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April 12-14, 2000. Chicago, IL. USA.

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30-31 March, 2000. Noordwijk, Netherlands

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Reports from the

Third International Workshop on Salvage Therapy for HIV Infection.

April 12-14, 2000

Chicago, IL. USA.

Paul Blanchard, HIV i-Base

The Workshop on Salvage Therapy for HIV Infection has established itself as an annual meeting focused on the needs of those patients who have continued viraemia and deteriorating clinical status despite receiving antiretroviral therapy. These so-called 'experienced' patients have a long history of treatment with a variety of agents often dating back to zidovudine monotherapy.

Increasingly, however, their ranks are now being swelled by those who were therapy naïve when starting triple combination therapy, but whose combination failed to make the grade either through inadequate potency, poor tolerability or difficult adherence.

The term 'salvage' is a much debated one, and being poorly defined, sits awkwardly in this meetings title - watch out for a possible name change for next years outing. Historically it has been noticed that virological response to any second-line regimen is always inferior to responses achieved in an antiretroviral naïve study population. This occurs despite exposure to new agents. Indeed, even second-line combinations which contain entirely new classes of agent and consist of components to which the patient is completely naïve still exhibit this blunted response.

Consequently, each serial attempt at virological control becomes that much harder to achieve. This leaves many patients and their physicians having to settle for less stringent goals where partial virological control and clinical stability is the most that can be achieved.

The causes of treatment failure for both initial and subsequent combinations are both multifactorial and complex. The following factors are currently being explored.

- Resistance - genotypic and/or phenotypic testing of viral isolates
- Pharmacokinetics - therapeutic drug monitoring
- Adherence / tolerability - talk to the patient!
- Toxicity - investigate drug levels, careful monitoring of liver function, triglycerides etc.

Inadequate knowledge and imperfect diagnostic tests make the determination of the role of each of these factors both difficult and imprecise.

The success of subsequent regimens, however, is strongly dependent on identifying (and eliminating) the contributing factors to failure of the previous regimen. Patients struggling with difficult regimens of inadequate potency deserve access to state-of-the-art diagnostics, even those yet to be perfected.

Indinavir plus ritonavir: *Might exposure to higher levels of indinavir overcome protease resistant HIV and prove useful to 'rescue' previously failed protease inhibitor based combinations?*

Combination of indinavir with lowered doses of ritonavir is a commonly used strategy to overcome the problematic short half-life of indinavir. Combining indinavir with ritonavir (IND/RTV) allows for twice daily dosing, does away with the fasting requirements of indinavir and still provides for a greater 'comfort zone' before indinavir levels might fall below required inhibitory concentrations. The user friendliness and potential for improved adherence achieved by combining these two protease inhibitors (PIs) means that few physicians will even consider prescribing indinavir as the sole PI component in an antiretroviral combination regimen.

There were three presentations of interest on IND/RTV at the Salvage Therapy Workshop. The first from Jon Condra of Merck Research Laboratories was an in-vitro study [1]. Historic pharmacokinetic data from single PI and ritonavir co administration was compared to known inhibitory concentrations for wild-type HIV-1 and inhibitory concentrations which had been determined for a panel of 20 clinical isolates from heavily PI experienced patients.

See Table 1.

Resistance is defined phenotypically as the fold increase in the concentration of drug needed to inhibit a particular HIV isolate. The reduction in drug susceptibility is signified by an increase in inhibitory concentration. If drug concentration can be raised above this fold increase then the viral isolate should be inhibited by the drug and no longer exhibit resistance. This means that drug resistance can be treated as a continuum rather than an absolute threshold phenomenon.

During dosing of PIs the plasma trough level or Cmin is often used as a conservative measure of the minimal drug exposure achieved during the dosing interval. When comparing this level to inhibitory concentrations measured in vitro caution must be observed due to the protein binding which is characteristic of all PIs. Protein binding 'locks up' a high percentage of free drug in the plasma and a protein binding correction must be applied which effectively raises the inhibitory concentration. Condra's data used inhibitory concentrations corrected for protein binding (by 50% human serum).

Plasma drug trough levels (Cmin) for single PIs were compared to the protein binding corrected IC95 (the inhibitor concentration required to achieve 95% inhibition)

Table 1

REGIMEN	DRUG	Ratio Cmin/ IC95 (wild-type) *	No. of resistant mutants from panel where Cmin ≥ IC95 * †
IDV 800 mg q8h	IDV	3.7	0/20
RTV 600 mg bid	RTV	2.4	0/20
SQVsgc 1200 mg tid	SQV	0.4	0/20
NFV 750 mg tid	NFV	1.8	0/20
NFV 1250 mg bid	NFV	1.2	0/20
APV 1200 mg bid	APV	0.9	0/20
DUAL PROTEASE COMBINATIONS			
SQV 400 mg / RTV 400 mg bid	SQV	1.7	0/20
	RTV	1.1	0/20
APV 1200 mg / RTV 200 mg bid	APV	6.7	**17/20**
	RTV	ND	ND
IDV 400 mg / RTV 400 mg bid	IDV	24.2	**13/20**
	RTV	2.9	0/20
IDV 800 mg / RTV 100 mg bid	IDV	28.6	**15/20**
	RTV	0.5	ND
IDV 800 mg / RTV 200 mg bid	IDV	68.5	**18/20**
	RTV	1.8	ND

ND = no data * IC95 corrected for protein binding † using IC95 of resistant mutant

for wild-type HIV-1. Most (but not all) PIs were found to maintain trough levels approaching or exceeding that drug's protein binding corrected IC95. Ratios of Cmin/ IC95 were calculated for each PI with the supposition that regimens achieving high Cmin/IC95 ratios would be expected to maintain more efficient viral suppression at trough than regimens with lower ratios (see table for ratios).

A panel of 20 PI-resistant clinical isolates were used by Condra's group and the fold-increase in IC95 determined for each isolate by phenotypic testing. These clinical isolates were from patients in whom indinavir had failed (14/20). 3/20 had experienced virological failure while receiving nelfinavir and 3/20 while receiving indinavir after a previous nelfinavir failure. All isolates had multiple substitutions in the protease gene typical of high level resistance to indinavir and/or other PIs. Indeed, they were the most 'genotypically resistant' viruses that could be identified in the groups collection and reflected the diversity of genetic patterns associated with virological failure to PIs in the clinical setting.

All PIs dosed individually achieve relatively low ratios of Cmin/IC95, even against wild-type HIV. It is unsurprising, therefore, that no individual PI could provide sufficient drug exposure to overcome the higher inhibitory concentrations characteristic of HIV-1 which has developed resistance to PIs.

It was hypothesised that the raised trough levels achieved by co-dosing saquinavir (SQV), amprenavir (APV) or indinavir (IDV) with ritonavir (RTV) may be sufficient to render HIV from this panel of resistant clinical isolates sensitive. The effect on the ratio of Cmin/IC95 of combining each of these PIs with ritonavir (at differing dosages) can be seen in the table. Notably there were substantial increases in the ratio for both amprenavir (from 0.9 dosed as a single PI to 6.7 dosed with RTV) and indinavir (from 3.7 as a single PI to 24.2 - 68.5 for various dosage combinations of IND/RTV). For SQV/RTV (400 mg/400 mg) the enhanced Cmin obtained (for both the SQV and the RTV) were still not sufficient to exceed the raised IC95 of any of the resistant viruses. The combination of APV/RTV (1200 mg/200 mg) achieved enhanced Cmin of amprenavir which was higher that the IC95 of 17/20 of the panel of resistant viruses. It should be cautioned, however, that the clinical isolates had sustained only a modest loss of susceptibility to APV and none carried the APV-associated I50V mutation. The high ratios of Cmin/IC95 for indinavir achieved with the IDV/RTV combinations translate to inhibition of the majority of the resistant isolates. The 400 mg/400 mg dosing produced a Cmin for IDV capable of inhibiting 13/20, the 800 mg/100 mg 15/20 and the 800 mg/200 mg 18/20. These data suggest that the amprenavir or the indinavir exposure achievable by co-dosing with ritonavir appears sufficient to suppress the replication of most viruses exhibiting high-level genotypic resistance to indinavir and other PIs.

Condra concludes that resistance may be overcome by increasing drug potency and/or exposure, even with the same drug that had initially selected that resistance. He goes on to speculate that combination PI therapies, especially IDV/RTV and possibly APV/RTV, may provide effective salvage in many instances of PI failure. He cautions that these concepts and conclusions must be verified in clinical practice, but that results of clinical studies using IDV/RTV as salvage of PI failure appear consistent with these predictions (see also studies below).

Clinical studies of indinavir/ritonavir as salvage therapy

Two studies were presented at the workshop, both retrospective chart reviews, of results obtained using IDV/RTV in patients with prior PI failure. The first was from a group at the University of Miami who identified 27 subjects who received IDV/RTV (800 mg/200 mg bid) after a prior PI failure [2]. These subjects were split into two groups on the basis of their response to IDV/RTV containing regimens as either responders (n=15) or non-responders (n=12) and factors associated with type of response determined.

Both groups of patients had extensive prior treatment histories and there were no differences between the histories of responders (R) and non-responders (NR). Similarly the baseline characteristics for gender, age, race, CD4 count, viral load (VL) and length of follow-up were the same in both groups.

