Therapeutic Drug Level Monitoring in Clinical Practice: Optimising First-line and Salvage Regimens

ATP Dr FAX Symposium III Report
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contents

Introduction from Co-chair 4

Introduction from ATP 5

Introduction to Pharmacology & Therapeutic Drug Monitoring (TDM) 6
Principles and Practice
David Back, Liverpool University

TDM in HIV Therapy: Does Measurement Lead to Clinical Benefit? 8
Richard Hoetelmans, Slotervaart Hospital, Amsterdam

Clinical Benefits of Therapeutic Drug Monitoring 11
TDM in Routine Patient Management
Ceppie Merrie, St James’ Hospital, Dublin

Special Patient Groups I: Pregnancy 14
Graham Taylor, St Mary’s Hospital, London

Special Patient Groups II: Paediatric Care 16
David Burger, Nijmegen University Hospital, Utrecht

Special Patient Groups III: Patients with Hepatic and Renal Dysfunction 20
Mike Berry, St James’ Hospital, Dublin

Interactive Discussion 22

Avoiding Failure: Optimising First-Line and Salvage Therapy 24
Mega-HAART: Definitions and Practice
Carsten Rotman, Goethe University, Frankfurt

The Role of Hydroxyurea 26
Mike Youle, Royal Free Hospital, London

Maximising Drug Synergism 29
Joep Lange, NATAC, University of Amsterdam

Practical Aspects of Developing a Therapeutic Drug Monitoring Service 30
Developing TDM Services: Learning from the Dutch Experience
David Burger, Nijmegen University Hospital, Utrecht

Role of Virological and PK Monitoring 31
Deenan Pillay, University of Birmingham Medical School

Roundtable Discussion 32

Summary of Issues 36

Appendix I - How to order TDM in the UK 37
Appendix II - List of Participants 38
introduction

David Back, Co-chair

Treatment failure is clearly multifactorial, and includes the development of antiviral resistance, poor adherence to therapy and pharmacokinetic reasons. The latter are particularly important for protease inhibitors (PIs), a group of drugs which exhibit considerable inter-individual variability in plasma drug levels and also have a marked potential for interactions which can lead to either excessively high or low PI levels. It is essential that individuals receive the optimal dose of all the drugs within a given regimen.

The rapid pace of drug development and the speed at which anti-retroviral drugs are licensed and introduced into clinical practice tends to outstrip our knowledge of how we should best use them. However, over the past couple of years, data have emerged demonstrating an important link between antiretroviral drug concentrations and efficacy.

As a result, the possibility of being able to monitor the plasma concentrations of antiretroviral drugs (particularly PIs) has arisen. Thus Therapeutic Drug Monitoring, which is part of patient management for drugs such as antiepileptics, digoxin, some antibiotics and immunosupressants is becoming an important topic for debate within the HIV community.

ATP organised this meeting to review the arguments for using TDM for antiretrovirals and at the same time look at some of the inherent problems that could potentially make TDM an exercise which has got limited value. They brought together an impressive line-up of speakers from the UK, Ireland, Europe and the US which produced a lively discussion.

One of the important features of the meeting was that here were people from academia, NHS, industry and the community genuinely seeking to understand the best way to proceed with TDM. Everyone who attended would surely have been convinced of the importance of understanding pharmacological principles to at least begin to move in the direction of ensuring that individuals receive the most appropriate dose regimens.

We deviated from the overall TDM theme in an excellent afternoon session on ‘Avoiding Failure: Optimizing First Line and Salvage Therapy’. There were presentations on mega-HAART (using TDM to check dosing), the role of hydroxyurea, drug synergism and immune-based therapies.

I hope this publication is a useful summary of the days deliberations. Thanks to ATP for the first rate organisation and tremendous enthusiasm to get things moving.
atp introduction

Simon Collins, Polly Clayden, Project directors, ATP

Although it is unusual for a treatment activist group to sponsor a series of scientific meetings, at ATP we believe that all positive people can understand and take an active part in their own treatment decisions. We have been publishing DrFax, our fortnightly review of latest research and treatment news for over 3 years and these symposium seemed a natural progression to stimulate a national forum with international input for discussing important treatment issues that could improve our care.

ATP has always taken the lead in pressing for what we see as the most important treatment advances - for triple therapy and access to protease inhibitors when dual therapy was still the standard of care, for the importance of access to both regular and ultrasensitive viral load tests (still not routinely available) and in the importance of treating to avoid resistance by aiming for suppression to less than 50 copies as long ago as summer 1997. We are committed to trying to make sure every HIV-positive person in the UK has access to the very best medical care.

Last October we focused on the potential of resistance testing, which led to the forming of a National UK Resistance Database Working Group and our last meeting looked not just at new drugs in the pipeline, but more importantly at how they could be used most effectively as they become available. We believe that TDM, has shown important results that justify raising the profile of this technology.

Every major conference seems to include small studies, or sub-studies reporting a significant percentage of people whose drug levels, when monitored, fell outside the defined effective therapeutic range. With up to 50% of treatment naive patients starting therapy not achieving or sustaining viral load suppression to less than 50 copies/ml, immediately limiting their long-term treatment options, it is important to look at any possible explanation. Knowing that individual TDM monitoring is integrated into routine care for all patients using PI or NNTRI combinations in the Netherlands - or St James’ Hospital, Dublin and that routine use in Liverpool was preventing sub-therapeutic dosing of PIs three years ago, we wanted this research to urgently have a wider profile.

TDM is not just a new test for the sake of it - the presentations highlighted in this report are firmly grounded in clinical relevance and practical solutions and we hope that both clinicians and patients feel more informed and confident in accessing this extremely under-utilised technology.

As always, we welcomed the opportunity to bring together people who do not usually have an opportunity to meet at a single event. As well as doctors pharmacists and other healthcare workers, we would like to thank the involvement of the industries who create these new technologies, researchers who explore their potential and people living with HIV themselves who ultimately hope to benefit from an increased awareness of new information.

Postscript:

We are happy to report that since the meeting, David Back has been successful in raising independent funding from the Monument Trust for the capital investment he needed. This will at least quadruple throughput of samples.

As a result of this meeting we are also pleased to be able to report that at least one pharmaceutical company, Roche, has agreed to cover the costs of testing drug levels of nelfinavir or saquinavir for patients starting combinations using these drugs or for existing patients who want to check levels due to toxicity or drug interactions. Hopefully other companies will follow this lead.

We'd like to think that we played a part in the practical benefit that access to these tests will bring.
The following introduction covers the most important terms used when studying pharmacokinetics and the issues around drug absorption. If you are not already familiar with these terms please refer back to these pages when they are used during the report.

Cmax, Tmax, T1/2 & AUC
When you take a drug by mouth the concentration of that drug in your blood gradually increases as it becomes absorbed by your body. The highest concentration reached is called the Cmax. The Tmax is the time taken to achieve that maximum concentration.

The half-life of the drug (T1/2), is normally taken as the time taken for the concentration of the drug to reduce by a half (i.e for your body to eliminate half of that drug). For practical purposes it usually takes about five half-lives for a drug to completely leave your body, although in fact very small and undetectable concentrations may continue for a lot longer.

The indication of the total amount of the drug within the systemic blood circulation is given by the area under the curve (AUC) shown in Figure 1.

MEC, IC95, IC50, Cmin & trough
The MEC is the minimum effective concentration of a drug which will be effective against the virus. If the concentration of a drug falls below this level at any time with anti-HIV medications this is the time when you are at risk of developing resistance. The MEC is usually based on the IC50 which is the concentration of a drug needed to inhibit 50% of viral replication during in vitro studies. Similarly, the IC50 is the concentration of a drug needed to inhibit 50% of viral replication in vitro.

After taking an oral dose of a drug, the concentration rises (to the Cmax) and then slowly falls. Dosing schedules are worked out so that when you take the next dose, the total concentrations of the drug rise before they are allowed to reach the MEC. The lowest concentrations reached, when regularly taking a drug, is called the Cmin or trough level. See Figure 2.

bioavailability
When you take a drug orally, a proportion of the drug is immediately filtered out by the gastro-intestinal tract or liver. If a drug is given intravenously - by injection into a vein (IV) - the concentration in the systemic circulation is much higher (and it is absorbed much quicker) because this first filtering does not occur.

The bioavailability of a drug compares the difference in blood levels when the same dose is given in each of these two ways. By looking at the area under the curve of the two doses - oral versus IV - we get a measure of bioavailability, which is given as a percentage. See Figure 3.

Clearance
Clearance is the term given for the removal of the drug from the bloodstream, and for the majority of drugs, clearance involves a mixture of actions by both the liver and kidneys. The majority (but not all) of antiretroviral HIV drugs are cleared by the liver.

Drugs that are extensively metabolised by the liver include zidovudine, nevirapine, efavirenz, delavirdine, indinavir, nefnafavir, saquinavir and ritonavir.

Drugs that are extensively excreted by the kidneys include ddI, d4T and 3TC.

Clearance can be worked out when you know the dose of the drug and the area under the curve, as long as you know the bioavailability after oral administration.

variability
Variability in blood levels of a drug, between different people, is one of the biggest issues in pharmacology. Although Patient A and Patient B take the same dose of the drug you may get a fourfold, fivefold, tenfold variability in the plasma concentrations. This variability can occur for all the above values - Cmax, Tmax, AUC or trough levels. The variability between different people is called inter-patient variability.

You also get variability within the same individual taking the same dose of the drug on different occasions which is called intra-patient variability. See Figure 4.

Harker-Peck model
A recent model for identifying the complex areas of variability in drug response is the Harker-Peck model:

Dosage Form: There is a potential variability from the dosage form and the kinetics of the release of the drug from the capsule or tablet - is it exactly the same with every capsule or tablet you take? From the pharmaceutical perspective, this is something which is closely regulated with strict quality control but that potentially could be where some variability arises.

Adherence: Within the area of adherence we also have potential variability through erratic timing, skipping an occasional dose, taking a drug break and poor awareness of actual adherence levels.

Pharmacokinetics: The main area of pharmacokinetics for this report includes the variability of absorption, distribution, metabolism and excretion.

The next issue though is the relationship between the drug concentration and the action of the drug. Whether, even if you attain exactly the same concentration of a drug in every individual, this will guarantee exactly the same antiretroviral effect.
This potential difference in pharmacodynamic response involves yet another variability.

**first pass metabolism & P-gp**
First pass metabolism is the set of barriers or filters, first in your GI tract and then in your liver, which reduce the amount of drug getting into the bloodstream when you take a drug orally.

The first barrier when the drug comes into the gastrointestinal (GI) tract are the cells surrounding the GI tract, called entrocytes which contain enzymes which can break down the drug (for example CYP3A4).

There is also the potential compromise of P-glycoprotein (P-gp) which is present in the apical membrane, or the membrane of the entrocyte. P-gp is a transporter which wants to efflux (forceably push) the drug back out of the cell and return it to the intestine. This mechanism has only recently been recognised and is still not completely understood. See Figure 5.

Enzymes like CYP3A4 which are present in the liver then try to metabolise the drug further.

**forgiveness**
The term forgiveness (F) describes the ability of a drug to maintain therapeutic drug action despite occasional lapses in dosing. It is defined in terms of the post dose duration of action (D) and the interval between the doses (I).

\[
F = D - I
\]

Forgiveness is equal to the post dose duration minus the interval between the doses. If, for example, the drug acts for 24 hours, and you are taking the drug every 12 hours, you've got a maximum forgiveness of 12 hours - you have the potential to miss a single dose and still maintain the effective concentration for the drug to act. This data, based on T1/2, often comes from studying single drugs in isolation, so that combination therapy may make this more complicated.

The possibility of safe window periods in which to take a dose of a drug varies considerably for different drugs (and may not exist at all for some), but has immediate impact on providing adherence guidelines and support for patients.

**inducers and inhibitors & CYP450**
Drugs are metabolised in the liver by the action of enzymes - an important group of enzymes being the P450 family. Individual enzymes are catagorised by additional letters and numbers such as 3A4 or 2D6.

The more of an enzyme that is present, the faster a drug is metabolised but this is a very complicated area because drugs themselves can alter the quantity of enzymes which are produced, including the enzymes which are responsible for their own metabolism.

For example, nelfinavir is an autoinducer - so that if you start taking the drug you will get pharmacokinetic accumulation in the first few days and then it will induce its own metabolism and the levels will come back down again. With ritonavir, you've got induction, for example, of certain enzymes including glucuronyl transferase which has an effect on oral contraceptives. If you’re looking at CYP3A4, for example, you can induce up the amount of enzymes. This increases the turnover still further, so you actually get more enzymes, but once that enzyme is increased you can inhibit that increased amount as well.

**therapeutic range**
Defining a therapeutic range is often difficult. Are we trying to maintain a drug above a certain concentration throughout the whole of the dosing interval, which is the minimum effective concentration. How safe are the margins? Should we be just above it, twice above it, five times above it? We also have to set the relationship with the Cmax for what is regarded as being realistically safe before risking side-effects.

One of the difficulties of establishing a true MEC based on the quoted IC95s is that this data is taken from studies done in the test tube, in culture. Extrapolating parameters from the laboratory data can become controversial when setting an MEC concentration to aim for in patients. Nevertheless, we settle on the following guide concentrations:

- Ritonavir to be above 2000 ng/ml.
- Saquinavir (originally 25), now >50, possibly >100ng/ml.
- Indinavir probably above 100ng/ml.
- Nelfinavir probably above 400ng/ml.

These figures have been extrapolated from in vitro data as minimum concentrations in vivo, although remember it may still be arguable as to whether these are exactly the figures we should be aiming for.
TDM in HIV Therapy: does measurement lead to clinical benefit?

Richard Hoetelmans, Slotervaart Hospital, Amsterdam

In discussing the therapeutic drug monitoring (TDM) of anti-retroviral drugs I will cover static models, HIV dynamics after start of therapy, with respect to the ADAM and INCAS studies, and an ongoing TDM study in the Netherlands, called ATHENA.

Inter-individual variability in PK parameters of protease inhibitors has been shown in many studies, and makes them particularly suitable for TDM application. Taking this further though, we need to show a relationship between the exposure that is measured and the antiviral efficacy or incidence of side-effects that is encountered.

TDM & long-term response

Static models normally look at the relationship between the exposure to drugs in patients and the antiviral HIV-I RNA response.

For example, one study looked at saquinavir exposure (Invirase) after 12, 24, 36 or 48 weeks of therapy. At each routine visit to the clinic from July 1996 to January 1998 treatment naive patients in the study had a blood sample drawn and the time that had elapsed between the last dose of the drug and the drawing of the sample was recorded. Results were interpreted using a validated reverse-phase HPLC assay.

Saquinavir concentrations were related to those we encountered in twenty reference patients from whom we had full 8-hour PK curves. The ratio of the observed concentration in the patient and the expected concentration in our reference population was then used to get a measure of the exposure.

All patients used Invirase at an increased dose of 1200mg TID. Because of the issue of poor bioavailability with this drug we used this dose routinely for all patients almost from the start of when it first became available. Although the saquinavir had to be started in the period of the study, some patients (in 1996) added the PI to background dual nucleosides.

In a multivariate analysis we found four parameters that independently predicted if a patient would be undetectable after 36 weeks of therapy:

• a low baseline viral load (p=0.011)
• a high baseline CD4 count (p=0.023)
• the introduction of two nucleosides (p=0.009)
• high saquinavir exposure (p=0.005)

Although we now know the importance of the first three factors, the pharmacologic exposure was very important in this population.

This showed the relationship between drug levels and response in the long-term but we also looked at the response in the short-term, this time within the ADAM study.

PIs and ADAM

Mathematical models looking at HIV-1 dynamics and initial clearance rates show a full, or at least a constant, inhibition in the patient by the drug that’s being used. We had observed a fair amount of variability in the initial clearance rates of HIV-1 RNA and wondered if the intra-individual variability in exposure to the drugs used was a factor that could explain this.

