 21 critical mutations had more than a 1-log drop in viral load at week 2, whereas people with eight of the 21 mutations did not respond. A score that included all IAS-USA protease mutations saw no difference in 2-week response until virus bore 13 mutations.

So at this point Boehringer predicts that most people with more than seven mutations from the set of 21 will respond poorly to tipranavir. But company virologists have not entirely tossed out the four-mutation set of changes at positions 33, 82, 84, and 90, arguing that they denote a highly resistant virus that tipranavir will struggle to control. But many may find it odd to juggle two scores – one that includes L90M and one that does not.

References

To view slides, abstracts and posters from the Third European HIV Drug Resistance Workshop, go to:

<http://www.hivpresentation.com>

1. Cooper D, Hicks C, Cahn P, et al. 24-week RESIST study analyses: the efficacy of tipranavir/ritonavir is superior to lopinavir/ritonavir, and the TPV/r treatment response is enhanced by inclusion of genotypically active antiretrovirals in the optimised background regimen. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. Abstract 560.
2. Schapiro J, Cahn P, Trottier B, et al. Effect of baseline genotype on response to tipranavir/ritonavir compared with standard-of-care comparator in treatment-experienced patients: the phase 3 RESIST-1 and -2 trials. 12th Conference on Retroviruses and Opportunistic Infections. February 22-25, 2005. Boston. Abstract 105.
3. Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir alone or in combination with saquinavir, amprenavir, or lopinavir: interim analysis of B11182.51. 5th International Workshop on Clinical Pharmacology of HIV Therapy. April 1-3, 2004. Rome. Abs34.
3. Larder BA, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. *AIDS* 2000;14:1943-1948.

European resistance workshop: CCR5 Antagonists

Mark Mascolini for NATAP

CCR5 antagonists - with Pfizer's maraviroc leading the development race - will be the next new antiretroviral class. These drugs block HIV docking to CCR5, one of two key coreceptors the virus can use to breach CD4 cells after grabbing hold of CD4 itself.

Acute HIV infection almost always involves virus that homes to the CCR5 coreceptor ("R5-tropic virus"). During advanced HIV disease the viral swarm may shift its focus to the alternate CXCR4 receptor ("X4-tropic virus") [1], but that happens in only about half of people with advanced disease.

Answers to two important questions about viral tropism will help determine how effective CCR5 antagonists will be, especially for people with virus resistant to the other classes:

- How often does HIV switch allegiance from CCR5 to CXCR4 in people with multidrug-resistant virus?
- How often will HIV jump from CCR5 to CXCR4 when pressured by CCR5 antagonists?

Partial answers to both questions emerged during the March 30-April 1 European HIV Drug Resistance Workshop in Athens.

Earlier this year Chelsea and Westminster Hospital's Graeme Moyle published a coreceptor tropism study involving 563 people, 19% of them infected with non-subtype-B virus [2]. Only 20% of viral samples homed to CXCR4 or to both CXCR4 and CCR5, and 60% of isolates from people with a CD4 count under 100 cells/ μ L tracked to CCR5. But a higher CD4 count and a lower viral load did independently predict a preference for CCR5. Treatment experience, viral subtype, and mutations in reverse transcriptase or protease did not correlate with viral tropism.

A longitudinal study presented at the workshop by Rolf Kaiser (University of Cologne) confirmed the predominance of R5-tropic virus in 42 people with heavy treatment experience and multidrug-resistant HIV [3]. And Kaiser found little coreceptor switching over time.

Half of Kaiser's cohort had AIDS, 64% had triple-class experience at the start of follow-up, and 82% had tried all three classes at the last follow-up point. All had subtype B HIV-1. The median CD4 count measured 240 cells/ μ L (range 10 to 1090 cells/ μ L) and the median viral load 27,000 copies/mL (range 276 to 1,750,000 copies/mL). Neither antiretroviral experience nor mutation patterns affected coreceptor preference. In fact the study turned up no clinical, immunologic, or virologic correlates of coreceptor tropism. But this was a small study.

Kaiser rated virus consistently R5-tropic in 25 people (59.5%) and X4-tropic in 12 (28.6%). In the other five tropism swung from X4 to R5 in two, from R5 to X4 in one, from X4 to R5 and back again in one, and from R5 to X4 to R5 in one.

HIV owes much of its infamy to a protean knack for adapting to any threat. And ever since development of CCR5 antagonists began, many have worried that virus blocked from its R5 port will simply sail on to X4. That happened rarely, however, in a Maraviroc monotherapy analysis presented by Pfizer's Elna Van Der Ryst.

Among 63 people who took Maraviroc and no other antiretrovirals, X4 viral variants cropped up in only two. Nonetheless, one of them enjoyed a 0.71-log drop in viral load and the other a 1.26-log tumble. But in a roundtable on coreceptor antagonists, Schering's Wayne Greaves warned that emergence of X4-tropic virus remains a threat during combination therapy including a CCR5 antagonist.

What makes HIV resistant to CCR5 antagonists? The answer appears to be different for different agents, according to results presented by Pfizer's Marilyn Lewis [4]. She ran serial passage studies with six CCR5-tropic patient isolates, exposing infected peripheral blood lymphocytes to rising doses of Maraviroc for 20 passages.

Resistance-related mutations never emerged from three of the six isolates. Mutations did arise in one subtype B virus and one subtype G virus, both of which retained their CCR5 tropism. The A19T and I26V changes that emerged in the subtype B strain were distinct from those reported with another CCR5 antagonist, a prototype of Schering's SCH-D. The changes Maraviroc evoked in the subtype G virus - a triple deletion in HIV envelope's V3 loop - differed from mutations that arose in another subtype G virus tested against SCH-C.

Maraviroc-induced mutations arose in another subtype B virus that switched tropism to CXCR4. But the same type of virus also evolved X4 tropism in a control experiment that did not subject it to Maraviroc.

So far, Lewis concluded, resistance experiments with candidate CCR5 antagonists have not elicited any apparent signature mutations. And research hasn't revealed whether CCR5-resistant virus exists naturally in viral populations not exposed to these drugs.

References:

To view slides, abstracts and posters from the Third European HIV Drug Resistance Workshop, go to:

<http://www.hivpresentation.com>

1. Spijkerman I, de Wolf F, Langendam M, et al. Emergence of syncytium-inducing human immunodeficiency virus type 1 variants coincides with a transient increase in viral RNA level and is an independent predictor for progression to AIDS. *J Infect Dis* 1998;178:397-403.
2. Moyle GJ, Wildfire A, Mandalia S, et al. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. *J Infect Dis* 2005;191:866-872.
3. Kaiser R, Boussaad I, Lehmann C, et al. Stable coreceptor usage of HIV-1 in patients with ongoing treatment failure on HAART. Third European HIV Drug Resistance Workshop. March 30-April 1, 2005. Athens. Abstract 60. Poster 9.5.
4. Lewis M, Westby M, Smith-Burchnell C, et al. A genotypic analysis of HIV-1 sequences from emerging resistant virus after in vitro serial passage with the CCR5 antagonist Maraviroc (UK-427857). Third European HIV Drug Resistance Workshop. March 30-April 1, 2005. Athens. Abstract 91. Poster 10.1.

