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CONTENTS

(hyperlinked)

EDITORIAL 2
CONFERENCE REPORT 2
XIII International HIV Resistance Workshop, 8-12 June 2004, Tenerife, Canary Islands
- Clear risk of NNRTI-resistance during STI: implications for SMART study
- Persistent nevirapine resistance following mother to child transmission interventions
- Tipranavir resistance and viral response: L90M did not reduce response, recommendation to use with T-20
- Resistance in the UK: new approach to epidemiological studies
- Low AZT activity against HIV-2 infection
- No evidence for cross resistance between nevirapine and d4T
- Case of MDR reinfection with MDR virus
- Experimental compounds to target viral expression in latent cells

CONFERENCE REPORT 11
Keystone HIV Pathogenesis and Vaccine Development Conference, 12-18 April 2004, British Columbia, Canada
- Keystone HIV Pathogenesis and Vaccine Report

TREATMENT ACCESS 18
- A round-up of news about access to treatments, with links to sources

ANTIRETROVIRALS 22
- CD4 entry criteria dropped for UK tipranavir named-patient access
- Tenofovir/FTC co-formulation expected in US by September
- Guidelines for T-20 (Fuzeon)
- Persistent HIV viraemia fosters immunologic harm and viral evolution
- Latent drug-resistant HIV harboured for years

DRUG INTERACTIONS 24
- Non-prescription simvastatin in the UK: contraindicated with many HIV medications
- Label changes for indinavir warn of several interactions including atazanavir and PDE5 inhibitors

WOMEN'S HEALTH 25
- Smoking during HIV infection may alter the natural history of HPV infection and increase the risk of cervical disease

PAEDIATRIC CARE 26
- Pharmacokinetic characteristics of ritonavir, zidovudine, lamivudine, and stavudine in children with HIV

PRIMARY INFECTION 26
- Sexual transmission of HIV by acutely infected individuals has a disproportionate effect on the spread of HIV and may explain the current pandemic

ON THE WEB 27
MEETING ANNOUNCEMENTS 28
PUBLICATIONS AND SERVICES FROM i-BASE 29

EDITORIAL

This issue includes reports from the recent resistance meeting in Tenerife – in which we include reviews of the research with the relevance to clinical practice – and Gareth Hardy provides an overview of the highly specialised Keystone meeting that took place in April.

We also round up some of the recent developments in international access to treatment. In the meantime, alarms were raised following the announcement on May 27th that the WHO had removed two Cipla products from its prequalification list: 3TC, manufactured as Lamivir and the AZT/3TC fixed dose combination, manufactured as Duovir, due to concerns over a bioequivalence study.

Although a gift to many detractors of generic antiretrovirals, a spokeswomen from MSF explained: "The fact that there is ongoing monitoring of drugs on the prequalification list by the WHO should be seen as a sign of an efficient process", Cipla must submit new data and we should expect a result by the end of July.

Our next double issue will be August/September and will cover the World AIDS Conference taking place in Bangkok from 11-16 July. The programme for this meeting is now online at:

http://www.ias.org

CONFERENCE REPORTS

XIII International HIV Resistance Workshop

8-12 June 2004, Tenerife

Simon Collins, HIV i-Base

This annual resistance meeting is an opportunity for over 200 key researchers to focus on current research into resistance and always provides some of the most interesting and important new data. Community, press and clinician attendance at this meeting is far more restricted than most other meetings.

The breadth of the meeting addressed in vivo research into cellular resistance to HIV replication and viral mutations driven by immune escape, in addition to specific complexities associated with resistance driven by drug pressure. A clear objective of the meeting is to move forward our understanding of the diversity, complexity and relevance of viral evolution and potential areas of future research.

Although there is a strong focus on preclinical and in vitro work, many of these studies have implications for clinical practice. As with HTB reports from previous meetings, this years' reports will also largely focus on those studies with the most important relevance for current clinical practice.

These include:

- Clear risk of NNRTI-resistance during STI: implications for SMART study
- Persistent nevirapine resistance following mother to child transmission interventions
- Tipranavir resistance and viral response: L90M did not reduce response, recommendation to use with T-20
- Resistance in the UK: new approach to epidemiological resistance
- Low AZT activity against HIV-2 infection
- No evidence for cross resistance between nevirapine and d4T
- Case of MDR reinfection with MDR virus
- Experimental compounds to target viral expression in latent cells

The abstracts and programme for this meeting are due to be posted to the conference website. This usually takes a few weeks, but encouragingly most of the full posters also become available online.

http://www.informedhorizons.com

Early reports from the meeting, including selected abstracts and some full text studies, are already posted to the NATAP website:

http://www.natap.org

Unless otherwise stated, all references in these reports are to the Abstracts and Programme of the XIII International HIV Resistance Workshop, 8-12 June 2004, Tenerife.

Clear risk of NNRTI-resistance during STI: implications for SMART study

Simon Collins, HIV i-Base

Several studies addressed the risk of resistance to NNRTIs developing during structured treatment interruptions (STIs).

Interest in two strategies using STIs: stimulating stronger HIV specific immune responses, and reselecting for wild-type virus prior to salvage therapy, is now largely reduced. However, various trials are underway that cycle treatment in order to reduce both toxicity and costs associated with long-term chronic treatment.

The largest of these is the international SMART study in which HAART is initiated and discontinued by CD4 count and response. This study is now recruiting patients in the UK. Several studies at the rsistance meeting provided important information that should inform patient management in this study.

Mireia Arnedo and colleagues from the University of Barcelona analysed baseline and post-interruption drug resistance in both plasma and proviral DNA, from 112 STI cycles in 35 patients from four clinical studies. All drugs were stopped at the same time.

Overall, 9/35 (26%) patients selected resistance mutations during 20/112 (18%) cycles just of half of which were not detectable at baseline in plasma or proviral DNA. Half the patients using 3TC and a quarter using NNRTIs showed resistance, approximately half of which were new mutations. Detailed results are shown in the table below.

New or archived mutations in four STI studies:

	Total	New	Archived
RTI (exc-184V)	6% (2/35)	3%	3%
RTI M184V	50% (9/18)	22%	28%
NNRTI	23% (3/13)	23%	0
PI	0%	0	0
Total	26% (9/35)	14%	12%

Results were also presented from a subgroup of eight patients who had genotypic and phenotypic samples tested at maximum levels of viral rebound, and these showed a good correlation between measures.

Lucia Palmisano and colleagues from Istituto Superiore di Sanita, Rome, presented further analysis from a large Italian study that randomised patients on successful HAART to either continue treatment of follow a course of four interruptions (of 1, 1, 2 and 2 month duration) at three month intervals.

Virological resistance occurred in 18% of the STI arm. Samples from a subgroup of 49 patients, with PBMC samples at baseline, half of whom developed resistance during the study were stratified by mutations detected during the STI. HIV RNA was measured with a test with a cut off of 3.5 copies/mL. 33% patients with mutations failed subsequent treatment compared to 12% of those who showed no resistance (p= 0.004). Resistance in resistance in baseline plasma and PBMC correlated.

This link to subsequent failure as a strategy to reduce side effects has ended by limiting long-term treatment options. This is a particular concern given that the study protocol for stopping treatment in this study had already tried to minimise risk of resistance to NNRTIs with long half-lives by stopping nevirapine three days earlier, and efavarenz one week earlier, than the nucleosides in each regimen.

C O M M E N T

The potential for NNRTI-resistance due to monotherapy when these drugs are discontinued is now widely recognised. Although many doctors already advise discontinuing the NNRTI one week earlier than their nucleosides, this may still not be sufficient as recent studies showed some patients can maintain therapeutic levels for several weeks after stopping treatment. [3]

Guidelines for stopping treatment within intermittent treatment studies such as the SMART study need to ensure resistance is minimised in patients in the intermittent treatment arms. SMART randomises patients on stable therapy to either maintain continuous treatment, or start and stop treatment by predetermined levels of CD4 count (250 and 350 cells/mm^3 respectively).

Resistance developed in this study will confound the real question on the potential benefit of CD4-driven treatment management and reducing long-term cumulative exposure to antiretrovirals. It will also jeopardise future options for these patients.

This is also an important issue for patients to understand too. The safest way to avoid resistance appears to be to switch the NNRTI to a PI for the last few weeks. This may involve additional short-term side effects such as nausea, diarrhoea, etc when the temptation is to stop treatment anyway, but the potential risk of NNRTI treatment for their next period on-treatment is actually far more serious than this short-term difficulty.

Nucelosides with long half-lives and low genetic barriers to resistance such as 3TC clearly also need to be considered. Although tenofovir has a long half-life, it has a higher barrier to resistance than 3TC. In the discussion, Michael Miller form Gilead reported that they have not seen new resistance in the limited numbers of patients stopping tenofovir in registrational studies, but it would be useful to see this reported as a separate study.

Links
http://www.smart-trial.org

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Persistent nevirapine resistance following mother to child transmission interventions

Polly Clayden, HIV i-Base

Three studies presented at this meeting evaluated resistance in women having received single dose nevirapine to reduce mother to child transmission.

Patterns of selection and "fading" of Y181C and K103N in women with subtype A vs D

A resistance substudy of the HIVNET 012 trial from Susan Eshleman and colleagues examined the impact of subtype A vs D on the selection and "fading" of nevirapine associated mutations K103N and Y181C in a group of women following a single dose of nevirapine to reduce mother to child transmission [1].

Genotypes were obtained at 7 days and 6-8 weeks and paired data were available for 159 women. Of this group 83 women had subtype A and 57 subtype D.

The investigators found a significantly higher overall rate of resistance (ie any nevirapine mutation) at 6-8 weeks than at 7 days, 47/140 (34%) and 31/140 (22%) respectively, in women with either A or D subtypes (p=0.013; OR 1,916; 95% CI: 1.287, 2.854). There was a higher rate of accumulation of mutations for subtype D vs A (OR 2.519; 95% CI: 1.136, 5.587).

The K103N mutation was detected at a higher rate in the 6-8 week samples: 41/140 (29%), than the 7 day samples: 18/140 (13%), (p=0.0001; OR 2.926; 95% CI: 1.287, 2,854) across both subtypes. Again the investigators noted a higher rate of accumulation for subtype D vs A although this was not statistically significant.

Conversely the detection rate for the Y181C mutation was higher at 7 days than at 6-8 weeks overall, 26/140 (19%) and 15/140 (11%) respectively (p=0.0145; OR 0.509; 95% CI: 0.297, 0.872. The investigators added: "Furthermore Y181 faded quickly in subtype A with little or no fading in subtype D."

These findings demonstrate HIV-1 subtype to influence patterns of emergence and "fading" (from detection) for the K103N and Y181C mutations The investigators also looked at G190A but the number of mutations detected were too small for meaningful statistical analysis (they also noted other nevirapine mutations eg V106 and Y 188C in a small number of women). They report that for all three mutations, the results suggest that nevirapine mutations are better tolerated in subtype D than subtype A viruses and conclude that these findings suggest that HIV-1 subtype should be considered in the design and interpretation of studies to determine whether single dose nevirapine compromises subsequent NNRTI containing treatment.

Surveillance of nevirapine resistance in Kwazulu-Natal, South Africa

The startling scale of 75% nevirapine resistance at two weeks following single dose nevirapine, reported in women with subtype C at this meeting last year provoked much speculation around the longer term consequences of selecting nevirapine resistant virus [2]. Will NNRTI containing drug programmes be effective if women have access to treatment for their own HIV?

In their surveillance report Gordon and colleagues write: "It is essential that the rate and pattern of drug resistance development is closely monitored. This is especially true for South Africa, in the light of the initiation of its national antiretroviral programme [3]." They examined nevirapine resistance patterns in 30 mother and infant pairs (including one set of twins) with HIV-1 subtype C who had participated in a single dose (to mother and infant respectively) mother to child transmission (MTCT) programme at a clinic in Hlabisa, South Africa.

At six weeks following the nevirapine prophylaxis, 12/30 (40%) of women and 40% of infants had detectable resistance. The K103N mutation was the most common mutation in 10/12 (83%) of the mothers. Other mutations reported in the mothers included: Y181C in 3/12 (25%), Y188C in 3/12 (25%), V106M in 2/12 (17%) and G190A in 1/12 (8%) Two or more mutations were found in 4/12 (33.3%) mothers.

Of the group of infants, the Y181N was the most common mutation and was present in 11/12 (92%) of the children (including one of the twins). Additionally 2/12 infants (17%) had the K103N and another 1/12 (8%) had a subtype C associated V106M mutation.

The investigators also reported that the K103N mutation resulted in the loss of a protein kinase phosphorylation site at codons 102 to 105 in reverse transcriptase. This was replaced with myristoylation site at codons 99 to 104 and a glycosylation site at 103 to 106. All infants with nevirapine resistance lacked a tyrosine kinase phosphorylation site at codons 174 to 181.

The investigators concluded: "Given the high rate of resistance in mothers and infants after single dose nevirapine, the search for safer regimens to prevent MTCT should be intensified."