Our hypothesis was that observed variability in plasma HIV-1 clearance rates after the start of therapy can, in part at least, be explained by differences in exposure to the drugs. The ADAM study (Amsterdam Duration of Antiretroviral Medicine) was an induction/maintenance study with an intitial regimen for all patients of d4T/3TC/ saquinavir (Invirase 600mg TID)/nelfinavir (750mg TID) in anti-retroviral naive patients.

The HIV clearance rate was estimated using an exponential model (first-order) elimination rate:

$$VL(t) = VL(0) * e^{-k*t}$$

k = elimination rate constant, t1/2 = ln 2/k
VL(0) = HIV-1 RNA at time t (copies/ml)
VL(0) = baseline HIV-1 RNA (copies/ml)
t = time after start of treatment (days)

We did this because we only had a limited amount of samples, at baseline, day 7 and day 14 after the start of the therapy (this study was never designed to look at these initial clearance rates). The quantification level of the assay that was used was 50 HIV RNA copies/ml.

Saquinavir and nelfinavir levels in all patients were assessed on each study visit and the concentrations were related to a reference population of 18 patients using the same drugs. Again a ratio was used as a measurement of the exposure to saquinavir and nelfinavir. We did not look at nucleosides because of their need to be intra-cellularly triphosphorylated before becoming active.

Of 34 patients, 29 had evaluable saquinavir and nelfinavir levels and supportive recorded times. Baseline characteristics were a median HIV-1 RNA load of 4.76 log and CD4 count of 410 cells/mm³. The half-life of the viral decay in the beginning had a median of 2.4 days and the interquartile range included a lot of variability.

The nelfinavir and saquinavir ratios that were observed were somewhat less than 1.0 - a figure that you would expect from this population - but the difference was not statistically significantly different. When we looked at various linear regression analysis we found that the two parameters that were associated with the initial decay rate of viral variants were the nelfinavir exposure and saquinavir exposure. The baseline CD4 count was nearly associated with the initial decline and the baseline for viral load did not have any relationship with the initial decline. When we looked at a multivariate analysis the only parameter that was significantly related to the initial decay rate was the exposure to nelfinavir.

Figure 2 plots nelfinavir exposure (1.0 is the expected
found that there was no difference between initial clearance rates of the two arms, and also that a high baseline viral load and a high exposure to nevirapine resulted in higher clearance rates.

Although this is preliminary, this still serves as an example of TDM levels and anti-viral activity for NNRTIs.

**ATHENA**

Those few studies discussed earlier, show that individual variability is important, but we have not yet run a large scale prospective trial proving that TDM eventually leads to a clinical benefit.

This is now being addressed, in a large ongoing study in the Netherlands called ATHENA. Virtually all HIV-1 infected patients in the country are included. There is a sub-group of 600 patients who are being followed more intensively (virological resistance, immunology, quality of life and pharmacology).

The pharmacologic sub-study has the sole objective of investigating whether the determination of the exposure to anti-retroviral drugs is a significant additional parameter that improves the treatment of HIV disease in patients. Plasma is isolated from a blood sample at each visit and frozen, and drug levels of all PIs and NNRTIs are assessed on line, within 3 weeks. A recommendation is then provided to the physician on whether to maintain, increase or decrease dosage.

Patients are randomised to a blinded group who don't get their drug level results or recommendations and an unblinded group who do. An interim analysis will be performed after 300 patients have a follow up of at least 6 months, or when 50 patients of a certain regimen have a follow up of 6 months. The results will be reported to the DSMB.

Endpoints for the analysis of the results are death, clinical complications, changes in CD4 counts, HIV-1 RNA, adverse events and laboratory effects. 295 of the 600 patients are currently enrolled, 148 are now in the intervention arm getting results plus a recommendation at each clinic visit, and 147 are now on the blinded arm.

**NOTES**


Mike Berry, Dublin: I’ve got a problem with the methodology of using only 18 patients as a reference profile. It ignores completely some aspects of variability and we’ll show you some profiles later on which demonstrate this (see page 21-22). I have a small problem using this to demonstrate the relationship between viral load and drug exposure but I have a much larger problem in actually altering people’s treatment based on this ratio. My own feeling is that you should really have a full profile.

Richard Hoetelmans: The models used for these studies are simple ones, but the ADAM study has now been analysed using population PK and the same results were produced. Use of those more complex population models are better, but the results, at least from the ADAM study, are the same. Our practice of increasing the dose for someone with low drug levels, has come from observations in our hospital. Patients with low drug levels did not become undetectable. When we increased their drug level, the majority responded well and went on to become undetectable. This lead to the basis of the randomised ATHENA study which will show any treatment benefit between the two arms.

Mike Barry: I don’t think ATHENA will show this, because if it doesn’t show a relationship between this ratio, it doesn’t mean that there is not one. You need to carry out a full profile.

Brad Kerr, Agouron: In the ADAM and INCAS studies, were the short-term changes in viral load predictive of long-term suppression in those patients?

Richard Hoetelmans: After 24 weeks, patients in the ADAM study were randomised to go to a double-drug regimen (it was designed as an induction/maintenance study) and most patients failed because their viral load rebounded. We then saw that some patients who remained undetectable, after reducing from four drugs to two drugs, had steeper declines at the start of the study. Unfortunately we only had drug levels for a few patients, but since we found a relationship between initial decline rates and drug levels it gives the suggestion that it is important. In the INCAS study, we are now looking at the patients who eventually became undetectable in the triple arm using AZT/ddI/nevirapine, and the only parameter that predicted if a patient went undetectable was nevirapine levels during the first two weeks. This was also associated with a higher clearance rate so there were indications that it was important, but we need more data.

Brad Kerr: In the ATHENA study, what sort of distribution of baseline viral loads are there?

Richard Hoetelmans: I don’t know off-hand what the average baseline viral load is but it includes naive and experienced patients. As it is a patient population of the Netherlands I would expect it to be generally representative.

Brad Kerr: I ask because, in some of our own studies with nevirapine, we see that a higher baseline viral load seems to be, maybe, a more important factor than drug levels. It looks like the importance of drugs levels may be of importance to patients with high viral load.

A poster by Courtney Fletcher, at Chicago this year, showed doing a concentration of base-dose adjustment, with indinavir and two nucleosides. It didn’t seem to work very well for them but I also noticed that there are patients with low baseline viral loads, so if you’re not successful in the ATHENA, in the gross analysis, you might try and focus on the patients with high viral loads.

Anne Hsu, Abbott: I am interested in the initial viral load decline relationship with drugs which we have also worked on. If a regimen is highly active and very potent one shouldn’t see a relationship with drugs because everyone should decline at a similar rate. If you see a relationship, I would tend to think that the regimen is probably inadequate. When you’ve seen this relationship, looking at a drug response curve, that means the treatment is inadequate.

Richard Hoetelmans: Yes, your presentation in Chicago achieved much higher saquinavir levels when used with ritonavir to boost it, than we obtained in the ADAM study using nelfinavir. We did not find a relationship because the drug levels were so high, so that might be quite true. It can still be used, however, to look at the dose that you need to get a good response, because if you increase the dose, and you see the viral load decline is steeper, it means the latter dose has more effect.

Anne Hsu: I agree too - you also see some relationship for a steeper decline to suppression below 20 copies/ml but the difference may be so small that I doubt how clinically useful that value is. The difference is 10%, maybe 15%, but there may not be statistical significance for long-term prediction below 50 or 20 copies.

Richard Hoetelmans: We don’t know at this moment, and this was also in naive patients, because you can also do something like that in pre-treated patients, and I think then the difference will be much higher decay rates.

David Burger: In the INCAS trial, is there a minimum drug level of nevirapine where you can see a break point between success and failure?

Richard Hoetelmans: I don’t know, because the analysis is still in progress, but we do know from studies with nevirapine that drug levels over 3.4 mg/ml are associated with a better response.

Diana Gibb, MRC: My question is about toxicity within the ATHENA trial. You may not be able to answer this, because you haven’t had a DSBM yet, but if you’re increasing your doses in your monitored group, then you can imagine that you might get more toxicity. Are you monitoring that as you go along?

Richard Hoetelmans: We are looking at it. We see that by increasing the dose in patients with low levels, they achieve higher levels but they are within the therapeutic range. We don’t see an increase in adverse events - and we’ve been doing this for three years now in our hospital. Because the individual variability is so large, a lot of patients using the lower dose, are also within the therapeutic range.

Rob Camp, EATG: In the ATHENA study the experts are giving recommendations. Do the practising clinicians have to follow them, or will it be like a GART study?

Richard Hoetelmans: No, they don’t have to follow them. It is a recommendation that’s made because we only see the drug levels, and we don’t know anything else about that patient at that moment, so there might well be a reason not to increase the dose. It is a recommendation that is being made, and the physician is not obliged to follow that.

Rob Camp: Isn’t that a concern because one of the things in the GART study was that 50% of the physicians didn’t follow the expert recommendation.

Richard Hoetelmans: Yes it is a concern - if they don’t do it, the answer will not be known. If there’s no difference between the two groups then there’s nothing to measure. There’s often good reasons for the physicians not to change, but in the Netherlands, physicians are quite used to using these drug levels to optimise their therapy.
TDM in Routine Patient Management

Ceppie Merry, St James’ Hospital, Dublin

TDM as a scientific discipline has been used for over 30 years and, with selected drugs, its use in clinical practice has reduced morbidity, mortality, lengths of hospital stay and adverse effects. This has established TDM as a standard of care in the treatment of many infectious diseases, but has not yet been applied to antiretroviral therapy.

When nucleoside analogues were the only available treatment, TDM would not have been practical for routine use. They are pro-drugs, which require intracellular phosphorylation, and meaningful PK data would require a cell separation - a technique which is costly, time consuming, and demands considerable expertise. However, the introduction of PIs merited a second look at the potential role of TDM in the day-to-day management of HIV infected patients.

Protease inhibitors are substrates for cytochrome P450 3A4 and P-Glycoprotein, which results in a potential for marked inter-patient variability. PIs are extensively plasma protein bound and undergo minimal renal elimination. So, from either a pure research or a pharmacologist’s point of view these drugs are ideal candidates for TDM. However, from the point of view, of either the patient, or the already overworked HIV physician, we need to show a practical benefit.

The now infamous data from Palella et al showed the superior efficacy of a protease containing triple regimen. In clinical practice, this response is assessed by patient history, physical examination and changes in the CD4 cell count and viral load but, in the short-term, these changes may, in fact, be solely due to the influence of the dual nucleosides. We need to look at the TDM of the PIs because it is otherwise impossible, or extremely difficult, to isolate out the relative impact of a protease inhibitor in any triple combination.

Subtherapeutic PI levels are undesirable for several reasons because:

- they compromise the response of the patient to the current regimen (Palella);
- resistance to PIs is progressive and exposure of a patient to subtherapeutic PI levels may confer pan class resistance on that patient, compromising the response to future PI containing regimens;
- these drugs are not inexpensive and carry a certain opportunity cost.

At St James’ Hospital Dublin, in collaboration with our colleagues at the Dept of Pharmacology, University of Liverpool, we have responded to specific questions which arose during routine clinical management, which we cannot answer any other way. The kinds of questions we have looked at are:

- are patients getting adequate drug exposure?
- what is the exact interaction between two PIs?
- what is the interaction between a PI and a NNRTI?
- can we manipulate the PK of a drug to optimise tolerability?
- what is the interaction between a PI and sildenafil (Viagra)?

i) Are patients getting adequate drug exposure?

In the first study we measured trough plasma saquinavir levels in 66 HIV infected patients, who were at steady state for the old formulation of saquinavir, and the results are shown in Figure 1.

There are two interesting features in this scatter plot. Firstly, there is marked inter-patient variability ranging from very low plasma saquinavir levels to a high of 731ng/ml. But secondly, a substantial number of patients have plasma saquinavir levels below the recommended level of either 25, 50 or 100 ng/ml.

Based on this study, we undertook a formal eight hour PK study of saquinavir in 17 HIV infected patients, and the results are shown in Figure 2. The bolder (centre) line on this graph represents median values (plus or minus standard errors) and at first glance we could all be forgiven for thinking that the 17 patients in this study actually have adequate plasma saquinavir levels. The real problem is that in clinical practice we don’t deal with medians or means, we treat actual patients. This group actually includes two outliers. There is a 40 year old haemophiliac man, with extremely high plasma saquinavir levels (a), and a 23 year old single mother, who has extremely low plasma saquinavir levels (b).

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- these drugs are not inexpensive and carry a certain opportunity cost.

Fig. 1 - trough saquinavir (Invirase)

Fig. 2 - Mean SQV (INV) and outliers
ii) Dual protease interactions

We first looked at the effect of ritonavir, at a dose of 300 mg twice a day, on steady state plasma saquinavir levels. In the presence of low dose ritonavir there was a 30-fold increase in saquinavir Cmax and a 58-fold increase in saquinavir AUC.

There was also a marked inter-patient variability. We knew that we had to dose-reduce, in order to avoid drug toxicity, but from this data we simply couldn’t recommend a single dose that would suit all patients, and so we set about really individualising the therapy.

There is a man who, in the fall of 1996, required salvage therapy. We started him on d4T/3TC/ritonavir (600 mg twice a day) / saquinavir (200 mg once daily). We were unhappy with this initial profile so we very quickly increased his dose of saquinavir to 200 mg twice daily, which results in the much more satisfactory profile shown in Figure 3. Two and a half years later, this patient remains clinically very well and fully virally suppressed.

In a similar study we found a five-fold increase in plasma saquinavir levels in the presence of nelfinavir. However, for some patients what that actually meant was we increased their dose of saquinavir from subtherapeutic to therapeutic levels, whereas for others we increased perfectly therapeutic saquinavir levels into potentially toxic levels.

iii) Interactions between PIs and NNRTIs

We studied the effect of nevirapine on steady state plasma saquinavir levels. In the presence of nevirapine, the absolute therapeutic saquinavir levels into potentially toxic levels. We knew that we had to dose-reduce, in order to avoid drug toxicity, but from this data we simply couldn’t recommend a single dose that would suit all patients, and so we set about really individualising the therapy.

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iv) Can we manipulate the PK of a drug to optimise tolerability?

Many of our patients taking ritonavir complained of maximal side-effects some 2 to 4 hours after taking their medication. So, in view of the apparent relationship between dosing, toxicity and maximum ritonavir concentrations we postulated that if we actually changed the dose of ritonavir from 600 mg twice daily to 300mg four times daily we could improve tolerability and yet maintain antiviral efficacy.

We took data initially from the published literature and we constructed proposed steady state ritonavir levels using the adjusted regimen of 300mg, four times a day. This regimen then avoids the very high maximum concentrations, which we assumed were causing the toxicity, but at all times we assured keeping plasma ritonavir levels above the recommended 2.1 micrograms/ml. We then carried out this study in 6 HIV infected patients and found that this is exactly the case. Using this altered regimen, we were able to keep 19 patients who were otherwise intolerant of ritonavir on this regimen.

A BID regimen has certain advantages from a lifestyle point of view over a QID regimen, but you must remember that this study was done at a time in Ireland when the only two PIs available were saquinavir and ritonavir.

v) Interactions between PIs and sildenafil (Viagra)

The prevalence of erectile disfunction in HIV-infected homosexual men is estimated to be 33%, compared to a population point prevalence of around 10%. Sildenafil is metabolised by, and acts as an inhibitor of, CYP450 3A4 and it also has an active metabolite the UK103,320.

Therefore, there is a potential interaction between sildenafil and the PIs. This study was a little different for us because it showed TDM in evolution - it was the patients who came to us and asked for a study and safe recommendation for adjusting doses if necessary.

We performed a two day pharmacokinetic study using indinavir with sildenafil. On day one, we measured plasma indinavir levels. On day two, patients patients received a single dose of 25 mg of sildenafil, in addition to their routine morning medication. One problem was that all patients were at steady state for indinavir. It would be unethical to even consider stopping the indinavir, so we don’t actually have baseline sildenafil data, but we have compared it to dose normalised data taken from published literature.

