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# SMART Living

## *Strategic Moves in AntiRetroviral Therapy*

**Satellite Symposium**
**Fifth International Congress on Drug Therapy in HIV Infection**
Sunday, October 22, 2000
15.30 – 17.30
Clyde Auditorium
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Glasgow, UK

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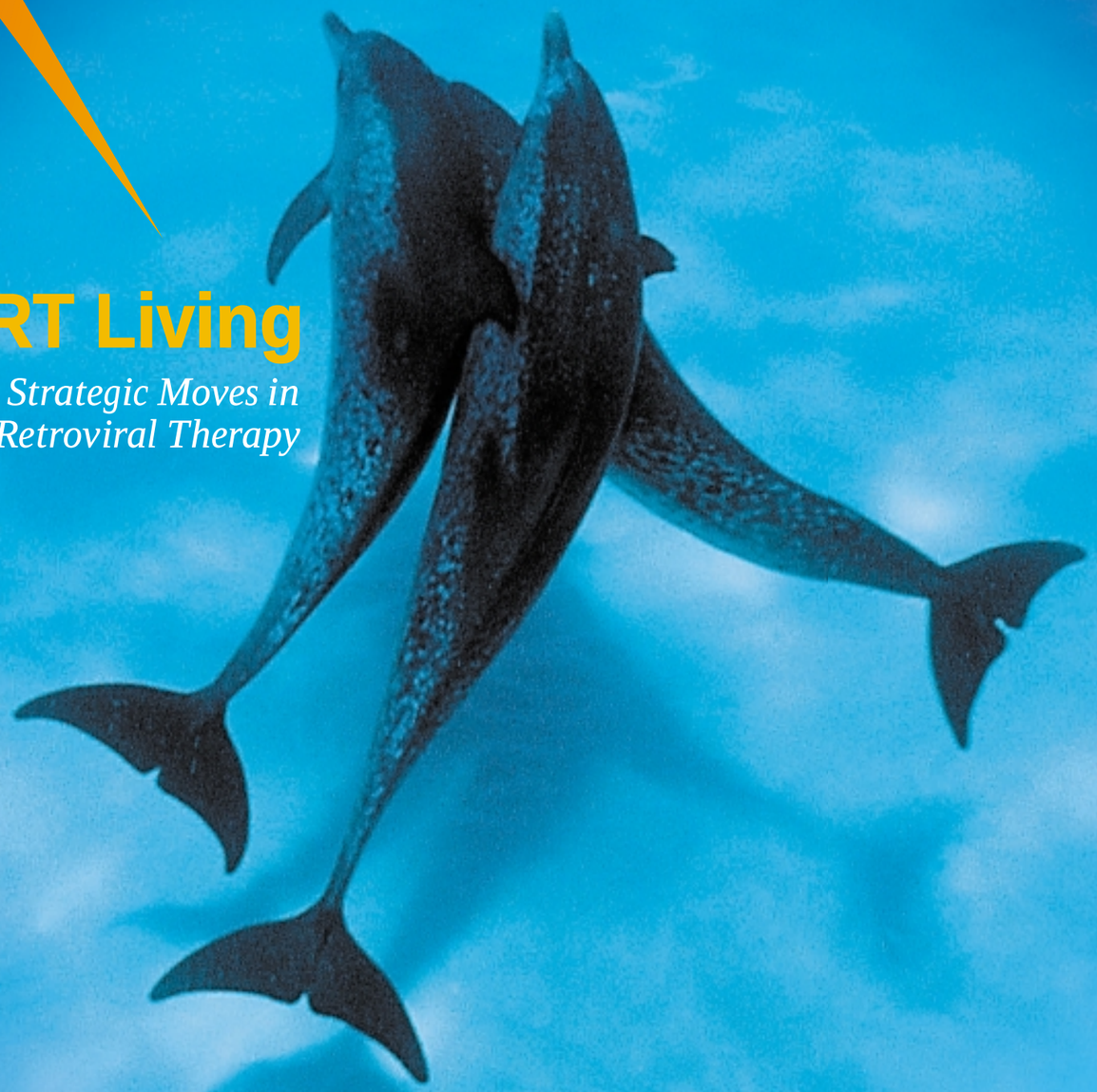