Persistence of nevirapine resistance: the Ditrame Plus study

A resistance substudy of the Ditrame Plus trial – in which women received single dose nevirapine in addition to short course zidovudine to reduce MTCT and the infants short course zidovudine and single dose nevirapine syrups – evaluated nevirapine resistance at four weeks post partum [4,5].

Baseline and four week samples were available for 63 women, of this group 21 had infected and 42 uninfected infants. Samples from the 26 infected children were also evaluated (21 children whose mothers had and 5 children whose mothers had not received nevirapine, but who had received the infant dose.

The investigators reported 21/63 (33.3%) of women having developed nevirapine resistance at week four, with the K103N being the most common mutation. They also reported the mothers with infected and uninfected infants developed resistance at the same rate (33.3%), 7/21 and 14/42 respectively. No zidovudine resistance was detected in this group. Additionally DNA-PBMC nevirapine mutations were detectable in 15/20 (75%) of women for whom DNA samples were available at week four.

Analysis of nevirapine plasma concentrations revealed wide inter patient variability with a median concentration of 648 (range 417-954) ng/ml. Resistance was significantly associated with a higher plasma concentration of nevirapine and among women who received two doses of nevirapine 3/4 (75%) acquired resistance.

The investigators described predictive factors for nevirapine resistance for the mothers as: median viral load 4.93 log10 copies/ml (nevirapine resistance) vs 4.54 log10 copies/ml (no nevirapine resistance) (95% CI: 3.11[1.04-9.29], p=0.020); median nevirapine plasma concentration 851 (633 – 1063) ng/ml (nevirapine resistance) vs 598 (315-885) ng/ml, p=0.014 and CD4 <350 cells/mm^3 81% nevirapine resistance vs 19% >350 cells/mm^3, p=0.06. Multivariate analysis revealed two factors to be independently predictive of development of resistance: viral load OR 95% CI: 4 (1.13 – 14.09) p=0.12 and plasma concentration 2 days post partum OR 95% CI: 1.05-1.50, p=0.31.

Additionally 6/26 (23%) of the infected infants developed nevirapine resistance detectable in plasma and DNA-PBMC at four weeks post partum, and follow up samples in two children – one at 3 and one at 12 months old – detected archive mutations in the DNA-PBMC.

Summarising their findings the investigators note that the association between high level nevirapine plasma concentrations suggests, "That a high level of nevirapine concentration induced a prolonged viral replication under suboptimal drug selective pressure which promote the emergence of resistant strains." Concerning the infants they write: "Recent studies have reported a negative impact of nevirapine resistance on a subsequent treatment including nevirapine; our results raise anxiety for those very young children presenting with resistant viruses."

C O M M E N T

More bad news for highly active drugs with long half-lives, given as monotherapy (or effectively as monotherapy). Although nevirapine resistant variants "faded" from detection in women in HIVNET 012 by 12-24 months using population sequencing methods, resistant variants will surely still persist as minority variants and rapidly return when drug pressure is reintroduced. "Fading" is an inconguous term in a room of viroloists that have warned of the risks from archived resistance for many years now.

Jourdain et al showed dramatically reduced response in women receiving NNRTI containing regimens following acquisition of nevirapine

resistance after receiving single dose nevirapine to reduce MTCT (at six months 75% unexposed, 53% of exposed but with no detectable mutations and 34% of exposed with detectable resistance were below 50 copies) [6]. Additionally when Mellors et al evaluated the role of minor NNTRI mutations, failure to achieve viral suppression was associated with previous NNRTI experience and NNRTI mutations at baseline [7,8]. However, genotyping failed to detect NNRTI mutations in 50/216 (23%) baseline samples in the NNRTI experienced patients, yet this group performed no better than those with detectable NNRTI resistance, and much worse that the NNRTI-naïve group who similarly showed no mutations.

Furthermore, as in the Thai study, adding nevirapine to background zidovudine is not associated with significantly less nevirapine resistance. The early emergence of the Y181C in the Uganda study (HIVNET 012) may help to explain the different rates of NNRTI mutations in mothers compared to infants, as previously reported and as seen in Kantor's study. The more rapid "fading" of the Y181C would seem to suggest that this mutation is "less fit" relative to both K103N and wild-type virus at least in sub-type A virus.

Better news is that no resistance was reported for zidovudine as prescribed in the DITRAME study and this should equate with less of an impact on future therapy.

These data, and emerging pharmocogenomic data, highlight the need for more thorough investigation of antiretrovirals, new and old, and their resistance patterns, paying attention to clade, gender, age and ethnicity.

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Tipranavir resistance and viral response: L90M did not reduce response, recommendation to use with T-20

Simon Collins, HIV I-Base

Tipranavir is an investigational protease inhibitor that is now being studied in Phase-3 RESIST studies, boosted with ritonavir (500mg TPV/200mg RTV, both BID), has activity against a broad spectrum of protease resistant virus.

Previous studies showed that tipranavir remained active unless four universal protease inhibitor mutations (UPAMs, at positions 33, 82, 84 and 90) were present, usually requiring upwards of 17 individual mutations. At this meeting, a more detailed breakdown of relationship between UPAMs and virological response to tipranavir.

Doug Meyers from Boehringer Ingelheim presented an analysis of baseline resistance and associated viral response from the tipranavir Phase IIb study BI 1182.51. [1] This study was designed for patients who were too treatment experienced for the tipranavir Phase-3 studies. Patients needed to be 3-class experienced with three or more UPAMs at baseline.

After resistance screening patients were randomised to open-label tipranavir/r, amprenavir/r, saquinavir/r or lopinavir/r plus in addition to optimised background regimens for two weeks. Tipranavir/r was added to the amprenavir, saquinavir and lopinavir arms after week two.

The PK and short term virological repsonse data were reported in HTB May 2004. [2] Short-term virological response for each arm was –1.15, –0.21, –0.29 and –0.38 $\log^{10}$ copies/mL at two weeks for these arms respectively. After tipranavir/r was added at week two, all arms had a >1 log (median) viral load reduction. However tipranvir/r significantly reduced AUC and trough levels of the other PIs.

The percentage of responders for each boosted PI was broken down by baseline individual and combinations of UPAMs and are shown in Figure 1 and 2 below.

Figure 1: Viral load response by key mutations

Percent with >1 log reduction at week 2

	TPV/r	APV/r	SQV/r	LPV/r
Mutation	64	71	71	78
33 (%)	27/52 (52)	16/62 (26)	15/67 (22)	23/67 (32)
82 (%)	24/45 (53)	11/52 (21)	15/53 (26)	18/59 (31)
84 (%)	23/43 (58)	10/39 (26)	5/36 (14)	14/35 (31)
90 (%)	23/60 (55)	16/66 (24)	13/61 (21)	22/72 (31)

Figure 2: Viral load response by key mutations

Percent with >1 log reduction at week 2

	TPV/r	APV/r	SQV/r	LPV/r
N	64	71	71	78
3 mutations	24/45 (56)	15/61 (25)	13/57 (23)	21/61 (34)
33, 82, 84	1/3 (33)	1/4 (25)	2/8 (25)	3/5 (60)
33, 82, 90	11/21 (52)	6/30 (20)	10/32 (31)	10/31 (32)
33, 84, 90	9/16 (56)	7/19 (37)	1/17 (16)	7/17 (41)
82, 84, 90	4/5 (80)	1/8 (13)	0	1/8 (13)
4 mutations	6/12 (50)	1/8 (13)	2/10 (20)	3/14 (21)

The numbers of responders in some of these groups are probably too small to comparative activity of each PI in each combination with any confidence. It would certainly be helpful to know whether tipranavir/r is more active than lopinavir/r when 82, 84 and 90 are present or with four UPAMs and less active against 33, 82 and 84, but this will require larger numbers and to control for activity of background therapy.

With small numbers the impact of other drugs used in the optimised background regimen that may have residual activity should be considered, Although these were patients who by definition have broad class resistance and therefore are unlikely to have any other active drugs, recent salvage studies have shown the importance of drug sensitivity in the background regimen. 14% of patients in the trial received T-20 and this would be expected to impact those individual responses.

However, lack of other active drugs was shown by the short-term nature of the viral load reductions that disappointingly returned towards baseline after week two, with further development of protease resistance and reduced sensitivity to tipranavir.

The study concluded:

- Patients with 3 or 4 UPAMs achieved ~ -1.2 log viral load reductions after two weeks exposure to tipranavir/r.
- Without supporting background regimens this response was short-term viral load generally began to increase again after week two.
- Different combinations of 3 UPAMs showed reduced efficacy for each of the boosted protease inhibitors studied.
- Tipranavir responses are reduced when 33, 82 and 84 are present.
- 50% of patients with 3 or 4 of these mutations had >1 log reduction in viral load.
- L90M did not affect TPV antiviral response, but is necessary to predict reduced responses to other PIs.

Although longer follow-up data and impact of individual drugs used in background regimen were not presented at the meeting it was made clear that concomitant use of T-20 had a significant impact on whether likelihood of a sustained response. Further data on these studies are expected at the ICAAC and Glasgow conferences this Autumn.

C O M M E N T

The lack of information on sensitivity to drugs in optimised background regimens limits the use that can be made on this resistance data,

but this early data will nevertheless be useful for clinicians who have the difficult task of selecting treatment for highly treatment-experienced patients.

People waiting to use tipranavir should strongly consider the importance of supportive active drugs if they are not to lose this option. Similarly, many people currently considering T-20, are likely to get a more durable response by also using tipranavir which is now available in the UK on an expanded access programme without CD4 entry criteria. This is in line with the current guidance for using T-20.

Although the RESIST studies allow other PIs, they do not allow therapeutic drug monitoring (TDM). This is clearly is a potential problem given the negative PK interaction data and that TDM is included in many European guidelines.

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Resistance in the UK: new approach to epidemiological studies

Simon Collins, HIV i-Base

Incidence of resistance is frequently presented from an analysis of single time point data from specific populations such as new infections, primary infection and national or local cohorts. This is often used to interpret prevalence and trends in resistance to specific drugs and drug classes.

However, these approaches do not provide an accurate estimate of the percentage of the population at any time who are resistant to a given class, or the characteristics of patients who are developing individual patterns of multi-drug resistance.

Annual reports from resistance databases only provide information relating to current or very recent treatment, as historical and archived mutations will not necessarily appear on in these results. The denominator used for these analysis can also be inappropriate depending on whether the total number of tests or the total number of treated patients is used.

A clearer indication of the incidence of drug resistance in the UK was presented by Deenan Pillay from six large database collaborating in the UK Collaborative HIV Cohort (CHIC). [1]

The number of annual resistance tests in this cohort rose steadily from 500 per year in 1997 to 2500 in 2000 and has remained stable at that level. Data was presented up to end of 2002.

Previous analyses of single time point analyses from this dataset have shown fairly stable percentages of tests with resistance to 1 class (75%), 2 class (55%) and 3-class (15%) resistance from 1998 – 2002. They also showed percentage of samples with NNRTI resistance overtaking PIs resistance in 1999 and remaining higher (50% vs 30%) in line with changes in prescription practice.

When the data was analysed by cumulative number of resistant classes compromised it became clearer to see the increase in 1-, 2-, and 3-class resistance in the population as a whole over time. Prevalence figures were obtained by using the number of patients on treatment in the UK (from SOPHID) as the denominator.

	>/=1 class	>/=2 classes	>/= 3 classes
Cumulative resististance in 2000	2250	1600	500
Cumulative resististance in 2002	3500	2500	800
Prevalence 2002 (% UK pt on Tx)	18%	12%	4%

Prevalence of resistance by class showed approximately 17% patients have resistance to any class, 16% to RTIs, 10.5% to NNRTIs and 7.5% to PIs. These figures represent a minimum lower level.Despite inclusion in treatment guidelines, resistance tests were not universally used in 2002.

The percentages in this study were from all resistance tests that were requested, and many of these patients would have been on failing treatment with suspected resistance. The definition of ‘class resistance’ was based on a single mutation in any one class.

A second poster from the same group, presented by Andrew Phillips, looked at results from resistance tests from routine care of patients from six clinics in London/Brighton who were using combinations of three of more drugs.

From 1996-2003, around 4450 patients started ART with >/=3 drugs. 56% started with an NNRTI, 41% with a protease

inhibitor. The cumulative risk of virological failure (two viral load >1000 copies/mL after 24 weeks from start of ART, unless during interruption) was 24% by 2 years, 34% by 4 years and 42% by 6 years.

Almost 1000 patients (22%) had a resistance test result at some time after start of ART, 859 of which produced an evaluable result. Cumulative risk of resistance is shown below:

	2 year	4 year	6 year
Cum. risk of vir. failure	24%	34%	42%
Resistance to any class	10%	20%	27%
Resistance to 2 classes	6%	14%	18%
Resistance to 3 classes	1%	2.5%	3.5%

Risks by 6 years for class-specific mutations were: M184V/I 18%, >/=1 TAM 15%, NNRTI 17% (25% when restricted to those who started with NN), major protease mutation 8% (10% when restricted to those who started with a PI).