In the presence of sildenafil, there is a 47% increase in indinavir Cmax and an 11% increase in indinavir AUC. In the presence of indinavir, there is a 4.4-fold increase in plasma sildenafil levels when the patients took a single dose of 25 mg sildenafil, when compared to the data taken from the literature. Furthermore, the terminal half-life is prolonged.

In view of the altered pharmacokinetics and, in fact, in view of the fact that many of our patients reported very prolonged pharmacodynamic effects - it would actually seem that a lower dose than 25 mg of sildenafil is actually more appropriate.

The practice of using TDM in Dublin therefore has the specific aim of individualising therapy in an attempt to optimise the risk-benefit ratio. Although proof of concept, when to sample and which samples to take need to be validated, and there are economic implications of adding another test to the standard of care for HIV therapy, the examples illustrated here all provided clinical benefit for the patients involved. Stefano Vella’s opening remarks at the 1999 Chicago conference said that ‘TDM should be added to the standard of care, with a single caveat that it should only be done once the current methodologies have in fact been validated’. They are remarks I completely agree with.
Steve Taylor, Birmingham: You showed, with the initial saquinavir data, that of 66 patients, nearly half of them had very low saquinavir levels, less than 25ng/ml. Is it possible that the Dutch group actually chose 20 patients in their curve groups who all had very low levels, and that therefore the ratios aren’t that important?

Ceppie Merry: This is the argument. There is huge patient inter-variability. You would hope that if you select patients, you will select from across the range. If you take a single point sample, it may be therapeutic or within the range for that patient, at that time. But with the inter-patient differences in bioavailability, a sample two hours later, or in fact one hour earlier, may have been subtherapeutic by our own standards.

Mike Youle, Royal Free: I was interested in the sildenafil data. Someone from Pfizer once said to me, luckily not in print, that they would never pay for a study that had HIV positive people in it. Did they actually contribute towards that study?

Ceppie Merry: Everything that I have shown today is TDM in clinical practice. We did it because we believed in it and the patients believed in it. We did not receive funding.

Mike Youle: Good. The point I was making was that the majority of the 50 or 60 of my patients that are regularly taking sildenafil are actually using doses of 100mg quite regularly on indinavir, ritonavir, and indinavir/ritonavir combinations. There are also reports of people using sildenafil as a recreational drug.

Ceppie Merry: I think it’s perfectly reasonable that there will be patients who can take saquinavir and indinavir with sildenafil at 25mg, 50mg and 100mg - because of the inter-patient variability - but having supervised the PI/sildenafil study, many patients experienced unpleasant side-effects. Many patients said they would not use it for recreational use because of these side-effects, which included drops in blood pressure, which were more severe than the data sheet suggests at 100 mg, severe headaches, dispepsia, rhinitis. Some patients will be able to take it at these doses, but where TDM is not available, in view of the data, a lower dose is probably most appropriate.

Mike Youle: Yes, and I think I would support starting at the lowest dose and working upwards for therapy, although it depends how much you ask someone to chew off their 100mg tablet.

Ceppie Merry: Lower than the lowest dose - less than 25mg.

Mike Berry, Dublin: I think the other interesting point about that study, and one that has a slight concern is that the patients who dropped their blood pressure didn’t actually get a tachycardia. The issue here is, is it interfering with the base receptors, and therefore your ability to compensate for the drop in blood pressure, and I think this is a worrying feature that should be looked at.

Duncan Churchill, St Marys: Can I just ask you to enlarge on the last point of your talk, when you said that the methodology needed to be validated. Did you mean validated in terms of being precise and accurate, or did you mean validated against clinical end points? That could take quite a long time.

Ceppie Merry: I mean that the methodology at the moment is far from validated because the Dutch group, as they have said, were quite experienced at this stage in measuring levels. But, at this point in time, we still believe that an AUC is the only way forward. Now obviously we want to move pharmacokinetics into the clinical realm, and the difficulty is that many people will feel that an AUC is just too troublesome, or takes too long. I personally don’t agree, so we need a consensus on which samples to take and how often, and I agree with you, we need a proof of concept clinical study. In Dublin we’ve started a large study, where we are actually going to do serial AUCs and see if it actually impacts on virological outcomes.
Pregnancy

Graham Taylor, St Mary's Hospital, London

In 1998, US guidelines for HIV-care during pregnancy recommended that women who would otherwise be on triple therapy if they weren't pregnant, should be on triple therapy if they are pregnant. This conclusion was eventually mirrored this year in the UK guidelines. 1,2

There is, however, still very little data on the safety of antiretroviral therapy in pregnancy, whether metabolism is altered in pregnancy and consequently the pharmacokinetics. There are pharmacokinetic data for AZT, ddI and a little on 3TC when taken in the last few weeks of pregnancy. 3,4,5

nevirapine in a triple combination

At St Mary's Hospital we decided to use nevirapine (with two nucleoside analogues, usually AZT and 3TC) as our third component because it is an easy regimen to take, has a good side-effect profile, has good anti-HIV activity and when given as a single dose in pregnancy, crosses the placenta and has a long half-life. However, the drug levels of nevirapine when it is given as part of a regular medication during second and third trimesters were not known and therefore we determined to measure the steady state blood levels in women prescribed this combination. Nevirapine (200mg once daily for the first two weeks and twice daily thereafter) was given with two nucleoside analogues. Concentrations were determined by HPLC at Liverpool University.

We have data from 18 mothers - samples were taken from 11 mothers at the end of the first two weeks of therapy (at the end of the daily dosing regimen) and the mean concentration of nevirapine was 3.55 µg/ml plasma. 22 samples were taken from the mothers whilst they were taking 200mg BID. The majority of these samples were taken at the end of two weeks on the full dose, the remainder at weeks 8 and 12 of therapy. Figure 3 shows the levels are quite high, but certainly within the published therapeutic range.

drug concentration in the placental cord

Thus far, eight babies have been born to the eighteen mothers and we have cord blood levels from four of the babies which show concentrations very similar to the maternal levels. After 24 hours the drug concentration was still within the therapeutic range. 6

We had aimed to take samples during routine clinic appointments (approximately four hours post dose), but in practice a number of the samples were taken much later after the previous dose and we therefore have concentration of nevirapine in plasma up to 24 hours after the last dose. Figure 1 shows the individual concentration levels of patients taking 200mg, twice daily. The range of concentration varies from 3.5 - 9 µg/ml - even out to 24 hours post dose. This is well above the 1µg/ml concentration that we were aiming to obtain, which is 100 times above the in vitro IC50.

Figure 2 shows the nevirapine concentration in the maternal, cord and the 24 hour post-delivery infant sample. Following a stat (single) dose of nevirapine given to the mother once labour is established, the concentration of nevirapine is similar in all three samples, which is due to the long half-life of nevirapine when first taken. These results are similar to the published results from the ACTG 316 study. However, different results were obtained where the mothers had taken multiple doses of nevirapine during the second and third trimesters of pregnancy.

Here we see that although the cord blood levels are again very similar to the maternal plasma level, the concentration of nevirapine in infant plasma at 24 hour is only 50% that of the cord blood at delivery. This indicates that for the infants who have been exposed to nevirapine in utero, the half-life of nevirapine is much shorter and suggests that additional doses of nevirapine would need to be prescribed to the baby to maintain therapeutic levels in these babies. This is rather than the single dose given at 48-72 hours, which was sufficient to maintain therapeutic levels for seven days in the ACTG 316 study.
We found no correlation between the nevirapine concentration and maternal body weight, or the gestation period, although these are all from samples taken in the second and third trimester. Although some mothers are leaving the doses a bit late, they nevertheless achieved good blood levels.

Two of the mothers developed a rash. One required interruption of therapy, but she was also taking Seprin and, when the rash settled, we reintroduced all her antiretroviral therapy (but not the Seprin) and she had no recurrence of the rash. The other mother continued with nevirapine, but delayed the dose increase from the 200mg once daily to BID. It is interesting to note that both of these mothers had nevirapine levels at the lower end of the range. We haven't seen rash in any neonates born to date.

One mother, not included in the overall analysis, who had a history of mild pre-eclampsia in an earlier pregnancy, was taking d4T/ddI/nevirapine throughout the second trimester and into the third trimester (see Figure 5). She then developed mild hypertension but had no proteinuria and was admitted for observation as a precaution. She quickly developed a severe complication of pregnancy called HELLP (a syndrome of haemolysis, elevated liver enzymes, low platelet count). She received standard management which involved lowering the blood pressure and an emergency Caesarean section. However, despite this she required intensive care for worsening hepatic and renal impairment, pancreatitis and airways obstruction due to facial oedema. She made a full recovery and both she and the baby are in good health now.

The main point of presenting this case is that the nevirapine levels at delivery were very high, even though the hepatic and renal impairment at that time had only just become apparent.

In this study we found that the dose of nevirapine doesn’t need to be changed when prescribed in pregnancy. We found that the regimen of nevirapine/AZT/3TC was easy to take and the adherence of the mothers was excellent. We were also keen to monitor the efficacy of this triple therapy in pregnancy.

In Figure 6 we plotted the viral load measurements in pregnant women treated at St Mary’s with triple therapy. At baseline plasma viral load ranged between 2,000 - 750,000 copies/ml. This includes mothers chiefly drug-naive, taking a triple including nevirapine, those who changed to a regimen including nevirapine and mothers who are chiefly drug-naive taking a triple therapy including nelfinavir. Given the small sample size, it is difficult to make any comparisons, but all treatments seem to work equally effectively in this group of patients.

We calculated the half-life of the virus following the initiation of treatment from the viral load reduction and it is about 2.75 days. There is no striking difference in the slope of the viral load in relation to the baseline viral load.

In summary, the dose of nevirapine that we are giving is the same in pregnant as for non-pregnant adults. The concentrations for nevirapine that are achieved are approximately 400 times higher than the IC50 of wild type virus in vitro and that is about the level of the IC50 of nevirapine mutant virus. We have found the treatment to be well tolerated. We have excellent adherence and this is confirmed by the therapeutic drug monitoring and the rapid and sustained reductions in viral load.

Q&A DISCUSSION

Question: Why did you chose 1µg/ml plasma as your minimal level when other groups have chosen 4µg/ml? I think that this implies the difficulty in trying to form a consensus on the therapeutic levels.

Graham Taylor: The concentration of 1µg/ml was chosen after reading earlier publications. 4µg/ml has been the average plasma concentration in these studies. 4µg/ml is also at about the IC50 of mutant viruses which have emerged during monotherapy with nevirapine, and therefore some have tried to obtain these levels in the hope that mutant virus will be suppressed if the concentration can be kept at such a high level.

We don’t know the minimum inhibitory concentration, but certainly the levels that we have found are similar to the published levels from studies in non-pregnant adults and those are the concentrations that we aiming for.

We were using TDM to make certain that we weren’t giving a medication, that would be handled in different ways at different time points in the pregnancy, that would give either very low levels or perhaps dangerously high levels.

NOTES

2. STI 1999;75:90-97
I am very glad that paediatrics is included in the programme of the first international symposium on TDM, as paediatric research, which should run in parallel, often lags behind that for adults by two or three years. In these discussions it is important that paediatric care is included from the beginning.

PK differences...

For HIV care, children are not simply small adults. From a pharmacokinetic point we know some examples:

- **Liver function:**
  
  Relative to the body weight or body surface area, liver function is higher in children; we often think that children are vulnerable to the effects of drugs but if you look at the PK you can see that the liver function is even better than for adults.

- **Total body fluid:**
  
  Total body fluid is relatively high in children and this is important for drugs that have a large volume of distribution. For example, soluble drugs can have a larger volume of distribution and therefore lower plasma levels.

- **Acid production:**
  
  To get acid production in children, especially neonates, it is not optimal, it is only maximal, at the age of two, and, for drugs that are given orally and require the presence of gastric acids, for instance indinavir, then you can have problems with absorption.

- **Absorption, dosing and diet:**
  
  Absorption of a drug that is influenced by food - that needs food or it doesn’t need food - is very important for children, especially young children who are fed many times a day, so it is often not possible to have an empty stomach for a long period.

  On the other hand if children go to bed at 6 or 7pm and they require an evening dose with food then that also is a problem particularly with strict Q12H and Q8H regimens. These PK issues are very important in children and quite different from adults.

Some of these aspects were shown in a PK substudy of indinavir in HIV infected children, carried out in Rotterdam, which aimed to find pharmacokinetic parameters, especially AUC, which were similar to those observed in adults. The study started in the spring 1997. As there was no PI available for children in the Netherlands, they decided to use indinavir (as it was the most widely used PI then).

The dosing was based on metabolic weight that has an equation of body weight 0.75 as a factor. You not only have to make an adjustment for body weight, but also for the increased liver function. The starting dose that we selected was 100mg/kg per metabolic weight per day, which is equivalent to 1250 mg/m² per day. We had a target AUC of 20mg/l.hr which is the average value in HIV infected adults.

We accepted a range of 10 - 30mg/l.hr and we measured AUC (not random samples) on days 14 - 28. Dose multiplication was applied at 50% or 100% if necessary.

Results from this study are shown in Figure 1. 19 children started with a dose of 100mg/kg metabolic weight, but only 53% achieved the target AUC of 20mg/l.hr. Only one child achieved a higher AUC and the remaining 42% only reached very low levels.

This resulted in a dose increment to 150mg/kg for most of these children (and for others that we later included in the study) which lead to 75% of the group then achieving the target AUC. Five children who initially achieved very low AUC of indinavir doubled the dose to 200mg/kg but this boosted AUC above 30 in four out of five and proved intolerable to all of them.

<table>
<thead>
<tr>
<th>Dose (mg/kg MW/d)</th>
<th>100 (n=19)</th>
<th>150 (n=17)</th>
<th>200 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (mg/l.hr)</td>
<td>17.1</td>
<td>15.1</td>
<td>19.7</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>9.4</td>
<td>8.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Cmin (mg/L)</td>
<td>0.15</td>
<td>0.06</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Figure 2 shows the average adult failures about 19 or 20 at AUC, a Cmax of 9.4 mg/L, and a trough level of 0.15mg/L. If you look at the starting dose of 100mg in the paediatric group, you can see that the AUC is only half this value and also the trough levels are lower.

The 150mg dose (which appeared to be the optimal dose) produced an AUC comparable to that seen in adults.
Although at this dose the Cmax is also comparable to that seen in adults, the Cmin is still much lower. In this study, the higher doses of indinavir needed to achieve a trough level comparable to that seen in adults, was not able to be tolerated.

Figure 3 shows the case of a 7-year-old boy. Because the starting dose was too low, we tried a 400 mg dose which was clearly too high and not tolerated. The reduced dose of 300mg TID produced an AUC similar to the adult average. Although they are similar, there is still a more rapid elimination of the drug and trough levels still remain lower than those seen in adults.

The variability that we observed in this study was also partly related to the age of the children (see Figure 4).

Although they all received indinavir, it was correlated for the metabolic weight, so not only for body weight but also for liver function and we found that the youngest children (<6 yrs) had a much higher indinavir clearance.

It is not totally clear that it is only metabolism that we are looking at, because this drug is given orally, so absorption may also be an issue. Nevertheless, children older than six reached an indinavir clearance which is similar to that seen in adults (about 0.7 l/hr/kg). So this may be, in part at least, a reason for the large variability, especially for the younger children who will require an even higher dose.

This data lead to the making of the dosing nomogram for indinavir shown in Figure 5. The original starting dose of 100mg/kg per metabolic weight was calculated based on the assumption that an 18-20 year old adult dose of indinavir should be 2400mg. This was a mistake because we should really have been looking at a child of about 12, when clearance of drugs is almost similar to that seen in adults.

If you look at this age, then you come to the optimal dose of 150mg metabolic weight. The 200mg (toxic) dose, is the adult dose already at the age of 10 - which is too early. Merck is also working on this and are investigating a dose of 1500 mg/m² which produces similar curve to the 150 mg/kg metabolic weight. So whether you look at metabolic weight, or whether you look at body surface area, you are in fact looking at the same. As most people are familiar with the use of square metres, and I think it is better to use this dose, or even a somewhat higher dose, we arrived at 1800 mg/m²/day.