Mean CD4 count and viral load prior to IDV/RTV was 283 cells/mm3 and 150 cells/mm3 (p=0.1) and 156,545 copies/mL and 228,231 copies/mL (p=0.1) for Rs and NRs respectively. Prior treatment history included a mean of 2.4 PIs received over 86 - 101 weeks.

Response to IDV/RTV was defined as achieving a nadir viral load less than or equal to 400 copies/mL on at least one occasion, non-responders as patients with a nadir viral load greater than 400 copies/mL. Virologic failure on prior PI regimens was defined as a rebound in VL to ≥ 1000 copies/mL after having < 400 copies/mL on at least one occasion or a failure to achieve VL < 400 copies/mL after ≥ 6 months on the original PI regimen.

Adherence to drug regimens was also routinely assessed through patient questioning. Adequate adherence to the IDV/RTV was defined as taking ≥ 85% of the doses. Inadequate adherence was defined as taking < 85% of the doses.

Both genotypic and phenotypic resistance to IDV and RTV was determined for responders and non-responders from stored plasma samples. Genotypic resistance was defined as the presence of one or more substitutions in or near the active site and phenotypic as a ≥ 4-fold increase in the IC95 of the tested strain relative to wild-type HIV-1. Phenotypic resistance to NRTIs and NNRTIs was also measured and no difference was found in either the presence of resistance or the number of agents of either of these two classes of drugs between Rs and NRs.

Association between resistance to IDV and RTV and adherence amongst Rs and NRs was compared using Fisher's exact test in 2-by-2 tables. Genotypic resistance to IDV and RTV at baseline was found in 13 subjects, 10 of whom were responders (77%) and no genotypic resistance in 14 subjects, 5 of whom were responders (36%). Adequate adherence was found in 17 subjects, 13 of whom were responders (76%) and inadequate adherence in 10 subjects, 2 of whom were responders.

Fisher's exact test revealed:

- Adequate adherence was positively associated with a favourable virologic response to IDV/RTV (p=0.007).
- Baseline genotypic resistance to IDV and RTV was associated with adequate adherence to IDV/RTV (p=0.05).
- Genotypic resistance to IDV and RTV was associated with a **favourable** virologic response rather than with therapeutic failure (p=0.05).

Phenotypic resistance to IDV and RTV (≥ 4-fold increase in IC95) at baseline was found in 4 subjects, all 4 of whom were responders (100%). Lack of phenotypic resistance (< 4-fold increase) was found in 15 subjects, 5 of whom were responders (33%). Adequate adherence was reported for 10 subjects, 7 of whom had a favourable response (70%). Inadequate adherence was found in 9 subjects, 2 of whom had a favourable response (22%). Fisher's exact test revealed:

- Baseline phenotypic resistance to IDV and RTV was associated with a **favourable** virologic response rather than with therapeutic failure (p=0.03).

The small numbers of patients with phenotypic resistance precluded the assessment of any possible relationship between baseline phenotypic resistance and adherence.

The group concluded from these data that IDV/RTV as part of salvage therapy is capable of adequately suppressing viral loads in heavily pre-treated patients failing PI-based regimens. Furthermore, this suppression is achieved using the same PIs on which patients had previously failed and to which they display both genotypic and phenotypic resistance. Adherence to therapy appears to be a critical factor in determining efficacy of this salvage regimen.

The second retrospective chart review presented by Howard Grossman covered 41 patients from 3 clinics in the U.S.A. receiving IDV/RTV (800 mg/200 mg bid) following virological failure on at least one prior PI containing regimen [3]. Virologic response, change in CD4 count and patient tolerability were assessed. At baseline prior to IDV/RTV median HIV RNA and CD4 count was 30,015 copies/mL and 258 cells/mm3 respectively. 100% of subjects were PI experienced (95% to IDV or RTV) and 73% were NNRTI experienced. The mean number of prior PI regimens was 3 (range 1-6). The IDV/RTV regimen in 29/41 subjects (70.7%) also included an NNRTI but only 7/29 patients were NNRTI naïve. Mean number of concurrent RTIs in the IDV/RTV based regimen was 2.

Data was extracted from charts at a mean follow-up time of 7.2 months (range, 3-17 months) on IDV/RTV therapy. Median change in plasma HIV RNA and numbers of patients below an assay cut-off of 400 copies/mL was presented (see table). Increases in median CD4 counts of 50 - 100 cells/mm3 between weeks 12 and 24 were also seen.

Table 2

Observed follow-up	N	Median Change (log10 HIV RNA)	% patients < 400 copies/mL
12 weeks	41	-1.65	51% (21/41)
24 weeks	30	-1.46	57% (17/30)
36 weeks	15	-1.66	63% (10/16)

Complaints related to tolerability were described which had warranted chart documentation. These led to discontinuation in only 2 cases, one for nausea and vomiting and one for alopecia. The investigators commented that the regimen appeared to be well tolerated and concluded that results for IDV/RTV (800 mg/200 mg bid) were encouraging for such highly treatment experienced patients.

C O M M E N T

Low absorption and pharmacokinetic limitations of currently available protease inhibitors has led to attempts at pharmacological enhancement either through administration with high fat meals, lipid rich capsule formulations, or co-administration with ritonavir, a potent inhibitor of cytochrome P450. The original approach to co-administration attempted to have both PI components provide plasma levels contributing to viral inhibition. This led to the much studied combination of RTV/SQV dosed at 400mg/ 400mg bid. Condra's data support this concept, but the levels of drug achieved with this approach would only be expected to inhibit wild-type virus. Additionally, tolerability is still problematic when RTV is dosed at these higher levels.

The more recent approach is to limit the role of ritonavir purely to that of a PK enhancer, and not to expect it to be acting as an antiretroviral at all. If you allow this approach, doses of ritonavir as low as 100mg may be sufficient to smooth out the PK and substantially raise trough levels of your primary PI. As Condra demonstrates, these raised trough levels (for indinavir and amprenavir) may even be sufficient to expect them to inhibit PI resistant virus. Indeed, this is the very approach taken by Abbott for ABT-378, a newer PI still in late stages of development. Co-formulation of ABT-378 with 'baby' doses of ritonavir, leads to ABT-378 providing trough levels of drug exceeding the EC50 of some PI resistant isolates. Thus, the rationale for the use of ABT-378/r and IDV/ RTV in salvage situations is the same.

Tolerability issues may, however, differ between ABT-378/r and IDV/RTV in salvage situations. Anecdotally clinicians report higher incidence of nephrolithiasis in patients receiving IDV/RTV at 800mg/200mg compared to those receiving 800mg/100mg. Additional side-effects of concern to patients such as dry skin, chapped lips and hair thinning might also be more common and severe at the 800mg/200mg dosage. These particular adverse effects to not seem to be an issue with ABT-378/r which appears to be extremely well tolerated. Given the data presented by Condra, clinicians might be confident in dosing IDV/RTV at 800mg/100mg in PI naïve patients, but may wish to consider the 800mg/ 200 mg dosing in PI-experienced patients.

There are additional considerations when trying to achieve high ratios of Cmin/IC95 with these combinations, regarding both resistance testing and therapeutic drug monitoring (TDM).

If such protease inhibitor regimens as IDV/RTV, APV/ RTV and ABT-378/r are sufficiently potent, neither genotypic resistance nor low-to-moderate phenotypic resistance may predict therapeutic failure. The results of such tests must be considered in light of the regimens overall potency and the drug exposure that can be achieved.

When using TDM to assess drug exposure it has been common to attempt to titrate dosage of drug to historical controls. When your primary aim is high trough levels, these historical controls are inappropriate. In such salvage settings should dose be standardised to those known to exceed the IC95 at trough of most resistant viruses? Should dose be titrated clinically by tolerability? Or should TDM be used in an attempt to titrate dose to achieve a Cmin known to inhibit that particular patients clinical isolate previously established by phenotypic testing?

References

1. Condra JH, Petropoulos CJ, Ziermann R et al. Resistance to HIV-1 protease inhibitors and predicted responses to therapy. Third International Workshop on Salvage Therapy for HIV Infection. April 12-14, 2000, Chicago, USA. Abstract 2.
2. Campo RE, Suarez GA, Miller N et al. Efficacy of indinavir/ritonavir-based regimens among patients with prior protease inhibitor failure. Third International Workshop on Salvage Therapy for HIV Infection. April 12-14, 2000, Chicago, USA. Abstract 7.
3. Grossman H, Luber A, Butcher D et al. Salvage therapy with twice daily indinavir 800mg plus ritonavir 200mg based regimen in clinical practice. Third International Workshop on Salvage Therapy for HIV Infection. April 12-14, 2000, Chicago, USA. Abstract 27.

Reports from

First International Workshop in Clinical Pharmacology in HIV Therapy

30-31 March 2000

Noordwijk, Netherlands

Simon Collins, HIV i-Base

The First International Workshop in Clinical Pharmacology in HIV Therapy was held from 30-31 March in Noordwijk, the Netherlands. Over 30 oral presentations and 50 posters provided information on new assays, quality assurance, drug interactions, adherence, sanctuary sites, PK related to efficacy and therapeutic drug levels monitoring. It was notable that over 40 of the 120 delegates present were from the US, and this reflected an increased interest in using TDM in clinical practice that has been generated by European researchers.