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# Welcome from the Chairs

*As we enter the fifth year of the HAART era, we can reflect upon the progress that has been made in treating HIV disease. At the same time, we are all too aware of the limitations of our current treatment approaches and the challenges posed by HIV drug resistance. Continued progress in HIV therapy requires rational combining and sequencing of the existing therapies to preserve and maximise the benefits of HAART. This can only be achieved through evidence-based decision making and the rapid incorporation of new learning and new therapies into our daily practices.*

Odontoceti Delphinidae *(the dolphin) is recognised as an 'intelligent' creature, highly adapted to its environment and able to communicate considerable information within its social group. We need to follow the example of these highly evolved creatures – sharing new information and experience, adapting our therapeutic strategies to a changing environment – all with the ultimate aim of out-SMARTing HIV.*

*This satellite symposium is dedicated to the art of SMART Living – using the wealth of existing data, and our ability to assimilate and interpret, to clearly define Strategic Moves that will enable us to optimise the benefits of AntiRetroviral Therapy over prolonged periods of time.*

*It is our pleasure to welcome you to this symposium, SMART Living. We have five leading experts to present the latest clinical and basic science data on new approaches for long-term therapeutic success – from intra-class drug sequencing, enhanced drug exposure and pharmacokinetic 'boosting', to the characteristics and clinical niches of forthcoming novel drugs.*

*This symposium offers a wealth of vital information for physicians looking to maximise the long-term benefits of HAART – we look forward to a productive exchange of information and opinions.*

**Nathan Clumeck MD**
**Margaret Johnson MD, FRCP**

# Introduction


**Nathan Clumeck MD**

*Head of Internal Medicine and Infectious Diseases and Director of AIDS activities, Saint-Pierre University Hospital, Brussels, Belgium*


*Dr Clumeck is Professor of Medicine and Infectious Diseases at the Free University of Brussels, Belgium. He is also Head of Internal Medicine and Infectious Diseases and Director of AIDS activities at the St. Pierre University Hospital, Brussels. Dr Clumeck's academic and research interests include AIDS in Africa, heterosexual transmission of AIDS and the treatment of HIV infection and related conditions. In 1983, he reported the first cases among African heterosexuals, and he has presented more than 250 scientific communications and has written more than 200 journal articles and book chapters dealing with the study of HIV infection. Dr Clumeck is a founding member and chairman of the European Aids Clinical Society (EACS).*

No-one needs any reminder of the revolution in the care and management of HIV infection that accompanied the introduction of protease inhibitors in the mid 1990s (see figure 1). The rapid emergence of PI-based HAART, followed later by NRTI-NNRTI based triple nucleoside regimens, transformed AIDS from a fatal disease into a chronic condition, manageable by life-long chemotherapy. Life-long because we now know that early optimism concerning the 'eradicability' of HIV after a few years on potent combination therapy was sadly premature. We cannot eradicate it by any means currently known, we can only suppress it, and the prospect of life-long suppressive therapy requires the development of a long-term strategic approach to HAART that would have been considered the product of pure pessimism just two or three years ago.

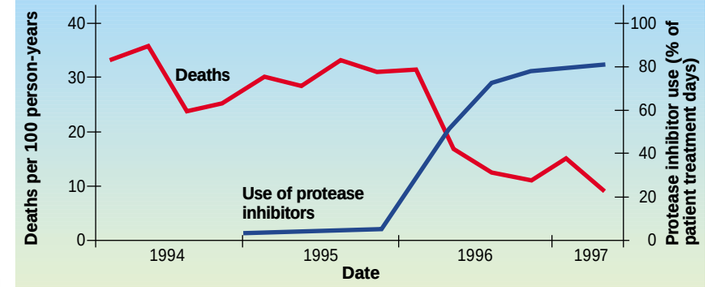
However, as remarkable as the impact of HAART has been, our current regimens are still far from optimal. Outside of clinical trials, with their carefully monitored cohorts, 'real-world' clinical experience shows some 30-50% of patients failing to achieve or maintain viral loads below the 50 RNA copies/ml limit of detection for our current assays – with implications for the evolution of drug resistance that have become only too familiar over the last few years.