CONFERENCE REPORT

Paediatric reports from 12th Conference on Retrovirus and Opportunistic Infections (CROI)

22-25 February, Boston

Abstracts from this meeting are posted to the conference website, and many pdf for poster presentations are already online:

<http://www.retroconference.org>

Once-daily lopinavir/ritonavir for children may offer advantages

Polly Clayden, HIV i-Base

A once-daily dosing schedule for HIV-positive children may offer an advantage to families and healthcare workers in terms of convenience and adherence. The currently approved paediatric dose of lopinavir/ritonavir (LPV/r, Kaletra) is 230/57.5 mg/m² taken twice daily with food. Gwenda Verweel and colleagues evaluated the pharmacokinetics, tolerability, and efficacy of once-daily dosing of LPV/r in children.

In this study children on stable treatment with a viral load < 50 copies/mL for at least 6 months received LPV/r 460/115 mg/m² once daily with AZT and 3TC. LPV/r was taken with food in the morning. Intensive pharmacokinetic studies were performed after observed drug intake during steady state at two weeks. Target for C_{min} was 1.0mg/L. After this period the time of dosing could be changed to the evening meal.

Single sample plasma levels were collected at day 28 and months 2, 3, and 6. Clinical assessment included plasma RNA levels, lymphocyte counts, biochemistry, haematology, and side effects monitoring.

Six-month follow up results were available for 14 children (7 boys and 7 girls) with a median age of 4.5 (range 3.3 to 9.5) years. The dose of LPV/r 460/115 mg/m² once daily, resulted in comparable LPV plasma levels to those in adults after an 800/200 mg once-daily regimen.

The authors report that: 3/14 children had a C trough that was considered to be too low (< 1.0 mg/L) and a dose increase was necessary; 11 children took LPV/r with their evening meal; and 44% (17 of 39) of the LPV/r plasma levels were higher than their corresponding values on day 14. 2/3 children taking LPV/r with breakfast had lower plasma levels than those on day 14.

All 14 children had viral load < 50 copies/mL after 6 months of treatment. CD4 cell counts did not change significantly during the study.

This once-daily regimen of LPV/r was generally well tolerated. Of the 14 children, 6 experienced mild gastrointestinal side effects but all were resolved after 2 months. Cholesterol and triglyceride levels were stable during 6 months of follow-up.

The authors concluded that LPV/r 460/115 mg/m² once daily led to LPV plasma levels comparable to adult data. In 3 of 14 children dose increase to 600mg/m² or 798mg/m² was necessary because of low C_{min} (24hr). Intake with a large meal (like dinner) is important to obtain adequate plasma levels when LPV/r is dosed once daily in children. They also noted that because of interpatient variability in plasma levels, TDM might be useful to guide the correct dose for children.

Lopinavir/ritonavir for young infants

Polly Clayden, HIV i-Base

Lopinavir/ritonavir is increasingly recommended for treating young infants but in the absence of published data. Ellen Chadwick and colleagues from the PACTG 1030 study group evaluated dose requirements for babies <6 months that provide systemic exposure similar to that which has been shown to be safe and effective in older children and adults.

Results were available for 12 infants (5 boys, 7 girls) and stratified by age: 14days to 6 weeks and 6 weeks to 6 months. A dose of 300 mg/m² lopinavir/ 75mg/m² ritonavir was studied in combination with two nucleosides.

Intensive PK studies were performed at two weeks with a dose adjustment if LPV/r 12-hour post-dose concentration (C₁₂) was < 1 mg/L; C₁₂ was measured every 12 weeks and intensive pharmacokinetic studies were repeated if there was dose adjustment at one year of age.

The study defined virologic success as viral load < 400 copies/mL at week 16; failure as never achieving < 400 copies/mL and late suppressors as achieving < 400 copies/mL after week 16. CD4 percentage was measured every 12 weeks.

Median follow-up at analysis was 50 weeks (range 19 to 112 weeks). At entry, median age was 9.4 weeks (range 3.6 to 25.7 weeks), log₁₀ HIV-1 RNA 5.6 (3.77 to 6.88) and CD4 percentage 37% (19 to 59%). Six of the 12 infants (50%) had virologic success, 2 (17%) virologic failure, and 4 (34%) were defined as late suppressors (< 400 copies/mL at week 32 to 48). The authors noted that poorer adherence contributed to poorer response.

In 6 infants studied through week 36, CD4 percentage showed a median increase of 8% (-9 to +20%) from baseline.

One infant required dose adjustment. Infants with virologic success vs virologic failure/late suppressors were significantly younger (median 5.6 vs 15.9 weeks, p = 0.004).

The authors found that the dose of 300 mg/m² LPV/r twice daily was well tolerated in young infants and produced encouraging results in those infants adherent to therapy. At week 2 lower plasma concentrations were reported than found in adults despite a surface area adjusted dose approximately 35% higher than recommended for adults.

To better define age-related differences in pharmacokinetics and response to LPV/r, this group will study a second cohort of 12 infants.

Dose finding atazanavir and atazanavir/ritonavir

Polly Clayden, HIV i-Base

Jennifer Kiser and colleagues reported findings from PACTG 1020, a prospective phase I/II open-label area-under the concentration time curve (AUC)-controlled study to determine the safety, pharmacokinetics, and optimal dose of once-daily atazanavir (ATV) powder and capsules with and without ritonavir (RTV) in HIV-positive children in combination with two nucleosides.

ART-naïve and -experienced children with viral load > 5000 copies/mL and ATV phenotypic susceptibility (< 10-fold wild type IC₅₀) were eligible for this study.

There are 8 study groups in PACTG 1020: groups 1 to 4 evaluating unboosted and in groups 5 to 8 boosted ATV. This poster reported preliminary PK data from 23 children in groups 5-8 receive RTV boosted ATV at a dose of 310mg/m².

Intensive PK studies were performed on day 7 and at week 56, plus 14 days after dose adjustment. A new ATV dose is calculated for children with: an AUC <30mg*hr/mL or AUC >90mg*hr/mL, increases of 25% in weight.

The authors reported week 1 pharmacokinetic results for 23 children ages 0.3-19.6 years. Overall median AUC and oral clearance (CL/F) were 60.8mg*hr/mL and 4.7L/hr/m² respectively.

In the youngest group (group 5, median age 1.0 [range 0.3-1.3] years, n = 6), median AUC and oral clearance (CL/F) were 53.6 (range 7.3-110) mcg*hr/mL and 8.1 (range 2.5-36) L/hr/m² in children receiving powder at a dose of 125 (range 50-

150)mg /298 (range 182-367)mg/m².

In older children receiving powder (group 6, median age 4.1 [range 2.6-12] years, n = 7), the median AUC and CL/F were 50.3 mcg•hr/mL and 6.2 L/hr/m² at a dose of 200 (range 150-500) mg/312 (range 268-327) mg/m². Older children receiving capsules (group 7, median age 10.5 [range 8.7-11.5], n=5) the median AUC and CL/F were 73.8 (range 60-134.2) mcg•hr/mL and 4.2 (range 2.2-4.7) L/hr/m² at a dose of 400 (range 300-500) mg/286 (range 274-349) mg/m².

In the oldest group of children receiving capsules (group 8, median age 17.7 [range 13.1-19.6], n=5) the median AUC and CL/F were 62.4 (range 51.5-84.7) mcg•hr/mL and 4.5 (range 3.4-6.0) L/hr/m² at a dose of 500 (range 400-600) mg/286 (range 281-311) mg/m².

The authors concluded: "The median ATV AUC and CL/F in adults receiving ATV/RTV 300/100mg once daily are 53.8 mcg•hr/mL and 3.2 L/hr/m² respectively. Thus ATV CL/F is age-dependent and faster in children than in adults, as seen with other protease inhibitors.

"As expected, the addition of RTV decreases the clearance and increases the AUC of ATV in children."