**Clinical relevance**

It is not only important to look at the pharmacokinetic data only, it is also important to look at whether this data is relevant to the clinical situation.

If a child had an AUC which was too low and resulted in a dose increment, we repeated the AUC afterwards. Finally, we looked at 22 children who received treatment for 6 months, and we looked at whether these children had a viral load below 500 copies/ml or not. We particularly looked at the AUC and if it was below 20mg/l (below the average adult value).

![Fig. 3 - IDV PK of 7yo boy, 21kg](image1)

![Fig. 4 - Indinavir age and clearance](image2)

![Fig. 5 - Indinavir dosing nomogram](image3)

![Fig. 6 - Virological response to below 500 copies/ml after 6 months treatment](image4)

- AUC < 20 mg/l.hr (N=11): 55% response
- AUC > 20 mg/l.hr (N=11): 100% response

Although we adjusted the dose based on the AUC, and we accepted the range between 10 - 30, the children with an AUC below 20 only had a 55% response, and the children who had an AUC above 20, and who tolerated this AUC, had a 100% response.

As a conclusion we recommend that you should target the AUC, at least in these children, to above 20mg/l.hr or higher as long as it is tolerated. A starting dose of 150 mg/kg metabolic weight/day (equivalent to 1800 mg/m²/day).

The dose can then be modified, based on the AUC observed and on the toxicity encountered. This study actually highlighted the need for an oral paediatric formulation and we then developed a liquid form presented in a study in Chicago by Patricia Hugen. The development included chemical and physical stability, taste panels and bioequivalence. The method of preparation...
for this liquid is now available to other clinicians and researchers.

**ritonavir/indinavir**

The TID dosing of agents is especially problematic in children and TDM monitoring in this population can provide a basis for dosing with ritonavir in order to eliminate the need for an afternoon dose being taken at school.

For example, a 7 year old girl who was on indinavir 400mg TID, was only achieving AUC figures around about 16-17mg/l.hr. Although viral load became undetectable after two months, it rebounded six months later despite strict compliance. Indinavir drug levels were boosted by adding a low dose of ritonavir to the 400mg indinavir dose, but this was now given BID, with food. No change was made to the background nucleoside therapy. On repeating the PK profile we saw a very large increase in the exposure to indinavir and also a very high trough level of indinavir - even after 10 or 11 hours. The virological effect was also there and the next time she came to the clinic viral load was undetectable again. This has continued for 5 months.

**nelfinavir - TID and BID dosing**

Nelfinavir was originally licensed for children in a TID dose of 20-30mg/kg. Measuring levels on an individual basis showed us that 20mg was obviously too low in a number of children. If you look at the AUC or the trough level of nelfinavir it is much lower than that observed in adults, so we now recommend a dose of 30mg/kg TID.

To achieve nelfinavir levels equivalent to adult values with BID dosing we found you need increased doses of 55mg/kg (not 45mg/kg). There was also a poster in Chicago showing that children that were weighing less than 25 kg needed higher doses than the 30mg/kg TID.

It is important that nelfinavir is taken with food, and especially for children to take the evening dose with food, even though they may have been sleeping. To just wake a child and give some of the powder is not enough. Figure 8 and 9 shows data for one child who crossed over from the TID dose to a 45mg/kg BID dose. The trough level after TID is higher than after BID given at 45mg BID.

PK in adults it is already complicated enough but these studies show why it is even more complicated in children. All children in the Netherlands are included in a study protocol with a research nurse and we do a pharmacokinetic profile, particularly AUC whenever is necessary. In addition to this we also perform routine TDM for children for the same indications applicable to adults.
Q&A DISCUSSION

Diana Gibb, MRC: I think it very important that these issues of PK in children are raised. You recommend that children are woken up to give them their drugs. But one of the reasons the studies have shown low trough levels is that often young children will sleep for 12 hours and get their three times daily doses packed into the waking 12 hours. If you are then looking at morning levels, you might not find anything there at all. In practice, the difficulties of waking children up to give them not only the powder but food as well, means this is not followed for many groups of children. The importance of looking at BID and practical dosing is extremely important.

Another issue is whether we calculate doses as metre squared or body weight. The nelfinavir dose is body weight, presumably through a relationship between metabolic weight and metre squared. Adult physicians find it very difficult to understand what on earth paediatricians do - some drugs they calculate on body weight, some on surface area some now on metabolic weight.

David Burger: I recommend dosing on body surface area using metre squared. The conclusion from one of the abstracts from Chicago was also that, for nelfinavir, dosing in children less than 25 kg should be higher and this is also the case for ritonavir.

Diana Gibb: Even though drugs are licensed based on body weight?

David Burger: Yes. Licensed recommendations are based on a study on only ten children between the ages of three and six, and on the observed intake of the medication with a standard breakfast - that is not routine clinical practice, especially if we accept that 18 or 20mg/l.hr is not sufficient.

Diana Gibb: This shows the difficulties of doing population PK on children and relating it to these standards from very small numbers of children who have had proper AUCs done.

David Burger: I am very happy that we did the AUC in this study and not routine random sampling.

Diana Gibb: What is your comment then about using random sampling in children?

David Burger: I wouldn't recommend using random sampling for children for the selection of the appropriate dose. I would always recommend a pharmacokinetic profile in any child. Afterwards, if you want to tackle problems with adherence or drug interactions, then you can do random sampling. In order to select the appropriate dose for each child you need an AUC.

Anne Hsu: For the indinavir study you have greater than 20 mg/l.hr AUC. Have you looked at the group that achieves a less than 55% response rate? Although this is a small study, do AUC minimum levels correlate better than the mean?

David Burger: The AUC correlated better. We selected the value of 20mg/l.hr because that was the average adult value. There were 22 children, and 11 were below and 11 above, so that was the exact point. It was not that you could say with 18mg/l.hr and higher you only have treatment response and below this you don't have any treatment response. There were children with an AUC of 15mg/l.hr, for example, who had a treatment response.

Rupert Jones, THT Yorkshire: I've got a child who thought that nelfinavir was disgusting and I find now a year later it hasn't changed - it might be the next line of treatment for my son. Who makes up the taste panels that you mentioned and is there anything we can do to improve the taste?

David Burger: The panels consisted of adult volunteers, not children because we didn't want children to ingest the medication. However, childrens' taste is certainly different from adults so we've also produced questionnaires for children who now use the liquid combination, although the data is too small to present.

Simon Collins: Was your indinavir paediatric solution developed privately, and do you have any marketing plans?

David Burger: Yes, privately. There was some support from the local company, but not from Merck International. We do not have any marketing plans for this, but it is available.

Diana Gibb: Have you seen much toxicity in terms of kidney stones in children and if not how do you manage to get them to drink additional water - especially very young children?

David Burger: Although we gave these children a higher dose than was used in the US we had a remarkably low incidence of kidney stones, or any other nephrological toxicity, so the children must have been drinking sufficient fluid. Differences in climate to the US or Italy may have been important, as much higher incidence than was used in the US we had a remarkably low incidence of kidney stones have been reported in children in those countries. We were also surprised with this low incidence but we don't have a very clear explanation for it.

NOTES

Liver dysfunction is a common complication with HIV disease, which is broadly classified as paracausal (hepatitis B/C/D, PCP, drug induced) or bilary (cholangitis, CMV, cryptosporidium, lymphoma, KS).

The parameters affected include plasma protein binding, liver blood flow and the activity of the drug metabolising enzymes themselves. Essentially, clearance of a drug is related to blood flow, and the extraction of the drug from the organ.

Figure 1 shows how complicated this side of pharmacology can get. Shand and Wilkinson demonstrated the intrinsic metabolic clearance and its relationship to hepatic extraction in 1975.1 Essentially, if you have a high intrinsic clearance, all or most of the drug will be extracted and metabolised. Low intrinsic clearance produces the opposite effect, with an almost linear relationship. With propranolol, for example, which has similar high clearance rate to PIs, liver blood flow increases as well as the clearance of the drug, but in sclerotic liver that blood flow almost by-passes the liver, avoiding drug metabolism altogether. A reduction in clearance tends to increase volume of distribution, because you have less plasma protein binding. This increases the half-life as the unbound fraction increases.

predicting PI response
There have been few studies looking at this for PIs though, and those that have been done do not help us draw general conclusions.

One small study (n=5) looked at nelfinavir and hepatitis B or C (two mild, one moderate and two severe). There was certainly a significant reduction in clearance for one mild and one severe patient but one patient with severe chronic liver disease retained good clearance (971 ml/min).2 So someone with severe liver disease can sometimes have quite normal drug metabolism.

A ritonavir study, comparing PK of six patients with underlying liver disease (increased LFTs x 4-10 times - Child Pugh, mild CLD) to 6 patients without, showed that the Cmax of ritonavir increased by 27% and the AUC increased by 50%.3

With efavirenz no real difference was found between the control group and chronic liver disease.4

what are the recommendations?
Both PIs and NNRTIs come with a suggestion that they should be used with caution in people with liver disease, but with few dose recommendations. Indinavir has been reduced to 600mg TID in some patients with liver dysfunction. The situation for patients then is really haphazard and although more studies may be useful, individualising treatment using TDM is the only real way to find out what is happening in such a fluctuating setting.

renal disease
Renal disease can be due to infective causes, malignancy and acute tubular necrosis amongst others and chronic renal disease certainly impairs the handling of drugs, particularly if this is the main route for elimination.

Again, there are two parameters that you can change: you can either use a lower dose at the same dosage interval, or you can use the same dose but extend the interval. Specific dose reductions are recommended here for nucleoside analogues; NNRTIs are again to be used with caution; and with PIs no initial dose reduction suggested (because they are predominantly metabolised by the liver).

full profile vs single point sample
For some anti-retroviral agents, such as PIs, significant PK variability already exists and the presence of renal or hepatic disease exaggerates this situation.

The idea of taking single time point levels and not interpreting them clinically is not TDM but a form of therapeutic anarchy. In my experience a single point reading is insufficient to provide a clinician with a reliable AUC levels in a particular patient - and certainly not for this to then be used as a basis for recommending dose changes.

Figure 3 shows a profile of saquinavir over the eight hour period dosing interval, compared to a patient who also has liver disease. A sample for this patient taken at three...
hours would be fine, but at one hour you get a different reading which would give a completely different impression.

Current strategies for anti-retroviral use may therefore be inadequate to ensure that the MEC will be consistently achieved by all patients, even when adherence is 100%. The only answer is to make full use of TDM, providing you do a full profile. Although it may seem inconvenient for the patient, this is not really either difficult or unusual.

In my hypertension clinic, for example, we put ‘cuffs’ on people at 9 o’clock in the morning. They take an hour to inflate and it does this every hour. I then bring them back again the following morning for more so that I have a full eight hour profile. With support, and an explanation of the importance of the results I have found this to be easily obtainable for patients within HIV-care.

The one rule that I always use in patient management is ‘what would I like to have done for myself?’ In this situation, knowing what I know, I would always like to have an eight hour profile of the drug and I’d like to have it assessed against the MEC!

**Q&A DISCUSSION**

**Steve Taylor, Birmingham:** I agree that the profile is the ideal method, but having done some of this in the clinic I think, unless you are doing a trial I think it is very impractical. We get some of our patients to come in at 8 o’clock in the morning and get a trough dose and hang around for two hours to get the peak dose and maybe repeat it a couple of times but we find it difficult for patients who are working. Taking blood samples at every hour takes up resources of doctors, nurses and patients.

**Mike Berry:** I think it is important enough for you to decide whether you want second-rate or the best? Many patients attend clinics for glucose tolerance tests which take several hours and clinics are able to manage this. Given full information I am sure that patients would be more than compliant.

**NOTES**

Interactive Discussion

Moderators: Heather Leake, Brighton Healthcare NHS Trust
Tom McManus, Newham General Hospital

TDM and sanctuary sites

The discussion began with a presentation from Steve Taylor and Deenan Pillay who have been studying HIV viral load in different body compartments, particularly the genital tract.

Deenan Pillay explained that one of the key issues in the effective suppression of viral replication is the different efficacy of drug combinations in sanctuary sites to that seen in the blood compartment. The male genital tract and semen are a physically separate compartment but also the source, of the major transmission of HIV worldwide. ‘We’ve generated data showing that there is some discordance between viral load suppression in blood and semen. With regard to the debate today, we’ve looked at drug levels within that compartment as a potential factor determining the different evolution of virus within that compartment.’

The most extensive data so far is with ritonavir and saquinavir, and it has produced very similar results to other findings with CSF penetration. PIs do not appear to penetrate into the semen very well at all, maybe at levels of approximately 2 - 4% compared to plasma, which are below the MEC.

Steve Taylor stressed that while there may be subtherapeutic levels in these cases, they don’t think that is necessarily going to be true for all drugs and are currently looking at both indinavir and nevirapine. ‘Discordant drug levels in the two compartments may have a great implications on both the development of resistance in each compartment and in the transmission of resistant virus to newly infected patients.’

This issue is complicated because there is hardly any protein in the CSF, the levels measured are practically all free concentrations. Although Anne Hsu in an Abbott study on saquinavir and ritonavir had found comparable reductions in both CSF and plasma, Joep Lange pointed out that this was not matched in the Prometheus study, where ritonavir/saquinavir was compared to ritonavir/saquinavir/344T. ‘While the triple drug regimen led to a decline of HIV RNA in the CSF in all the subjects investigated, the ritonavir/saquinavir alone arm did not achieve this for a considerable number of subjects, even though the plasma viral load went down. This difference may be explained though by the timing of taking the sample. In the first study this was after 48 weeks whilst Prometheus was after only twelve weeks.’

While protein binding for the PIs is generally 98%, this is not the case for indinavir which has 60% protein binding in plasma. Alfred Saah referred to work by Diana Havler at UCSD which showed indinavir penetration in the CSF and a correlation showing actual measured levels above the inhibitory concentrations of the virus. Again though, this was qualified by the fact that these studies were within combination therapy rather than indinavir monotherapy and nucleoside analogues lead to an RNA decline in CFS by themselves.

non-linear relationships

Avneet Chowdhuey from Barts asked the pharmacologists whether there are there any drugs that display non-linear or saturable kinetics, and whether they had any specific warnings about this.

David Burger had seen with indinavir, and in paediatric studies with saquinavir, that these two PIs clearly exhibit non-linear pharmacokinetics, and urged caution with dose increments. So a with a trough concentration or an AUC which is 50% below what you should expect, doubling the dose will more than double the concentration possible to a hazardous level.

Other PIs and NNRTIs have may have some degree of non-linearity, and this can include the effect working the other way round.

Increasing the dose of nelfinavir, for example, produces a less than proportional increase in plasma concentrations, although it isn’t known whether this is because of an absorption limitation of some kind or due to a dose dependent enzyme induction effect.

Ritonavir, at low doses, exhibits a non-linear increase, for example, for 100mg ritonavir and 400mg ritonavir the difference is about tenfold, when the dose difference is only fourfold. Abbotts interaction studies with indinavir found indinavir by itself to be non-linear, but becomes relatively linear when it is given with ritonavir.

AUCs vs single point

One of the points which came up in discussion after Dr Barry’s talk was that the relative practicality of doing AUC measurements rather than single time point measurements the discussion focussed on the difference between the ideal situation and what we may be limited to in practice?

The discussion attempted to clarify the relative importance of the speed of response, durability of response and Cmax versus AUC versus the Cmin. If the major concern is Cmin would it not be possible to just trickle the drug in just above Cmin for the eight hours?

Anne Hsu thought the Cmin to be more important, particularly for PIs, because the viral replication is very fast and the equilibrium is also very fast. ‘If there is difficulty in determining AUC you could opt for Cmin but AUC the difference is about tenfold, when the dose difference is only fourfold. Abbotts interaction studies with indinavir found indinavir by itself to be non-linear, but becomes relatively linear when it is given with ritonavir.