Our current regimens can be compromised by a number of factors; adherence being one of the most important. The emergence of multi-drug HAART regimens has led to increased dosing complexity and high pill burdens that can significantly impact on the consistency with which medication is taken. Procedures to simplify dosing schedules and ease dietary restrictions are required to encourage long-term adherence, as are ways of reducing the number of tablets to be taken.

Toxicity and tolerability are another pair of related issues compromising both adherence and the prospects for long-term therapy. Powerful drugs can have powerful side-effects, and the effective management of these – and of emerging adverse events related to long-term antiretroviral drug exposure, such as lipodystrophy and cardiovascular disease risk – is an obvious and essential prerequisite for any strategic approach to HAART.

Figure 1

**Impact of PI-based HAART: mortality HIV-infected subjects with <100 CD4 cells/mm³**




Palella *et al. NEJM*, 1998

Perhaps the newest and most potentially significant issue for HIV management is our improved understanding of the impact of pharmacokinetics on therapeutic success. Bioavailability issues and drug-drug interactions are factors that need addressing in therapeutic planning; but the emergence of pharmacokinetic boosting to raise drug exposure and simplify dosing requirements has significant implications for our strategic goals.

And then, of course, there is drug resistance and cross-resistance: easily the most important influences on therapeutic prospects from the very earliest days of zidovudine monotherapy. No attempt to plan for sustained therapeutic success can avoid this almost inevitable concomitant of therapeutic failure, and the identification and development of successive, sequenceable drug options is a vital part of any long-term view.

We have three licensed classes of antiretroviral at present: targeting two viral enzymes at different stages of the virus life cycle. An increasing number of candidate drugs from these classes are entering pre-clinical and clinical studies, but without new targets and drug classes no amount of new compounds will represent more than an incremental step forward in the treatment of HIV disease. The potential for the sort of cross-resistance already observed amongst the existing antiretrovirals makes any major leap forward dependent upon the introduction of drugs for which there *is* no existing

cross-resistance. In addition, there is a need for us to develop a more comprehensive understanding of the interplay between the virus and immune system and to develop therapies to augment the host response against the virus. While we wait for the introduction of these new classes of drug, we cannot afford to squander those drugs we have. The benefits of HAART must be preserved by intelligent use of the existing agents within a framework of optimized therapy based on the best available knowledge in every pertinent field.

To this end, Dr Jonathan Schapiro, Dr Andrew Zolopa and Dr Julio Montaner will describe the basis and most recent developments in the optimization and sequencing of HAART regimens, focusing primarily on the protease inhibitors. We will see that our increasing knowledge can turn the complex pharmacologies and patterns of resistance for which the PIs are well known into exploitable factors for strategic therapy.

Dr Joep Lange and Dr Anton Pozniak will discuss the future, and the most promising of the experimental new drugs in classes yet to be introduced into clinical practice. We need novel new agents for a variety of reasons – not least to treat the steadily increasing number of people whose virus is resistant to the current classes. To use them well, however, we need to learn from what has gone before to ensure their intelligent incorporation into strategies for long-term management. And we must continue basic investigations to identify and explore novel opportunities for chemotherapeutic intervention in HIV disease.

To sum up, since we cannot eradicate HIV we must build an effective framework for the indefinite continuation of tolerable, potent therapy. To this end we need to apply the lessons of the past to the construction of a new paradigm of extended care that not only makes the best use of those drugs we have but can seamlessly incorporate new drugs and drug classes as they become available. In turn, these drugs must also be viewed as valuable tools to further our understanding of HIV and possible new approaches to treatment. Such a strategy must make the best use of both clinical and basic science data on resistance, pharmacokinetic and adverse event management, regimen simplification and drug sequencing, if it is to succeed.