The study noted that these are lower limit estimates as test results were not available for many with virological failure, and resistance below sensitivity limits of assays will be missed. Factors presented in poster.

Significant factors associated with development of resistance in a multivariate analysis included:

Viral load <100k	0.64 (0.51-0.79) (vs10-99k)	p < 0.001
Previous AIDS	1.33 (1.10 – 1.61)	p = 0.003
No PI or NNRTI	1.83 (1.32 – 2.52)	p<0.005
Using >3 drugs	0.71 (0.52 – 0.97)	p=0.03

Although most patients achieve durable suppression using 3 or more drugs, this study shows that an appreciable number do not.

References:

1. Pillay D et al on behalf of UK CHIC Group. Estimating HIV drug resistance in the UK treated population. Abstract 77. Antiviral Therapy 2004; 9:S88.
2. Phillips AN et al on behalf of UK CHIC Group. Risk of development of drug resistance in patients starting antiretroviral therapy with three or more drugs in routine clinical practice. XIII Intl HIV Drug Resistance Workshop, 2004. Abstract 135. Antiviral Therapy 2004; 9:S151.

Low AZT activity against HIV-2 infection

Simon Collins, HIV i-Base

Although AZT is widely used to treat HIV-2 infection recent studies showing difference in response compared to patients with HIV-1. This prompted Garcia-Lerma and colleagues from CDC Atlanta USA to evaluate in vitro selection experiments with strains of each virus.

5/5 HIV-1 strains rapidly selected for resistance after 3-6 passages (in increasing AZT concentrations of four-32 fold). In contrast 0/5 HIV-2 virus acquired mutations after 10 passages (1024-fold increase in AZT concentration). In the presence of both AZT and ddI, HIV-1 viruses selected mutation for both drugs, while HIV-2 selected only for ddI (K65R and M184V).

All HIV-2 viruses replicated efficiently in concentration of AZT that was 2800-fold higher than the EC50 for HIV-1 and were 200-fold less sensitive. Sensitivity to ddI was similar for both HIV-1 and HIV-2.

RefL Reid P, MacInnes H, Garcia-Lerma JG et al. Natural resistance of HIV-2 to zidovudine. Abstract 32. Antiviral Therapy 2004; 9:S38.

No evidence for cross resistance between nevirapine and d4T

Simon Collins, HIV i-Base

Two articles published last year (Blanca et al JBC 2003, Baldanti et al AIDS 2003) reported that resistance to d4T (stavudine) was related to the nevirapine-associated Y181C mutation. This included a report that Y181C/I should eight fold resistance to d4T in a recombinant virus assay.

Prompted by the important implications of such cross-resistance on current interpretation systems for resistance reports Klaus Korn from the University of Erlangen-Nuremberg looked for corroborative evidence from a database of 500 RT genotype samples and corresponding phenotypic data to d4T.

427/511 samples without Y181C showed a median resistance factor for d4T of 1.8 (IQR 1.0-2.9). The 84/511 samples with Y181C had a corresponding resistance factor of 2.7 (IQR 1.3-5.4). However this difference was explained by strong linked

to RTI mutations in the same sequences. The 3/84 samples without RTI resistance had resistance factors of 1.0, 1.1 and 1.4. Similarly only 16/59 samples with phenotypic resistance to d4T > 8-fold had Y181C.

The study therefore failed to find an association between Y181C and d4T sensitivity and concluded that d4T should not be avoided as a treatment option on the basis of this genotypic mutation.

Ref: Korn K, Schmidt B, Walter H. No evidence for stavudine resistance due to nevirapine-selected mutation Y181C in HIV-1 reverse transcriptase in a large genotype/phenotype database. Abstract 43. Antiviral Therapy 2004; 9:S49.

Experimental compounds to target viral expression in latent cells

Simon Collins, HIV i-Base

Earlier studies were have investigated the use of IL-7 to stimulate latently infected CD4 cells to express HIV and therefore render them susceptible to effect of antiretroviral treatment. If this response was sufficiently extensive and robust, this would re-open discussions on possibilities of HIV eradication.

An abstract at the meeting reported further ex-vivo research in cell cultures with IL-7 and two previously unreported drugs: valproic acid (VPA), an inhibitor of histone deacetylase (HDAC), a host mediator of gene expression; and an investigational p38 kinase inhibitor that should similarly inhibit HDAC. All three drugs induced outgrowth in cells from 4/4, 5/5 and 2/2, patients 'at concentrations achievable in vivo' of IL-7, VPA and the p38 KI respectively, without inducing cell activation.

C O M M E N T

This preliminary work is complementary to research using other approaches aimed at draining the latent reservoir, such as prostatin. Novel agents which can either selectively kill HIV infected cells (virucidal agents) or induce expression of virus in the latent reservoir so that the currently licensed virustatic antiretroviral drugs can clear that remaining virus are the most promising leads we currently have towards viral eradication.

However a serious problem with viral induction is that promotion of global T-cell activation leads to highly problematic inflammatory consequences.

Such approaches have been investigated before, for example using combined IL-2 and anti-CD3 monoclonal antibody therapy, and were extremely toxic (ref: Kulkosky J *et al*. Prostratin: activation of latent HIV-1 expression suggests a potential inductive adjuvant therapy for HAART. Blood. 2001; 98:3006-15).

The new strategy described here, which does not involve cellular activation, is unlikely to be dogged by the same problems.

Ref: Margolis DM, Lehrman G, Archin NM et al. Targetting reservoirs of HIV infection: inducing latent viral expression without host cell activation. Abstract 68. Antiviral Therapy 2004; 9:S77.

Case of MDR reinfection with MDR virus

Simon Collins, HIV I-Base

Incidents of HIV reinfection or superinfection are generally difficult to isolate and report as the structure for patient management are not geared to be able to look for this. When cases are identified (see report on last years meeting in HTB 4/7, Aug/Sep 2003) they tend to be picked up by clinicians who notice unexpected virological rebound or increases, that are linked to a personal patient history, and then confirmed by technology that is not generally easily accessible to practicing clinicians.

In one case of multiple drug resistant (MDR) transmission with low level viremia reported by Brenner and colleagues from McGill University AIDS Centre, Montreal, superinfection occurred with a second heterologous MDR strain. [1] This was confirmed by phylogenic and clonal analysis of viruses from the index case and source partners. In cell culture, both of these transmitted MDR species showed reduced replication capacity relative to the WT virus isolated from the first source partner after treatment interruption.

This report came from a larger study looking at transmission of resistance in the Montreal Primary Infection Cohort, which included wild-type infection in 15 patients, resistant infection in ten patients and nine patients infection with MDR virus.

Longitudinal follow up of this group over 2-6 years showed that mutations in patients infected with resistant virus (other than M184V) generally persisted over time, including those patients with MDR infection. This was in contrast to reversion to wild-type virus, in a number of source partners for these MDR infections, following a treatment interruption.

The global history of HIV clades and recombinant viruses clearly shows the epidemiological significance of recombination.

Several presentations at the meeting looking at recombination including a study from Frank Maldarelli and colleagues [2]. This study estimated similar rates of recombination in treatment naïve and experienced patients and suggested that at relatively low rates of viral load of 3000 copies/mL this pool of infected cells is sufficiently large to permit frequent recombination.

Although a fine point, it is clinical important to realise that, for example a strain with M184V mutation from earlier treatment history combines with, for example K103N resistant strain from later use of NNRTI, to form a dominant strain that contains both 184V and 103N. A crude estimate from sequential samples from a recently infected patient was that >20% of infected cells in vivo are likely to be infected with two or more proviruses.

Reference:

1. Brenner BG, Turner D, Wainberg MA et al. Natural history of transmitted drug resistant and wild-type infections and superinfection in the Montreal Primary HIV-1 Infection (PHI) Cohort. Abstract 90. Antiviral Therapy 2004; 9:S101.
2. Maldarelli F, Kearney M, Coffin J et al. HIV-1 populations are large, highly diverse, and characterised by frequent recombination in drug-naïve and drug-experiencecd individuals. Abstract 45. Antiviral Therapy 2004; 9:S54.

C O M M E N T

The growing collection of documented case reports or reinfection or 'superinfection' clearly establishes this as certain possible risk.

This doesn't mean that HIV-positive people have to use condoms every time they have sex, but it does mean that other risk factors are important when both partners are HIV-positive – especially when they have different treatment histories and resistance patterns.

Risk is a continuum. For example, any additional risk is likely to be extremely low for monogamous couples, who both have undetectable viral load, and the same treatment and resistance history. Higher viral load, as with all cases of infection, is likely to be an independently increase the risk.

Someone who is treatment naïve, or currently on successful treatment could jeopardise future health and treatment following reinfection from a partner who has any drug resistance, however extensive, and it is plausible that risk of reinfection is likely to increase with traditionally associated factors: viral load, mode of exposure, concurrent sexually transmitted infections etc.

CONFERENCE REPORT

Keystone HIV Pathogenesis and Vaccine Development Report

12-18 April 2004, Whistler, British Columbia, Canada

Gareth Hardy PhD, for HIV i-Base

This year's Keystone Symposia on Molecular Mechanisms of HIV Pathogenesis (X7) and HIV Vaccine Development (X8) was held in British Columbia's Whistler Resort, Canada, from 12-18 April 2004.

This highly specialised and relatively small annual meeting is often not attended by community activists or press. The focus on basic science means that much of what is presented and discussed has little, if any, direct implications for clinical practice. However, the meeting attracts some of the world's experts on HIV immunology and pathogenesis as a forum to exchange and discuss ideas and data. Collaborations were also as likely to be forged between sessions as *on-piste* on The Cougar and The Harmony Ridge slopes on the heights of the Whistler and Blackcomb Mountains.

From year to year, the feeling of these meetings can shift from optimism and excitement, to a mundane business-as-usual mood, to an urgent knuckle-down and crack-on intensity. This year's meeting was somewhere between the latter two.

An abundance of data was presented on the "infectious synapse". This is the juncture between the uninfected $CD4^+$ T cell and the virus loaded dendritic cell, ready and waiting to drop its lethal bomb. Following virus binding to specific receptors on the dendritic cell (DC) surface endocytosed viral particles may i) establish infection ii) be degraded after fusion with lysosomes in which constituent viral antigenic peptides are loaded onto MHC molecules for presentation to T cells or iii) be diverted to target CD4+ T cells. Two distinct forms of HIV infection of DCs have become apparent. In the first, *trans* infection, HIV appears to pass straight through the DC. Initially virus binds to the cell surface adhesion molecule dendritic cell-specific ICAM-3 grabbing nonintegrin (DC-SIGN) in the mucosa. Following endocytosis virus appears to be "protected" within the DC and is packaged for release onto target CD4+ T cells in the lymph nodes which then support explosive virus replication. Thus in *trans* infection an intracellular phase of the virus life cycle is completed within the DC without virus replication. In the second form, *cis* infection, virus is actually degraded and/or infection of the cell occurs. Processed viral peptides may then be presented to T cells by MHC class I and II molecules.

David McDonald's group at the University of Illinois, Chicago, USA, first demonstrated that HIV forms an "infectious synapse" bringing virus and receptors into proximity on the cell surface. [1] This finding was backed up by Vincent Piguet of the Department of Dermatology and Venerology, University Hospital of Geneva, Switzerland, who showed that infectious synapse formation could be impaired by experimental suppression of DC-SIGN expression on DCs using a lentiviral-mediated RNA interference mechanism. [2] DC-SIGN negative DCs were unable to facilitate HIV infection of T cells *in trans*. Teunis of the Department of Molecular Cell Biology and Immunology, University of Amsterdam, the Netherlands, found that DC-SIGN and CD4 recognise distinct sites on gp120. [3] Furthermore DC-SIGN binding to gp120 appears to enhance CD4 binding to gp120. Teunis suggests this could be due to DC-SIGN binding inducing a conformational change in gp120 favoring subsequent CD4 binding. However, it is probably more likely to be due to an increase in stability and thus avidity between the virus and DC surface, which may facilitate gp120 binding to CD4. Teunis went on to say that in contrast to other DC-SIGN ligands, HIV-1 and hepatitis C virus (HCV) appear not to become targeted to lysomal compartments where they may be degraded, but instead appear to be preserved in endosomes. Teunis concluded that HIV-1 and HCV target DC-SIGN in order to circumvent rapid lysosomal degradation, which is vital to their dissemination and survival.