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Brad Kerr agreed that those parameters for any given regimen tend to be so highly correlated that it is difficult to distinguish within a study any difference between once/twice/three times a day regimens. With nelfinavir, Agouron found that the two-hour concentrations were more strongly related to response than pre-dose levels, although he thought that maybe there was more noise in the trough concentrations. They were untimed samples with a lot of
variability in the time since last dose whereas the two-hour samples were very tightly controlled.

**Ritonavir / Indinavir Dosing**

The issue of trials being driven by marketing considerations was raised by David Campbell-Morrison, where the studies from Abbott promote high doses of ritonavir and those from Merck favour high doses of indinavir. ‘I think scientifically we may be getting complete oblation of the cytochrome P450 at even a 100mg BID dose of ritonavir - so there’s really not much point in further increasing the dosage. The 800mg BID dosing of indinavir can produce a very high level of toxicity. Patient consideration has been left out of the equation and I don’t think there’s very much scientific work going on to produce studies on optimal regimes in pharmacokinetic terms.’

This produced a heated discussion between ‘heavyweights of the pharmacokinetic world’ and leading researchers and members of the community on the benefits and necessity of clinical trials for these combinations.

Joep Lange regretted the restrictions on European studies due to limited independent funding. He had proposed a study two years ago comparing 100/800 to 400/400 in a real life situation but was not supported by either company because the end result, whatever the result would require fewer total drugs to single PI use. Following independent investigator-driven studies, showing the benefit of using these drugs together is too significant for either company to ignore, the debate has now focussed on the dosing.

On the scientific question of efficacy it was interesting to hear that both Merck and Abbott actually have some consensus on this. Alfred Saah: ‘Anne Hsu and I were on the phone to a group in California who were trying to decide on a dose for HIV infection in women and ... we both agreed that there would be no difference in efficacy’.

On the surface this may make it very difficult to get an efficacy answer with clinical endpoints from a trial comparing different dose combinations. If the synergistic relationship of double drug potency in the 400/400 dosing raised by Joep Lange is important though, then this difference may become apparent through looking at early RNA decline. ‘I am not making value judgments here about which is the better one efficacy wise - but if synergy is important you will get an answer. You don’t need clinical end points.’

While the sample size to show differences in efficacy would have to be very large, smaller studies could show any variation in the early slope of decline and just as importantly, differences in toxicity - what actually happens to the patient - and whether there is a higher drop out rate for either regimen.

There seemed to be a demand from the clinicians present for a clinical trial in order to know whether any difference was relevant as this will be the only way to verify if current assumptions are correct. Several other contributions returned to the issues of toxicity, and whether other doses could be as effective but more tolerable. The higher AUCs produced can be higher than we are used to when using each drug separately and may be far in excess of anything that could be predicted to be suppressing HIV. A higher AUC may be a predictor of toxicity in terms of lipodystrophy, cholesterol disorders and cardiovascular and diabetic type complications. James Deutsch highlighted ‘how massively higher both AUC and the Cmin were with all the ritonavir/indinavir combinations compared to when either of the two drugs are taken alone. It is astonishing to know that the AUC and the Cmin levels when we are using these PIs singly are considered acceptable in comparison.’

There was also a broad agreement that for individual patients, tolerability and forgiveness may be in reality become the key factor in settling for the dosing ratio. Currently, without the benefit of results from comparison arms, individualising patient care may only be possible with the support of TDM, thankfully going someway to validate the subject of the whole meeting!

The balance between optimum antiviral activity and side-effects is obviously crucial. One response from someone who had just achieved undetectability on their third combination stressed the importance of forgiveness as being ‘the thing I really go for, I then start worrying about the side-effects later’.

**Microbial Model**

At the end of the discussion, Alfred Saah returned to the historical model for TDM being rooted in the study of infectious diseases, where you are able to measure any microbial level. ‘In terms of antimicrobial susceptibility, some people are treated with antibiotics who have resistant organisms and they have still recovered and others with susceptible organisms have been successfully treated and they’ve died - so it’s not just all the antibiotic, or all the PK, there are the other things that we don’t know that are not measurable.’

In the case of HIV we are missing significant pieces of information such as the susceptibility of the bug, and the effects of other drugs on viral suppression. To only maximise the concentration of the PI in this regard and trying to correlate it with historical information on viral suppression may require more information. ‘This doesn’t mean we shouldn’t continue to look ... if in fact we think we need to measure drug levels toward some optimal level and hope for the best.’
The failure of HAART is a serious issue especially in the long-term treatment of HIV. Often due to multiple sequential therapies, now considered sub-optimal, which allowed emergence of resistance and cross-resistance in many patients and severely reduced choices for the future treatment.

The options for patients in this situation include:
- stopping treatment to wait for new agents
- switching to sub-optimal treatment (which allows viral replication but hoping that the resistant virus has an impaired fitness)
- replacing the protease inhibitor and new RTIs (if available) if naive to NNRTIs (and vice versa)
- adding hydroxyurea (to boost RTI levels)
- using multiple drug salvage regimen - mega-HAART

Mega-HAART (MH)

Mega-HAART can be defined as combining the maximum number of tolerated drugs in order to increase the total antiviral activity by both additive and synergistic effects. By increasing plasma drug levels we also hope to get a better chance of inhibiting partially resistant virus populations. In practical terms this means that we combine 3 - 5 nucleosides with an NNRTI and preferably three PIs. Sometimes we use only two PIs, but ritonavir should certainly be included, if possible, as a booster.

The first patient we treated with this concept was a 34 year old woman diagnosed in 1986. She had some minor HIV associated diagnoses but then experienced an AIDS defining event with CMV retinitis in 1995. In 1996 she started ritonavir in combination with two nucleosides; her CD4 count improved little bit but viral load remained very high at 800,000 copies/ml, even including ritonavir. She experienced a two relapses of retinitis. We didn’t have any proven options for this patient because she was pretreated with every class of drug. She was being treated with the best combination available at that time, and had failed clinically and virologically, so we devised a HAART combination that consisted of AZT/3TC/ddC/ddI/ritonavir/nelfinavir/indinavir.

This combination brought viral load down below 20 copies/ml - in this case the first time she had ever become undetectable. The patient was treated with that combination for 32 weeks but because this is a very hard combination to follow we tried a simplified once-daily maintenance regimen, with ddl/3TC/nevirapine. Viral load rebounded quickly because of a pre-existing resistance to NNRTIs so we initiated MH again which was slightly modified later on and she became undetectable again. Her CD4 count continued to rise (it is now around 500 copies/mm$^3$) and since last summer she was treated with a protease-sparing maintenance regimen which she continues to take.

Maintaining therapy for almost one year still below the limit of detection meant that these results were accompanied by a clinical benefit as she has been able to discontinue prophylactic treatments for both CMV and PCP.

Incidently, this woman was monitored very closely for both CMV and PCP. Treatment was on an out-patient basis and the patient has got a 7 year old daughter and she took care of her all the time and she is very well. Nevertheless she has developed considerable fat redistribution which is still progressing even though she is now treated with a non-protease containing regimen.

This first patient encouraged us to conduct a pilot study. This analysis is preliminary from 37 patients with a history of multiple drug failure who have been treated with at least six drugs. A medium follow up time of 8 months and baseline resistance was available for a subset of these patients. A more comprehensive analysis of 97 patients with a medium follow up time of 12 months is being produced which confirms these results.

24 patients received 6 drugs, 11 patients were treated with 7, and 2 patients got 8 drugs. The majority received 3 PIs and the rest at least 2 PIs. Most patients were treated with ritonavir as a booster. We looked for the maximum virus reduction that was achievable by the proportion of patients that were dropping down below 500 or 20 copies/ml respectively and the number of patients maintaining that viral load. We also looked at the CD4 responses.

The median viral load at baseline was 320,000 copies/ml and median CD4 count was 110 cells/mm$^3$ and Figure 1 shows the extent of pre-existing resistance in the 24 patients with available analysed data. Most had started their treatment in the era of monotherapy and had already been treated with protease containing salvage regimens.

The median maximum viral load reduction in this study was about 3 logs and over 2 logs in 32 patients. 29 patients achieved viral suppression < 500 copies/ml and 15 patient of these were <20 copies/ml. The median CD4 increase was 95 cells/mm$^3$ and 19 patients had a CD4 rise of more than 100 cells/mm$^3$. Nine patients were switched to simple therapies, now considered sub-optimal, which allowed emergence of resistance and cross-resistance in many patients and severely reduced choices for the future treatment.

The options for patients in this situation include:
- stopping treatment to wait for new agents
- switching to sub-optimal treatment (which allows viral replication but hoping that the resistant virus has an impaired fitness)
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- using multiple drug salvage regimen - mega-HAART

Figure 1 - Baseline resistance

(available for 24/37 patients)
- > 10-fold AZT resistance: 15/24
- > 4-fold abacavir resistance: 11/24
- NNRTI resistance: 16/24
- > 4-fold resistance to 3-4 PIs: 13/24
- > 10-fold resistance to 3-4 PIs: 6/24
- 16 patients recycled 3TC: (9/16 with evidence of returning susceptibility)
maintenance treatments as seen in the first case report but only three remain undetectable whilst on that maintenance therapy now.

Mega-HAART combinations therefore represent a salvage therapy option for patients after the sequential failure of HAART but we still need more studies. The factors associated with response or failure need to be elucidated and the contribution of resistance to success or failure needs to be established.

Tolerability was relatively good although the most side-effects were due to the protease inhibitors, especially ritonavir. We did a dose reduction in these combinations which is not recommendable in other regimens or situations. The MH combination obviously is not suitable for long-term treatment so the development of maintenance options is required. You have to keep in mind that this preliminary analysis is based on volunteers with a high motivation but these very compliant patients have shown a proof of concept for this type of treatment.

Q&A DISCUSSION

Joep Lange: Julio Montaner has done something similar with mega-HAART showing that the success rate falls with long-term the follow up. In fact, after only 24 weeks, only 16% of patients were <50 copies. Do you see a similar trend or do you see that once people get down to <20 copies they stay there?

Carsten Rotman: Yes, almost. The data from the 1997 paper, which is about to be published, shows a similar viral load reduction of around 2.7 logs compared to the 3 logs here. We had a drop out rate because of intolerance and viral rebound of 25%.

Joep Lange: Does that mean that the successes are transient?

Carsten Rotman: In some patients, but not in all of them of course. This is a strategy worth trying it. We need to find out other factors contributing to long-term response in addition to resistance. We also hope that even a short-term reduction of viral load may have a sustained clinical benefit.

Maxime Journiac: How to you determine the doses for the drugs in these regimens?

Carsten Rotman: We only dose adjust for the protease inhibitors and we are guided by adverse experiences as well as measuring levels using TDM. We worked together with Richard Hoetelmans and performed drug concentration level testing in these patients. On this basis we were able to quadruple the dose of indinavir for one patient to obtain therapeutic levels although this wasn’t continued because of tolerability.

Maxime Journiac: How did you manage the dosing for people who were taking PIs with NNRTIs because they can affect each other. Did you find lots of variation?

Carsten Rotman: I haven’t seen the results from the PK analysis yet, but nobody can predict what is going to happen if you combine 3 PIs with a NNRTI. It’s a desperate salvage situation when we try this mega-HAART dose.

Giovanni Alunni, NADIR, Italy: Can you comment on whether a washout period before starting a salvage therapy would be useful and, in that case, what should be the appropriate length?

Carsten Rotman: We have experience with drugs holidays but they are longer than they need to be for a washout period. In another analysis we have 50 patients who took a break from treatment before starting a salvage regimen and in 29 of these patients we have seen a switch back to wild type after a median time of 12 weeks. This correlates with later response in salvage treatments, so a drug-free period may be suitable for some patients to enhance the response rate. At the moment it is not clear how long the break ought to be. If CD4 counts drop dramatically we restart treatment - otherwise we monitor closely and try to wait.

Joep Lange: Data presented at the Canadian salvage conference showed that for every month that you stopped there is a 15% increase in the virological success rate but there’s also considerations for not stopping too long. It was interesting to see that increase in period off treatment can be correlated with a better response rate.

Mike Youle: The data from the Royal Free showed that for every month off therapy before salvage you’re 15% more likely to respond and for every log higher baseline viral load you are 40% less likely to respond. This is the big problem.
Hydroxyurea (HU) has only recently received wider attention for the treatment of HIV, probably because it is so cheap and therefore less attractive to a commercial developer - and I think that is an important issue. The cheaper and easier something is to use, the less likely it is to be developed.

Hydroxyurea has been around for over 30 years and it is currently licensed for use in certain cancers. In HIV it is used at much lower doses which is important when we come to talk about toxicity.

**why use HU for HIV?**

Mechanisms of action that have been suggested for hydroxyurea are that it:

i) **inhibits HIV DNA synthesis**

Instead of your normal DNA synthesis you actually deplete your ability to do that and this has a direct implication for toxicity. The idea of nucleoside toxicity is becoming increasingly important - just when we thought nucleosides were not doing very much and the protease inhibitors were those nasty drugs that were rotting your liver and causing lipodystrophy.

ii) **potentiates NRTI activity (ddI but also others)**

With hydroxyurea you get a potentiality of NRTI activity, mainly because the odds are stacked in favour of ddI in terms of chain termination, because you've got a reduction in your precursors. Data from a Franco Lori study in Figure 1 shows short-term viral load results from patients given either ddI or ddI/hydroxyurea. There is clearly some difference between the two groups and more importantly this was sustained.

Of these patients with long-term follow up, 11 out of 12 using just HU/ddI maintained undetectable levels of viral load. This may offer important potential for treatment in resource-poor settings.

Other data was shown by Steve Miller and a physician from Botswana who both looked at using this combination in populations who otherwise have no access to anti-retroviral treatments. ddI/hydroxyurea is half the price of ddI/d4T (or other double nucleoside combinations) at present, and they actually showed equivalents of the two regimens.

iii) **compensates for ddI resistance**

Is there any evidence that hydroxyurea compensates for ddI resistance? This is the theory that you are actually competing against a reduced nucleotide pool and whether that might allow you to re-establish the ratio although I'm not sure that there is any hard evidence for that to date.

iv) **enhances phosphorylation of NRTIs**

NRTIs require intracellular phosphorylation for 'activation'. Hydroxyurea arrests cell cycle in G1-S phase, potentially increasing the activity of intracellular kinases and therefore phosphorylation of NRTIs. If NRTI phosphorylation has been impaired, hydroxyurea could be a rational part of a salvage treatment containing thymidine (e.g., d4T) or cytidine (e.g., 3TC) analogues, and this is being studied in patients whose NRTI regimes have failed.

v) **modulates the immune system**

There appears to be some evidence for modulation with the immune system with the cytostatic effect of hydroxyurea both on CD4s and CD8s. In this kind of setting, where CD8 activation has been suggested to have an impact on both the immunological benefits of therapy and also be part of clinical disease processes, there may be a role for hydroxyurea within this. This is based on the hypothesis that excess CTL activation without HIV elimination is basically working overboard. The Zinkanargel hypothesis was debated heavily at the RIGHT meeting and certain of the American scientists thought that this was definitely not an issue.

In the same way that hydroxyurea downregulates CD8 activation, and inhibits HIV replication, you might get a benefit of the drug where it is softening this response between the CD8s and CD4s, and not ending up with this clearance of CD4.

**what are the practical issues?**

One of the difficulties with research that is not backed by a major drug company or FDA and MCA driven agenda, is that it tends to be small studies, that then move into population studies and then somebody comes up with the idea of doing a decent study. Having said that, I am not so sure that we make our decisions on what is good or bad on a big study I'm not sure that Delta told us that AZT and ddI was better than a single drug - I think we already knew that. What we didn't know was whether that was either sustained or safe.
Larger studies are really telling you what you already know and confirming what might already be clinical practice within the treatment environment.