# Notes

# Strategic optimisation of antiretroviral therapy

**Jonathan Schapiro MD**
*Department of Medicine, Center for AIDS Research, Stanford University School of Medicine, USA and National Hemophilia Center, Tel-Hashomer, Israel*

*Dr Schapiro is Director of the AIDS Service at the National Hemophilia Center, Tel-Hashomer, Isreal and Clinical Assistant Professor at the Center for AIDS Research, Stanford University School of Medicine, USA. During a distinguished research career that has been acknowledged by the receipt of numerous awards, Dr Schapiro has investigated causes of protease inhibitor failure, the importance of drug resistance mutations, adherence and drug levels and the correlations between viral load and mutations in different body compartments before and following antiretroviral therapy. Currently, Dr Schapiro combines clinical and educational activities with research interests that focus on resistance and cross-resistance between protease inhibitors, the clinical utility of resistance assays and of salvage therapy and the mutational correlates of drug failure.*

In the last five years, the armamentarium of antiretroviral drugs has rapidly expanded such that patients and physicians are confronted with a bewildering choice of different combination therapies. The selection of which combination to use, and when, is based upon personal judgement and a reliance on data that is frequently non-comparative and non-uniform in the way in which it is analysed. Superimposed onto this is the enormous complexity of the data relating to HIV drug resistance and drug pharmacokinetics (PK).

Compounding these issues still further, is the difficulty in viewing key data such as drug efficacy, drug exposure and drug resistance as inter-related elements that comprise an overall continuum. Each element does not exist in isolation of the other and on its own may convey limited and maybe even inaccurate information of relevance to a specific clinical situation. This situation can be likened to trying to complete a puzzle, where we look sequentially at each individual piece, trying to work out the whole picture from it. Obviously, what we need to do to 'get the correct message or picture' is to put them all together and view them as a single unit of inter-related elements.

The determination of drug potency provides an excellent example of the importance of viewing as a single continuum, efficacy data and a wide range of other factors such as drug resistance and pharmacokinetics.

Intrinsic antiviral potency or efficacy is commonly reported as a 'simple' single statistic – either the inhibitory concentration, $IC_{50}$, $IC_{90}$ or $IC_{95}$, or the effective concentration, $EC_{50}$, $EC_{90}$ or $EC_{95}$. The simplicity of a single-figure assessment of drug potency allows for a number of potentially inaccurate assumptions: that drug potency is a definitive measurement, that there is little or no variance in the potency reported, that the measurement applies to all clinical situations, that measurements can be compared between drugs, that assays are standardized and that the 'environments' in which the measurements are made are uniform. These assumptions are generally false and we need to look beyond a single number for an accurate picture of potency.

The $IC_{50}$ and $IC_{90}$ are the *in vitro* concentrations of drug required to inhibit viral replication by 50% and 90% respectively. These values can be determined in the laboratory using a variety of assays. The number of variables that contribute to the determination of $IC_{50}$ and $IC_{90}$ values means that they can vary dramatically[1] depending on factors such as:

- which markers of HIV replication are evaluated
- which cell types were used in the assay
- the sensitivity (resistance) of the predominant viral strain
- the different methods of adjusting for protein binding.

The inaccuracy of IC values as a single measurement of drug potency is reflected in the wide range of values quoted in prescribing information for protease inhibitors (see figure 1).

Generally when the inhibitory concentration of a drug is determined *in vivo*, it is known as the 'effective concentration' (EC). ECs are likely to be more accurate determinations of antiviral drug activity, since they are a direct measurement of *in vivo* drug potency taking into consideration complex viral dynamics in the patient and do not require adjustment for protein binding. However, it should be understood that EC figures are derived from patient data to which a mathematical modelling technique known as exposure-response modelling has been applied. Ultimately then, the $EC_{50}$ is the *in vivo* plasma concentration of drug (e.g. trough) required to achieve 50% of the maximal reduction in viral replication as predicted by the exposure-response model. For example, if therapy results in a maximal 2-log reduction in viral load, the drug concentration required to produce a 1-log reduction in viral load (i.e. 50% of the maximal reduction) is the $EC_{50}$. $EC_{50}$ values can only be determined in clinical trials in patients because the values are determined from actual drug levels and the corresponding decrease in viral load which can only be measured in patients' blood plasma. $EC_{50}$s are, therefore, rarely obtained outside of the clinical trials setting.