In order to better understand the mechanisms behind DC-SIGN-mediated transfer of HIV-1 to $CD4^+$ T cells, Rahm Gummuluru, of the Department of Microbiology, Boston University School of Medicine, Massachusetts, USA, engineered cell lines of divergent cellular origin to express DC-SIGN which were then compared to immature DCs for their ability to facilitate *in trans* HIV-1 infection. [4]

HeLa/DC-SIGN cells were unable to transmit captured virus to $CD4^+$ T cells. In contrast, THP1/DC-SIGN cells were similar to DCs in their ability to transmit captured virus to $CD4^+$ T cells. However, both HeLa/DC-SIGN cells and DCs rapidly internalised virus into intracellular compartments that were trypsin resistant. Electron microscopy and immunfluorescence analysis revealed a pattern of virus particle trafficking to perinuclear lysosomal compartments in HeLa/DC-SIGN cells, whereas in DCs and THP1/DC-SIGN cells viral particles localised at the plasma membrane. Kinetic measurement by ELISA for cell-associated p24 demonstrated that this lysosome associated virus in HeLa/DC-SIGN cells was degraded within 8 hours post virus exposure, in contrast to DCs and THP1/DC-SIGN cells which steadily released virus into culture supernatants over time. Gummuluru also explained that in DCs as much as 75% of internalised virus may end up in lysosomes where it is degraded and co-localises with MHC Class II. However, the remaining viral particles are retained in endosomal compartments as infectious virus and are trafficked to the infectious synapse for release into the cell free compartment.

Gummuluru concludes that the nature of the intracellular compartment into which HIV-1 particles traffic following DC-SIGN binding, plays a crucial role in determining the efficiency of *trans* infection. The question as to whether or not DC-SIGN mediated infection of DCs can give rise to antigen presentation via MHC Class II is a very important one. It may be the case that differential levels of HIV antigen presentation arise from *cis* as opposed to *trans* infection, or that the quality of that antigen presentation is markedly different between the two forms of infection, or indeed that the maturational status of the DC may be differentially effected by either *cis* or *trans* infection which would dramatically effect the functional outcome of antigen presentation. These questions remain to be answered.

David McDonald of the University of Illinois, Chicago, found that activated DCs facilitated *trans* infection much more effectively than immature DCs. [5] In his experiments DCs were experimentally activated using lipopolysaccharide (LPS). Immunoflourescent analysis revealed that virus in activated DCs was often concentrated into a single subcellular region both proximal and distal to the infectious synapse, where it co-localised with the cell surface molecules HLA-DR (MHC Class II), DC-SIGN and the co-stimulatory molecule CD86 (B7.2) in addition to the tetraspanins CD63, CD9 and CD81. CD81 co-localisation with HIV-1 was particularly pronounced, with the majority of its constituent total cellular signal concentrated within the compartment. Over several days of culture, HIV-1 and CD81 remained concentrated, with decay of virus within this compartment correlating with decreasing infectious transmission. Importantly, the compartment lacked early and late endosomal markers as well as HLA-DM, a molecule involved in antigenic peptide loading onto MHC Class II, indicating that the compartment was distinct from lysosomal or Class II processing vesicles. Subsequent recruitment of the compartment to the infectious synapse resulted in exposure of its luminal contents at the DC surface, with delivery of both HIV-1 and co-stimulatory molecules to the $CD4^+$ T cell surface. McDonald concludes that because of this compartment's staining profile and its apparent multilamellar composition it is likely that it is a multivesicular body (MVB) that is normally reserved for the sequestration of intact antigens within DCs.

Another key area of interest was the increasing body of data on anti-retroviral cellular factors. APOBEC3G (also known as CEM15) is perhaps the most talked about of these. The mechanism of action of APOBEC3G is catalysis of the destructive deamination of deoxycytidine (dC) to deoxyuridine (dU) in viral cDNA intermediates that arise during reverse transcription. In order to do this APOBEC3G must be carried forward into newly infected cells by the viral particle itself. Thus APOBEC3G is first packaged into new viral particles in the infected cell. However the action of the APOBEC3G enzyme is blocked by HIV Vif and can only be demonstrated functionally using *vif* deficient HIV.

Michael Malim of King's College, London, [6] shows that *vif* expression disrupts APOBEC3G packaging through at least three separate mechanisms: inhibition of cytoplasmic APOBEC3G incorporation into virions; reduction of the efficiency of APOBEC3G translation; and induction of APOBEC3G ubiquitination in virus producing cells leading to degradation of the

enzyme by the 26S proteasome. Warner Greene of the Gladstone Institute of Immunology and Virology, University of California, San Francisco, USA, [7] further elaborates on this by showing that Vif prevents virion incorporation of APOBEC3G by depletion of its intracellular stores in infected T cells. Vif both inhibits APOBEC3G mRNA translation by 40-50% and reduces the intracellular halflife of the enzyme from more than eight hours to two hours by ubiquitination and subsequent targeting for degradation by the 26S proteasome. Malim suggests that the Vif/APOBEC3G regulatory axis is a potential target for therapeutic agents.

A number of interesting presentations were given on the evolution and pathogenesis of simian immunodeficiency virus (SIV) infections in non-human primates. HIV-1 and HIV-2 are thought to have arisen following cross species transmission to humans of SIV from chimpanzees (SIVcpz) and sooty mangabeys (SIVsm) in sub-Saharan Africa, though other SIVs exist in numerous primate species from this area. Understanding the complexity of these different SIV's evolution is considerably difficult because there appear to have been multiple instances of cross-species transmission and recombination among divergent different SIV strains.

Paul Sharp of the Institute of Genetics, Nottingham University, UK, has used multiple phylogenetic analysis to identify a core set of non-recombinant SIV lineages. [8] This SIV phylogeny was then used as a backbone onto which to map the mosaic recombinant viruses. Sharp explained that SIVcpz is a hybrid virus that has emerged from recombination between the SIVrcm lineage and an ancestor of the clade comprised of SIVs from mona, mustached and greater spot-nosed monkeys. This virus then disseminated throughout the population of central chimpanzees (*Pan troglodytes troglodytes*) and then into eastern chimpanzees (*P.t. schweinfurthii*). Sharp went on to explain that HIV-1 groups M, N and O have arisen as a result of SIVcpz transmission to humans on three independent occasions.

Sharp contested current thinking that HIV-1 has undergone rapid evolution following these transmissions, saying he can find no evidence for this. In addition, an apparent lack of parallel coincident amino acid substitutions in the sequences of groups M and O during their evolution suggests that SIVcpz adapted readily to its new human host.

Mario Santiago of Howard Hughes Medical Institute, University of Alabama, USA, confirmed the SIVcpz source of HIV-1[9]. Using full and partial length sequences from SIVcpz viral RNA found in 581 urine and 606 fecal samples from more than 250 wild chimpanzees in more than 15 habituated and non-habituated communities in Ivory Coast, Uganda, Rwanda, Tanzania, Cameroon and the Democratic Republic of Congo, phylogenic analysis reinforced *P.t. troglodytes* and not *P.t. schweinfurthii* as the source of HIV-1.

One very important feature of SIV is the lack of any AIDS-like disease in all known infections in natural hosts. However transmission of SIVs to other primate species, such as humans or rhesus macaques, that are not natural hosts causes persistent infection associated with progressive CD4+ T cell loss and disease development. Mark Feinberg of Emory University, Atlanta, Georgia, USA, points to the SIV-infected sooty mangabey as an interesting example. [10] In this species an AIDS-like disease does not develop despite chronic high level viraemia and attenuated cellular immune responses. Feinberg says that this implies "high level virus replication alone can not account for the progressive $CD4^+$ T cell depletion leading to AIDS." Feinburg goes on to suggest that what prevents disease developing in this species is their failure to mount antiviral immune responses which may result in indirect bystander killing of uninfected T cells contributing to $CD4^+$ T cell depletion and compromising immune regenerative capacity. Feinberg's group has been investigating the immunological distinctions between SIV infection in sooty mangabeys and rhesus macaques. In particular they have observed that from within the first days of infection onward there are significant numerical and functional differences in DC populations between sooty mangabeys and rhesus macaques, which could thus turn out to be pivotal determinants of disease outcome in SIV infection. However these findings may also indicate critical determinants of disease outcome in HIV infection as well. Similar observations have been made with regard to DC numbers and function in HIV infected humans. As discussed above, we still don't understand many details of what HIV is doing to DCs. These cells are likely to play an important role in the immunopathogenesis of HIV. After all they are responsible for initiating the entire immune response.

Marie-Claire Gauduin of the New England Regional Primate Centre, Harvard Medical School, Southborough, Massachusetts, USA, presented the results of a study investigating the effects of $CD8^+$ T cell depletion in rhesus macaques that had undetectable viraemia following discontinuation of early HAART. [11] Three rhesus macaques were infected with pathogenic SIVmac239 and treated with HAART within 5 – 10 days of infection. Viral loads peaked at 7 – 10 days following infection (mean value 7.1 log copies/mL) and decreased to below detection within 20 weeks following treatment. At 40 weeks HAART was discontinued which gave rise to a transient rebound in viral load. Subsequently viral load became controlled in association with broad SIV-specific $CD4^+$ and $CD8^+$ T cell responses, measured by IFN-gamma ELISpot, intracellular staining and tetramer staining. At the time of $CD8^+$ T cell depletion using the anti-CD8 monoclonal antibody cM-T807, all 3 animals had maintained undetectable viraemia for more than 40 weeks, which then rapidly rose within another 10 days (peak levels 10^5 – 10^7 copies/ml). Twenty days after treatment with cM-T807 there was a rapid decline in viraemia which coincided with recovery of $CD8^+$ T cells into the periphery, and expansion of SIV-specific $CD8^+$ T cell responses in the lymph nodes. Gauduin says that "these findings provide direct evidence for the role of $CD8^+$ T lymphocytes in controlling viraemia in the setting of early antiretroviral therapy followed by treatment interruption."

On the vaccines front, Gary Nabel of the Vaccines Research Centre, National Institute of Allergy and Infectious Disease

(NIAID), NIH, Maryland, USA, announced the development of vectors carrying modified HIV *env* DNA designed to express gp160 with altered variable loops expected to enhance immunogenicity. [12] The modified DNA vaccine candidates have been shown to improve cellular and humoral immunity in combination with a gag-pol-nef immunogen in primates and thus phase-I trials in humans have begun including multiple clade envelope constructs.

Richard Koup of the National Institutes of Health, Maryland, USA, presented data on a therapeutic vaccination trial in which 12 mamu rhesus macaques were challenged with SIV after which they received HAART (X8, no abstract). The animals were vaccinated in various regimens with an ALVAC gag-pol-env construct in some cases with IL-2 or IL-15. At 41 weeks ART was discontinued and CD8 T cell responses were monitored using MHC class I tetramers. Vaccination in these animals failed to confer durable protection from viraemia despite induction of T cell responses. Furthermore shifts in the expansion of $CD8^+$ T cells with different specificities confirmed observations made by David Watkins of the University of Wisconsin, USA (X8, no abstract) that virus rapidly escapes from the $CD8^+$ T cell responses that initially control viral replication. As a consequence, $CD8^+$ T cell clones with new specificities subsequently become predominant after the first few weeks of the $CD8^+$ T cell response.

While clinical studies in humans have taken place using canary pox (ALVAC) as a vector, such as the QUEST trial discussed later below, investigations of other vaccine vectors are underway. Richard Compans of the Department of Microbiology and Immunology at Emory University, Georgia, USA, discussed new approaches to improving the efficacy of virus like particles (VLPs). [13]

VLPs are being constructed at Emory to induce broadly cross neutralising antibody responses, $CD8^+$ T cell responses and mucosal protection from infection with three important modifications to previous VLP constructs:

i) the surface structure of the expressed *env* products (gp120) have been modified to delete glycosylation sites and variable loops;

ii) adjuvants have been added to enhance responses, most particularly mucosal responses; and,

iii) inclusion in the VLPs of additional surface proteins expected to have an adjuvant effect, such as influenza HA protein or targeting effects such as membrane anchored forms of dendritic cell growth factors.

In one study in rhesus macaques SIV VLPs containing sufficient gag to enable viral budding were administered in a prime-boost regimen with a DNA vaccine prior to challenge with SIV. Compans showed that the DC targeted VLPs were able to induce maturational co-stimulatory molecules such as CD80 (B7.1) and CD86 (B7.2) on DCs. Induced IFN-gamma T cell responses measured by ELISpot were fairly robust in comparison to lymphocyte proliferative responses which were negligible. Viraemia was not contained following SIV challenge. The lack of lymphocyte proliferative responses induced by this vaccine despite the DC targeting mechanism which may be considered to help generate such responses is a concern here, indeed T cell IFN-gamma responses may not be the magic marker of T cell function we have considered it to be of late. This is discussed further below. Alternative approaches to modifying the envelope protein carried by similar vectors are likely to hold more promise in terms of generating broadly cross neutralising antibody responses.

One of the main reasons why these responses don't arise naturally is because "neutralization" epitopes on gp120 are masked by hypervariable domains of the protein, which attract useless antibody responses. However some of these neutralisable epitopes do become transiently exposed when CD4 binds gp120 inducing a conformational change in its structure. One such epitope is that recognised by the broadly cross neutralising monoclonal antibody 17b.