These data are preliminary and the optimal dose of ATV/RTV has not yet been established. The authors added: "Further evaluations are underway in P1020 to establish the optimal dose of ATV/RTV in subjects 91 days to 21 years in the United States and South Africa."

Switching d4T to tenofovir and protease inhibitor to efavirenz

Polly Clayden, HIV i-Base

Alessandra Viganò and colleagues reported findings from a study to assess the strategy of replacing protease inhibitor (PI) by efavirenz (EFV) and stavudine (d4T) by tenofovir (TDF) in HIV-positive children with long-lasting viral suppression.

In this study, 27 HIV-positive children (age range 5.0 to 17.5 years) with viral load < 50 copies/mL for the last 48 weeks, on HAART containing lamivudine (3TC) + d4T + 1 PI were randomised either to switch d4T to TDF and PI to EFV at baseline (n = 14; group A) or at week 24 (n = 13; group B).

All children maintained 3TC and were followed with clinical assessment, viral load, CD4 count, fasting metabolic, and renal parameters for 48 weeks.

The authors reported from baseline to week 24 and at week 48, both groups had unchanged CD4 count 884, 759, 848 vs 809, 795, 754 cells/mm³; HIV RNA < 50 copies/mL; unchanged and normal levels of serum creatinine, phosphate, calculated creatinine clearance; absence of proteinuria and glycosuria.

The children in Group A, from baseline to week 24, showed a significant decrease on total cholesterol (-20%, p < 0.03), triglycerides (-35%, p < 0.05) and total cholesterol/HDL ratio from 3.5 to 3.0, p < 0.006; and at week 48, the authors reported stable cholesterol levels and a further decrease of triglycerides and HDL cholesterol. Children in this group with elevated (> 95th percentile for age and sex) cholesterol and triglyceride levels showed a marked decrease of both over the study period (from 43 to 0% and from 36 to 7%, respectively).

In Group B, from baseline to week 24, the children showed unchanged cholesterol, triglycerides, HDL cholesterol and percentage of HIV with elevated cholesterol and triglyceride levels; at week 48, the authors reported a significant decrease of cholesterol (-14%; p < 0.03), triglycerides (-41%; p < 0.05), and HDL cholesterol (from 3.9 to 3.2; p < 0.006). The children with elevated cholesterol and triglyceride levels showed marked reduction of both after the initiation of the new regimen (from 46 to 8% and from 54 to 0%, respectively).

No adverse events were reported throughout this study.

The authors concluded: "The replacement of PI by EFV and d4T by TDF in HIV-infected children who had been receiving a HAART regimen containing 3TC+d4T+PI who had long lasting viral suppression provides continued virological suppression, stable CD4 response.

References:

1. Verweel G, van der Lee M, Burger D et al. 6-Month follow-up of once-daily lopinavir/ritonavir in HIV-1-infected children. 12th CROI Boston 2005 Abstract 769.
2. Chadwick EG, Rodman J, Palumbo P et al. A prospective evaluation of pharmacologic, virologic, and immunologic parameters of lopinavir/ritonavir for HIV-1-infected infants < 6 months of age. 12th CROI, Boston 2005. Abstract 766.
3. Kiser J, Rutstein R, Aldrovandi G et al. Pharmacokinetics of atazanavir/ritonavir in HIV-infected infants, children, and adolescents: PACTG 1020A. 12th CROI, Boston 2005. Abstract 767.
4. Viganò A, V Giacomè V, Beretta S et al. Switching stavudine to tenofovir and protease inhibitor to efavirenz results in a favourable clinical outcome in HIV-infected children. 12th CROI, Boston 2005. Abstract 770.

CONFERENCE REPORT

40th European Association for the Study of the Liver (EASL)

13-17 April 2005, Paris, France

An excellent selection of over 20 reports from this important European meeting are available on the NATAP website, including:

- Incidence and predictors of emergence of resistance to adefovir after 4 years follow-up
- Age & ribavirin dose reductions reduce SVR to peginterferon+ribavirin
- Cost effectiveness of peginterferon in HCV/HIV coinfection
- Albuferon: new HCV drug
- New HCV drug NM283: 24 week data at EASL
- New HCV drugs in development: EASL Report

<http://www.natap.org>

TREATMENT ACCESS

Millions in Global Fund grants go unused: Indian government bureaucracies kill off people living with AIDS

Richard Stern, Agua Buena Human Rights Association

While hundreds of millions of dollars in assistance for AIDS pour into India from international donor sources including the Global Fund to Fight AIDS, TB and Malaria, only 5,000 People Living with HIV/AIDS (PLWA) are receiving antiretroviral treatment through the public sector. Incredible negligence on the part of the National AIDS Control Organisation (NACO) and the Health Ministry combine to systematically create a form of "bureaucratic genocide," contributing to the deaths thousands of PLWA who need treatment now.

According to the World Health Organisation (WHO), 700,000 people in India urgently require treatment. About 100,000 die each year, nearly 300 each day.

As of this moment, all public sector treatment in India is provided by government funds, channeled through NACO. Yet \$122 million in additional funds for ARV access has been available for nearly a full year from the Global Fund but not one dollar has been disbursed from Geneva to India for antiretroviral access

While the money remains in the bank, Mumbai's JJ Hospital is the only publicly funded facility in that city where PLWA currently receive free treatment. Two overworked counselors try to see 180 patients each morning who come to the Clinic. Counselors must deal with adherence and other issues for the 1,350 PLWA now receiving free treatment at this hospital. Yet hospital staff have indicated that as of 1 April no more PLWA can be placed on treatment. The Mumbai AIDS Control Centre has decided that the JJ program is saturated.

Mumbai is India's largest city with a population of 16 million. Experts agree that at least 30,000 people in Mumbai need treatment now. The government will supposedly begin providing free treatment at three additional hospitals, called "medical colleges," in the near future but the cap for each of these hospitals will be 500 patients, meaning that a total number of 2,800 people, could be placed on treatment by the end of 2005 in Mumbai, leaving 27,000 or 90% still without ARV access. Of these 27,000 an estimated 8,000 will die during the year.

No treatment for children with AIDS

Although Mumbai AIDS Control Centre staff acknowledged that 1,500 children are known to need treatment, and despite a thriving low cost generic manufacturing industry, incredibly there are no paediatric AIDS suspensions available. Children over 13 are given pills for adults but there is no treatment for children under 13. The WHO representative for Mumbai, Dr. Dilip Vasvani informed me that there are "plans" to begin providing treatment for children at a facility in Northeast Mumbai that already provides medical services for children but he would not be specific about a date.

Few if any of the PLWA we met in Mumbai had any information about the Global Fund or the reason for the delays in disbursement. In India's first AIDS related Global Fund project, approved in round two, over two years ago, \$100 million was made available to India by the Fund. Incredibly, India's "Country Coordinating Mechanism" (CCM) – the umbrella body that oversees Global Fund applications for India - only asked for funds to treat 5,000 people over a five year period. At current prices, treatment for 5,000 people represents only about \$800,000 out of the total approved of \$100 million, less than one percent. However,

it is a moot point, since none of the people who could be treated with Global Fund money have even been placed on treatment at the time of writing. Global Fund projects are "country driven" meaning that the Fund does not mandate that a country ask for funds for treatment in their proposals. A year and a half later, in the fourth round, India did ask for funds for treatment access, but the grant agreement has never been signed (See Table summarising Global Fund grants below).