Standardisation and quality control

In the UK, where all TDM is currently performed at Liverpool University, validated assays are already established and results from studies there correlate closely with groups from the Netherlands, who are similarly experienced. However, as new laboratories develop assays to offer this service, it is vital that a quality control programme is supported and maintained between sites. To this end, the International Inter-laboratory Quality Control (QC) Programme for TDM has been established by David Burger at the University Medical Centre, Nijmegen, the Netherlands.

Evaluations are based on analysing drug-free plasma spiked with weighed concentrations (low, medium and high) for each approved PI. The results from this study showed a 20% variation between assays used at different sites (sites remained anonymous in the results), which is actually very close to the 12-15% inter-assay susceptibility accepted for similar assays.

The variations detected between sites were believed to come from differences in weighing of the drug used when calibrating each test and hope to be resolved by increased standardisation of the HPLC-UV or LC-MS systems that are used. Based on these encouraging results, a second round of QC is already underway, and it will be important that new sites providing TDM support are enrolled in this scheme.

This QC programme will involve monitoring samples from each site on a quarterly basis, and the frequency and continuous nature of this approach is itself expected to lead to a further refining of this technology. [1] These results, are also a significant improvement on the fivefold difference found between US labs, in an Agouron study, that was presented last May at the AIDS Treatment Project (ATP) Symposium on TDM.

TDM in clinical practice

Some of the most forthright commentary on using TDM in clinical practice was provided by Dr Ceppie Merry, who began with a quotation from J. Schentag that *'if we continue in the practice of 'one dose for all' we will quickly enter unmanaged chaos and total irrationality'.*

Dr Merry previously worked closely with David Back lab in Liverpool to provide TDM for all patients attending St James Hospital in Dublin. For the last ten months Dr Merry has been involved in clinical practice in Chicago. As more patients see their second and third-line therapies fail, and only a limited number of really new drugs look likely to reach the market in the next couple of years *'it is far from certain that the pharmaceutical industry alone can help us out of this situation. Maybe we have to make better use out of what we have now, especially for those patients who have run out of other options.'*

Dr Merry highlighted the differences between scientific approaches to the introduction of resistance testing and that of TDM, as *'one of the double standards in HIV therapy today'.* While debate will no doubt continue to refine the therapeutic ranges for individual drugs and the most useful sampling points, it is now at least generally recognised that there is a relationship between drug concentrations and outcome, and that the critical factor is time above minimum inhibitory concentration (MIC).

Caveats against use of TDM given in the recent JAMA guidelines for treatment of HIV include cost, quality assurance and uncertainty about optimal use - but these are all factors that remain to be proven for resistance assays, although theses are now routinely provided in the US. In practice, integrating TDM 2-3 weeks into a new regimen offers the potential not only to ensure adequate drug potency when its is most needed, but by increasing the duration of that regimen, will reduce the need for more costly resistance tests upon treatment failure.

Dr Merry concluded by suggesting that the experience of doctors and researchers interested in this area who were present at the meeting, many of whom had been involved in using TDM for PIs for over five years, may be best focused as an expert advisory panel. This would be an important practical outcome from this symposium and we hope it is one that is taken up by the organisers of the meeting. [2]

ATHENA - Early results from first randomised study of clinical benefits of TDM

18 months ago, two large randomised studies designed to look at the clinical benefit of TDM, were both being planned. While the UK's MRC sponsored and long awaited OPIUM has yet to enrol, and indeed is still dependent on

a last-minute reprieve, early results of the Dutch ATHENA study were presented at this meeting. ATHENA will randomise 600 patients (50% treatment naive, 50% experienced) from 22 sites in Holland, to one of two study arms. The intervention arm involves drug concentrations being determined at regular intervals and the results reported to the treating physicians, together with advice from a pharmacologist; in the control arm the results of the tests are not reported. MIC levels for each PI were determined at 0.1mg/ml for indinavir, 0.4 mg/ml for nelfinavir. 2.1mg/ml for ritonavir and 0.05 mg/ml for saquinavir (SGC). Target values for the concentration ratio (CR) were between 0.75 - 2.0 population values (ie if CR < 0.75 a dose increase was recommended and if CR >2.0 it is thought safe to recommend dose reduction). It was stressed that individual patient treatment histories provided by clinicians are essential in order to be able to provide a recommendation. By refusing to run tests unless this history was provided, produced a 95% adherence by clinicians for these forms. Results and advice were available within four weeks.

Results to December 1999 include 391 patients (34% treatment naive), with 1828 sample levels, evenly split between the intervention and control arms (938 vs 890).

Table 3

	Number of measurements *	% < 75%of pop. values	% > 200%of pop. values
IDV	387	28%	5.9%
NFV	378	26%	5.0%
RTV	404	27%	9.9%
SQV	287	41%	11.5%
NVP	372	10%	3.5%

** from both arms combined*

Early results indicate that at least a quarter of patients on each of these PIs lead to a recommendation to prompt adherence support and/or increased dosing. Although a smaller number of samples showed levels more than double the target level, in practice recommendations to reduce doses were rarely followed unless high toxicity was reported. TDM is already routinely available for all patients in the Netherlands, and this was one of the difficulties for patients in the blinded arm. This study identified a disturbingly high percentage of patients failing outside a very broadly defined therapeutic range for each drug and further results of this and other studies and needed urgently. [3]

TDM for individualising dosing - practicality and efficacy for PIs and RTIs

Courtney Fletcher, from the University of Minnesota, is one of the key pharmacologists in the US who currently prioritises this area of research. Dr Fletcher provided up-dated data from one of several of his studies presented at the last ICAAC. The primary aim of this randomised open label study was to evaluate the safety and feasibility of individually adjusted concentration controlled (CC) regimens, compared to standard dosing (STD). All patients received AZT/3TC/indinavir. Intensive PK studies were performed at weeks 2, 28, and 56 if eligible, and steady-state target concentrations were 0.19mg/l for AZT, 0.44mg/l for 3TC and a Cmin of 0.15 mg/l for indinavir. Dose adjustments included TID dosing for AZT and 3TC and occasionally QID dosing for indinavir. In addition to a statistically significant improvement in obtaining optimum dosing concentrations shown below the median time taken to reach undetectable HIV RNA (<50 copies) was 110 days in the CC arm compared to 176 days in the STD dosed arm.

Table 4

	% Patients achieving target dose	
	Standard dosing	Concentration Controlled dosing
AZT	8/13 (62%)	11/11 (100%) *
3TC	10/13 (77%)	11/11 (100%)
IDV	3/13 (23%)	9/11 (82%) *

** p = < 0.05*

Table 5

	Time to BLQ (<50)	BLQ at wk 24
Standard dosing	176 days	9/13 (75%)
Concentration Controlled dosing	110 days *	10/11 (91%)

** p = 0.056 (Mantel-Cox)*

Adherence was monitored by count of returned pills (patients were provided with medication for several additional days with each monthly supply), and was found to be equal in both arms, despite more complicated regimens in the CC arm.

Secondary aims of this study involved quantitating intracellular AZT- and 3TC- triphosphate, which are more critical to nucleoside activity, and the relationship to antiretroviral response. Results from 8 subjects (with a total of 69 paired plasma and PBMC samples) found no relationship between plasma clearance of AZT and 3TC but a significant correlation between PBMC concentrations of the triphosphate levels of each drug ($r=0.7$, $p<0.001$). Lower CD4 baseline was also found to lead to higher triphosphate levels and the rate of HIV RNA decline correlated with higher levels of TP in each drug. [4]

TDM and adherence

Perhaps the least effective use for drug level assays is for assessing patient adherence. Aside from overtones of *'big brother'* surveillance, random testing only provides information about the *'last dose'*, and can be complicated

by *'white coat adherence'* - where a patients takes medication on the days s/he know they have a doctors appointment. Reassuringly a similar reaction came from both clinicians and patient advocates in the audience although several other presentations detailed thorough and complicated methodologies from deriving adherence data from random sampling.

Nevertheless, John Urquart, Professor of Pharmco-epidemiology, Maastricht University, provided a plenary, aimed at establishing both the importance of adherence for successful treatment and many of the practical issues involved for doctors. Cross-referencing with adherence studies from other disease areas, HIV patients are actually remarkably compliant - a fact not attributable to the severity of the illness. Several studies in other disease areas show that success rates for adherence are apparently not related to the severity of symptoms or risk of future illness and studies for glucose intolerance, epilepsy and pain management were cited.

A recent article in the BMJ by Judith Jones showed that adherence rates drop to 40% after six months for patients prescribed other 'lifelong' medications. Diaries, histories and even TDM can overestimate adherence compared to electronic monitoring (MEMS). However, accurate feedback from patients to their doctor about actual adherence, will require allocating time to adherence issues in every consultation.

Doctors developing this area would also do well to bear in mind Dr Urquart opening remarks in his lecture, that pointed out that one of the key obstacles faced in improving adherence was the fact that *'doctors strongly believe that their patients do what they tell them'*. [5]

Drug interactions

Fourteen of the presentations reported on specific drug interactions, some of which had been reported at earlier meetings.