Figures 7-8 show data from a Swiss study using d4T/ddI plus or minus hydroxyurea and looking at evaluations over a period of time and the baseline characteristics of these. There were 72 in each group, and they were mainly people who were naive, and here there were reasonably high CD4 counts and not particularly high viral load. Here is what happens and I think most people will have seen this data before.

There was a less rapid response perhaps in the people given hydroxyurea, but that you actually got a fairly sustained response out of 48 weeks of treatment with a better effect in the people who were on hydroxyurea containing regimens.

There is some blunting of the CD4 response (Figure 8) of the people on the hydroxyurea containing regimens, and I think that most people have seen that in clinical practice. This may suggests that there might be an initial period where you have to have antivirals without hydroxyurea - or perhaps the other way round - and several studies looking at whether giving hydroxyurea either after initial viral load reduction or at initial treatment.

In our study at the Royal Free, 82% of our patients are on hydroxyurea and we are finding some blunting effect of the CD4 response. There is some suggestion from a few patients in early infection that there may be a benefit.

Another study of 10 patients, presented in Chicago, using HU/ddI and a PI within a few months of infection showed all patients achieving viral load< 50 copies/ml. It also showed a higher naive ratio than in untreated controls and that you actually got bigger CD4/CD8 anti-HIV T-cell responses. I don't think you can draw much from 10 patients but it was an interesting finding. There were two patients who showed no infectious virus recoverable following in vitro cell stimulation who were given ddI and hydroxyurea.

Another Lori study treated six patients prior to seroconversion with a ddI/HU and a PI. No patients had seroconversion illnesses and the CD4 and CD8 ratios returned to normal very rapidly with undetectable nodal RNA in two patients despite searching 44 million cells. These are all anecdotal cases, but here you have 2 people on dual therapy which previously perhaps would have been thought not to give such good responses, and one of these patients discontinued without rebound.

The Berlin Patient took ddI/indinavir/HU - viral load became undetectable, stopped therapy, rebounded, started therapy, rebounded, stopped therapy and went on and off 3 times but then has had a prolonged period without any viremia.

One salvage study at Geneva involved patients being given only d4T/3TC/hydroxyurea - and received criticism for sub-optimal treatment. However, a reasonable log drop in patients who were experienced in 3TC and d4T, although not from all patients.

At the Royal Free we’ve got 63 patients with a median CD4 of 128 very much similar to Schlomo’s details - not 1.7 it is 3.02 so we’ve got exactly the same viral load drop in these patients however our median CD4 count interestingly is now about 128 cells/mm³ so it is blunted compared to

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**hydroxyurea - proposed mechanisms of action** (Slides courtesy F. Lori)

1. **HU inhibits HIV DNA synthesis**
   - HU inhibits HIV DNA synthesis
   - DNA replication is blocked
   - DNA synthesis is prevented
   - decreased HIV production

2. **HU potentiates NRTI activity**
   - HU enhances phosphorylation of NRTIs
   - NRTIs potentiated by HU
   - Increased anti-viral activity
   - HU enhances antiviral activity

3. **HU compensates for ddI resistance**
   - HU lowers IC50 of ddI-resistant variants of HIV-1
   - IC50 of ddI-resistant variants

4. **HU enhances phosphorylation of NRTIs**
   - NRTIs require phosphorylation for 'activation'
   - Hydroxyurea arrests cell cycle in G1, S phase, priming the activity of intracellular kinases and therefore phosphorylation of NRTIs
   - If NRTI phosphorylation has been impaired, hydroxyurea could be a rational part of a salvage treatment containing Thymidine (e.g. d4T) or Cytosine (e.g., 3TC) nucleosides
   - Studies are currently underway to determine the potential utility of this approach in nucleoside "failures" (Slides courtesy F. Lori)

5. **HU modulates the Immune System**
   - Cytostatic effects of HU on CD4
     - Low rates of CD4 cell division
     - Low rate of viral replication
   - Cytostatic effects of HU on CD8
     - Down-modulation of excessive activation
     - CD8 exhaustion is prevented

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AIDS Treatment Project September 1999

Therapeutic Drug Monitoring in Clinical Practice
what you're seeing. The question is, how durable is that response? In fact we have had only two rebounds from the people in that group who continued to take therapy. There is a maintenance in those patients over a median 30 week follow up now. 9

There are some randomised studies looking at earlier disease which are important. At the moment we have no idea what dosage to use particularly in terms of toxicity. Figure 12 shows the dosage regimens within this study and they are picking up on the triple drug regimen. One of the difficulties with previous studies is that have mainly used combinations with indinavir which may not be the best strategy. (Figs 11-12)

The 3D study with Christina Katlama in Europe and Rob Murphy in the US will actually produce some hard evidence for what we are seeing because they are randomising HU or non-HU containing regimens with three relatively easy to take and relatively well tolerated drugs in naive and experienced patients and that data should be about ready by the middle of next year. (See Figure 13)

The safety concerns: we have an extensive track record so we know the long-term toxicities which are myelosuppression, some people get nausea and I think this is significant in HIV and other diseases. I have yet to see a skin reaction. Alopecia does occur in a number of patients, and mouth ulcers, and I think you have to look at those in terms of dose reduction.

Q&A DISCUSSION

Deenan Pillay: Are you concerned about the use of hydroxyurea with other nucleosides for side-effects? If it enhances the potency it is likely to enhance the toxicity?

Mike Youle: Neuropathy is a major problem in late stage patients and there’s a lot you can do about it. It hasn’t been a problem in our group of patients but I am very aggressive with treating with L-acetyl carnitine as soon as it occurs and we now have only 2 people out of 60 with neuropathy. It is certainly a concern though, which needs evaluating.

David Campbell-Morrison: Would you like to comment on what effects hydroxyurea might have on neutrophil function. It has been suggested you can have an increased incidence of bacterial infections, without neutropenia due to hydroxyurea down regulation of neutrophils

Mike Youle: I’m not an expert on this but it is probably likely in the same way as CD4 rises are probably partly going to be functionally delayed and therefore you get your rise and you might get neutropenia without neutrophil dysfunction and vise versa, or a combination of the two.

NOTES

1. Lori F, Chicago, 1997
There are two types of synergism:

i) Summation (or addition) occurs when the effects of two drugs having the same action are additive: $2 + 2 = 4$.

ii) Potentiation occurs when one drug increases the action of another and this is one of the instances where $2 + 2 = 5$! If we come back to ritonavir and indinavir, where the choice of dosing of each drug has been an issue that has already generated a lot of heated discussion, I would argue that summation is present in one and potentiation in another.

While looking at synergy in two-drug combinations is possible, the more drugs that are introduced in a combination, the more complex it becomes. Data on current drugs is limited and we extensively use drug combinations in the clinic that have never even been tested for synergistic or additive effect in vitro.

Apart from the pharmaceutical company work, the academic institute that has done most work on synergy is Martin Hirsch’s group at the Harvard Medical School, utilising multiple drug effect analysis of Chou and Talalay. They have consistently published, from the very early days of antiviral agents, plotting of dose-effect curves for each agent and for multiple diluted fixed-dose combinations of these agents.

Most anti-HIV drug combinations that are being used, which have been tested, have been additive but the real concern is probably avoidance of antagonism. Martin Hirsch’s group has also discovered, in these in vitro studies, some antagonism between particular drugs. In fact, they discovered this in a study looking at various triple and double nucleosome combinations, and triple drug combinations including saquinavir and nevirapine.

They looked at the relationship between AZT and d4T, in HIV isolates from a patient both before and after being treated with AZT monotherapy (and developing AZT resistance). They found that there was an additive or synergistic effect between the two drugs in the naive isolate, but there was antagonism in the isolate that was AZT resistant.

Nevertheless, an ACTG study was done looking at this particular combination, in both AZT naive and pretreated patients, and the prediction from the in vitro data was actually confirmed by the in vivo data from the clinical trial, because in the AZT pretreated patient there was a rapid drop in CD4 cells rather than a rise.1 Seeing this, maybe we should be paying more attention to the in vitro testing of all anti-retroviral combinations, before we start using them in our clinics, and maybe it is not so clever to run clinical trials of drugs that have been proven to be antagonistic in vitro.

Hirsch’s group also showed some data showing antagonism between indinavir and saquinavir.

Another antagonistic combination is that between AZT and ribavirin. This work was published over ten years ago by Marcus Vogt, again from Martin Hirsch’s group. He showed that ribavirin inhibits HIV cross correlation and that there is an overlapping pharmacological toxicity which you would generally always try to avoid.2

This is becoming particularly relevant now, because chronic hepatitis C is a big problem in the HIV infected population and the drive towards treatment of HCV is rapidly becoming interferon and ribavirin. A number of clinicians don’t know about this interaction and we need to be cautious of combining these two drugs.

This may be an ideal situation for use of early viral decay slopes for in vivo testing of synergism or antagonism. If you look at early viral decay, taking multiple blood samples over the first days of treatment you should be able to find synergism or antagonism if you compare it with the standard regimen. With the data from the ADAM trial showing that nelfinavir concentrations do matter when you look at viral decay, we should be able to detect synergism or antagonism at this time and we could make far more use of these techniques.3

Some people argue that if you have synergy you may use lower doses of individual drugs in order to reduce the risk of toxicity. I think this may be a dangerous assumption because even with the most potent anti-HIV therapies - for example five-drug regimens - there is still evidence of residual virus replication.4 Potency is still an issue and it is still important, allowing of course for tolerance, to hit as hard as possible.

The mechanism of action of drugs is not always predictive of synergistic or additive effect. For example, a lot of people said that it didn’t make sense to use two PIs together, as you can only fit one PI in the same pocket. The same argument is now being used for NNRTI combinations, yet we now know there are double PI combinations that do have an advantage.5 Other factors may be involved, such as drug distribution and the targeting of different cell and tissue reservoirs. No two drugs are exactly the same in that regard there and there may be PK interactions that are exploited.

Another reason to still look for combinations of drugs in the same class, that may not be immediately a logical choice, is that resistance profiles of agents in particular classes may not be completely overlapping. We already see the clinical use of NNRTI combinations. For instance, in the Canadian mega-HAART regimen, they use a combination of nevirapine and delavirdine although, as far as I am aware, this was without having done PK studies.6 Without looking at any PK data, this shouldn’t be done, because you may be doing more harm than good. If we are going to look at unconventional regimens we have to use the resources we have, and this includes therapeutic drug level monitoring, to at least try and do it properly.

NOTES
5. Moyle et al. on behalf of SPICE team. 5th Conference on Retroviruses and OIs, Chicago 1998. [Abstract 394b].
Practical Aspects of Developing Therapeutic Drug Monitoring

Developing TDM Services:
Learning from the Dutch Experience

David Burger, Nijmegen University Hospital, Utrecht

When the PIs became available in Europe in the summer of 1996, there were only two sites in Holland that were active in pharmacological research with HIV. One was run by Richard Hoetelmans, at Slotervaart Hospital, Amsterdam, and the other by myself, at University Hospital, Nijmegen. We both saw the importance of starting clinical pharmacological research of these new drugs and divided the work, so that Richard should start with ritonavir and saquinavir assays, and we started with indinavir. By January 1997 we had assays available for these three compounds.

Once these were available we started to collect population data - just asking random patients to come to our clinic and to approve a pharmacokinetic profile. We aimed for a random selection to not be biased by patients with either good or bad responses, using 15-20 patients to do a full pharmacokinetic profile of 8 or 12 hours. At the same time, we started the TDM service and we provided it for all the Dutch physicians. We made it a routine assay. It was only investigational, trying to collect data from as many patients as possible, but at the same time we knew that other physicians would have patients who they wanted to have plasma level monitored as a routine measurement for specific indications.

We already knew there could be interactions and a risk of sub-optimal therapy. We provided the tests and analysis free of charge, so long as the physicians filled in the application form completely, in order the make the tests as widely used as possible. It has also resulted in very good cooperation from physicians.

If the physician sends us the sample without giving us the information, then the sample is not analysed. And it is still remarkable that 95% of the applications that we get are with complete information, and that when we ask the other 5% for additional information we get it for almost all samples. Maybe only 1 in 500 samples is discarded because of incomplete information.

We also participated in NATEC trials and our early development of the assays and our incorporation of them into clinical care and clinical trials has already resulted in a number of published studies, including showing viral clearance rate related to plasma nelfinavir levels.1,2,3,4

We analysed approximately 5000 samples in 1998. There are about 2500 to 3000 patients in the Netherlands, so nearly every patient had one or two drug levels measured though the year.

TDM is paid for by the hospital itself. In Nijmegen, we pay for it from government-based funding for HIV clinics. Each HIV clinic in Holland receives funding for the additional costs of treating HIV patients, based on the number of patients they have. Hospitals are free to spend the money as they like, but in Nijmegen, for example, there is a committee that determines additional costs and distributes the money. Since 1998, TDM is included in this budget.

Although pharmaceutical companies sometimes sponsor us to develop assays, they never pay for routine patient care.

The ATHENA study (see page 9) will hopefully provide proof of concept of TDM although even if the result of this trial is negative - that does not mean that TDM is not beneficial. It only means that the way that we are doing it now, working with concentration ratios and with the specific advice to recommend dose adjustment, is not the most effective way. It can still mean some of the TDM service may be beneficial to subgroups of patients.

Q&A DISCUSSION

David Back: If you have three hospitals geared up and another four geared up making seven, why in the UK do we only have one? Can we send samples from the UK to Holland?

David Burger: Yes, of course!

NOTES

The causes of why patients fail virologically include drug resistance, compliance, plasma drug levels, cellular triphosphate levels, differential activity of the drug between organs and cells and other immunological host factors which we don’t currently understand.

So, how can we improve monitoring standards for patients?  

i) we can predict who is likely to achieve an optimum response, and to which drugs  

ii) we could identify the causes of when a patients treatment has failed virologically  

iii) we can use the information they provide in order to maximise available drugs

**access to current diagnostics**

In addition to using viral load tests for monitoring routine treatment, we could be using them at the start of treatment to study the dynamics of first phase slope of decline in more detail. Following a successful response to treatment, regular monitoring is essential in order to be sensitive to early treatment failure. This relies on ultra sensitive assays but many clinics still do not routinely have access to either these, or even regular, assays when they want them.

We currently have crude assessments of compliance, despite knowing the difference it can have on likely treatment success. We don’t routinely access more intensive compliance tools, although many centres are beginning to offer this to some or all of their patients.

Although it may be currently unclear whether we should be testing all treatment naïve patients for resistance, we should certainly be using these assays for all patients with primary infection. Yet they are still only rarely provided and their use is decided on a financial basis.

Most clinics do not have access to resistance tests for treatment failure and where they are provided, they are not financed from an NHS budget. Current availability is largely through clinical antiretroviral trials or studies sponsored by the diagnostic companies themselves and this very limited access reaches only a small proportion of patients failing in the UK.

Establishing TDM services, without the routine availability of viral load (or resistance) testing or adherence support, is therefore unlikely to be straightforward. These examples should not discourage us but they do reflect some of the problems we are likely to encounter.

**introduction without evidence base**

There will always be difficulties of establishing an evidence base for any new treatment, and the parallels between viral load and resistance tests and the situation with TDM are very close.

John Mellors’ data at Vancouver in 1996, showed viral load levels at baseline predicted the risk of progression to either AIDS or death. This produced an immediate increase in demand for this technology, even though there was no evidence to suggest that a reduction in viral load following initiation of therapy would reverse this risk. In this case, strong biological plausibility arguments were used to bring the test into routine clinical management, and these indeed have borne out to be true. Nevertheless, we successfully introduced viral load testing before we had the evidence base to monitor treatment in a formal sense.

We are experiencing a similar situation now with regard to resistance tests. Although two prospective studies, GART and VIRADAPT, have come up with statistically significant results in favour of resistance testing, the data is limited by being short-term and on largely experienced patients. Again, we are still pushing forward with resistance testing even though the evidence base is not as robust as we would like.