The WHO's Dr Vasvani acknowledged that he himself knows little about the Global Fund roll-out in India. He indicated that ARV roll-out would be slow at first to assure quality of care, but could not explain why the "cap" of 2,800 had been placed on access for Mumbai for the year 2005, when so many are urgently in need of treatment. In all of India 5,000 people are on treatment in six major centres, but NACO had originally announced that treatment would be available for 100,000 by the end of 2005. In early February, the NACO estimate was dramatically lowered, in spite of available funds, and the goal is now to have 100,000 people on treatment by the end of 2007, a decision that defies logic given the resources available to the government from donor sources.

For most questions I posed regarding the Global Fund and general ARV policy, Dr Vasvani referred to me Dr Alka Gogate, Director of the Mumbai AIDS Control Centre, the local branch of NACO which is responsible for Maharashtra state.

In spite of a confirmed appointment that I had made directly with Dr Gogate for Tuesday March 29th, at 3 pm she failed to appear and left no note or message relating to the cancellation of this meeting. Although I never spoke with Dr Gogate, documents provided by NGOs, indicated that in March 2004 she had announced that medications for children would be a priority in Mumbai. She also indicated in the same report that in Mumbai, no one would receive treatment unless they had a "responsible accompanying person" to ensure adherence. I had no chance to ask her if she was aware that this policy was against all "best practice" that entitles a person with AIDS to confidentiality.

Global Fund money still not released

However, information available on the Global Fund website reveals that \$37 million has been available since the fourth round AIDS project was approved in June 2004 for ARV treatment access to be provided at several major sites throughout the country, during a two year period, with an additional \$85 million available for the following three years. However, the grant agreement, which would release these funds, has still not been signed, and there is still no specific information about when it will actually be signed. According to the website, the \$37 million would provide treatment for 44,300 people during the first two years of the project.

Informed sources claimed that the delay in signing the contract and disbursing the funds was due to a range of issues related to internal government and health ministry approvals and other "bureaucratic" problems. The Department of Economic Affairs of India is the "Principal Recipient" for the grant and would implement the project. It is astounding and disheartening that \$37 million has been available to provide treatment for nearly a year, and could potentially have saved 45,000 lives, yet the CCM and Principal Recipient have not been able to complete the requirements needed in order to receive the funds and begin implementation of treatment. More perplexing is the fact that NACO has been able to complete requisites for the small government financed treatment access roll-out, but not for the Global Fund roll-out which will cost the government nothing at all.

The Global Fund claims that it is trying to use partner agencies including WHO and UNAIDS to speed up this process, but obviously the outcome remains lethal.

The total amount available over the entire five year project for scaling up from the 4th Round HIV grant would be about \$122 million, with a goal of placing 137,000 people on treatment during a five year period. Yet, according to our calculations based on current medication prices, for every \$10 million available, about 50,000 people should be able to receive treatment.

Ironically, a fourth round grant agreement was signed just weeks ago for \$4.2 million, with a Consortium of five Indian NGOs. But of this money, over \$1.9 million is allocated for "infrastructure, human resources, and planning and administration," while only \$62,000 is for drugs, in this case drugs to treat opportunistic infections.

Informed sources in Geneva indicated that India's various Global Fund grants could be canceled due to lack of follow up as the two year review process approaches for the Round Two grant, and implementation is still bogged down in delays due to bureaucracy.

The reality for PLWA in the streets and hospitals of Mumbai, is that the windfall of resources available in Geneva and New Delhi is being delayed by a small army of paid bureaucrats, while those who need treatment simply find a place to die.

Hospices in Mumbai

Nestled in the far northeast corner of the city, six kilometers from the end the Mumbai railroad line is the Niramay Niketan AIDS hospice. The day I visited about 50 PLWA were living there, but none had access to ARVs.

"Not all of them are terminal," said Frank Furtado, Director of the programme. "For those who can be treated for their OIs, we try to get them out in 15 days. Still, Furtado acknowledged that about 150 PLWA die each year at the hospice and an unknown number die after they have left. Furtado expressed skepticism about placing hospice residents on antiretrovirals unless sustainability was guaranteed.

Founded in 1885 as India's first leper hospital, Niramay Niketan still houses 40 people suffering from leprosy. The stigma and suffering of untreated AIDS patients holds interesting parallels to earlier leper and TB sanatoria, while today, despite the fact that cheap and effective remedies exist, 98% of AIDS patients in Mumbai and throughout the country are abandoned to die.

The Neketen AIDS programme began in 2002 in a new building constructed with donations obtained by Furtado, and the entire project including leprosy and AIDS care, functions on a budget of US \$5,000 per month.

Furtado, although he has directed the project since its opening, was completely unaware of the Global Fund or the money sitting unused in Dehli and Geneva. Nor had he been told about the possibility of applying for a 5th round grant.

Furtado mentioned that there is a great shortage of staff at the centre but indicated that part of the problem is that there are not enough qualified nurses who are willing to work with PLWA.

Since my visit coincided with lunchtime, nurses and assistants were busy serving ample portions of food to the residents. Two wide-eyed, but emaciated children, perhaps 5 years old, stared at the pale-faced intruder.

Each of the five AIDS units has its own TV and the centre is immaculately clean, in spite of the staff shortages. Furtado proudly mentioned that his institution has always been willing to accept "eunuchs" as transgendered people are known in India.

Sex workers condemned to death

Interestingly, at the JJ Hospital Centre treatment programme, only four women out of 600 enrolled in the programme are sex workers, even though Mumbai's infamous red light district is just three kilometers from the hospital. An estimated 8,000 sex workers are HIV-positive. According to one source, when sex workers begin to be ill, the men who run the brothels send them back to their home villages to die. They avoid sending them to the hospital for fear that the authorities might obtain information about illegal activities from the sick women.

In another AIDS hospice, Jyothis Terminal Care, 50 kilometers north of Mumbai, the Director, Mrs Bede, informed me that all 73 available beds were filled. Only four of 73 PLWA have ARVs, those four as a result of donations made to the hospice, Mrs Bede confirmed that hospice records showed that of 800 people who were admitted to the hospice during the past five years, 400 are known to have died, but no information is available on several hundred others who eventually left the hospice. Fewer than 100 are known to be alive.

I asked Dr Vasvani why no attempt was being made to utilise the hospices for disbursement of antiretrovirals, given the fact that both Jyothis and Neketen have physicians and nurses on staff. He replied: "You have to move slowly with these kinds of things." In fact, in Mumbai there seems to be no shortage of infrastructure available in the health care system, an issue frequently referred to as an obstacle in sub-Saharan African countries and rural areas. But in Mumbai, doctors and clinics abound and with the funds that should be flowing, could be enlisted in ARV roll-out programmes.

While I was in India, a large paid advertisement appeared in one of Mumbai's English language newspapers (*Mid-Day*) soliciting proposals from NGOs for the fifth round of Global Fund projects, but no such announcement appeared in any Hindi papers. It is estimated that 95% of PLWA in India speak no English, but many NGO directors as well as most government officials are fluent in English. No mention was made in the advertisement for proposals related to care and treatment. Global Fund projects are country driven, according to Global Fund board mandates, so there will be no intervention by the Fund to mandate proposals that would focus on access to ARVs for PLWA. With all the delays in disbursement of funds in previously approved grants, it is questionable why India would even be applying for a Fifth Round grant.

Country coordinating mechanism fails PLWA

Obviously the CCM in India is a lot better at writing lucrative proposals than at implementing them. One wonders if the CCM should not be devoting its efforts to implementing current proposals, and what the real motivation is for soliciting Fifth Round grants from a plethora of NGOs. Perhaps the promise of money strategically delivered to some leading NGOs by the CCM may actually discourage meaningful activism, because some NGOs become reluctant to place pressure on the various agencies involved for fear of losing their funding.