Jason Hammonds of Vanderbilt University, Tennessee, USA, presented his continuing work developing pseudovirions which express stable natural trimers of gp120 with these CD4 induced conformational changes. [14] Hammonds showed for the first time that these gag-env pseudovirions indeed present the 17b epitope in the context of trimerised gp120. However in guinea pigs unadjuvanted pseudovirions were not able to induce high titre neutralising antibodies. Experiments are ongoing to investigate the effects of adjuvanted pseudovirions. Such approaches which are designed to expose conserved regions of gp120 in potential vaccine constructs have a much greater chance of stimulating *in vivo* B-cell production of high titres of broadly cross neutralising antibodies than previous constructs which have just included straight env and gag sequences, such as the currently tested ALVAC constructs.

Adenovirus may also prove to be a useful vector for an HIV vaccine as discussed by Dan Barouch of the Beth Israel Deaconess Medical Centre, Boston, Massachusetts, USA. [15] One problem here is the high seroprevalence of antibodies to adenoviruses which Barouch explained is 45% in the US and Cameroon and 80% in Thailand. However serotypes exist with low seroprevalence that are also immunogenic such as serotype 35. Barouch showed that a rAd35-gag vaccine induced good IFN-gamma and IL-2 responses in ELISpot assays as well as demonstrating the ability to transduce dendritic cells in mice.

Stephen Udem of Vaccine Discovery Research, Wyeth Research, New York, USA, discussed the use of vesicular stomitis virus (VSV) as a vector (X8, no abstract). The attraction of VSV is that it is typically a minor pathogen of livestock and in humans is non-pathogenic, where infection is limited to the mucous membranes and respiratory tract. Furthermore there is little pre-existing immunity to VSV in humans and it induces good mucosal and systemic immune responses. Udem explained that VSV has proven to be a safe and effective vector for *gag* and *env* constructs in pre-clinical trials. [16] In macaques intranasal

administration of VSV-gag and VSV-env following DNA vaccine priming resulted in robust and durable IFN-gamma T cell responses in comparison to the use of the DNA vaccine alone. One concern with this vector is possible neuropathology. However Udem explained that insertion of an additional gene into the virus genome and truncation of its glycoprotein gene sufficiently attenuates it. Thus VSV vaccines are approaching acceptability for use in humans, and have been safely administered to more than 50 macaques conferring a high degree of protection from SHIV challenge.

Alexandra Trkola of the Department of Infectious Diseases, University Hospital Zurich, Switzerland, investigated the ability of autologous virus replication to stimulate humoral immune responses in the Swiss structured treatment interruption (STI) cohort. [17] Longitudinal analysis of neutralising and binding antibody production was conducted in patients receiving short and long term STIs. Trkola explained that in this study neither pre-existing or induced $CD4^+$ or $CD8^+$ T cell responses correlated with protection from elevated viraemia during ART discontinuation in 4 STIs. Induced antibody titer increases to p24 and gp120 were low during 4 short-term STIs and did not become significant until after a fifth long-term interruption. While neutralising antibodies were not boosted by STIs, high levels of pre-existing neutralising antibodies were associated with potent control of viraemia. Interestingly Trkola found that pre-existing and evoked levels of non-neutralising binding p24 antibodies correlated with significantly lower viral set points following the STIs. However binding antibodies to gp120 did not have this correlation.

Trkola also presented data on a small number of patients who were treated with a cocktail of broadly cross neutralising monoclonal antibodies (including 2F5, 2G12 and b12) demonstrating a period of complete viral suppression to below detection limits following ART discontinuation in some, but not all treated patients. In one patient however, this suppression was particularly short-lived and viraemia rapidly rebounded suggesting viral escape from neutralisation. This was possibly due to existence of pre-treatment viral variants with sufficient immune escape mutations in the neutralisation epitopes of their envelope sequences to rapidly overcome the pressure exerted by the administered monoclonal antibody cocktail. This data demonstrated firstly that neutralising antibodies can suppress viral replication at least as well as HAART and secondly that vaccine induced B-cell production of broadly cross neutralising antibodies may have a far better chance of overcoming immune escape than a cocktail of four or five monoclonals with broadly cross neutralising activity.

Sophie Holuigue of the Department of Immunology and Molecular Pathology, University College London, UK, re-investigated the role of antibodies in viral control during primary HIV infection. [18] Previously the decline in high level viraemia at primary infection to the viral set point has been attributed to $CD8^+$ T cell responses which coincide with this viral decline, in contrast to neutralising antibodies which arise subsequently. Using either early virus isolates or recombinant viruses containing gp120 directly amplified from patients shortly after infection, Holuigue confirmed previous findings first detecting neutralising antibodies 3 – 24 months after infection. However virus inactivation was detected as early as 12 days after onset of symptoms when sequential patient sera was assessed for virus inactivation in the presence of active complement. This inactivation coincided with the initial decline in viraemia, closely following the appearance of $CD8^+$ T cell responses. Complement subsequently increased virus "neutralisation" titres 2-fold at later time points. The presence of complement in the assays shifted the neutralisation of heterologous virus to earlier time points, in some cases to the same time points as that of autologous virus. Holuigue suggested that this implies antibodies working in concert with complement may contribute to the initial control of viraemia and concluded that the implications of this for vaccine development are promising as non-neutralising antibodies may have a much broader and greater antiviral activity than observed in traditional *in vitro* assays.

Of significant interest was a presentation entitled "Evolution of HIV is focused in HIV-specific $CD4^+$ T cells" by the group of Dean Hamer at the National Cancer Institute together with the group of Daniel Douek at the vaccine Research Center, both at the NIH in Maryland, USA. [19] Douek previously showed that HIV-specific $CD4^+$ T cells harbour a large proportion of the pro-viral DNA that makes up the latent reservoir of virus. In this presentation Hamer not only showed that HIV-specific $CD4^+$ T cells are infected, but that they are also activated by HIV. $CD4^+$ T cells from patients treated with HAART early in infection (i.e. before any major loss of $CD4^+$ count) were stimulated with HIV antigens p24, p66 and gp120, with CMV antigen, or anti-CD3, and the replication competent virus induced was sequenced. In addition pro-viral DNA was also sequenced from purified HIV-specific $CD4^+$ T cells.

The env sequence of viruses infecting HIV-specific $CD4^+$ T cells was found to have an 8-12% divergence from the env sequences of viruses infecting T cells stimulated by CMV and anti-CD3. Phylogenic tree analysis showed that these viral variants were diverse and distinct from viruses populating other $CD4^+$ T cells. In general polyclonal (anti-CD3) stimulated $CD4^+$ T cells appeared to have very homogenous sequences representing the original infecting strains, though during untreated chronic infection virus sequences were found to be highly heterogenous both in HIV-specific and polyclonal $CD4^+$ T cells. Hamer explained that the HIV present in HIV-specific $CD4^+$ T cells continues to evolve even in individuals who initiated antiretroviral therapy shortly after infection.

Mathematical modeling based on these findings suggested that boosting HIV-specific $CD4^+$ T cell frequency could increase viral load and decrease functional help. The argument here is that while highly active anti-retroviral therapy may inhibit 99.9% of viral replication, the remaining 0.1% of virus that is replicating, is doing so in HIV-specific $CD4^+$ T cells. The reason for this is logical enough: the population of $CD4^+$ T cells that are most likely to be continually activated in HIV infection are HIV-specific ones, even in the presence of antiretroviral therapy, due to the ongoing presence of HIV antigen. Such activation of these cells subsequently leads to high turn over of the virus they harbour.

Though not particularly surprising, the implications of this data are profound. This may explain why one HIV therapeutic vaccine after another cannot induce sustained HIV-specific $CD4^+$ T cell proliferative responses. We can induce those responses, but time and time again, they emerge as a transient phenomenon only to mysteriously disappear again. Such short-term responses are the hall mark of effector T cells which have a very short half life, and not central memory T cells which should be sustained for many years. Indeed Hamer explained that the half-life of these HIV-specific $CD4^+$ T cells, once activated, was less than 1 day. Hamer concludes that "The ability of HIV-specific $CD4^+$ T cells to serve as a distinct reservoir for HIV growth and variation suggests that vaccines and treatments aimed at augmenting HIV-specific $CD4^+$ T cell responses should be undertaken with caution." However many immunologists argue that we need to ensure preservation of these responses, perhaps by using more effective HAART regimens, which fully penetrate all anatomical and cellular compartments, thus preventing the small amount of virus replication that is taking place in the HIV-specific $CD4^+$ T cells. Indeed these responses need to be expanded in a manner in which they can be sustained, in order to help achieve long-term control of viral replication in the absence of anti-retroviral treatment.

Bruce Walker of Massachusetts General Hospital, Boston, Massachusetts, USA, presented an update on his structured treatment interruption study in primary HIV infection. [20] Fourteen patients underwent up to three structured treatment interruptions. Treatment was restarted if the viral load increased to more than 5,000 copies/mL for more than 3 weeks or if the viral load increased to more than 50,000 copies/mL on any single occasion. Following interruption, 11 patients (79%) maintained control of viraemia for more than 90 days, despite lack of HLA alleles associated with protection. 57% achieved control of viraemia for 180 days, 43% for 369 days and 21% for 720 days. However over time there was a gradual decrease in CD4 counts and increase in viral loads. The total magnitude of $CD8^+$ T cell responses increased 3.5, 2.1 and 1.78 fold at the first, second and third interruption and transiently detected HIV-specific $CD4^+$ T lymphocyte proliferative responses declined with recurrence of viraemia. Walker concludes that "despite initial control of viraemia, durable immune control in persons following treated acute infection occurs infrequently".

In response to this, Dean Hamer made a passionate request to Walker that he would now denounce the practice of treatment interruptions, acknowledge the potential risks of drug resistant evolution within them, and agree that they offer limited real clinical benefit. However there was little agreement on this and Walker did not seem to share Hamer's view that structured treatment interruptions were dangerous.

One particularly interestingly element of Walker's data was his finding that $CD8^+$ T cell responses measured by IFN-gamma release in the ELISpot assay did not correlate with protection from viraemia in his patients. In contrast measurement of HIV-1 specific $CD8^+$ T cell proliferation by CFSE staining revealed a very impressive correlation with protection from viraemia. This concurs with previous data published by Migueles *et al*, [21] demonstrating that HIV-1 specific $CD8^+$ T cell perforin expression, known to be deficient in HIV chronically infected individuals, is correlated with proliferation. Thus while proliferation is coupled to effector function, we are now experiencing a gradually dawning understanding that IFN-gamma expression is not part of this picture. The implication here is that the commonly used IFN-gamma assay, now the assay of choice in many immunotherapy and vaccine trials, may not be telling us the correct information about functional T cell responses in HIV infection

Brigitte Autran of the Hôpital Pitié-Salpétrière, Paris, France, presented the results of the first international, randomised, double blind, placebo-controlled, phase-I therapeutic vaccination trial: QUEST. [22] Here 79 individuals with primary HIV-1 infection were treated with HAART >72 weeks before being randomised to one of three immunotherapy arms. Group A continued to receive ART alone, group B received the ALVAC-HIV(vCP1452) therapeutic vaccine in addition to ART and group C received both ALVAC-HIV(vCP1452) and Remune therapeutic vaccines in addition to ongoing ART. ALVAC-HIV(vCP1452) was given I/M at weeks 8, 12, 16 and 20 following randomisation in groups B and C and Remune was given I/M at weeks 0, 4, 12 and 20 following randomisation in group C. In all groups ART was discontinued 24 weeks following randomisation and patients were followed up for an additional 24 week period. The primary endpoint was a viral load <1000 copies/mL at week 48 (24 weeks after stopping ART) without restarting ART. Secondary endpoints were maintenance of viral load <400 copies/mL throughout the 24 week ART interruption and time to reaching viral load above 1000 copies/mL after stopping therapy. In all cases restarting HAART was considered failure in the intention to treat analysis.

Preliminary analysis of the data (vaccinated patients in groups B and C have not been unblinded) reveals that while vaccination successfully induced T cell responses measured by IFN-gamma ELISpot, the virological endpoints of this study all failed. In vaccinated patients the median p24 specific CD4 ELISpot response was 180 spot forming units/cells (SPU) per 10^6 PBMC (n=32) versus a median of 0 for the ART alone treated group (n=18) (p=0.006). The median CD8 IFN-gamma response to gag was similarly high for the vaccinated patients at 275 spu/10^6 PBMC (n=34) compared to 0 for the ART-alone treated group (n=18) (p=0.002). Of the 52 vaccinated patients 15.4% received the primary endpoint of a viral load <1000 copies/mL plasma at the end of the 24-week treatment discontinuation period. Of the 27 ART-alone treated patients 22.2% reached this endpoint. There was no statistically significant difference in these values. There was also no statistical difference in the number of patients achieving viral load <400 copies/mL during the ART discontinuation period or the median number of days to a viral load more than 1000 copies between the ART alone and vaccinated groups.