The evidence base for routine testing of pharmacological parameters at the moment comes from individual clinics that have already discovered clinical benefits from the information that the tests provide. On this basis they have integrated TDM into the routine care of some, or all, of their patients, and convincing examples of which are included in this report.

If we are going to increase the availability of TDM to other clinics, using the protocols that have been developed, we will have to rely on collecting the data that is acquired from them to provide the evidence base. In other words, using development of techniques to justify their further use.

**real costs & expertise**

One vital lesson, particularly from the introduction of viral load testing, is to minimise regional differences in provision of any new service. Working together to generate a national consensus would establish a greater nationwide equality to treatment. It would save the small fortune that is currently spent duplicating meetings between virologists, clinicians and purchasers within every health authority, to justify any funding changes that are required at each local level. It would also reduce the upheaval of patients changing clinics, or registering at different centres.

Most importantly, we need to get an accurate idea of the true costs that will be involved, so that a diagnostic service can be set up which includes the relevant back-up, robustness and quality control. This has to allow for capital investment, training and running costs.

When laboratory tests are used in routine practice, but funded by either pharmaceutical company trials or diagnostic companies, or, as is currently the case with TDM, by research within academic organisations, then that is not a true cost. It is unfair to expect academics to carry the costs on the back of their already difficult to obtain research grants.

These are complicated assays and we need to develop more laboratories able to perform the tests and additional expertise within them to provide the necessary interpretation of results.

Underpinning all this, is not just access to tests according to an established and validated protocol, but access to results in real time, and the ability for clinicians to be able to discuss the meaning of the results that are produced.
Roundtable Discussion

Joep Lange, Mark Nelson, Deenan Pillay, David Burger, Maxime Journiac, Simon Collins

consensus parameters

One immediate issue was whether there could be agreement on parameters for TDM to work with.

Deenan Pillay: I'd like to look to the pharmacologists for whether Cmin, Cmax or AUC are the most clinically useful measurements. Clearly there's very little way that we can go forward, unless there is some sort of consistency, or at least an agreement as to what sort of ongoing measurements are required for that assessment, and that if there is going to be measurement results have to be available in real time. The second thing: what sort of studies are possible in real life practice now and is there a role for studies? And thirdly, if not, is it worth starting to address the issue of what measurements get currently done in routine practice, documenting those and trying to build a network within the UK and with the expertise there is in the rest of Europe. A European-wide network, as this area develops, would feed information back to inform our future practice. The consistent agreement among pharmacologists though, is needed in order to progress.

David Burger: If you look at the research on pharmacology on microbiological disease, which has taken ten or twenty years, mostly in animals models, when you can have an infection in that animal, you can make a distinction between AUC and Cmax and Cmin. That is not possible for HIV, where it is very difficult to make a distinction between the relevance of each parameter at this moment because to test it in patients would make a very complicated trial.

It is very difficult to get an answer within a year or two, to whether it should be the AUC or the Cmin but I don't think there is very much inconsistency between the pharmacologists. I would want to have an AUC for each patient every day if possible - of course it is not, not even every week - so if you can do a full profile when the patient starts treatment, to see if there's some problems with absorption or anything else then that's okay. That may be possible in routine management and after that you should proceed with random samples because you cannot do (and may not need) a full profile every month.

Saye Khoo, University of Liverpool: I do not think that this Cmax, Cmin, AUC debate is something that the pharmacologists should decide - this is essentially a virological question and it is a question of how the virus replicates. I think it is dangerous to extrapolate to the aminoglycoside situation, where there is a concentration dependent kill and a post MIC effect. To my knowledge there is no evidence that there is a post MIC effect with HIV - you've got an organism that has a very short replication half-life, you've got a huge viral load in sites where drug penetration is already poor and to my mind the gold standard has to be AUC. If you had to do something easier than AUC a better guess would be trough level, where there would be a better chance of a significant breakthrough into blood from sanctuary sites. We really need the virologists for this.

David Burger: I can agree with that completely. The Cmax has relevance only for toxicity. It is important but for virological efficacy you need the AUC or the trough level and the both are related to each other.

clinical trials

Mark Nelson: I'd like to say that I agree with Dr Lange's presentation earlier, in that we need clinical trials. I don't think that nine out of ten patients showing GI side-effects shows no low levels of intolerance, and I think many companies can stand up and show similar things for their drugs. We should be trying to do with TDM exactly what is going on in Holland and what we need is a clinical trial, which the MRC should be doing in this country to take this forward as it is clearly an exciting subject.

Simon Collins: At every conference there are always two or three studies that show that a proportion of people just don't get the therapeutic drug levels that they need. Even with optimal therapy in treatment naïve individuals, 50% of people aren't getting their viral load levels below 50 copies. It gets put down to either resistance - we don't have access to resistance tests - it gets put down to potency of the drug - and potency of the drug is obviously very closely tied up to the levels of drug and it gets put down to adherence - where patients get the blame for that generally. Sub-therapeutic drug levels could account for a significant number of people whose treatment fail. When we see that these tests are available routinely in the Netherlands, they have been available in France and for patients in Liverpool, it becomes very frustrating.

Mark Nelson: You've got to remember that compliance is important. It is no use doing TDM on someone who isn't taking the tablets. What we really need to do is to understand what are we going to do with the results. As with resistance tests, clinicians will need the tests to be interpreted for clinical practice. I think we need to put it into perspective. The way forward, like with everything, is to do clinical studies to really answer the question. If they showed from the study that TDM is not useful then of course it shouldn't be done and we need to answer how useful it is before it goes into clinical practice.

Graham Taylor, St Marys: I don't wish to sound negative but I do want to bring a word of caution into all this. One of the things that struck me was that when Mark asked people for scenarios he wasn't overwhelmed by the response and I think that means that we've got more questions today than we've got answers and we're trying to run before we can walk. We are talking about setting up national programmes and we don't know how we are going to interpret the data, what implications it is going to have, whether it is going to be beneficial. We've seen this with other tests, we're still going through it with resistance testing; we've had all kinds of problems with viral load testing and sub-types so I think we actually need to define some scenarios and then test the hypothesis.

Mark Nelson: That's exactly what I was saying we need - the only way to answer it is proper clinical studies.

Simon Collins: We do also have examples though of clinics that are routinely using this for every patient starting on a PI or an NNRTI regimen already, and it is in practice for every patient for some clinics. It is very frustrating when you see this happening from a patient point of view.

Combination therapy is an incredibly fragile thing to use and if you're really lucky it is going to work. We've got options here of minimising the chance of it failing and so making access to TDM is an important thing to move forward on. There isn't an easy way of getting round the fact that when you see a group of twenty people and you've got two or three outliers there, whose trough levels are higher than other people's peaks, then that is something that needs looking at very urgently.

The argument that we heard earlier, and its the same argument for using resistance tests before starting a regimen, is that if you start someone on triple therapy, two of those drugs will hold someone for six months until the treatment fails and TDM on starting treatment may prevent that risk. There may also be an argument for including TDM within an expanded access.

You could set up a trial, but part of the agenda for today is also to
do with individualising patient care, particularly in the area of salvage therapy. Using TDM immediately, on an individual basis, should be an important option now, for example, for people on a salvage regimen.

Mark Nelson: Yes, with salvage therapy there are certainly more things at stake and you don’t want to get things wrong. What I would hope is that by running clinical trials that would increase immediate access and availability for many people, particularly those outside London.

Joep Lange: I am totally in favour of anything which helps drugs get on to the market sooner but they should only be available in the context of systematic gathering of data. The problem now is that a lot of money is being spent when the drug or test comes on the market, but we are not gathering the information we need. Yes, people should have access straight way to these new therapies but the they should be also be willing to allow for data collection.

Ceppie Merry: We are currently collecting a database on all our patients. We are looking at other parameters like lean body mass, cigarette smoking, use of theophylline, to see if in the future we could take a single sample - we just don’t know what that sample is at the moment. In the meantime we are doing AUCs and we are looking to see if we can do multivariate analysis so that if we looked at somebody’s lean body mass and other variables in weight we could pick a single sample for that person in the future. Although our use of TDM started off as part of the research, these drugs we are prescribing now for anti-retroviral care are so expensive and it is really hard to justify spending x-thousand pounds on a drug in a year when £200 will actually get us TDM. The best time is at the start of treatment and then at any change so, even if you add the costs to repeat it, it is not a lot of money in a year in terms of the overall cost.

A show of hands from a question prompted by Mark Nelson showed that none of the physicians present would object to recruiting their patients into a TDM trial.

A second show of hands showed that there none of the individuals present who are living with HIV would be unwilling to enter a TDM study and MRC members present hopefully noticed the results.

John Walsh: If you’re talking about a randomised control study then there might be patients who wouldn’t be prepared to go into the placebo arm or the arm where their physician didn’t know the area of the TDM, particularly if you’re doing area under the curves where they have to have eight or ten samples taken with no benefit to them at all.

David Burger: I would recommend doing a randomised control trial on drug monitoring in a country which doesn’t currently have access to these tests. In the Netherlands, it’s almost routine for every physician to ask for a drug level monitoring now and physicians want to have those results even if the patient is in the blinded arm. It’s difficult to construct this trial for us but you should certainly do it in the UK.

Steve Taylor, Birmingham: I think there are very briefly two issues you need to address with TDM. I don’t think it’s that much use once the patient has failed and resistance has developed because whatever interesting thing, whatever wrong thing with the drugs, happened six months ago or a year ago.

Firstly, will TDM increase the proportion of people achieving maximum suppression, that is to say viral load less than 50 copies/ml in three months - will it increase that proportion from 50%?

Secondly, will it increase the durability of response. We need studies need to look at both these things and we’re in the process of talks with the MRC and other people to try and do this - early induction and maximising the impact of initiation and maximising durability.

Virco: I would just like to add on that, when we were looking at our retrospective and prospective studies that we set up two years ago for resistance testing, we found that PK was clearly also a parameter. We have developed in-house an assay that can measure with the same sample for resistance testing, TDM for all available drugs (except nelfinavir). We found out that Cmax/Cmin modelling has not helped so now we are building up a correlative model using resistance testing and TDM. When a physician sends in a sample we hope to provide information on how the trough level is compared to the IC50 or the IC90 of that patient. It’s not available commercially at the moment but we hope to present data at ICAAC later this year.

access and capacity

Yasmin Motala: I have a practical question for David Back. Even in the absence of evidence - there is a lot of interest. How would someone currently access your tests and how will you respond to an increase in demand for these tests, given you are the only UK site at the moment?

David Back: There is a form on our website. You can contact us by phone or through the website and request TDM and we will provide full details of exactly how to send the samples and the turn around time.

Demand is going to have to be weighed up to see how many samples we can we turnaround. At the moment we are pretty near our own capacity, with new technology which we hope to have by the summer, we hope to be able to increase this three- or four-fold. Everyone is on short-term, one or two year contracts through in the UK. When you haven’t got a single person with a stable post this presents certain difficulties.

answers from purchasers

Maxime Journiac: Perhaps because I come from a country where we have apparently less problems to access to National Health Care, but as an activist I don’t think it is my concern who should have it or not. I think we have clear evidence so far that a lot of people can have a better use of their drug regimen by having access to these tests. They are not that expensive to run on a regular basis and with anything new you have to make an effort in investment. I do not believe any European country doesn’t have that kind of resource to put in and it is very difficult to discuss this topic when we don’t have, for example, NHS commissioners present. It is useless for patients and physicians to discuss who should get it and who should not when we don’t have the people present who control the budgets.

Deenan Pillay: Sure that’s the big point is that there is no one here that can actually make the decision about where the money is coming from, that’s a disgrace. I know they have repeatedly been asked but I don’t think they’ve been to any of these meetings. I think the problem is if we go and ask people directly for money they wouldn’t give it to us. They’d say there’s not enough data and - we’re better off if we can set up a trial straight away - very quickly then at least a certain percentage of people are going to get it.

Mark Nelson: But someone like the MRC has to do it … there must be someone here who is part of the MRC who will volunteer to take it forward at the MRC.

costs and finance

Mark Nelson: Somebody mentioned the horrible word “costing”. I think for the first time we’ve got one of the commissioners of purchasing here? Because there is the problem of cost and budgets …

Deenan Pillay: I am still unsure whether TDM is for all patients before starting therapy, after failing therapy, or routinely to assess before potential failure, and by what sort of tests? With regard to cost - that is related to the sites that currently offer this. Now within the UK or Europe we’ve heard what’s happening in Europe. Virco are developing this service but it isn’t currently available. Other than David Back’s lab in Liverpool there are no other site
within the UK who are able to respond to a request on a clinical sample?

David Back: David Burger mentioned providing their tests free of charge. Can you expand on this please?

David Burger: We started as purely a research project. The number of samples we received is clearly increasing now though and we been discussing this year whether to charge. We decided not to do that this year but perhaps for next year. The problem is getting bigger and it is difficult for us to continue as we are. We combine routine patient samples with research projects - we are running the assays for research purposes and we just add in the samples for routine patient care. The technician is already working in the lab and she can also do the patient samples. But the number of patients samples for routine care is increasing.

David Back: If you’re going to be running these assays in seven hospitals in the Netherlands and you’re going to be getting answers to PIs and NRTIs, you’re talking about a lot of money to actually set up that infrastructure.

David Burger: We set up the assays with some funding from the companies and also from the hospitals themselves, again as a part of Richard Hoetelmann project. I don’t know how the hospitals that are not involved in HIV research are going to set up the assays. I think they are waiting for when they can charge for the tests. For us it is quite simple because we are doing research, but other hospitals I think expect to be paid for it.

Maxime Journiac: I would like to ask how much does it cost in the Netherlands to run a test and what investment was involved? Do you need a special training of the technicians? - We’ve been told in France, that training people is a limitation - otherwise the price is not that expensive, about 800 francs, £80.

David Burger: The price of one sample is about US$25 - the investment that we usually ask for to set up and validate an assay is about US$10,000 and the technicians that are working on it are also working on HPLC for other drugs as a routine patient care - not always for HIV but other diseases in the hospital, so these people have the experience to work with HPLC and no further specific training is needed.

Maxime Journiac: How many tests can a technician run a day?

David Burger: About forty.

Deenan Pillay: I immediately get worried when costs get thrown around from different scenarios, and I’m not disagreeing with your experience, but if we’re talking about setting up a comprehensive service within the UK we need to think about the number of samples that will be sent and the number of sites required. The cost of an assay for our purposes should be defined by the cost of consumables, the cost of labour and the overheads, together with start-up costs in a lab including the training, the buying or rental of equipment, the capital charge and so forth. It is a sophisticated calculation and I think there’s a danger of taking a single cost like that. I’m sure that what will come out will be that it costs $25 for a drug level and that is not the case if we are talking about setting something up. Building it into UK purchasing plans has to include these factors.

David Back: We’ve been doing all the drugs by separate high performance liquid chromatography systems but we are changing over in the summer to measuring by mass spectrometry. This requires £115,000 worth of hardware which we have got to raise capital for. If we go to the MRC, and we’re lucky, the committee will meet in about two years time and then decide maybe they’ll have to think about it for another year. In practice we will have to get the money from somewhere else.

pharma support for costs

Mark Nelson: What we are talking about is cost effectiveness. I’d like to turn it on its head. It might be cost effective for the pharmaceutical industry - who will keep people on their drug for longer because it’s going to be more effective, you’re going to reduce the toxicity and perhaps what we ought to be looking at is putting all the drug companies in a room together and ask them what are you going to come out with to help the doctors keep the patients on your drugs for longer. I think that is maybe a way of looking at it. I’m not going to pick on anyone from the pharmaceutical industry but could someone comment on that or whether they’ve thought about promoting TDM for their drugs?

Yasmin Motala: We met with Neil Buss from Roche over the weekend and he indicated they would meet these costs for plasma monitoring for anyone on a saquinavir containing regimen...

Mark Nelson: Has that stimulated anyone from the other companies to say yes to this? John, you’re from Roche - are you going to say you’re not going to do it?