Interactions between St John Wort and antiretrovirals have received extensive publicity recently *(see HTB no.1)*, which were further strengthened by a new study at this meeting, showing that nevirapine levels were reduced by 19% when co-administered with hypericum [6].

Other studies though were also new to this meeting. In fact, learning of new interactions between anti-retrovirals that are already widely available and already being used together in combinations, emphasised the practical importance of being able to confirm dosing by measuring drug levels that are actually achieved. This is especially important in the context of multi-drug (often mega-drug) combinations that are providing optimistic results for patients in salvage therapy. Triple-PI, dual-NNRTI and multiple PI/NNRTI combinations are already being reported, and it in not possible or realistic for every combination to be studied in a trial setting before use.

The take home message from all these studies is that TDM should play a key role whenever considering combinations of drugs for which there is no clear interaction data. As many of these unknown interactions will come from the new of compounds in salvage studies and expanded access programmes, this will only be possible if manufacturers work together with independent laboratories to enable drug-level assays to be produced for use in expanded access programmes.

Availability of pure compound to enable labs to produce these assays prior to availability in expanded access became one of the more political requests made to the pharmaceutical companies present from both pharmacologists, clinicians and activists present.

Baby-dose ritonavir improves amprenavir profile

Although not approved by the EMEA at its first application for licensing, amprenavir may in fact offer advantages over other PIs if it is shown to provide a distinct resistance and side-effect profile. As with some other PIs though, it's optimal use is likely to be when co-administered with ritonavir, which leads to a reduced pill count and improved PK profile. This was supported in a study by Lamotte and colleagues from X.Bichat-C.Bernard Hospital Paris, which showed wide inter-patient variability in Cmin of amprenavir when used alone. This boost provided sufficient to enable efavirenz to be used concomitantly with APV/RTV. Efavirenz reduces levels of APV AUC by around 36% and the two drugs should otherwise not be used together.

As shown in Table 6, co-administration of these BD regimens resulted in APV Cmin at least 10-fold higher than when APV was used alone. Inter-patient variability was also wide. [7]

Data was not provided on Cmax or AUC levels but a Glaxo-Wellcome study in HIV-negative subjects presented at the 7th Retrovirus Conference showed that RTV (300mg BD) increased AMP (450mg BD) Cmax by 9%, Cavg by 238% and Cmin by 1325% and pointed to further studies within QD regimen. [8]

Ritonavir and indinavir with efavirenz

Aarnoutse and colleagues showed indinavir Cmin reduced by -48% and AUC by -19%, in 18 HIV-negative volunteers (at steady state with bid IDV/RTV 800/100) following 14 days of concomitant efavirenz (600mg QD). No dosage adjustment was recommended. [9]

Interaction of ABT-378/r (lopinavir/LPV) with PIs

Now available in the UK through both named-patient and the open label safety evaluation programmes, there will undoubtedly be a group of patients who look to LPV with other PIs in a salvage context. Ann Hsu presented results of a PK study where single doses of saquinavir, indinavir and nelfinavir to HIV-negative volunteers induced following 10 days 400/100 BID lopinavir. A second study added amprenavir/ritonavir (450/100,750/100 BID) for 5 days to steady state (17day) LPV.

See Table 7 for PK results were with lopinavir (L) and

Table 6 - Summary of APV Cmin (target 100ng/ml):

	RTV/APV/EFV			APV	RTV/APV		
RTV/APV dose	100/450	100/600	200/600	0/1200	100/450	100/600	200/600
Mean	1492±1580	1662±1522	1598±847	111±79	2344±1128	1730±797	2473±2061
Range	438-5090	553-5356	723-3260	0-295	517-4692	331-3067	602-5689
Median	1181	1294	1269	85	2360	1581	2669
N	36	9	10	36	12	14	5

Table 7 - Results were with lopinavir (L) and compared to historical data.

	sqv+L	sqv alone	idv+ L	idv alone	nfv+ L	nfv alone	apv+L1	apv+ L2	apv alone
dose	800bd	1200td	600bd	800td	750bd	1250bd	450bd	750bd	1200bd
AUC24	26	9.4	45	51	48, 40	42, 15	21	30	37
C max	1.3	1.0	3.5	9.0	2.3, 1.8	4.0	1.7	2.4	5.4
C trough	0.32	0.09	0.44	0.21	0.8, 0.6,	0.7	0.54	0.74	0.28

compared to historical data.

Dosing recommendations with lopinavir (400/100 BD) from this study were:

SQV 800mg BD
IDV 600mg BD
APV 750mg BD
NFV 750mg BD

Although at the above doses, nelfinavir had the most significant effect by reducing lopinavir AUC by 23% and C trough by 42% further NFV dose reductions are not recommended.

This study provided important information from single dose interactions in HIV-negative volunteers. [10]

L-Acetyl Carnitine (LAC) improves symptoms of peripheral neuropathy (PN): Evidence for increases in cutaneous innervation

Although somewhat tenuously linked to clinical pharmacology, the implications for this study are sufficiently important to justify early presentation at any HIV-related meeting.

Peripheral neuropathy can be one of the most difficult symptoms to manage, and one that significantly effects the quality of life. Estimates range from 10-35% of HIV positive patients and from 11-55% patients who use ddC, d4T, ddI or 3TC. For people who have no other remaining choices for antiretroviral therapy, or where the severity of symptoms has been underestimated and neuropathy has progressed, there are currently no effective pathogenesis based therapies.

The mechanism for nucleoside analogue -related PN is thought to be impaired neuronal mitochondrial DNA synthesis and repair which disrupts energy metabolism causing die-back of long peripheral axions. L-acetyl carnitine is an amino acid that enhances retrograde neurotrophic support of sensory neurons, and which suffers a decrease in serum levels in HIV neuropathy.

This open observational cohort study by Mike Youle performed lower leg skin biopsies on four patients with established PN (Grade 2-4) before and after 6 months oral LAC treatment (1500mg BID). Frozen sections were immunostained using fibre-type specific primary antibodies (PGP, GCRP, VIP) and FITC-labelled secondary sera, and were examined by fluorescence microscopy and optimised by digital photography. All sections were stained and analysed at the same time. The system used for computerised image analysis for each of three skin areas (epidermis, dermis and ecrine sweat glands) has already been validated for use in diabetes-related neuropathy.

Results showed an increase in area of immunostaining of 40% (p=0.22) for all fibre types and 493% (p=0.002) for small sensory fibres. The study noted a trend towards greater percentage increases with increased duration of neuropathy. In sweat glands the mean increase was 293% (p<0.001) for all nerve fibres and 273% (p<0.001) for sympathetic efferents.

All patients reported an improvement in symptoms and three of these four patients had continued nucleoside treatment throughout the study. Clinical grade of dysaesthetic pain improved from grade 3-4 at baseline to grade 1-2 following treatment with LAC. [11]

References

1. Aarnoutse R et al. International Interlaboratory quality control (QC) program for therapeutic drug monitoring (TDM) in HIV infection: first results. Abstract 1.4. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.
2. Merry C et al. TDM of PI Therapy: PK-PD considerations - Abstract 6.1. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.

3. Burger D, Hoetelmans R, Hugen P et al - ATHENA: A Randomised, Controlled Clinical Trial to Evaluate whether Therapeutic Drug Monitoring (TDM) Contributes to Reduced HIV-related Morbidity and Mortality. Abstract 6.6 First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.
4. BFletcher C et al. Concentration Controlled Antiretroviral Therapy. Abstract 6.2. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.
5. Urquhart J - The Challenges of Patient Non-Compliance with Antiretroviral Drug Regimens. Plenary 2. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.
6. De Maat MMR et al. A Potential Interaction between St Johns Wort and Nevirapine. Abstract 2.8. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.
7. Lamotte et al. Amprenavir Plasma Concentrations are Dramatically Increased by Association to Ritonavir in Baby Doses in HIV-infected Patients: Possible Combination with Efavirenz. Abstract 2.7. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.
8. Sadler et al - Phamacokinetic Drug-Interaction between Amprenavir and Ritonavir inHIV-Seronegative Individuals. Abstract 77 - 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA.
9. Aarnoutse et al. PK Study to Investigate the Influence of Efaviranz on a BID Regimen of Indinavir/Ritonavir (800/100mg) in Healthy Volunteers. Abstract 2.3. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.
10. Hsu A et al. Interaction of ABT-378/ritonavir with Protease Inhibitors in Healthy Volunteers. Abstrat 2.4. First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands
11. Hart AM, Terenghi G, Johnson M, Youle M - L-Acetyl Carnitine (LAC) Therapy Increases Cutaneous Innervation and Improves Symptoms in Antiretrovital Therapy Related HIV peripheral neuropathy. Abstract 7.2 First International Workshop on Clinical Pharmacology, 30-31 March 2000. Noordwijk, Netherlands.

ANTI-RETROVIRALS

Dosage adjustments for coadministration of lopinavir (ABT-378/r) and efavirenz

A recent report from Study M98-957, an ongoing Phase II study in which efavirenz was co-administered with ABT-378/r (lopinavir), has found an interaction between this protease inhibitor which is still in development and efavirenz . The study is being conducted in patients who are experienced with multiple protease inhibitors, but who have not been treated with non-nucleoside reverse transcriptase inhibitors. The study shows that efavirenz lowers the trough levels of lopinavir in the blood. High trough levels of lopinavir may be important for achieving maximum antiviral activity in patients who have previously experienced failure of PI containing regimens. According to officials at Abbott Laboratories (the developers of lopinavir), about 25% of participants in Abbott's expanded access program (EAP) are taking this combination (out of a total of 2256 participants).