The fact that vaccination here proved immunogenic in terms of T cell IFN-gamma responses, but yet failed to translate into

any discernable clinical benefit further adds credence to the notion postulated by Bruce Walker that IFN-gamma is perhaps the wrong marker of immune function to be measuring in our immunotherapy trials. It is becoming increasingly clear from the published literature that IFN-gamma production is not tied to T cell function in the manner perhaps we once thought it was. Indeed it is possible that because of this, assays measuring IFN-gamma release tend to churn out lots of positive results. These are popular as everyone likes to show positive results. Thus IFN-gamma production assays validate the immunogenicity of various strategies tested, while these responses yield very little clinical benefit because they have limited or no functional impact that could affect long-term clinical outcome.

Walker advocates the CFSE dye dilution assay (flow cytometry based lymphocyte proliferation assay) as an accurate measure of HIV-specific $CD8^+$ T cell function. Functional assays for measurement of HIV-specific $CD4^+$ T cells that offer clinically relevant alternatives to singly evaluating IFN-gamma production in the CD4 subset have previously been shown by other groups. Anna Vyakarnam's group at Kings College Hospital, London, demonstrate the superiority of IFN-gamma and IL-2 double positive intracellular staining by flow cytometry [23] and Frances Gotch's group at Chelsea and Westminster Hospital also in London demonstrate the superiority of the traditional lymphocyte proliferation assay incorporating radioactive labeled thymidine [24].

If we are to get a handle on useful immune responses that candidate vaccines or immunotherapies should be inducing, we need to be using assays which correlate with clinical outcome. This means that immunology laboratories and investigators need to be a little more adventurous in terms of the assays with which they choose to evaluate their immunotherapy trials. Hopefully the work in this area already laid out by some groups will be verified in larger immunotherapy studies and by other groups in the not too distant future. But until then the incremental acquisition of failing immunotherapy data continues to generate a business-as-usual feel to not really understanding why our chosen immune-based interventions are not working. Its back to the flow cytometer for me, and until then a few last runs down the Harmony Ridge with my snow-boarding buddy from Sydney, while the bars down below roar to the opening matches of some strange local game called "ice-hockey".

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TREATMENT ACCESS

A round-up of news about access to treatments, with links to sources

Graham McKerrow, HIV i-Base

US trade deals threaten access to medicines

Trade deals being negotiated between the United States and individual countries or regional groups could severely restrict access to essential medicines for millions of people around the world according to the international medical humanitarian organisation Medecins Sans Frontieres (MSF). MSF warns that the negotiations are part of a US strategy to build a network of agreements that undermine international consensus reached at the World Trade Organization (WTO) about the appropriate balance between the protection of private intellectual property and the protection of public health. These agreements will make it impossible for dozens of countries to ensure access to affordable medicines for their populations.

The MSF reports says: "After being forced to compromise in multilateral negotiations, the United States has turned its attention to regional and bilateral free trade agreements (FTAs) that will affect every region of the world. These bilateral and regional agreements are attracting little public attention, are often highly technical in nature, and are being negotiated in secret, despite repeated requests from civil society to open them to public debate. The United States' goal in such negotiations reflects the wishes of the group of industry representatives advising the US Trade Representative."

Links to the report "Access to Medicines at Risk Across the Globe: What to Watch Out for in Free Trade Agreements in the United States"

English:

http://www.accessmed-msf.org/documents/ftabriefingenglish.pdf

Spanish:

http://www.accessmed-msf.org/documents/ftabriefingspanish.pdf

USA and multinationals move to introduce fixed dose combinations

The US Food and Drug Administration (FDA) and several of the world's biggest pharmaceutical companies issued statements on the same day in apparently coordinated moves to outflank the smaller generic producers by planning to market drugs made by different companies in single pills, or as separate pills distributed together in the same packages. The announcements refer to providing treatments to developing countries, and the US government statement is explicit that this will be part of the United States' multi-billion dollar programme to tackle HIV in certain specified countries. The multi-drug pills are called Fixed Dose Combinations (FDCs) and having pills with different drugs in the same packages is referred to as 'co-packaging' or 'co-blisters'.

By offering FDCs the generic manufacturers are able to provide not only cheaper treatments but also treatments that are more effective because they are easier to take and therefore adherence is likely to be better. There have been demands dating back several years for the multinational pharmaceutical companies to produce FDCs but to no avail. It is only since the production of FDCs by the generic manufacturers and the availability of billions of dollars, from the US government and the Global Fund to Fight Aids, TB and Malaria, that the pharmacos have acted on this issue.

Below are summaries of the announcements and links to the full statements.

FDA process for fast track Fixed Dose Combination (FDC) approval

The US FDA announced on May 16 a guidance document that describes a process to expedite approval of co-packaged and fixed dose combination (FDC) therapies "so that high quality drugs can be made available in Africa and developing countries around the world under the President's Emergency Plan for AIDS Relief."

The new process simplifies procedures for submitting clinical safety and efficacy data, virology, chemistry and bioavailability information for treatments. A marketing application cannot be approved to permit sale in the United States until relevant patents or exclusivity protections expire, but the FDA could grant "tentative approval," showing that a product had met all FDA scientific standards for safety, efficacy, and quality. Such tentatively approved products would then be available for procurement under the $15 billion President's Emergency Plan for AIDS Relief.

Link to the Federal Register Notice, Availability of Guidance:

http://www.fda.gov/OHRMS/DOCKETS/98fr/cd0466.pdf

Link to the draft Guidance Document:

http://www.fda.gov/oc/initiatives/hiv/hivguidance.html

Details of the FDA announcement can be found on the US government website:

http://www.fda.gov/oc/initiatives/hiv/default.htm

On the Net:

FDA AIDS site:

http://www.fda.gov/oashi/aids/hiv.html

UNAIDS outlook:

http://www.who.int/mediacentre/releases/2004/pr33/en/

MSF says new procedures sidestep international standards

Médecins Sans Frontières has criticised the new US procedures for approving FDCs and co-packaged medicines, saying that rather than creating "a unilateral system which unnecessarily complicates and delays matters", the US should support the existing World Health Organisation prequalification system, and lend the technical expertise of FDA officials to the process.

A statement issued by Rachel M Cohen, US Director of the MSF Campaign for Access to Essential Medicines, says: "The US has repeatedly been invited and encouraged to take part in the prequalification project and has consistently refused to collaborate.

"It is the World Health Organisation, and not the US Food and Drug Administration, which has the mandate to set international standards for quality, safety, and efficacy. There is no justification for further delaying the availability of medicines that are already saving lives and that are already certified by the WHO as meeting stringent international standards for quality, safety, and efficacy."

The full MSF statement is at:
http://www.accessmed-msf.org/prod/publications.asp?scntid=1852004132172&contenttype=PARA&

Other links:
http://www.doctorswithoutborders.org/
http://www.accessmed-msf.org/

Gilead, Merck and BMS announce plans for FDC

A joint announcement was made on May 16 by Bristol-Myers Squibb, Gilead Sciences and Merck saying that the three companies were in discussions on the development of a once-daily, fixed-dose combination of three anti-HIV drugs and were also considering co-packaging options for the individual products.

The potential three-drug, fixed-dose combination would include two Gilead drugs, Viread (tenofovir disoproxil fumarate) and Emtriva (emtricitabine). In March, Gilead filed applications in the United States and Europe for approval of a single-tablet formulation of these two drugs. The third drug in the proposed combination, is efavirenz, which is marketed in the United States, Canada and certain European countries by Bristol-Myers Squibb as Sustiva and elsewhere by Merck under the brand name Stocrin.

The companies also are discussing a co-packaged version that would include the three products as an interim step until a fixed-dose combination product could be made available.

Although joint company collaborations are to be welcomed and patients in the West will be able to be able to benefit from the lead taken by generic companies, it is difficult to know how with current formulations this resulting FDC could be compressed into one pill. In this case the options of two pills QD will already be available in the existing formulations.

Boehringer and GSK announce co-packaging talks

Boehringer Ingelheim and GlaxoSmithKline issued a joint statement in Ingelheim, Germany, and London, UK on 16 May saying "both companies welcome the United States' continued involvement in the global response to HIV/AIDS". Boehringer Ingelheim and GSK have entered into discussions to assess the development of co-packaging of anti-retrovirals for the treatment of HIV infection in the developing world.

The full statement is at:
http://www.boehringer-ingelheim.com/corporate/asp/news/ndetail.asp?ID=1814

The world health report 2004 - changing history

A World Health Organisation report, *Changing History*, calls for a comprehensive HIV/AIDS strategy that links prevention, treatment, care and long-term support. At a crucial moment in the pandemic's history, the international community has an unprecedented opportunity to alter its course and simultaneously fortify health systems for the enduring benefit of all, says the WHO

The report comments that by the end of 2004, WHO will have achieved only 25% of the "3 by 5" target but many believe the figure that 25% is itself overly optimistic.

Among all possible HIV-related interventions, the report says it is treatment that can most effectively boost prevention efforts and in turn drive the strengthening of health systems and enable poor countries to protect people from a wide range of health threats.

WHO world health report:
http://www.who.int/whr/2004/en/
WHO press release:
http://www.who.int/mediacentre/releases/2004/pr33/en/

Cote d'Ivoire activists angry at slow disbursement from Global Fund

Activists are angry that six months after Cote d'Ivoire received a US$91 million grant to fight the disease, not a penny of the money has been spent fighting the spread of HIV or helping those living with AIDS. The first tranche of $28 million from the Global Fund to fight AIDS, TB, and Malaria was made available to the government of Cote d'Ivoire in December last year after being held up by several months of infighting between different ministries over who would get to spend it.

The representative of one Ivorian non-governmental organisation (NGO) said: "Projects have been submitted to the committee that is coordinating how the funds will be spent, but nothing has been done yet."

The representative of another Ivorian AIDS NGO, who was equally unwilling to be named, pointed out that Cote d'Ivoire had also received $2.5 million to fight AIDS from the United States and $760,000 from Belgium over the past year, but this money too had yet to be spent.

"The AIDS epidemic is getting more money that anything else in Cote d'Ivoire, but you can't see its impact on the ground," he complained.

The full text of the report by the UN Office for the Coordination of Humanitarian Affairs 2004 is at:
http://www.irinnews.org/AIDSReport.ASP?ReportID=3363&SelectRegion=West_Africa&SelectCountry=COTE_D_IVOIRE

700 PLWA in Panama face 'death by bureaucracy'

Unbelievable as it seems, 700 People Living with HIV/AIDS (PLWA) in Panama have been without their anti-retroviral treatment for over two months due to bureaucratic "errors", report Richard Stern and Guillermo Murillo, of the Agua Buena Human Rights Association

Most of these 700 people receive ARVs through the Panamanian Ministry of Health at one major inner city hospital and come from the country's working classes, and informal labor force, and are therefore among the nation's most impoverished people. Meanwhile, 1,100 employed middle and upper class PLWA who receive treatment through the government run but semi-autonomous "Social Health Institute" continue to receive their treatment care system.

Dr Gladis Guerrero, National AIDS programme director, acknowledged that because of "human error," the Health Ministry program failed to carry out purchases to ensure continued treatment for those who receive their ARVs through its programmes. Dr Guerrero would not say when the problem was expected to be resolved, only that she hoped that it would be "as soon as possible."

The full article is at:
http://www.aguabuena.org/ingles/articules/plwapanama.html

20 of the world's 41 richest nations have promised nothing to the Global Fund for 2004 and 2005

Aidspan, the US-based independent watchdog that follows the work of the Global Fund to Fight AIDS, TB and Malaria, says that almost half of the 41 richest nations have not promised a dollar to the Global Fund for this year or next year.

The group analysed the Equitable Contributions Framework, which was drawn up in 2002 to decide the level of contributions each country should make to the fund. They found that only 14 countries have given 100% of their equitable share.

Aidspan worked on the basis that the Global Fund declared that it needs at least $1.4 billion this year and $3.3 billion next year. They followed the proposal made by President Jacques Chirac of France and others and accepted by the US Congress, that the USA should provide one third of the total, Europe should provide a third and the rest of the world should give the final third. Within each 'third' the donations should be in proportion to the countries' gross national product (GNP). Aidspan looked at the records of the 41 countries that are defined by the World Bank as "high-income".

Only two nations, France and the Netherlands, have promised 100% or more of their equitable share for both years.

The good news is that the total promised to the fund for this year is $1.515 million, which is slightly higher than the $1,400 million goal. More than half (53%) of the 2004 money has come from the EU nations, which have 27% of the world's GNP, 36% from the USA, which has 32% of the world's GNP and 11% from the rest, which have 41% of the world's GNP, although half of this GNP share is attributable to more than 100 non-high income countries.

Total money promised for next year is $842 million, which is only 26% of the $3,300 million needed. This has come 69% from the EU nations, 24% from the US and 8% from the rest.

There are four high-income countries that are represented on the board of the Global Fund but are still significantly below their equitable contributions for this year. They are Austria, Canada, Japan and Switzerland.