John Drake, from Roche: I am sure Roche are very keen to do something but we want to know how best to do it and I think we’ve heard today that there’s a dichotomy of feeling whether you should do an AUC or a spot Cmin and I’m trying to think what scenarios are best to do it.

I can think of, say, one patient group where you’ve got a fairly simple regimen, viral load has gone down and CD4 has come up for a long period of time you may not need to do TDM on that patient because the patient is doing well.

Then you have the case David Campbell-Morrison described - of someone on a good regime, whose viral load has come down but he’s getting toxic effects and he is faced with the alternative of changing to another regimen. An AUC in this example could maybe have modified the dose and cut out the peaks, and here you need a Cmax to indentify toxicity.

Many patients choosing therapy will have limited options - they maybe have to use saquinavir and efavirenz - where you know there’s going to be a major interaction. You know that some people will absorb a lot of saquinavir and others won’t. This may be a case where you could utilise TDM after a week or two to see whether that patient can safely use a regimen that at the moment is not recommended.

Those would be three scenarios where you could get useful information to modify treatment and I would be very keen to do that. This means that different parameters are required depending on the type of information that you are after.

pharmaceutical support for assays

Maxime Journiac: I think we have to make sure that every pharmaceutical company collaborates with this work. It is very important and as a treatment activist, I would argue refusing approval for drugs where companies have not provided the pure compound formulation necessary to conduct those tests.

It is a problem now in France - Gilles Petavrin, a key pharmacologist cannot get hold of these products, particularly, I think, efavirenz. I don’t think this is reasonable behaviour.

Mark Nelson: We have a similar problem with some of the companies in the UK at our own hospital.

Kitty Smith, DuPont: We are in the process of working with David Back to set up an assay in the UK - I’m afraid I don’t know about the situation in France but I will be meeting with people in DuPont involved in this area and we will discuss this. I don’t know what the situation is in France but certainly the aim at the moment is to set up an assay in the UK. It should be possible for other countries to send samples there, although that is not ideal by any means, and it should be available in other countries.

ribavirin

David Back: I’d like to pick up a couple of things that Joep mentioned - the NNRTIs for example, that’s one, and the other one was on interferon, ribavirin and backbone - is there an issue of backbone nucleosides. I don’t know if you would like to expand on that at all...

Joep Lange: I don’t think it is necessary. I think people should be aware of the potential antagonism between ribavirin and AZT if
they want to combine it. If they have other options than AZT they might prefer to use them. It is not only AZT, d4T also, and there is literature on d4T and AZT which are supposedly antagonistic; there is literature on ddI which is synergistic.

Maxime Journiac: In France there is a trial starting that is looking at the effect of ribavirin on coinfected individuals taking up therapy with any of the nucleosides AZT, d4T or 3TC. I think it starts recruitment at the end of the summer so hopefully we'll get results in the spring of next year.

Joep Lange: I hope they do some pharmacology in that study... but you have no pharmacologists!

who benefits most?

David Back: Given that it is not going to be feasible within the UK to immediately use TDM on everybody, can we come to some consensus on who may benefit most? For example, people who commence therapy, who switch therapy, who are maybe on failure, drug interactions, toxicity, is there a ceiling here that is going to be useful? Given the debate on Cmin versus AUC, I wonder if today we can begin. We are privileged in a sense in our own set-up with Dublin, and for Liverpool and Manchester we do AUCs but it is not going to be feasible to do AUCs on everybody.

Mark Nelson: It's fine doing them but can you tell us what to do with the results on everyone. It's fine to get back a result and saying they need to increase their dosage or decrease their dose but can you actually tell us from the patient history given, what to actually do with the patient.

David Back: I think that decision is different for every patient. Using the example of someone with indinavir side-effects on the 800/100 indinavir/ritonavir dose then a decision has to be made whether to reduce indinavir to 600mg or whether 100mg ritonavir can be reduced further. I am not convinced that 100mg is the lowest we can go for ritonavir.

Mark Nelson: Part of the problem is that Mike Youle's data, which is impressive on 800/100, includes heavily PI-experienced patients. It may be because you are getting such high levels that the drugs are working and in this case you are better off trying to deal with the toxicity in another way rather than reducing the dose. That is what worries me about toxicity - it's easy to reduce toxicity but as you reduce the dose down you risk losing efficacy.

David Burger: But those patients on 800mg indinavir, who suffer from indinavir related toxicity, are those who have the highest concentrations, so if you decrease the dose to 600mg in such a patient you get an average value for 800/100.

into clinical practice

Ceppie Merry: A number of people have asked what kind of technology you would need to introduce TDM into routine clinical practice - it's the same exact that you need for viral load. You take a blood sample you spin it down in the same cabinet and you store it in the freezer. So there really is no magic - we've already done it for viral loads so I don't see why we can't do it for TDM. In terms of feasibility, we've done it now for three years. We must have done hundreds and hundreds of AUCs.

I want to say that I completely disagree with other people's concerns about the difficulty of getting patients to attend for a longer period. AUC is practical in routine clinical practice if you tie it in with a clinical visit - we have not yet ever been turned down. The difficulty is the patient must understand why you are doing it. You must always report back the results and we always give the patient a print-out of their AUC with IC50 and IC95 values and that is feasible in the real world.

Steve Taylor: I'd just like to go back to what Ceppie was saying in one of her slides - that one of the most important areas of measuring is at the beginning of therapy, because you do not know to what degree the other two drugs in the combination of three is actually driving your viral load down. You could well have subtherapeutic levels of protease, then develop resistance and you might as well be throwing your money down the drain. I think this is more useful than the failing patient when six months damage has already been done. I think the MRC are actually doing this in the FORTE study for plasma levels of nelfinavir and nevirapine after two or four weeks treatment.

Martin Fisher: I would use it for prevention. Individual patients come with their own priorities and you have to respond to those cases individually. I don't think you can have a blanket definition for TDM use and say we are only going to do it here. As with everything else it is always a combined process between the doctor and patient in deciding this.

quality control

Duncan Churchill: I have a question for the pharmacologists about external quality control. This was highlighted in the session this morning. It's quite clear some labs can get this completely wrong. One of the things that David said earlier on implied that there wasn't any exchange of samples between Holland and Liverpool for example. Do either of your hospitals do external quality control?

David Burger: Yes we are doing it. We have in fact a national quality control programme and we have asked several pharmacological companies to send samples to us so that we can send samples to them. At this moment only Agouron have agreed to do that and the other companies do not. We also want to do it with David Back of course, to develop an external quality control programme. There are data and literature on nelfinavir and AZT, but it is very important to do that quality control. I was really shocked by the data that Brad Kerr showed to us from the US labs this morning. It's terrible. Because if we are looking at the relevance of drug level monitoring and we can't even measure a correct level we should go back to our work and not sit here.

Richard Hoetelmans: Trying to summarise the debate has highlighted that different questions are being asked by therapeutic drug monitoring and in having to prioritise them, this mirrors to some extent what we had with resistance testing maybe three years ago. Doing a clinical trial does not preclude pushing to develop a service. Both of those different approaches - developing a service, auditing and doing studies within that routine service - can answer questions that may not be answered within a formal study.

I think is highly laudable that David, say, is developing a study, and I think that should have the support of the meeting because we've identified that as a need. But secondly we need to know how we go forward because requests for TDM will be increasing, whatever we say. I think there is a need for a strategy to pool the data the tests provide, in a similar way to our plans following the resistance symposium. It is perhaps a bit easier with TDM than resistance testing, because within the UK, there seems to be only two labs doing those assays. This makes it much easier to pool that data together with the associated clinical information. I would propose that that is a way in which we could go forward - the details of which may need another meeting of those concerned.

Conclusion

AIDS Treatment Project September 1999

Therapeutic Drug Monitoring in Clinical Practice
Summary of Issues

parameters
There was a certain consensus that different parameters for TDM are required for different circumstances.

- Cmax is more important when looking to explain or minimise side-effects
- Cmin and AUC are used to guard against sub-optimal dosing and risk of resistance.
- AUC preferred to single point trough
- compromise sample at 0, 1, 2 hours would pick up individual PK variation if full AUC is not possible

The debate over use of trough level only, or full profile, seemed to fall back on two main concerns. The preference for a full profile, given an ideal world, was tempered largely by concerns over whether patients would put up with the inconvenience of several additional hours at the clinic.

However, the response from doctors currently using TDM within a clinical setting, was that once the importance of the tests are explained to the patient, this hasn’t caused any difficulties in practice.

There was universal interest from PWAs attending the symposium in accessing TDM for their own care, within either a trial or clinic setting.

The pitfalls of single-point trough concentrations were pointed out in several populations and a compromise of 0, 1 and 2 hour samples seemed to win general approval.

In the longer term, we can work towards an extensive database, referenced to body weight and other variables that may allow for more accurate single point predictions in the future. In the short-term we need to collect the results of the tests we are currently running in order to produce an evidence base which justifies further use of TDM.

Nevertheless studies using single point trough levels have been able to show a direct relationship between plasma concentrations of both PIs and NNRTI’s and reduction in viral load.

immediate use
Nevertheless, there are also many people whose care could benefit immediately from integrating (currently nominally inexpensive) tests and who should not have to wait for the results of those clinical trials. Salvage therapy, paediatric dosing, pre-existing or suspected liver/kidney damage, individual dose interactions with other compounds.

- Use on individual basis, and in specific populations, justified by smaller studies
- Justified for use in salvage combinations where any chance to increase success may be justified
- Protocols and information for this exist (through University of Liverpool)

indications for use
- Confirm dose of any PI or NNRTI within regimen
- Toxicity / dose reduction
- Sub-therapeutic doses / antiretroviral responses
- Unknown drug interactions (EFV/SQV/RTV etc)
- Renal or hepatic dysfunction
- Pregnancy
- Paediatric dosing
- Interactions with methadone or Viagra

validation
Validation of tests and systems was highlighted as crucial if we are hoping to be able to safely make dosing adjustments in individual patients on this basis.

The major centres for this study in Liverpool and Netherlands already co-operate and, if they haven’t already, intend to cross validate each other samples. On a local (UK) level, this should provide confidence in the quality of the assays.

Where specific expertise has not been developed, or where assays are not independently assessed, the variability is very worrying and the examples shown from some of the US labs demonstrated this.

pharmaceutical sponsorship
This was highlighted throughout the day as offering two-way benefits. Some promises were made, we look forward to following them up. Involvement could include:

- meeting TDM costs for patients using their drugs
- integrating TDM into all PI/NNRTI containing trial arms
- provide pure compound to independent researchers to develop their own assays
- participate in quality control programmes

efficacy & trials
It was encouraging that all doctors present showed an active interest in making use of TDM, certainly within a trial setting, and there was a definite interest in using TDM in routine clinic care.

We heard of several trials currently either planned or running, which we hope will provide clearer answers, including an MRC joint initiative in the UK. These studies are important, not least from an NHS purchasing point of view, and in practice may make tests available quickly to a group of people who are otherwise unlikely to receive it.

- Clinical trials still needed to prove clinical benefit for routine use (some already underway)
- MRC initiative proposed by the meeting
- Collection of data from currently performed tests may provide their own evidence base
- Follow-up meeting could provide a structure for this (similar to that being developed for resistance tests)
Appendix I: How to order TDM in the UK

Contact:
David Back or Sara Gibbons, Univ of Liverpool
Tel: 0151 794 5553
Fax: 0151 794 5540
hivgroup@liv.ac.uk
http://www.liv.ac.uk/hivgroup/

Drug Analysis Available
Protease Inhibitors:
Saquinavir, Ritonavir, Indinavir, Nelfinavir
NNRTIs:
Delavirdine, Nevirapine (Efavirenz currently under evaluation)
Others:
Sildenafil, Methadone

Sample Details
Please complete the sample requisition form, including strict timing of dosing and last meal, with as much information as possible to aid us in the interpretation of the results.
The form is available from the website as a Word 97 document, an Acrobat pdf file or as a web page.

Sample Volume
Blood samples should be collected in heparinised tubes and plasma obtained by centrifugation.
The minimum plasma sample volume required is 1 ml per drug analysed, e.g. if a single sample is analysed for saquinavir and ritonavir 2 ml of sample is required.
Please do not overfill tubes.

Sample Storage
Plasma may be stored at -20° C or lower, prior to transport.

Transportation
Please notify us of your intention to send samples so we can ensure prompt handling on their arrival.
We would prefer that large numbers of samples are transported frozen, on dry ice and securely double tubed. However, studies have shown that samples may remain at room temperature for 48 h with no effect on drug levels. Small numbers of samples may be sent via the Royal Mail so long as all the requirements for the packing of pathological specimens are met.
If sending samples through the post, please post early in the week so that packages do not remain in the University's mail room over the weekend. The use of Special Delivery to guarantee next day delivery may also be considered.
If you require any further information please contact Sara Gibbons.

Inactivation of Samples
The inactivation of samples will be performed in our laboratories.

Cost
The cost of analysis is £25 per sample, per drug.
For example, a single sample to be analysed for both saquinavir and ritonavir will cost £50.
HIV Focus, Roche, have recently announced that they will fund the analysis of saquinavir and nelfinavir. Other pharmaceutical companies may offer similar programmes in the future.

Results
Samples will be analysed as soon as possible and the present turnaround of results is approximately 2 weeks.

Delivery Address
Please mark all packages for the attention of Sara Gibbons or Prof David Back and send to:
Dept of Pharmacology & Therapeutics
University of Liverpool
Ashton Street
LIVERPOOL
L69 3GE
## Appendix II - List of Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Position</th>
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<tr>
<td>Jonathan Ainsworth</td>
<td>North Middlesex Hospital</td>
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<tr>
<td>Celia Aitken</td>
<td>St Bartholomew’s Hospital</td>
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<td>Ian Alexander</td>
<td>Perriford Hospital</td>
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<td>Giovanni Anunziata</td>
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<td>Jane Anderson</td>
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<td>Rob Campbell</td>
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<td>Mike Youle</td>
<td>Royal Free Hospital</td>
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AIDS Treatment Project: who we are...what we do...

ATP is a volunteer-led organisation made up predominantly of people who are HIV+. For the last three years we have been providing treatment information, training and support to HIV+ individuals and organisations as well as to clinicians and healthcare professionals within the NHS. ATP is a registered charity.

**ATP Guide to Second-line and Salvage Therapy**
First patient produced booklet on Salvage Therapy - August 1999 edition rewritten to include information about mega-HAART, drug holidays, resistance tests etc.

**ATP Guide to Combination Therapy**
Both guides are written in simple and easy-to-understand language and cover the difficult areas of HAART.

**DrFax**
Our highly respected fortnightly review of the most important latest research, conference coverage and original reports. Edited by Paul Blanchard. Available free by fax, e-mail or post. Currently at issue 74.

**PTN**
Bi-monthly magazine, *Positive Treatment News* is distributed free at treatment centres (and individually by post) focusing on presenting treatment news in an easy-to-read but in depth format. Currently at issue 6.

**Symposia**
Individual, one-day events established as a forum for important areas of HIV treatment. No comparable events are available in the UK where leading nationally and internationally respected experts debate current issues amongst clinicians, researchers, informed positive people, industry representatives, activists, pharmacists... etc. A full report is produced following each meeting.

**Symposia Reports**
- Resistance Assays & Clinical Practice
- New Compounds & their use in Salvage Therapy
- Therapeutic Drug Level Monitoring (TDM)

**AIDS Treatment Project Information Phoneline**
- mon/tues/wed afternoons 3pm - 6pm, mon & wed eve 6pm-9pm

Last year the ATP Treatment Information Phoneline (staffed by HIV positive volunteers) handled over 1200 calls each averaging over 30 minutes. All calls are confidential and charged at local rates from anywhere in the UK. We offer a postal information request service with each call and in the same period sent out 750 researched responses, sometimes with up to a dozen articles.
This event was sponsored by unrestricted educational grants from the following companies:

Abbott • Agouron • Bristol-Myers Squibb • Chiron • Du Pont • Glaxo
Wellcome • Merck Sharpe & Dohme • Pharmacia & Upjohn • Roche • Virco