Lopinavir is a co-formulation of ABT-378 with the drug ritonavir. Abbott recommends that the dose of lopinavir be increased to 4 capsules (a total of 533 mg ABT-378 and 133 mg ritonavir) every 12 hours if efavirenz is being coadministered. The normal dose is 3 capsules every 12 hours. The adjusted regimen is now included in the informed consent forms for new EAP applicants and all EAP sites have been notified of the change.

ABT-378/r (lopinavir) now available on named patient basis in UK

Abbott Laboratories have announced the availability of ABT-378/r, a protease inhibitor still in development, on named patient basis in the UK. Physicians may request supply of ABT-378/r to individual patients and there are no restrictions in terms of patient criteria.

This named patient program is in addition to the open-label safety evaluation study (M99-046UK) which also provides ABT-378/r to patients meeting the study criteria.

Physicians requiring further information, or needing to request ABT-378/r for individual patients should contact the Named Patient Administrator on 01628 644370.

Source: Abbott Laboratories, 4 April 2000

Enteric Coated ddI available on named patient basis in UK

A named-patient programme is now available for didanosine enteric coated capsules (ddI/EC). Supplies are limited, and Bristol-Myers Squibb ask clinicians to be guided by the following the entry criteria:

- Treatment naïve

or
- Failure on last regimen or resistance suspected/ confirmed

or
- Intolerant to 200mg tablet formulation of didanosine

Dosing for ddI/EC is one 400mg capsule daily. Food restrictions remain the same as for earlier ddI formulations. Capsules must be taken on an empty stomach (at least two hours after food), and patients should not eat for 30 minutes after dosing.

There will be an administrative charge of £193.60 for a month's supply of 30 enteric coated capsules of ddI provided in a bottle.

These supplies will be administered on a named patient basis, which as you may know does entail certain legal responsibilities including serious adverse event/ serious adverse drug reaction reporting requirements for the requesting physician.

For further information please contact the named patient administrator by telephone on **020 8754 3788,**
or by e-mail:

virology.namedpatient@bms.com

Source: Bristol-Myers Squibb, 25 April 2000

Nelfinavir Potency Concerns From PI Perspective 29, April 2000.

Results from several recent studies may help clarify how to best use anti-HIV drugs as part of first line therapy. These results seem to suggest that nelfinavir (Viracept), the most widely used protease inhibitor, may not be as potent as other drugs in its class or some of the non-nucleoside RT inhibitors (NNRTIs). This article provides an overview of the studies.

EuroSIDA Study EuroSIDA, an observational study that has enrolled over 8,500 people in over twenty European countries, recently reported several findings. Of note is one that suggests nelfinavir is a less potent first line protease inhibitor in a typical three-drug combination (along with two nucleoside analogue drugs) than indinavir, ritonavir or two protease inhibitors together.

An analysis of about 1,500 people showed that those starting therapy with either hard gel saquinavir or nelfinavir were less likely to achieve viral loads below 500 copies within 24 weeks of therapy. They were also more likely to have their viral loads rebound above 500 copies compared to people who started with indinavir, ritonavir or two protease inhibitors.

Eighty-five percent of the participants used three drugs; the rest used four or more. People who started with high viral loads and low CD4+ cell counts and those who started with one or two new drugs were least likely to have sustained responses.

Although this was expected in the case of hard gel saquinavir, known to have serious absorption problems, it was a surprise for nelfinavir. No obvious reason was given as to why nelfinavir fared so poorly. While there are limitations to observational studies, two other recent studies raised similar questions about nelfinavir, including ACTG 364 and the European COMBINE study.

ACTG 364 ACTG 364 compared nelfinavir alone, efavirenz alone, and both drugs together. All groups also received two nucleoside analogue drugs (NAs). Those receiving nelfinavir used the standard dose, given three times per day. ACTG 364 showed that people taking nelfinavir fared less well than those taking efavirenz, though people who used both did the best of all. In addition to nelfinavir, efavirenz or both drugs, all 189 participants took ddI+d4T, d4T+3TC or ddI+3TC depending on which NARTIs they had used before. After 48 weeks, the results showed the following.

Table 8 - Percentage pts < 400 copies/mL at 48 wks

Regimen	% with viral load <500 copies HIV RNA
NFV+2 NAs	35%
EFV+2 NAs	60%
NFV+EFV+2 NAs	74%

NFV=nelfinavir, EFV=efavirenz

Those taking combinations including efavirenz or efavirenz + nelfinavir were more likely to maintain good HIV control than those taking only nelfinavir. There was no difference in the suppression of HIV between these two groups. No difference in the rate of side effects was seen among the three groups.

Another surprising finding was that all study groups looked equivalent at the end of 16 weeks, originally planned as the end of the study. However, longer-term follow-up showed a real difference developed between the regimens. This should remind us that short-term studies can be misleading.

The COMBINE Study The COMBINE study compared nelfinavir (1,250mg twice daily) + AZT/3TC (Combivir) against nevirapine (200mg twice daily) + AZT/3TC. The study followed 142 people taking HIV treatment for the first time. Results seen in the two groups after 24 weeks were as follows. The outcome, favouring nevirapine, was equally true in people who began with either high (over 100,000 copies) viral load or low viral load (below 100,000 copies).

Table 9 - Percentage pts achieving < 20 copies/mL

Regimen	All patients	Baseline VL > 100,000 c/mL
NFV+AZT/3TC	33%	22%
NVP+AZT/3TC	58%	57%

NFV=nelfinavir, NVP=nevirapine

Source: PI Perspective 29, April 2000. From 'Project Inform'. For more information, contact the National HIV/AIDS Treatment Hotline, 800-822-7422, or visit our website, www.projectinform.org.

C O M M E N T

These are troubling findings given that nelfinavir is the most widely used protease inhibitor. Agouron Pharmaceuticals, its manufacturer, has tried to explain these results. It claims that a disproportionate number of people with mutations related to nucleoside analogue resistance were in the nelfinavir arm. Other scientists dispute the role this may have played. Agouron has not commented on the EuroSIDA or COMBINE studies.

What complicates this further is that the current federal (US) guidelines lists nelfinavir-based combinations as preferred and the nevirapine-based ones as less desirable-the opposite of these new findings. Since the approval of nelfinavir, Project Inform has publicly questioned whether it offers the same potency as indinavir and ritonavir. Now that studies have raised the same question, the burden is on federal authorities to decide what to do. One study suggesting inferiority may not be enough to question the value of a drug, but aren't three studies enough?

For people already using nelfinavir and having a good response, these findings may not warrant changing regimens. But it suggests more frequent checking of viral load. For those making their first treatment decisions, the new data should become one more fact in deciding which therapy to begin. There are now so many options for first-time treatment that learning about the reduced potency for one of them doesn't necessarily create a crisis.

PAEDIATRICS

Liquid formulation of efavirenz available for children in the uk on named patient basis

A named-patient programme is now available for a new liquid formulation of efavirenz, for use in paediatric HIV-care in children aged three years or older. The programme may also be extended if there is sufficient demand.

The liquid is a clear, strawberry-flavoured solution administered once-daily and may be taken with or without food. Participants will be dosed with efavirenz based on their body weight. Efavirenz has not been adequately studied in children weighing less than 13 kg or in children under three years of age and should not be given to children falling into these categories.

Currently, 100 mg and 50 mg capsules of efavirenz are available for paediatric use.

Contact DuPont Pharmaceuticals on 01438 842613.

Most reconstituted CD4 cells naive after HAART in children with HIV

Immune repopulation after highly active antiretroviral therapy (HAART) is different in children than in adults, according to a report in the April 15th issue of the Lancet.

In particular, reconstituted CD4 cells in adults tend to be memory cells carrying the CD45RO marker, while new CD4 cells in children tend to be naive T cells carrying the CD45RA marker, Dr D M Gibb, of the Medical Research Council Clinical Trials Unit, in London, UK, and other investigators for the Paediatric European Network for Treatment of AIDS Steering Committee say in the journal.

The investigators monitored immune repopulation in 25 vertically HIV-infected children for 1 year after HAART. Treatment with HAART brought about a 3-log reduction in plasma HIV RNA load that lasted for at least 1 year. Treatment also induced a *'substantial increase in median CD4 cells,'* the authors write, from 403 cells/mm3 at baseline to 650 cells/mm3 at 24 weeks and 631 cells/mm3 at 48 weeks.

At 48 weeks, 71% of the reconstituted CD4 cells in these children were naive cells, Dr Gibb and colleagues say. This contrasts with adult patients, in whom *'the initial rise in CD4 cells after HAART is due to expansion of CD45RO memory cells.'* The team attributes this difference to the presence of functioning thymus tissue in children.