The full Aidspan report is downloadable as a pdf at:

http://www.aidspan.org/globalfund/index.htm

Portion of its Equitable Contribution that each of the 41 high-income countries has pledged for 2004 and 2005

(*Asterisks denote countries represented on the Global Fund's board)

	2004	2005		2004	2005		2004	2005		2004	2005
Andorra	0%	0%	**Denmark***	**>100%**	**0%**	Kuwait	0%	0%	Singapore	3%	1%
Antigua & Barbuda	0%	0%	Finland	0%	0%	Liechtenstein	>100%	0%	Slovenia	0%	0%
Australia	40%	6%	**France ***	**>100%**	**>100%**	**Luxembourg ***	**>100%**	**0%**	**Spain ***	**100%**	**33%**
Austria *	**0%**	**0%**	Germany	100%	35%	Malta	0%	0%	**Sweden ***	**>100%**	**0%**
Bahamas	0%	0%	Greece	0%	0%	Monaco	0%	0%	**Switzerland***	**0%**	**0%**
Bahrain	0%	0%	Iceland	37%	0%	**N/lands ***	**>100%**	**>100%**	UAEmirates	0%	0%
Barbados	0%	0%	**Ireland ***	**>100%**	**0%**	New Zealand	0%	0%	**UK ***	**>100%**	**30%**
Belgium *	**>100%**	**0%**	Israel	0%	0%	**Norway ***	**>100%**	**0%**	**US ***	**>100%**	**18%**
Brunei	0%	0%	**Italy ***	**>100%**	**84%**	Portugal	0%	0%			
Canada *	**51%**	**44%**	**Japan ***	**33%**	**0%**	Qatar	0%	0%			
Cyprus	0%	0%	Korea, South	2%	0%	San Marino	0%	0%			

Roche announces lower prices – MSF disagrees

Roche announced in June fresh price cuts for nelfinavir (Viracept) and saquinavir (Invirase) for developing countries. However the company was immediately contradicted by Médecins Sans Frontières, who said the company had made the announcement in Swiss Francs, but a translation into dollar prices showed price increases.

Roche said it was cutting the cost of a pack of 270 250-mg tablets of nelfinavir from CHF90.90 to CHF88.40, and a pack of paediatric nelfinavir powder from 49 CHF to 39.50. It said it was reducing the price of a pack of 270 saquinavir capsules from CHF 95.40 to CHF 89.60.

A company spokesman said Roche sells the drugs at no profit to sub-Saharan Africa and other poor countries and reviews its prices annually to ensure they still reflect the cost of production.

Sean Healey, the Information Officer for the MSF Campaign for Access to Essential Medicines, said in an email response: "In US dollar terms, the prices actually rise for nelfinavir 250mg tabs and saquinavir 200mg caps in sub-Saharan Africa and LDCs [least developed countries], and also for nelfinavir 250mg tabs, nelfinavir powder for suspension and saquinavir 200mg caps in low-income and lower-middle-income countries. Roche, who corporate HQ is in Switzerland, is virtually the only major drug company to still quote their prices in a currency other than US dollars.

Healey continued: "Nelfinavir and saquinavir are both important drugs, but unfortunately Roche still doesn't take its responsibilities to patients seriously. In our view the Roche communication was in fact misleading."

MSF calculates that the price of 270 tablets of nelfinavir has risen from US$65.61 to $69.76, that 270 200-mg capsules of saquinavir have risen from $68.57 to $70.71.

Source: Roche and MSF press announcements

ANTIRETROVIRALS

CD4 entry criteria dropped for UK tipranavir named patient access

Polly Clayden, HIV I-Base

From June 14 the entry criteria for the Named Patient Supply of the investigational protease inhibitor tipranavir have broadened. There are now no restrictions on the basis of CD4 count or viral load.

Inclusion criteria that remain include being triple-class experienced with at least two previous PI based regimens. Women need to have a negative pregnancy test if they are of childbearing potential and be willing to use effective barrier method of contraception.

Exclusion criteria include:

- Female patients who are pregnant or breastfeeding
- Previous significant hypersensitivity to the active or any of the excipients of tipranavir or ritonavir
- Baseline AST/ALT > 5 x ULN OR total bilirubin > 3.5x ULN
- Baseline AST/ALT > 2.5 x ULN AND total bilirubin > 2x ULN
- Use of other investigational drugs (until TPV/r receives marketing authorisation)

Preliminary pharmacokinetic data on double boosting with saquinavir, amprenavir or lopinavir/r indicated negative interactions and significant reduction in plasma levels of these PIs (see HTB May 2004) [1]. If used, close clinical and laboratory patient monitoring should be undertaken.

If a physician wishes to start a dual boosted PI regimen the potential risks and benefits of the regimen should carefully be discussed with his patient. Clinical and laboratory monitoring of triglycerides, amylase / lipase and transaminases must be undertaken.

The safety of tipranavir in renal insufficiency is unknown. The risk/benefit for each patient has to be determined by the treating physician on a case-by-case basis.

There will be an administration fee for provision of tipranavir from August 7 2004. The cost will be £490 per 120 capsule pack.

Doctors who wish to enroll patient in this programme or who have further questions should contact Sarah Jones at Boehringer Ingelheim 01344 741282/742539.

Source: Boehringer Ingelhiem

Reference:

1. Large reductions in plasma PK levels of saquinavir, amprenavir and lopinavir/r levels when given with tipranavir/ritonavir
http://www.i-base.info/pub/htb/v5/htb5-4/Large.html

Tenofovir/FTC co-formulation expected in US by September

Gilead Sciences announced on May 17 that the US Food and Drug Administration (FDA) had granted priority review status to the New Drug Application (NDA) for the fixed dose co-formulation of the company's anti-HIV medications tenofovir (Viread) and FTC (emtricitabine, Emtriva). Gilead submitted its application to the FDA on March 12, 2004 and had anticipated a decision by January 12, 2005 based on a 10-month traditional review. Under priority review, the NDA will be reviewed with in six months and the action date by which the FDA will make a decision is September 12, 2004.

The proposed tablet will contain 300 mg of tenofovir and 200 mg of FTC and will be administered in combination with at least one other anti-HIV medicine. The company said that following approval of the fco-formulation, each drug would continue to be sold individually.

The full statement is at:
http://www.gilead.com/wt/sec/pr_572624

Guidelines for T-20

Guidelines for using T-20, (enfuvirtide, Fuzeon), have been produced by an international panel of experienced clinicians following a Roche-sponsored roundtable meeting and were published in 21 May issue of AIDS. They provide in greater detail a similar approach to that recommended in the British HIV Association (BHIVA) Guidelines.

The guidelines address:

- Use of resistance history and testing to optimise background therapy
- Optimal and less-than-optimal uses of T-20
- Safety and toxicity: injection site reactions, pneumonia and hypersensitivity
- Importance of training and support from healthcare professionals to assistant patients in successfully introducing T-20 into their daily routines
- Investment in patient training programmes to yield significant returns in the maintenance of adherence, patient confidence, and in the benefit of T-20 therapy.

The full guidelines are only available online to subscribers or as a pay-to-view article but reprint copies are available free from the Roche Drug Information Department on 0800 328 1629.

C O M M E N T

The changes to the expanded access programme for tipranavir (see earlier article) should mean that patients waiting to use T-20 with additional active drugs, now have a more supportive regimen.

Guidelines for using T-20 in London have been produced by the London Drugs Advisory Group of the HIV Commissioners Consortium, and this is posted to the BIVA website:

http://www.bhiva.org/consortium/t20.html

Persistent HIV viraemia fosters immunologic harm and viral evolution

David Douglas, HIVandHepatits.com

Persistent low-level HIV viraemia is associated with ongoing immune activation and antiretroviral treatment failure, according to a report in the 30 April issue of AIDS. In untreated HIV infection, HIV replication, HIV-specific T-cell responses, and T-cell activation contribute to disease outcome, the authors explain. How these factors interact in the setting of antiretroviral therapy is not well understood. Dr Steven G Deeks from the University of California, San Francisco, and colleagues assessed HIV-specific CD8 T-cell responses, T-cell activation, and phenotypic drug susceptibility during a longitudinal study of treated HIV-infected individuals experiencing sustained viral suppression, intermittent viraemia, or persistent low-level viraemia.

Ten of 18 patients with persistent low-level viraemia experienced virologic failure during the median 27 months of follow-up, the authors report, compared with 8 of the 15 patients with intermittent viraemia and none of the 13 patients with sustained suppression. The HIV-specific T-cell response was 12-fold greater among patients with persistent low-level viraemia and 9.5-fold greater among patients with intermittent viraemia than among patients with sustained viral suppression, the report indicates. Patients with intermittent or persistent viraemia also showed a greater breadth of HIV-specific immune responses than did patients with sustained suppression.

HIV-specific T-cell responses were stable over time in patients with suppressed and persistent viraemia, the researchers note, whereas the responses rose and fell with HIV RNA levels in patients with intermittent viraemia.

The median level of activated CD8 T cells was substantially higher in patients with persistent viraemia (16%) than in patients with suppressed or intermittent viraemia (6% and 9%, respectively), the investigators report. Most patients with persistent low-level viraemia also experienced an increase in the level of drug resistance under stable therapy.

“Our study suggests that persistent HIV replication during therapy drives ‘generalised’ immune activation, and that the activated immune system in turn supports viral evolution and a greater risk of virologic rebound,” Dr Deeks told Reuters Health. “In contrast, brief or transient periods of HIV replication do not have a measurable impact on immune activation. Thus, our data suggest that short-term exposures to a vaccine will not be harmful.

“Ongoing work in our group is focusing on the nature of these activated T cells,” Dr Deeks added. “We are particularly interested in the antigenic specificity of these cells. We are also interested in the question as to why some individuals exhibit high level immune activation during HIV infection while others do not.

“Although our study focused on HIV pathogenesis in the setting of highly effective antiretroviral therapy, we believe that our

data have direct clinical implications," Dr Deeks said. "For example, low level viral replication-as defined by persistent levels of detectable HIV RNA-is associated with immunologic harm and ongoing viral evolution. Such individuals may require a treatment modification." "Also, our data suggest that specific immunomodulators during incompletely suppressive therapy may prove to be very useful," Dr. Deeks said. "My hope is to see such drugs developed for this purpose."

C O M M E N T

Increasing or persistent levels of virus activity are likely to induce T cell responses. However knowing that these responding T cells can express IFN-gamma is not enough. It is important we know more about the quality of those responses i.e. not just their antigen specificity but the degree to which they can perform effector functions such as cellular proliferation, IL-2 production and cytotoxic perforin release.

It would appear that the HIV-specific IFN-gamma responses detected in this study show as little correlation with protection from viral activity as those described by Walker and Autran (see Keystone Report, this issue of HTB).

Ref: Karlsson AC, Younger SR, Martin JN et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viraemia. AIDS. 2004 Apr 30;18(7):981-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15096800

Latent drug-resistant HIV harboured for years

David Douglas, HIVandhepatitis.com

Among patients who had previously shown drug resistance, drug-resistant strains of HIV still existed in blood cells even though the patients were responding successfully to highly active antiretroviral therapy (HAART), Belgian researchers recently observed.

Dr Chris Verhofstede and Ghent University Hospital colleagues studied 11 patients who were successfully treated with HAART for a mean of 59 months. All patients had a history of suboptimal therapy and had developed drug resistance. Of these patients, 10 still had previously evolved drug-resistant HIV detectable in peripheral blood mononuclear cells.

"We were able to show that all drug-resistant HIV-1 variants that arise during therapy failure remain archived in the cells of the infected person for a very long period of time - at least 7 years and most probably much longer," said Verhofstede. The resistance was detectable "even if drug pressure was removed or if a patient subsequently responded well to a new drug combination."

"These findings indicate that once resistance arises against an antiretroviral, the activity of this drug will remain reduced for several years and possibly life-long, even after a withdrawal period of years," said Verhofstede. "Recycling drugs is therefore not an advisable option if other alternatives are available." He further noted that the results "argue against a possible benefit of therapy interruptions as a way to improve the effect of a subsequently introduced salvage regimen containing recycled drugs."

Ref: Verhofstede C, Noe A, Demecheleer E et al. Drug-resistant variants that evolve during nonsuppressive therapy persist in HIV-1-infected peripheral blood mononuclear cells after long-term highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2004 Mar 15;35(5):473-483.

DRUG INTERACTIONS

Non-prescription simvastatin in the UK: contraindicated with many HIV medications

Simon Collins, HIV i-Base

Mainstream press and TV items recently reported that Britain will soon become the first country to allow the sale of the cholesterol-lowering drug simvastatin (Zocor) without a prescription. This is in a move to cut the number of heart attacks and strokes. Low dose simvastatin will go on sale at pharmacies this year.

Simvastatin however is contraindicated for HIV patients who are on treatment because of significant interactions with indinavir, lopinavir, nelfinavir, ritonavir and saquinavir. There are also potential interactions with amprenavir, nevirapine, efavirenz and delavirdine.

Clinicians and pharmacists should ensure that patients with elevated cholesterol using these antiretroviral are aware that simvastatin is not an option for them.