Whereas most NGO directors we spoke to tended not to be overly critical of the AIDS treatment roll-out, one PLWA told me through an interpreter: "You are in India, but you don't understand. To the Indian government, people living with AIDS are unwanted. They would happily be rid of us."

India has long been a centre of international activism as a result of various Indian generic companies which produce ARVs that are exported throughout the world at cheap prices. While I was in India the new Patent Act was passed despite the strong protests of Indian as well as international activists. This law may have significant long-range impact on the exportation of these drugs. There was major coverage in the press regarding the Patent Act. But, over the years with all the attention focused on the Indian generic companies little or no attention has been focused on the fact that 98% of all Indians themselves lack access to the inexpensive ARVs that are manufactured by numerous companies in their own country.

I obtained the detailed minutes of the regular monthly ARV scale up meeting held in New Delhi on 3 February of this year,

and attended by WHO, and NACO employees, as well as many international donor sources and civil society groups. Even as government representatives were explaining the newly reduced goals in terms of scaling-up, no mention appears anywhere in the minutes of the untapped Global Fund resources.

Lethal Global Fund policies

The Global Fund's own "country driven" orientation, which mandates only minimal intervention in national decision-making regarding fund implementation is inextricably linked to the "genocidal" bureaucracy that is apparent in India. It is clear that neither the CCM nor the Principal Recipient in India is concerned about the fact that nearly 100,000 people may have died of AIDS since the Fourth Round grant was approved. But the Global Fund does not intervene (because of its "board policies") to implement project safeguards that would stop the deaths of Indian PLWAs and get treatment to them. So the Indian CCM and Principal Recipient feel little or no pressure from the funding source to fulfill their obligations in a way that would be congruent with the life or death urgency of the situation. Ultimately it is the Global Fund and the National AIDS programme that are failing the multitudes of poor Indians who need treatment.

One of only three civil society Global Fund board members worldwide works in New Delhi at a large international agency, but even her presence at the heart of where the struggle should be, seems to have generated little or no impact.

The Global Fund continues to describe itself as a funding source only, and also as more of a "bank" than an implementing agency. This is distressingly accurate. Just the interest on \$140 million dollars sitting in a Swiss bank for a year, at 6% interest, would yield about \$8 million, enough money to purchase ARVs for 40,000 PLWA for one full year at current prices.

Current Status of India's Global Fund Grants that Focus on AIDS Treatment, April 2005

(Please note that approximately 200,000 People have died of AIDS in India since the Round Two grant was approved, approximately 80,000 of these have died since the Round Four grant was approved.)

Project title	Date approved	Amount approved and available for the five year grant	Amount disbursed as of April, 2005
HIV prevention and care for PLWA through scaling up PMTCT services and public/private ARV treatment	January, 2003 (Round 2) 28 months ago	\$100 million	\$4.7 million
Acces to Care and Treatment	June 2004 10 months ago (Round 4)	\$140 million	\$800 million
Totals		\$240 million	\$5.5 million

*\$122 million of this amount is available to the government for treatment access, and \$18 million is for an NGO consortium that will not be providing treatment.

**\$800,000 has been disbursed to the NGO consortium, but not for ARV access.

Richard Stern is Director of the Agua Buena Human Rights Association, Costa Rica

rastern@racsa.co.cr

www.aguabuena.org

ANTIRETROVIRALS

Draft BHIVA treatment guidelines online for comment

The 2005 revision of the UK treatment guidelines produced by the British HIV Association (BHIVA) have been posted to the BHIVA website in draft format for comment.

The BHIVA Treatment Guidelines for 2005 are prepared by a writing sub-committee, who jointly take responsibility for the recommendations, which are based on published data and evidence-based medicine. The guidelines are updated to reflect

the latest findings and are subject to a consultative procedure that encourages comments from its membership, community organisations and pharmaceutical companies.

<http://www.bhiva.org>

PAEDIATRIC CARE

US guidelines on paediatric care updated

The American Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection were updated on 24 March 2005. The appendix, '*Characteristics of available antiretroviral drugs*' has been extensively modified to include up-to-date drug information, including updated information about paediatric dosing and new drug formulations.

The updated appendix also includes a matrix based on Table 18 in the Adult Guidelines (adverse drug reactions) and three matrices based on Tables 19-21 in the Adult Guidelines (drug interactions between antiretrovirals and other drugs).

The paediatric guidelines were developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, which reviews new data on an ongoing basis and provides regular updates to the guidelines.

The updated guidelines document is available in the Paediatric Guidelines section of the Guidelines page on the AIDSinfo site:

http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=51

<http://aidsinfo.nih.gov>

C O M M E N T

There are so few changes to these guidelines that anyone who has already printed either the January 2004 or November 2004 guidelines would do better to save their paper, and just note the few new additions.

If this is the first time you have looked at the document, then it does contain a wealth of background information and references. that form a useful resource This latest version however is virtually unchanged: the only differences appear to be in the Appendix listing 'Characteristics of Available Antiretroviral Drugs' that now include links to Black Box Warning matrices for various drugs, particularly abacavir; and half a dozen references have been removed.

Interestingly no publications from 2004 appear to have been reviewed for the 2005 guidelines, not even Katherine Luzuriaga's NEJM paper recommending 4-drug, PI-containing therapy for infants.

The indications for starting treatment in children less than or more than 12 months of age are unchanged. This is despite inclusion in Table 3 and Figures 1-4 of the HIV Paediatric Prognostic Markers Collaborative Study Group (HPPMCSG) data that clearly show that the CD4% cut-offs should be higher in younger infants and lower in older children. [1]

Please refer to the current PENTA guidelines for a discussion as to how these data can be used in practice. [2]

Striking differences persist in prescribing habits between the US and Europe, particularly with regard to the use of abacavir as part of first line therapy for children. These guidelines will not change these discrepancies. There is no discussion of the pros and cons of treatment interruptions in children.

Hopefully the next version of the guidelines will include a reflection on the data from the HPPMCSG and will acknowledge that judiciously delaying initiation of treatment may be in the best interest of selected children.

References

1. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet* Nov 2003; 362: 1605-11.
2. Castelli-Gattinara G et al. 2004 PENTA guidelines for the use of antiretroviral therapy in paediatric HIV infection. *HIV Medicine*, July 2004 (Volume 5, Supplement 2). Available to download free at:
<http://www.pentatrials.org>

HEPATITIS COINFECTION

UK guidelines for liver transplant in HIV-positive patients

These guidelines, written on behalf of the British HIV Association (BHIVA) and The UK and Ireland Liver Transplantation Centres, and reviewed and endorsed by British Transplantation Society Standards Committee, are now published on the BHIVA website, and are available to download as pdf and Word documents.

This document was written following a consensus meeting of specialists in the field of HIV and liver transplantation in June 2004.

<http://www.bhiva.org>

Sexual HCV reinfection of HIV-positive gay man while receiving PEG-interferon plus ribavirin

Simon Collins, HIV i-Base

Although sexual transmission of HCV occurs in <1% of monogamous heterosexual couples who do not use condoms, an increasing number of cases of transmission to HIV-positive gay men has been reported in the UK over the last two years. Transmission in these cases is linked to anal intercourse without using condoms, multiple partners, active and receptive fisting, and recreational drug use. [1]

Sexual transmission of HCV to HIV-negative men has not been reported, but it has not been established whether HIV plays a role in these cases of transmission or whether transmission related to a highly infectious pathogen being exposed during higher risk activities to groups of men who already decide to only have sex with other HIV-positive partners.