The findings *'raise important questions about therapeutic strategies to be followed in children,'* the investigators note. *'Compared with adults, the presence of a functioning thymus in children may allow alternative approaches to treatment, including removal of memory cells, the major reservoir of HIV-1, which would not be possible in adults.'*

Ref: Lancet 2000;355:1331-1332.
Source: Reuters Health

OTHER NEWS

Decreased bone mineral density and HIV protease inhibitors

A possible connection between the use of protease inhibitors and decreased bone mineral density was first raised at the 1999 Conference on Retroviruses and Opportunistic Infections. Since then, several anecdotal reports of bone problems in PI-treated patients have been made. In the March 10 issue of AIDS, the link between these drugs and the risk of bone mineral density loss has taken a step closer to confirmation.

Researchers at the Washington University School of Medicine in St. Louis recruited 112 men for their study. Sixty of the men were taking combination antiretroviral therapy that included protease inhibitors. Thirty-five others were HIV-positive but were not receiving protease inhibitors and 17 were HIV-negative.

The researchers assessed the subjects' overall bone mineral density as well as that of their lower spine and thigh bone. Based on these measurements, the researchers found that 50 per cent of the subjects taking PI-therapy showed signs of bone diseases such as osteoporosis. In fact, the risk of osteoporosis in the PI-treated subjects was more than twice as high as that in HIV- subjects not taking protease inhibitors. Osteoporosis is a condition that weakens bones and makes them more vulnerable to fracture. It is most commonly observed in post-menopausal women and is often responsible for the 'shrinking' stature of the elderly.

Decreasing bone mineral density is a natural side effect of aging. The risk of accelerating that loss by the use of PIs is worrisome, particularly as many people taking these drugs venture further and further into middle age.

Ref: AIDS 2000;14:F63-F67. Source CATIE-NEWS. 'From Community AIDS Treatment Information Exchange (CATIE). For more information visit http://www.catie.ca'

GM-CSF beneficial for patients with advanced HIV disease

In a phase III multicentre trial of patients with advanced HIV disease, granulocyte-macrophage colony-stimulating factor (GM-CSF) significantly increased CD4 T-cell and neutrophil counts, delayed the time to first infection, and reduced the incidence of overall infection.

Dr Jonathan B. Angel, of the University of Ottawa, Ontario, Canada, and colleagues from the Leukine/HIV Study Group randomised 309 patients to receive either placebo or GM-CSF for 24 weeks. The patients' CD4 cell counts were between 50 million and 100 million cells per litre, they had previously had an AIDS-defining illness, and they were on stable antiretroviral therapy.

Adjuvant GM-CSF significantly increased CD4 and neutrophil counts after 1, 3, and 6 months of therapy, as reported in the March 10th issue of AIDS. Sixty-seven percent of patients receiving GM-CSF developed an infection, compared with 78% of patients receiving placebo. In addition, GM-CSF delayed the time to first infection to 97 days, compared with 56 days for placebo.

The study showed that there were no differences between groups in cumulative opportunistic infections or changes in HIV RNA.

The authors suggest that the addition of GM-CSF to an effective regimen of antiretroviral therapy could delay virologic failure. *'Whether the ability of GM-CSF to maintain viral suppression as observed in the advanced HIV population will translate to individuals with earlier stages of HIV disease remains to be evaluated.'*

Ref: AIDS 2000;14:387-395. Source: Reuters Health

INTERVIEW

A view from the lab: Interview with Professor Clive Loveday.

Polly Clayden, HIV i-Base.

A Foundation Chair in Retrovirology at the Royal Free Hospital School of Medicine was established in 1996 and Professor Clive Loveday was then appointed as the first UK Professor of Retrovirology in April of that year. The department was built during the rest of that year and the new laboratories commissioned in January 1997 at which time departmental activities could commence. We talk to him about his work...

Where were you working prior to this appointment, can we have some Clive Loveday history?

At University College, with Richard Tedder, for about eight years, and I did a high professional training in virology there. If you go back historically, I did a degree in science and a PhD at Middlesex Hospital, and then I was working for an immunologist who said 'You should do medicine if you really want a rounded career in research', so I actually went back to med school, and that took us up to the early eighties, and while I was doing my house jobs, that's when HIV first appeared.

So I started reading about it, with an interest in infectious diseases and a background in microbiology and thought, 'this is an area that I should start working in'. So I applied back to University of London and I got what was called a 'New Blood Lecturer' post in GU medicine at Middlesex. I went back there in '84 and my first job was looking after newly recruited patients with HIV infection - we'd just got the anti-body test.

They'd just got a big MRC grant to study the natural history of HIV. Our job was quite simple - people got their antibody result and just came straight to us with a result and no one really knew what to do with it. We basically explained what it meant, what we knew and (mostly) what we didn't, and offered to recruit them on to this MRC cohort. It meant they were at least part of a group being followed and then could take advantage of any benefits that were forthcoming as quickly as possible. We had about four or five hundred patients that we saw every three months, but if they had any problems they could be called straight up to us. It was horrendous really and the learning curve was exponential, we didn't know what was going on and the patients didn't know what was going on. Every time a patient coughed they thought they had PCP...

When I knew I was coming back to this post, I quickly, in my last year, did a general practice vocational training so I became a qualified GP - I promised my wife I would have some sort of post-graduate medical qualification in my back pocket before I entered the heady world of research.

In case you had to step down from your ivory tower?

That's right, they dump you, in just two years, three years, four years -incredibly insecure. I always said though, that in those three and a half years when we were looking after that cohort, in fact what I probably used most of all was my general practice because that's what we were doing really - looking after the community.

When did you go back to the lab full time?

In the late eighties, I wanted to get into harder core research and moved into Richard Tedder's department who was the consultant virologist. I got an appointment, which was a Wellcome Fellowship appointment, called the HIV/AIDS Research Fellow; it was actually looking after the virology of the same group of patients. PCR had just appeared and my main brief then was to set up the molecular technologies for HIV within the department. We made a viral load assay by 1990 and we made a resistance assay by '91, using those for our local patients and MRC studies, but they were what you would call 'home brew' now and when the kits came out it was easier for us to change over. Companies wanted us to do studies and

they wanted to use the kits anyway, but it was used in the first combination study of AZT/3TC which we did with Glaxo, anyway that's all history now and I got this appointment in '96.

The school provided a building, set the labs up and provided an infrastructure and basically launched me on the world...

So you find support from outside monies?

Basically, yes - and it certainly focuses your mind.

And the objectives of your department?

In the modern jargon the 'mission statement' is, to set up the molecular technologies for HIV/AIDS to carry out research and development and support the clinical care of the patients at the Royal Free - we have a very strong commitment to them. To develop a programme of work around HIV and AIDS that would raise the profile of this institution. To publish, develop an academic profile. The model of the department, which I had in mind, because clearly retrovirology is a sub-division of virology so people would always ask 'Why aren't you part of virology'. By and large though in virology, you simply carry out virological procedures, you may give a virological opinion on a result but that's all you do and you don't have any other interactions outside; it's very limited.

My concept was much more of a hybrid department that wasn't just developing measures but actually we were working both in virology and interacting with everybody - clinical, epidemiological, statistical, pharmacological, and immunological and trials level. It's a model that does upset some of our school political masters, because it's not what you call conventional.

You grew remarkably quickly both in terms of reputation and turnover of activities; did you have a strict business plan?

In terms of the business plan we didn't want to be dependant on any one group - trusts, collaborative work with the MRC, external collaborations with international commercial and academic groups and some teaching and training. We started with a view that we'd do any job basically. I said that no project was too small, if a company just asked us to do one measure we did it, we were looking to give high quality and individualised attention to anybody that came to us and what happened was they'd come back with ten viral loads next time and then a hundred. And that's the way things grow...

And the academic side of things...

I always emphasised the academic dimension with everyone we collaborated with - even with people we were doing service work for in other trusts. Effectively what happened with them would be, someone would ask for a viral load or a resistance because they needed it and then they'd say 'we're going to send you everything, it's good it's efficient, it's quick'... We never really mail dropped anybody, more and more people started phoning up, at this point in time we probably work for about thirty-five trusts around the country plus our work for the Royal Free. What I've tried to do now is draw them into an academic, clinical research group so we can put together results from everything we're providing for them to support their patients. We can also do bigger analyses and when we publish we'll publish on behalf of the retrovirology academic research group - kind of a co-op element to it.

The thing is to keep the prices down as low as possible and to get the most academic, scientific information and push forward the frontiers all the time. In terms of the business plan everything went pretty much according, but there was a slight change because we discovered we had non-B viruses.

You've anticipated my next question. What about non-B clades in this hospital, did this discovery change things, what percentage of your patients are non-B?

I had to do a quick appraisal - this was '97, we did a quick audit study about the size of the problem, and it looked like about ten to twenty percent of our patients might be non-B. We did a study of the whole clinic - everyone gets a serological sub typing now; we're beginning to build up databases. Because the MRC recognised we were doing that, they gave us quite a big award last year to set up an epidemiological study for the next three years of all those patients, so we'll try and find out who they are, where they came from, what viruses they had, what are the distributions and then look at their relative responses to therapy and their relative progression rates, in relation to sub type-B. We're beginning to build up a picture.

What about the technology?

As you know, all the technologies we use for viral load and resistance are based on PCR, and if you have divergent viruses that are potentially non-B, the primers used in PCR may not fit. Most of the primers are developed in kits for laboratory strains of sub type-B because that's all they make in America basically. We've told the companies about missing samples, and we hope they can improve their primers and start to pick up European viruses.