Extensive drug-drug interaction charts are available on the excellent Liverpool University drug interaction website:
http://www.hiv-druginteractions.org

Label changes for indinavir warn of several interactions including atazanavir and PDE5 inhibitors

Graham McKerrow, HIV i-Base

Several changes have been made to the product label for indinavir (Crixivan) to warn of interactions with a number of drugs and to say that it should not be coadministered with atazanavir and that patients and doctors should be alert to interactions with the phosphodiesterase type 5 (PDE5) inhibitors sildenafil (Viagra), tadalafil (Cialis) or vardenafil (Levitra).

Indinavir (800 mg every 8 hours) coadministered with a single 10 mg dose of vardenafil resulted in a 16-fold increase in vardenafil AUC, a 7-fold increase in vardenafil Cmax, and a 2-fold increase in vardenafil halflife.

Taking indinavir with atazanavir (Reyataz) is now not recommended because both sometimes cause increased levels of bilirubin in the blood.

Text was revised in *Ritonavir* section to clarify PK when 100mg or 200mg ritonavir boosting is used.

Patients are now advised to tell their doctor if they are taking calcium channel blockers (eg amlodipine, felodipine), antiarrhythmics (eg quinidine), anticonvulsants (eg phenobarbital, phenytoin, or carbamazepine) or steroids (eg dexamethasone).

Advice on methadone has been revised to say: “Administration of indinavir (800 mg every 8 hours) with methadone (20 mg to 60 mg daily) for one week in subjects on methadone maintenance resulted in no change in methadone AUC. Based on a comparison to historical data, there was little or no change in indinavir AUC.”

Terfenadine (Seldane) was deleted and amiodarone (Cordarone) and D.H.E. 45, Migranal, Ergotrate, and Methergine were added under the “Medicines you should not take with indinavir” section of the patient package insert.

The revised product label says delavirdine (Rescriptor) inhibits the metabolism of indinavir such that coadministration of 400 mg or 600 mg indinavir three times daily with 400 mg delavirdine three times daily alters indinavir area AUC, Cmax and Cmin, but that indinavir had no effect on delavirdine pharmacokinetics.

The complete revised label is at the US Food and Drug Administration site:
http://www.fda.gov/cder/foi/label/2004/20685slr046,047_crixivan_lbl.pdf

WOMEN’S HEALTH

Smoking during HIV infection may alter the natural history of HPV infection and increase the risk of cervical disease

HIVandHepatitis.com

Human papillomavirus (HPV) infections in women are both common and clinically important. They have been linked to the development of cervical intraepithelial lesions and to invasive cervical cancer. The frequency of HPV infections and related lesions has been shown to be particularly high among HIV-infected women.

HPV-related cervical diseases have also been linked to smoking, which, like HIV, may play a role in the development of cervical disease, in part through an effect on the immune response to HPV.

A review published more than a decade ago cited 33 epidemiological studies of the association between smoking and cervical cancer. The majority of those works found such an association, and many of those that did not were said to have methodological flaws.

The author of the review concluded: “The evidence would seem to support the conclusion that the association between cigarette smoking and cervical cancer is causal” (p. 955); the results of subsequent work have supported these conclusions. In a recent study, which found a link between smoking and cancer among women with oncogenic HPV infection at baseline, the authors concluded: “Subsequent studies should examine the role of smoking in the multistage pathogenesis of cervical cancer.”

In the current study, HIV-infected (*n* = 1797) and HIV-uninfected (*n* = 496) women were assessed every 6 months for type-specific HPV DNA. Smoking status was self-reported. Covariates included age, parity, sexual behavior, HIV load, CD4 cell count, and antiretroviral therapy. Smoking was positively associated with HPV prevalence at baseline in HIV-infected women (*P* = .002) and was significantly associated with type-specific HPV. In Cox models, detection of HPV was significantly associated with smoking in HIV-infected women (*P* = .003), but HPV persistence was not (*P* = .72). The overall likelihood of acquiring persistent HPV was higher in smokers (*P* = .023) because of greater incidence.

Among HIV-infected women, smoking is associated with a significantly higher prevalence and incidence of HPV infection. Smoking during HIV infection may alter the natural history of HPV infection and increase the risk of cervical disease.

Ref: Minkoff H, Feldman JG, Strickler HD et al. Relationship between smoking and human papillomavirus infections in HIV-infected and -uninfected women. J Infect Dis. 2004 May 15;189(10):1821-8. Epub 2004 Apr 27.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15122518

PAEDIATRIC CARE

Pharmacokinetic characteristics of ritonavir, zidovudine, lamivudine, and stavudine in children with HIV

HIVandHepatitis.com

The aim of the current randomised, open-label, multicentre study was to evaluate and describe the parameters and characteristics of different drug regimens in children infected with HIV. The study settings were paediatric HIV research clinics in the United States and Puerto Rico.

Twenty-one HIV-infected children, aged 3-14 years, who were clinically stable and treated with the same antiretroviral therapy for 16 weeks or longer, were included. In step 1, children were randomised to receive one of three treatment regimens: zidovudine (Retrovir, AZT) plus lamivudine (Epivir, 3TC), ritonavir (Norvir) plus zidovudine and lamivudine, or ritonavir plus stavudine (Zerit, d4T). Patients originally assigned to the zidovudine plus lamivudine group in step 1 were eligible to progress to step 2 if their HIV RNA values at week 12, 24, or 36 were 10,000 copies/ml or greater but 100,000 copies/ml or less. In step 2, they received a regimen of ritonavir plus stavudine and nevirapine.

Seven children were randomised to each of the three treatment regimens. Concentrations of the agents were quantitated at steady state after observed doses, and the pharmacokinetic parameters were determined. Nevirapine concentrations were not determined. One child was excluded from analysis because pharmacokinetic parameters could not be estimated. Ritonavir oral clearance was slower in the pooled cohort of children who received stavudine compared with zidovudine and lamivudine. Stavudine oral clearance was marginally faster when combined with ritonavir and nevirapine compared with only ritonavir.

Therapy for HIV is complex, and pharmacodynamic data indicate that relationships exist between systemic concentrations of antiretroviral drugs and virologic response. Careful drug interaction studies have not been conducted for all treatment regimens, and it will not be surprising if unexpected interactions are found.

Pharmacokinetic studies to address these considerations should be viewed as a fundamental component of antiretroviral drug development, as they represent a tool to improve pharmacotherapy for HIV-infected children.

Ref: Fletcher CV, Yogev R, Nachman SA et al. Pharmacokinetic characteristics of ritonavir, zidovudine, lamivudine, and stavudine in children with human immunodeficiency virus infection. Pharmacotherapy. 2004 Apr;24(4):453-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15098798

PRIMARY INFECTION

Sexual transmission of HIV by acutely infected individuals has a disproportionate effect on the spread of HIV and may explain the current pandemic

HIVandHepatitis.com

A large number of observational studies has estimated the average probability of male-female transmission of HIV per unprotected coital act to be 1/384—1/2000 transmission events per coital act during established (ie no-acute) HIV infection.

In a study using survey-based data on sexual behaviours in the United States, Pinkerton et al calculated that these probabilities of transmission per coital act would result in low rates of lifetime transmission (0.190.40 infected partners/man; 0.090.18

infected partners/woman), which, by themselves, could not sustain an epidemic.

The fact that genital fluids (not blood) are the principal vehicles for sexual transmission of HIV presents a particular problem for modeling the likelihood of HIV transmission during acute HIV infection on the basis of blood data. This is because acute HIV infection represents the period of initial establishment of anatomic HIV reservoirs; therefore, the viral dynamics in blood, which have been well described for acute HIV infection, cannot be assumed to apply to the genital tract.

Researchers in the Quest Study Group and the Duke-Emory Acute HIV Consortium examined whether viral dynamics in the genital tract during the natural history of acute HIV-1 infection could explain efficient heterosexual transmission of HIV. The investigators measured HIV concentration in blood and semen samples from patients with acute and long-term HIV infection. They than explored the effect of changes in viral dynamics in semen on the probability of transmission per coital act, using a probabilistic model published elsewhere.

Considered over time from infection, semen HIV concentrations, in men with acute infection, increase and decrease in approximate parallel with changes occurring in blood. Modeling suggests that these acute dynamics alone are sufficient to increase probability of heterosexual transmission by 810-fold between peak (day 20 after infection, based on the model) and virologic set points (day 54 and later after infection). Depending on the frequency of coitus, men with average semen HIV loads and without sexually transmitted diseases (STDs) would be expected to infect 7%-24% of susceptible female sex partners during the first 2 months of infection. The predicted infection rate would be much higher when either partner has an STD. The authors conclude: “Empirical biological data strongly support the hypothesis that sexual transmission by acutely infected individuals has a disproportionate effect on the spread of HIV infection. Acute hyperinfectiousness may, in part, explain the current pandemic in heterosexual individuals.”

The present study provides empirical evidence that men with acute HIV infection are biologically hyper-infectious because of increased genital shedding of HIV. In addition, the present study has provided evidence that, during acute infection, HIV load increases and decreases in semen in approximate parallel with changes occurring in blood, which have been well described. The present model of viral dynamics in semen suggests that, on average, individuals are hyper-infectious beginning before the onset of the acute retroviral syndrome and continuing for approximately 6 weeks thereafter.

Ref: Pilcher CD, Tien HC, Eron JJ Jr et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis. 2004 May 15;189(10):1785-92. Epub 2004 Apr 28.

ON THE WEB

Online medical resources:

HIV in-Site Knowledge Base

New or updated chapters from May and June include:

- **Antiretroviral treatment monitoring in developing countries: related resources**

http://hivinsite.ucsf.edu/InSite?page=kbr-03-01-19

- **Dosage adjustments for ARV-ARV drug interactions (adult dosing)**

http://hivinsite.ucsf.edu/InSite?page=md-rr-24

- **Dosing for ritonavir-boosted protease inhibitors: a table of dosage adjustments for treatment regimens including ritonavir-boosted protease inhibitors**

http://hivinsite.ucsf.edu/InSite?page=md-rr-23

- **Warning of interactions between trazodone and 3A4 inducers/inhibitors.**

http://hivinsite.ucsf.edu/InSite?page=ar-alert

Hopkins report – May 2004

http://hopkins-aids.edu/publications/report/report_toc_04.html

- **Genes, ethnicity, and efavirenz response: clinical pharmacology update from the 11th CROI**
- **HIV superinfection: can patients be infected twice?**
- **Syphilis rates climb again**
- **Travel advice for HIV-infected individuals**

Medscape (Requires one-time free registration)

Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmocokinetics and avoidance of drug resistance

http://www.medscape.com/viewarticle/477466

Identification and management of neurologic and psychiatric side effects associated with HIV and HAART

http://www.medscape.com/viewprogram/2960

PRN Notebook - June 2003

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

- **Pharmacokinetics, pharmacogenetics, and HIV**
- **Update on the treatment of acute and early HIV**
- **HIV and cardiovascular disease: responding to the risk**
- **Diagnosis and management of HPV-associated anogenital dysplasia in HIV-infected men and women**
- **Antiretrovirals for the World: needs and challenges**

MEETING ANNOUNCEMENTS

2nd European Advanced HIV Course

August 25-27, 2004

The European AIDS Clinical Society (EACS) is running its second course on 'Antiretroviral Therapy and Comprehensive Care for People living with HIV/AIDS' focused on the clinical management of HIV, in Montpellier (South of France) from 25th to 27th August 2004.

For further information please contact the EACS office for an application form:

sylvie-chatelin@eacs.ws

or download it from our website:

http://www.eacs.ws

IAPAC Conference in London

23 - 24 September, 2004
Royal College of Physicians, London

The International Association of Physician in AIDS Care (IAPAC) announces the first-ever IAPAC Sessions-Europe, taking place 23 - 24 September 2004 at London's Royal College of Physicians.
For the past three years IAPAC has hosted this symposium in the United States, providing HIV-treating physicians an opportunity to discuss and debate the latest issues on HIV clinical management with their fellow IAPAC members.

The association is pleased to bring this unique gathering to its European membership.

To register and/or receive further information (including the program) on sessions, please contact

Nicole Burnham at:

nburnham@iapac.org

or Ben Collins at:

bencollins@sbcglobal.net

PUBLICATIONS AND SERVICES FROM i-BASE

Introduction to Combination Therapy – July 04

We have updated our non-technical patient guide to treatment.

This guide provides everything you need to know before starting treatment.

Printed or pdf versions of this guide are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. To order copies, see below and the back page.

Guide to changing treatment: second-line and salvage therapy

This is a non-technical patient guide to second-line and salvage therapy. 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. To order copies, see below.

Guide to HIV, pregnancy & women's health

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.

Guide to avoiding & managing side effects

A comprehensive 36-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.

Chinese, French, Italian and Spanish translations of this booklet are also available.

HIV Treatment Bulletin (HTB)

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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.

World CAB Report: focus on international drug pricing

This is a report of a meeting held in San Francisco over three days in February 2004 of community advocates and three major pharmaceutical companies that focused on pricing issues and global access to treatment. To order copies, see below.

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 eighth meeting, are posted to the i-Base website.

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

The i-Base website

http://www.i-Base.info

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http://www.aegis.com/pubs/i-base/2004

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h-tb

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