A letter in the 8 April issue of AIDS from den Hollander and colleagues from the South Rijnmond Medical Centre in Rotterdam describes the case of patient who was sexually reinfected with a different HCV strain while receiving pegylated-interferon plus ribavirin treatment for his initial acute HCV infection. [2]

This patient, diagnosed with HIV since 1998, seroconverted to HCV genotype-1 between January and May 2003, with a HCV-RNA load up to 1.92×10^9 copies/ml. HCV testing was prompted after elevated AST failed to normalize after switching nevirapine to lopinavir/r, and he mentioned participation in group sex parties where one of the other participants was HCV-positive. From 1998 to 2004 he was treated for several sexually transmitted diseases (gonorrhoea, syphilis, rectal lymphogranuloma venereum).

Treatment with PEG-IFN-alpha 2a, 180 ug/week and ribavirin 1000 mg/day was started, and lopinavir/r/3TC/tenofovir was continued. HCV RNA was cleared after 12 weeks and AST levels normalised. At month 13, still on PEG-IFN/ribavirin therapy, AST levels increased and HCV RNA became detectable. Genotyping showed HCV genotype-2. The patient admitted he had participated in one more 'fist-fucking' party at month 11 in Berlin. The patient denied IVDU at any time.

The letter reports that this is the first case of reinfection during HCV treatment, and that PEG-IFN and ribavirin did not prevent infection with HCV.

C O M M E N T

There are a number of comments to this study that are worth making in addition to the conclusions of the authors.

Firstly, there was a good response to PegIFN and RBV despite HIV co-infection and genotype-1 infection

Secondly, re-infection was the most likely cause of the second surge of HCV viraemia (different genotype) and that pegIFN did not protect against this, reflecting the patient's susceptibility to HCV infection probably related to HIV induced immune suppression.

Finally, the important conclusion must be to spread the 'safe sex' message and increase awareness with regard to mucosal traumatic 'sexual' transmission of HCV in this group of patients and the importance of continuing to offer early treatment to prevent long-term progression to end-stage liver disease and HCC.

References

1. Danta M, Brown D, Bhagani S et al. Evidence for sexual transmission of HCV in recent epidemic in HIV-infected men in South-East England. 11 BHIVA Conference, 20-23 April 2005, Dublin. Oral Abstract 25.
2. den Hollander JG, Rijnders, BJ; van Doornum, GerardJJ et al. Sexually transmitted reinfection with a new hepatitis C genotype during pegylated interferon and ribavirin therapy. Letter in AIDS: Volume 19(6) 8 April 2005 p 639-640.

First European recommendations for the treatment of patients co-infected with HIV and HBV/HCV

The following is an edited version of a press release from the European Consensus Conference

The First European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV Co-infected Patients, which was held in Paris in March, ended with the adoption of recommendations on treating patients using the best therapeutic protocols available.

The two day conference attracted more than 950 participants and brought together leading European and North American specialists on AIDS and liver disease. On the basis of the presentations, discussion and debate, a jury of ten physicians from eight European countries, presided by Professor Alfredo Alberti from Italy and Professor Nathan Clumeck of Belgium, drew up the recommendations. "Our goal is to ensure that a consistent therapeutic approach is adopted at the European level, and to increase the number of patients who are diagnosed and treated," said Professor Clumeck. "Today there is too much variation from one country to another. Our recommendations are adapted to the European context, both in terms of the patients and the health care systems."

Co-infection with HIV and the HCV or HBV is common: more than one quarter of HIV-positive individuals are infected with HCV and nearly 10% with HBV. The increased life expectancy of HIV-positive patients has brought to the fore the problem of hepatitis, a disease that progresses relatively slowly. Cirrhoses and liver cancer due to hepatitis C have become the number one cause of mortality among AIDS patients. For these patients, hepatitis C develops into cirrhosis in five to ten years on average, compared to 30 or so years for the general population.

Such co-infections are especially common in certain high-risk groups, especially IV drug users (in this group, 90% of HIV-positive patients might be infected with HCV or HBV), and among immigrants. Treatment of co-infections is therefore doubly complex: first, because treating two viruses simultaneously requires choosing the right combination of medicines, and second, because patients in the most widely affected groups need particular psychological and social support to help them adhere to the treatment regimen despite the side effects and the constraints of taking pills regularly.

The recommendations concern two main areas:

1. Overall patient care:

Routine treatment of the hepatitis C virus should be adopted since today there are drugs that can eliminate the virus in 15 to 60% of patients depending, in particular, on the viral genotype. Treatment for HBV does not eradicate the virus, but can prevent progression toward liver disease. At the European level, only a small minority of patients are treated for hepatitis viruses. Multidisciplinary teams composed of doctors, psychologists, social workers and patients' organisations must provide support for patients to ensure treatment adherence and observance.

A multidisciplinary approach is also necessary for alcoholic patients, since alcoholism aggravates hepatitis B and C.

Patients infected with HIV but not HCV or HBV should be vaccinated against these viruses. If their immune status is too weakened for vaccination to be effective, the vaccine should be given following the implementation of anti-retroviral treatment for HIV and once the immune defenses have been built up.

Prevention campaigns must be organised to stop the transmission of HCV and HBV, especially through vaccination and with programmes specially targeting IV drug users (to avoid needle sharing, for example), since the prevalence of these viruses is on the rise.

2. Therapeutic protocols:

Protocols differ for HCV, which can be eliminated, and for HBV, for which drugs can only slow or stop progression of the disease.

HIV/HCV: Treatment consists of a combination of pegylated interferon and ribavirin. The consensus meeting recommends increasing the dose of ribavirin among patients infected with genotype 1 HCV, which is more resistant to treatment than the other genotypes. After the first three months of treatment, efficacy can be assessed to determine whether or not to continue to the end of the treatment period (48 weeks).

HIV/HBV: Antiviral compounds are effective against both HIV and HBV, but they are complex to administer because both viruses may develop resistance to the drugs. The choice of which combinations to use must be made according to identifiable resistance and the specific biological parameters of each patient.

For patients whose immune system has been significantly depressed (low CD4 counts), antiretroviral treatment for HIV must first enable the CD4 count to rise, before treatment for HCV can begin.

There is a need for further studies to better understand the natural progression of co-infections and to determine exact treatment dosages and durations. Data about infection with HBV and HIV/HBV co-infection is especially lacking. One of the pressing questions that must be addressed is whether or not to continue HBV treatment, perhaps with reduced doses, when the viral response is not very satisfactory, in order to slow progression toward liver disease or the worsening of hepatitis B

disease. The members of the jury also recommended that studies to evaluate new drugs currently under development be conducted at an earlier stage among patients co-infected with HIV and hepatitis B and C viruses.

These recommendations are now published in the May 2005 issue of Journal of Hepatology.

OTHER NEWS

Newly acquired HIV infections are key to transmission

Graham McKerrow, HIV i-Base

The rate of HIV transmissions in heterosexual sex was highest during early-stage infection, in a retrospective study of 235 monogamous, HIV discordant couples in a Ugandan population-based cohort. [1] Observers are already pointing to the study as evidence for the need for new approaches to HIV prevention strategies and the authors themselves conclude that their findings have implications for HIV prevention and for projecting the effects of antiretroviral treatment on HIV transmission.

The US-Ugandan study enrolled 15,127 adults into a community randomised trial of STD control for AIDS Prevention in the Rakai district of Uganda. Wawer and colleagues retrospectively identified 235 monogamous HIV discordant couples and estimated rates of transmission per coital act by the index partner's stage of infection – recent seroconversion, prevalent or late-stage infection - and the adjusted rate ratio of transmission per coital act was estimated by multivariate Poisson regression.