Were companies concerned at first, because presumably they weren't missing any in America?

One of the biggest problems I had was I'd say 'oh look this is a real problem you're missing so many...' and they'd say 'no we're not, what, where' (all sub type-B there, so it wasn't a problem). I'd say 'I'm sorry you're missing them in Europe, and the way things go these viruses are going to swarm across Europe and arrive in the United States', and they have. Now in 2000, at the last conference, the US has 'discovered', non type-Bs, so it's become an issue.

What systems do you run?

We established all the molecular viral load systems in the department, that is, the main three (Roche, Chiron and NASBA), and that was all done cost-free. We managed to impress people and get their support. The same for the

resistance systems as well. We were in a unique position as the first Department of Retrovirology in the UK; we were trying to do comparisons between them within one institution. Also we looked at the relative sub-optimal performance of different assays, you'll remember in '96,'97,'98 the Roche 1.0 wasn't detecting or was sub-optimally detecting, we were quite an important part of actually sorting all that out and sharing those viruses with Roche. We helped to field trial the new versions of the kit, the so-called 1.5.

How much work do you do with the MRC?

I've had a long working relationship with the MRC. When I was with Richard Tedder, I was a grant holder and virologist on Concorde, and from then I was a virologist on DELTA...Since then I've been part of the MRC studies and tried to support that activity. At the moment I'm the virology principle investigator for ERA and PERA and that's quite a feather really to get a virologist as a principle investigator.

I now actually give the MRC a session a week going over everything we're doing; we've got INITIO, FORTE, ERA and PERA. We've also been running the Vanguard with Mike Youle and steering that.

How's ERA study doing?

What I also do for ERA that has not been done before, is that every resistance measure that comes out of Virco to go back to the physicians, I'll have a copy sent to me as well, so I can have a quick look at it and sign it off. We don't want to interfere with the study but just make sure that there's nothing absolutely nonsensical about the result. So if you like we're maintaining a clinical standard for that, if they don't hear from me there's not a problem, if there is we'll discuss it. That's new for the MRC, normally once things are running they like to cut virologists and physicians out of the loop and go onto autopilot.

What's your turnaround time for viral loads?

I was the first one to propose real time virology for HIV so we turn our viral loads round in one or two days, that's what everyone likes. Someone from Aberdeen phoned me and said 'how long will it take, four weeks, six weeks?' I said 'you send it; I'll get it tomorrow, and you'll get the result either in the evening or the next morning'. She's been sending everything ever since.

Having worked as a physician, the one thing you do need is those sort of results on the desk the next time a patient comes in, if you're running tests once a week or once a fortnight it's just not satisfactory, we do a run every day.

And resistance?

It's harder with resistance, it's a much more complex test, we're having failures at the moment all that isn't sorted out yet. We have a sign off form and it says 'date sample received' and that's signed 'date test done' and that's signed by the technician date test signed off by the lab and then I sign it off, so we will be able to audit these quite soon and see how long it's actually taking but I have to say my sign-off date is getting much closer to the day of the test being done now.

The turnaround time is not optimal at the moment, we looking for a working week, which we're achieving yet, but I think that it's a good target. But this is against a background of being terribly under-resourced; if you throw money at something you can always achieve your target.

How many resistance tests did you do last year?

About 1000 to 1200, since we started so that's just over a year. Some of those have been part of studies.

So who's paying?

All sorts of sources - with Mike Youle we've begged and borrowed and stolen, calling things studies and audits...

You must be getting all sorts of information out of this creative accounting...

Yes, it's actually evolved quite an interesting group of patients that we're following in a salvage therapy audit and looking at resistance in that group. That's evolving some interesting results, which you'll see quite soon, in terms of strategies that might be used in patients who are very drug experienced, because clearly there are big problems that need to be resolved and they're not going to go away. Mike's actually presenting some results at the Salvage meeting in Chicago.

Other monies - we ask people to pay for tests, that is we ask clinicians who have research funds. We've been charging £210 per test, up to the beginning of the year, and considering that the kits cost £180 we are doing them for next to nothing. The price is going to go up just a little bit quite soon, to I think to £234. Still pretty cheap!

Which clinics? Is the pattern changing?

We've always worked with Brighton and with Ealing; we did quite a lot for Barts before they got set up, a whole host of centres around London and outside. From Cardiff to Aberdeen, it's quite interesting there was a time when Aberdeen were discussing a resistance result with a key opinion leader in London and the key opinion leader was saying 'How the hell did you get a resistance result?'

How aware are doctors of these tests, did you have to work hard to raise awareness?

That's an interesting question, we always tried with whatever we did in virology to raise awareness and to develop a very intimate relationship, a personal service for people and this was never more important than in terms of resistance. So what I actually did was - we had a formal sign-off sheet which was based on the computer interpretation, I then signed that off, writing quite a detailed report of what I thought patients were resistant to. I never recommended treatments but just said what drugs I regarded as being a no-no and that point in time and I always wrote on the bottom 'Please call me.'

What sort of reaction did or do you get to the interpretation?

About forty percent would call me, and in the early days calls would take about half an hour, I did a little tutorial and told them what we were doing how we were doing it, told them what you would see and did an explanation. But now, with the group I work with anyway, they're enthusiastic about the tests, they're going to lots of research meetings and developing a greater understanding, so we skip that part now, the calls are quicker.

What do you think would help doctors learn more about interpretation?

People within our co-operative group now are actually publishing, for example Martin Fisher's group down in Brighton have recently presented at BHIVA. As that happens and as it is disseminated to grass roots everyone will understand more and more about what we know and what we don't know and what are the applications.

Can patients actually call you direct?

I have spoken to patients. I regard the relationship between a doctor and a patient as so important that, basically, if a patient gets through to me I'd talk to them and that's not a problem. The frustrating thing is that it's not always easy to get through to me. If people are patient enough to keep trying then I just talk to them, one of my failings is I like to chat about my work...

What are your views on resistance guidelines?

Do you know, I still haven't seen the BHIVA guidelines, one thing I found almost a conflict having written American guidelines and then European guidelines, to start addressing another set is actually quite difficult. As I wasn't on that guideline committee, my opinion was that they'd reach the same conclusion as the other two committees. But I still haven't actually seen a copy.

The US Guidelines for the International AIDS Society are completed; they're going to be published in JAMA. The European Guidelines, you probably know where they are, we've all fed back after the Frankfurt meeting, and they're doing the final draft now, I think they're targeted to Lancet.

I'm excited because, unlike the '98 guidelines, both the committees I've worked on, they're putting their money where their mouth is. They are saying either recommend or consider for different patient situations and the groups have basically discussed the evidence or lack of evidence and often that may result in 'well, consider doing it'.

What sort of trials do you think would be needed to persuade people these tests are worth funding once and for all?

A good single randomised controlled trial is what one would say is required to justify it becoming a guideline, but it actually becomes a protocol at that stage, you don't need a guidelines committee. But the complexity of resistance measurement and everything that surrounds it in terms of pharmacoeconomics, and so on is such that I don't think one trial will answer those questions.

I think what we're both saying, is no matter what trial you do, someone who doesn't want to pay the money can find a reason... And all we can do is generate more trials that will address the problems; at the moment there are about eleven trials underway in Europe and America, trying to develop that information. ERA will go out for longer and ask the question 'does the benefit last for six month or a year?' PERA will be the first one I'm aware of in children and that's an important area because you've got less drugs to offer your patients in the first place. We will be enhancing the data basically to show there is a benefit.

All the evidence that has been put down so far is in patients who are quite or very experienced and have been followed up for a very short time. So I suppose less experienced patients, and ERA includes that group, and maybe first change.

Do you recommend people having resistance tests before they start therapy first line?

I personally do, it's something I feel quite strongly about. But most of my guidelines colleagues for one reason or another don't feel as strongly or haven't come down on that side of the argument. But if it were you, would you like to think that the first therapy you're embarking on would be optimal therapy? I'd probably be prepared to pay for it. So yes is the answer to that.

What do you think about the nevirapine resistance data at Retrovirus?

In terms of the 103N in pregnant mums who have a single dose to prevent vertical transmission - clearly the benefit of that strategy to the greater group of patients is enormous, if prevention can be carried out, because there's one thing we've seen from the strategies like the French had following the 076 study was that they practically eradicated vertical transmission in France. But equally drugs, which can become or generate highly resistant viruses just by the development of a single mutation, so called low genetic barrier, are to be approached with caution if used alone.

Back to other sorts of diagnostic tests, at one meeting you said that viral load was only going to go so far, and eventually we were going to need to use quantitative DNA testing. Can you elaborate?

Essentially my own view is that if we get another class of drug like the protease inhibitors - which could well be the fusion inhibitors - and we are giving patients these three classes of drug, I think we'll see another quantum drop in viral load. At the moment we're going along at less than fifty or less than twenty copies and that technology won't go any lower, PCR itself will only detect one copy. You can really see we're getting pretty close to the bottom of the river, but we do know that proviral DNA is stored in cells, and attempts to quantify that have been carried out and been quite successful.