After seroconversion of the index partner, the rate of transmission (0.0082 per coital act) within the first 2.5 months was almost 12-fold higher than that observed in the prevalent index couples (0.0007 per coital act). The rate increased significantly again at about two years before the index partner's death.

The overall rate of transmission observed in these couples is consistent with previous estimates from Rakai, Europe and North America, but this analysis provides the first empirical data on the substantial variation in transmission by stage of infection.

The data were collected from stable, heterosexual couples, whose primary risk was through vaginal intercourse, and additional studies are required to examine transmission by stage of infection in other epidemic settings. "Nonetheless, our data have a number of clinical and epidemiological implications," write the authors

The highest rate of transmission per coital act and the highest proportion of transmissions occurred at a time when few seroconverters know their HIV status or receive antiretroviral treatment. "Thus," write Wawer and colleagues, "ART, initiated relatively late during infection, under current guidelines, may have only a modest impact on HIV transmission. Also, because most HIV transmissions occur before index cases are eligible to receive ART, the heterosexuals spread of drug-resistant HIV may be modest in this population. Measures that prevent primary HIV infection or reduce early viraemia (as may occur with HIV vaccines) are likely to have a greater effect than ART on the spread of HIV."

They also draw attention to the advantages of increasing efforts to identify people with early-stage infection in order to promote safer behaviour and to consider the provision of treatment.

An editorial commentary in the Journal of Infectious Diseases says: "Wawer et al have confirmed the remarkable threat of HIV transmission posed by people with newly acquired HIV infection. The challenge now is to waste no time in finding the most creative strategies to incorporate these results into global HIV prevention efforts." [2]

Both the editorial commentary and the full article are available on-line as free articles.

C O M M E N T

The point of including this article was not to suggest that antiretrovirals should be used to slow down transmission on an epidemiologically relevant level. Condoms are still the best and most and cost effective approach with any stage of HIV-infection; the primary focus of antiretrovirals is always to treat HIV-positive patients for their own healthcare.

It does however provide important data to support what forward thinking clinicians and prevention workers have realised for a long time: that a key driving force behind the epidemic is the behaviour of recently infected, undiagnosed individuals, who consider themselves HIV-negative, and behave as such, while in fact being the most highly infectious group in the population.

Recent behavioural studies – including a study presented at the BHIVA meeting in Dublin – show that receiving an HIV diagnosis leads to more extensive behaviour change towards protecting partners of unknown status than any other intervention. [3]

References:

1. Wawer M, Gray R, Sewankambo N et al. Rates of HIV-1 Transmission per Coital Act, by Stage of HIV-1 Infection, in Rakai, Uganda. The Journal

of Infectious Diseases 2005;191:1403-1409

<http://www.journals.uchicago.edu/JID/journal/issues/v191n9/33445/33445.html>

2. Cohen M and Pilcher C. Editorial Commentary: Amplified HIV Transmission and New Approaches to HIV Prevention. The Journal of Infectious Diseases 2005;191:1391-1393
<http://www.journals.uchicago.edu/JID/journal/issues/v191n9/34190/34190.html>
3. Fox J, McClure M, Weber J et al. Risk factors for the acquisition of HIV in individuals known to have recently seroconverted. 11th BHIVA Conference, 20-23 April 2005, Dublin. Oral abstract O15.

Calls to i-Base phonenumber now free from Orange mobile networks

Mobile phone network Orange has announced that it will not charge contract or pay as you go customers to call freephone helplines who are members of the Telephone Helplines Association (THA) – which includes the i-Base treatment information phone service.

Although Orange previously had a policy that they did not charge contract customers to call any freephone number, pay as you go customers still faced hefty charges for calling freephones - and that included charity helplines. Orange has now confirmed that although contract customers will in future be charged to call commercial freephone numbers, all of its customers will now be able to call any freephone helpline that is a member of the THA and their call will not be charged nor itemised.

The i-Base phone number is on 0808 800 6013 and can offer information in English or French, usually provided by positive treatment advocates, and is open Mondays, Tuesdays and Wednesdays from noon to 4pm.

Request for overseas volunteers

The following was received from Katie Graves-Abe, a Programme Coordinator at The International Centre for Equal Healthcare Access (ICEHA).

I am writing to you to request your assistance in recruiting volunteer physicians and nurses to improve the capacity for providing care to HIV-infected patients in developing countries.

ICEHA is a non profit organisation of physicians and nurses who volunteer their expertise on HIV care and infectious diseases to clinics in developing countries. ICEHA's volunteers equip local healthcare professionals with the skills needed to take care of their own patients and enable developing countries to fight the HIV epidemic from within. ICEHA is always in need of new healthcare providers to volunteer in our programmes overseas.

As part of an effort to recruit more volunteers, we are contacting reputable publications that cater to healthcare providers to see if they can help get the message of these volunteer opportunities out to potential volunteers.

More information about ICEHA is available on our website:

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

ON THE WEB

Conference reports:

Community impact of New York case of HIV infection with multidrug-resistant dual-tropic HIV-1 and rapid progression to AIDS

Ben Cheng, MS

<http://clinicaloptions.com/hiv/ev/2005-3-cheng.asp>

Community newsletters and journals:

PRN Notebook

http://www.prn.org/prn_nb_cntnt/current.htm

Can the HIV/AIDS Epidemic in New York City Be Stopped? - Thomas R. Frieden

Use of Androgens in HIV-Infected Men and Women - Steven K. Grinspoon

Lipodystrophy: What's Going On? - Donald P. Kotler

Advances in Immune-Based Therapies for HIV Disease - Laura A. Napolitano,

The President's Emergency Plan for AIDS Relief - Mark Dybul,

ACRIA Update – Substance use and HIV

Spring 2005 - Vol. 14 No. 2

http://www.acria.org/treatment/treatment_edu_springupdate2005.html

- **Substance use and HIV**
- **HIV care and treatment as harm reduction**
- **Much ado about meth**
- **Drug interactions: HIV medications, street drugs and methadone**
- **Personal perspective: living with(out) crystal meth**
- **Drug use: the effect on HIV progression, adherence and the relationship with medical providers**
- **Buprenorphine: the new kid on the block**

Integration of buprenorphine into primary HIV care

Report from the Forum for Collaborative HIV Research

Opioid dependence and HIV both represent serious public health threats to the US. The Drug Addiction Treatment Act of 2000 allowing prescription of Schedule III-V drug dependence treatment medications in office-based practices, and the approval of buprenorphine and buprenorphine/naloxone provide promising new directions for the treatment of opioid addiction and particularly, for improved care of patients with HIV-infection *and* opioid dependence. However, the integration of buprenorphine into HIV primary care has not been as rapid or extensive as expected.

The Forum for Collaborative HIV Research convened experts in HIV medicine and/or opioid dependence treatment from academia, community and private practices, patient community, US government agencies and industry to review issues associated with the integration of buprenorphine into HIV primary care, identify barriers to this integration and develop recommendations for increased uptake of this new opioid treatment modality into HIV primary care settings.

The report may be downloaded from:

<http://www.hivforum.org/uploads/Buprenorphine.pdf>

For workshop presentations, please see:

<http://www.hivforum.org/projects/Buprenorphine.htm>

For hard-copy requests, please contact: ipsitad@gwu.edu

<http://www.hivforum.org>

Online medical resources:

HIV inSite Knowledge Base

Updated resources from April 2005.