If you have an image in your mind of someone responding to therapy as it is at the moment, you'll see a fall in viral

load. Over twelve to sixteen weeks it goes undetectable. If you measure DNA in those patients it would have a certain value and it may, over six months drop less than a log - there's a little shallow curve for DNA in cells. What I think will happen is if you get this extra fall in viral load, so it goes really seriously undetectable, you'll actually change the curve of the DNA and you will start to see a fall in the way that we currently see plasma viral load. So what we are going to end up measuring, as a routine is DNA fall, we may do viral load when someone first comes in or if someone's failing otherwise we may not need it.

More thoughts about the future?

In terms of the disease, of pathogenesis and virology, we're getting to a very interesting stage. I think in terms of therapy at the moment, we're very near the cusp. If you look at how the host handles infectious disease; it's a combination of the therapy that we give them and their own immune system - that's always been the balance for any infection. Without the host's immune system functioning as well, usually infections are devastating.

I think when we introduce another new class of drug and it produces a much more profound effect we will shift the whole balance of what the host does in relation to the disease. In other words the pathogenesis of the disease will change once we get a successful third class. What we'll see is much lower viral loads allowing a much better immune reconstitution - just think what immune reconstitution was like just after PIs in relation to what we had before. The balance of the disease may truly shift towards a chronic, quiescent infection. I'm very excited about that next step - this is all theoretical though but with what we have already, I think it will happen.

Do you think this will have a profound effect on all patient groups, including very late stage and experienced?

There are always going to be exceptions, but if you think - and I know what happened to some of our late stage patients with protease inhibitors when they first came out - it was miraculous and so potentially, it's an option. The thing against it is if you're very late stage you may loose certain clonal memories in the immune system, which just cannot be regenerated, but if you're regenerating the immune system anyway and you have naive cell populations, there's the issue of re-immunisation with traditional antigens, which may also encourage the immune system to become whole again.

The whole model then shifts if what I speculate becomes fact, all viral load systems then get thrown out the window and we'll be looking at completely different issues.

What about the future for your department?

What the future now offers is the opportunity to develop and break the department up a little. So that we have a research department doing academic research, we have our clinical research activity being done as a unit of activity and maybe even a third group working there. What we're trying to set up is an academic clinical research unit.

In terms of where we're going now - we've got sufficient funding to set up a separate site. We're looking at doing it with the trust, as the school doesn't have enough room geographically. There are a number of options locally or we may even rent something a little bit further away. That will be the site for academic, clinical research and the core of it is around resistance. We've got a grant award for the next two years to evaluate the system that has been set up to measure resistance, that's genotypic resistance, and develop it so that it will function as a clinical research tool as opposed to just a research tool. At the moment it's a research tool, it's a single unit with maybe one plate reader with it. We get ten samples, which we can run in that system and of those five works, five don't work. We report the five that work, of the five that don't, we'll play with, juggle with, try extracts on, and we'll maybe make another three work. The last two we finally have to give up on. That's a research way of doing it.

If you think how a diagnostic lab needs to run, they need to run that system with a guaranteed throughput, it needs to have the flexibility to handle ten samples one day and maybe a hundred the next because they'll be a mixed demand and it's unpredictable. What we have persuaded the company to do is to set us up with their optimum system so it can do eight resistance measures per hour. It's not a big machine - it's a single computer reading system - but you just have more and more of these towers, each one is running a gel and one computer will take up to eight of these.

What we're going to then do, is research and evaluate how it performs in terms of speed of production of results and how it will handle an increasing number of samples. So the research is all about developing the system to have a routine virological process, the by-product is the resistance measures. What we're actually evaluating is the machinery and the technicians that run it. Those measures will provide results for patient care. We've contracted to evaluate the system using 2000 measures a year, so that's one strategy to get reduced costs.

Finally, what do you feel is the role of an activist group such as ours?

My view is having been in HIV right from the start it is a disease that has actually revolutionised medical care. Community group responses have made patients question every step of the way what it is they've got, what it's doing, what it causes and what they're going to do about it. Prior to that medical practitioners of all shapes and sizes had never ever had that sort of response to a disease before and had never been asked those questions.

It troubles me not at all to say to a patient 'I don't know' and that is the most important hurdle. It's an enormous benefit and it has dragged clinical care kicking and screaming into the 21st century, particularly with the Internet and I think you have to take a lot of credit for making that happen. You have my hearty support.

The European Agency for the Evaluation of Medical Products
Evaluation of Medicines for Human Use

London, 12 April 2000
EMEA/11260/00

EMEA PUBLIC STATEMENT ON VIRAMUNE (nevirapine)
— SEVERE AND LIFE-THREATENING CUTANEOUS AND HEPATIC REACTIONS —

The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP), has recently been made aware of additional reports of serious cutaneous and hepatic reactions, sometimes fatal, associated with Viramune[1] (nevirapine). This has led to a re-assessment the benefit risk profile of nevirapine.

This assessment confirmed that severe and life-threatening cutaneous (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) and hepatic reactions are the major clinical toxicity of nevirapine. The **first 8 weeks** of therapy are a critical period which therefore require a close monitoring of the patients to disclose the potential appearance of severe and life-threatening skin reactions or serious hepatitis/hepatic failure. Some of the severe cutaneous reactions were associated with risk factors such as not following the dose escalation regimen or delaying seeking medical attention when the symptoms appeared. Furthermore, most of the cases of hepatitis were reported to be within the **first 8 weeks** of treatment, some of them were associated with hypersensitivity reactions (such as fever, rash, arthralgia, myalgia, hypereosinophilia or acute renal failure).

Following a review of the above information, the EMEA wishes to draw attention to the following:

- **Concerning cutaneous reactions, the initial dosing of nevirapine of 200 mg daily and for patients 2 months up to 8 years 4 mg/kg once daily during the 14 days lead-in period must be STRICTLY adhered to.**
- **Patients should be intensively monitored during the first 8 weeks of treatment. Nevirapine must be permanently discontinued in patients developing a serious cutaneous reaction i.e. Stevens-Johnson syndrome, a toxic epidermal necrolysis or a severe rash accompanied by hypersensitivity reactions (characterised by rash, constitutional symptoms such as fever, myalgia and lymphadenopathy, and visceral involvement such as hepatitis, cosinophilia, granulocytopenia and renal dysfunction).**
- **Concerning hepatic reactions, a close liver monitoring of patients must be performed especially during the first 8 weeks of therapy (see below). Nevirapine should be stopped and never readministered in patients with ASAT or ALAT greater the 2ULN associated with hypersensitivity reactions (characterised by rash, constitutional symptoms such as fever, myalgia and lymphadenopathy, and visceral involvement such as hepatitis, cosinophilia, granulocytopenia and renal dysfunction) or hepatitis.**

As an urgent measure, the prescribing and patient information has been modified through a rapid procedure at the request of the marketing authorisation holder. The EMEA thought it necessary to provide this new information to the public. The complete revised product information is available in the European Public Assessment Report of Viramune published on the EMEA Website.

[1] Viramune is a non-nucleoside inhibitor of the reverse transcriptase of the HIV virus and indicated for antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infected patients with advanced or progressive immunodeficiency. The European Commission granted marketing authorisation for the European Union tro Boehringer Ingelheim International GmbH on 5 February 1988 for the medicinal product Viramune 200 mg tablets and on 18 June 1999 Viramune 50 mg/5 ml oral suspension, which contains the active substance nevirapine. Viramune 200 mg tablets is marketed in all EU Member States and Viramune 50 mg/5 ml oral suspension is marketed in Austria, France, Germany, The Netherlands and United Kingdom.

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RECOMMENDATIONS FOR LIVER MONITORING

Monitoring of hepatic function must be performed every two weeks during the first 2 months of treatment, at the 3rd month and then on a 3-6 monthly basis. It is also recommended that monitoring of the liver function should also be performed if the patient experiences signs or symptoms suggestive of a hepatitis and/or hypersensitivity reactions.

Activity of aminotransferases	**Clinical symptoms of hypersensitivity (Such as fever, rash, arthralgia, myalgia, hypereosinophilia, acute renal failure)**	**Recommendations**
ASAT or ALAT > 5ULN	No	The treatment should be stopped immediately. **When liver function test return to baseline values,** it may be possible to reintroduce nevirapine on a case by case basis at the starting dose of 200 mg/day for 14 days followed by 400 mg/day. If significant liver function abnormalities rapidly recur, nevirapine must be **permanently discontinued.**
ASLT or ALAT > 2ULN	No	Nevirapine can be continued provided that the patient is closely monitored
	Yes (or signs or laboratory findings of hepatitis)	Nevirapine should be stopped AND NOT READMINISTERED
Unknown	Yes	Liver function testing should be performed

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COMMENT

This statement, including the complete revised product information for nevirapine, highlighting the changes is available in pdf format from the EMEA website at http://www.eudora.org/emea.html

The risks of these adverse events with nevirapine were previously known . However, particularly given that some of the serious cutaneous reactions were associated with not following the strict dose escalation regimen, or delaying seeking medical assistance, the focus on more careful monitoring, particularly during the first months of treatment is welcomed. Closer monitoring indeed is something that would probably add benefit to combinations with other agents.

The additional clinic visits required may also provide a valuable opportuity to provide simple adherence support for patients in their new treatment.

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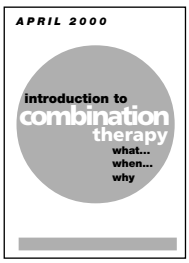

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