Community-based care in the developing world

<http://hivinsite.ucsf.edu/InSite?page=kbr-03-03-07>

Women and HIV

<http://hivinsite.ucsf.edu/InSite?page=kbr-03-01-12>

Pregnancy and prenatal care of women with HIV

<http://hivinsite.ucsf.edu/InSite?page=kbr-03-01-13>

Primary care of infants and children with HIV

<http://hivinsite.ucsf.edu/InSite?page=kbr-03-01-14>

Malaria and HIV

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

Pneumocystosis and HIV

<http://hivinsite.ucsf.edu/InSite?page=kb-05-02-01>

The science of HIV vaccine development

A collection of material about policy and scientific issues in HIV vaccine development.

<http://hivinsite.ucsf.edu/InSite?page=kbr-02-01-06>

PUBLICATIONS AND SERVICES FROM i-BASE

i-Base website redesigned

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

The website has been totally redesigned so that it is faster and easier to use, and is more accessible for those with impaired sight. For those who understand these matters, all pages conform to at least the W3C-WAI Level A and most to level AAA.

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

All i-Base publications are available at our website, including 2005 editions to three treatment guides. The site gives details about i-Base, the UK Community Advisory Boards (UK-CABs), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as pdf files).

An average of almost 1700 pages a day are served from the site.

i-Base distribution figures

In March and April, individuals and organisations ordered from i-Base:

- 161 *Adherence Support* pads;
- 942 copies of *Guide to Changing Treatment: What to do if Your Treatment Fails*;
- 785 copies of our *Guide to HIV, Pregnancy and Women's Health*;
- 1363 copies of our *Introduction to Combination Therapy*;
- 1693 copies of the *Guide to Avoiding and Managing Side Effects*, and
- 1,267 *Treatment Passports*.

In the same month we received 179 new orders for *HIV Treatment Bulletin* on top of the 4,229 regular print subscriptions and 1,066 email subscriptions.

UK-Community Advisory Board: reports and presentations

The UK-Community Advisory Board (UK-CAB) is a network for community treatment workers across the UK. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

Reports and presentations for the ninth meeting, held on 31 May 2004, are posted to the i-Base website and are available in printed format. The training session at this meeting included an introduction to the immune system, a summary of community involvement in UK-based research into vaccines, microbicides and other new prevention technologies, an introduction the International AIDS Vaccine Initiative, an update on post-exposure prophylaxis and updates on microbicides.

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

Transcriptions and slides of training sessions from previous meetings also on the site include:

- An introduction to statistics, by Dr Caroline Sabin
- Genetics, resistance and HIV - Professor Clive Loveday
- Approaches to Salvage Therapy - Dr Mike Youle
- Pregnancy, HIV and Women's Health - Dr Karen Beckerman
- Fertility treatment and sperm-washing - Dr Leila Frodsham
- Access to treatment for UK visitors, refugees and asylum seekers - Linda McDonald
- Resistance, Lipodystrophy and IAS Report - Simon Collins
- TB and HIV coinfection - Dr Anton Pozniak

World CAB: International drug pricing

Report from a meeting in February 2004 of community advocates and three major pharmaceutical companies that focussed on pricing issues and global access to treatment.

Available to download as a pdf file. See website below

Introduction to Combination Therapy

June 2004 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 pdf versions of this booklet are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish.

Guide to HIV, pregnancy & women's health

New 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 you are on therapy or not and includes information for your own health and for the health of your baby.

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

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

New 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 your treatment fails.

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

Guide to avoiding & managing side effects

New 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.

It is written by people who are HIV-positive, who have been on most of the treatments, who have had many of the side effects and who have learnt to negotiate their own healthcare.

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.

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 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.

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

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

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

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

h-tb

HIV Treatment Bulletin

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

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

by sending an email to:

subscriptions@i-base.org.uk

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

Editor in Chief: Paul Blanchard

Editor: Simon Collins

Associate Editor: Graham McKerron

Commissioning Editor: Polly Clayden

Medical Consultants:

Dr Sanjay Bhagani, Royal Free Hospital, London.

Dr Karen Beckerman, Bellevue Hospital, New York.

Dr Gareth Hardy, Royal Free Hospital, London.

Dr Saye Khoo, University of Liverpool Hospital.

Prof. Clive Loveday, International Laboratory Virology Centre.

Dr Graeme Moyle, Chelsea & Westminster Hosp, London.

Dr Stefan Mauss, Düsseldorf.

Dr Graham P Taylor, Imperial College, London.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

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

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

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

Articles written and credited to i-Base writers, as with all i-Base originated material, remains the copyright of HIV i-Base, but these articles may be reproduced by community and not-for-profit organisations without individual written permission and reproduction is encouraged. A credit and link to the original author, the HTB issue and the i-Base website is always appreciated.

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies. All editorial policies are strictly independent of funding sources.

HIV i-Base

Third Floor East

Thrale House

44-46 Southwark Street

London SE1 1UN

T: +44 (0) 20 7407 8488

F: +44 (0) 20 7407 8489

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

**HIV i-Base is a registered charity no 1081905
and company reg no 3962064.**

HTB is also known as DrFax



HIV i-Base

All publications are available free or charge including bulk orders because any charge would limit access to people who most need this information.

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

STANDING ORDER DONATION

THANK YOU FOR YOUR SUPPORT

Title: _____ First Name _____ Surname _____

Address _____

_____ Postcode _____

Email _____ @ _____

Telephone (s) _____

Please pay HIV I-Base £ _____ each month until further notice

Please debit my account number _____

Name of account (holder) _____ Bank sort code ____/____/____

Starting on ____/____/____ (DD/MM/YY)

Signature _____ Date ____/____/____ (DD/MM/YY)

To: Manager: (Bank name, branch and address)

Please complete the above and return to: HIV I-Base, 44-46 Southwark Street, London SE1 1UN

(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA, Sort Code 60-12-14. Account Number: 28007042)

ONE-OFF DONATION

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

GIVE AS YOU EARN

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

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

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.

HIV i-Base

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



Subscription Fax-Back Form

Please use this form to amend subscription details for HIV Treatment Bulletin (DrFax) and to order single or bulk copies of other publications. *All publications are available free, but if you would like to make a donation please use the form on the inside back page.* i-Base currently receives no health authority or statutory funding.

Name: _____ Position: _____

Organisation: _____

Address: _____

Tel: _____ Fax _____

E-mail: _____

I would like to make a donation to i-Base - **Please see inside back page**

HIV Treatment Bulletin (HTB) by Email (PDF format) by Post

HIV Treatment 'Passports' - Booklets for patients to record their own medical history

1 5 10 25 50 100 Other _____

Guide To HIV, Pregnancy and Women's Health (Spring 2005)

1 5 10 25 50 100 Other _____

Introduction to Combination Therapy (June 2004)

1 5 10 25 50 100 Other _____

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

Changing Treatment - What To Do If Your Treatment Fails (April 2005)

1 5 10 25 50 100 Other _____

Guide To Avoiding and Managing Side Effects (February 2005)

1 5 10 25 50 100 Other _____

Also available in SPANISH as a print version and in FRENCH, SPANISH, ITALIAN, CHINESE as pdf files on the i-Base website

Paediatric HIV Care - March 2001 - Report from i-Base Paediatric Meeting

This 44-page comprehensive report is now only available in pdf format and on the i-Base website.

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

1 5 10 Other _____

Office use:

Please fax this form back or email a request to HIV i-Base:

020 7407 8489 (fax) subscriptions@i-Base.org.uk

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