Since $IC_{50}$ and $IC_{90}$ values depend not only on variables such as viral strain, cell type and assay method, the relative *in vivo* potency of two PIs can not be reliably compared using *in vitro* values. Comparisons can be made between $IC_{50}$s in wild-type and $IC_{50}$s in resistant strains but comparisons of potency between drugs can *only* be truly defined in a clinical trials setting.

Figure 1

**Inhibitory and effective concentrations for the PIs**

| PI | $IC_{50}$* (nM) | $IC_{90}$* or $IC_{95}$* (nM) | $EC_{50}$** (ng/ml) |
|---|---|---|---|
| Saquinavir | 1–30 | 5–80 | 50.44 |
| Indinavir | NA | 25–100 | NA |
| Ritonavir | 4–153 | NA | NA |
| Nelfinavir | NA | 7–196 | NA |
| Amprenavir | 80–410 | NA | NA |
| Lopinavir | 4-27 | NA | NA |

NA – not available
*Require further adjustment for protein binding
**Based on trough, does not require further adjustment for protein binding

Figure 2

***In Vitro* potency of existing PIs against wild-type and recombinant mutant HIV clones**

| | $IC_{50}$ (nM) | | | | |
|---|---|---|---|---|---|
| Inhibitor | Wild-type | 10/48/82/90 | 20/46/63/82/84 | 20/46/54/63/82/84 | 10/84/90 |
| SQV | 5 | 269 | 8 | 25 | 29 |
| AG1776 | 12 | 8 | 10 | 25 | 21 |
| BMS 232,632 | 2 | 47 | 12 | 30 | 7 |
| ABT-378 | 8 | 35 | 85 | 222 | 23 |

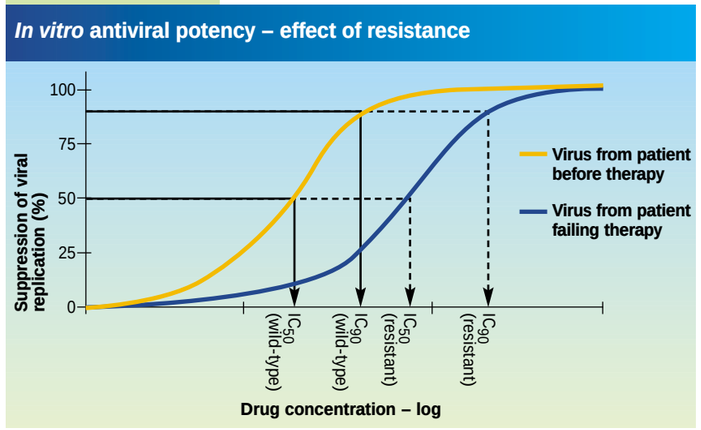
Knowing how measurements of drug potency are assessed, we can understand how important is the impact of viral sensitivity (resistance) on these figures. Drug potency is inter-related and dependent on the predominant viral strains used in the assay.

A useful initial screen to evaluate drug potency is to determine the fold-change in $IC_{50}$ compared to wild-type virus, in recombinant clones of resistant strains (see figure 2).

The significant effect of viral resistance on $IC_{50}$ and $IC_{90}$ values can be clearly demonstrated in graphical terms (see figure 3).

It is important to point out that, just as drug potency should not be viewed as a single definitive unit of numerical data (IC value), so also drug resistance should not be viewed as a simple binary record of 'resistant' or 'sensitive'. Resistance is in itself, a continuum and our ability to quantify resistance in such terms as 'fold increase' may satisfy our desire for quantification, but at the same time, encourages us to believe that this information alone provides a definitive answer to our questions. We must remember to look at the 'whole puzzle' and not the single piece. As such, a shift in $IC_{50}$ or $EC_{50}$, as might be expected for virus with decreased sensitivity to a given drug,

Figure 3




may not simply indicate drug resistance precluding the use of this drug but may rather call for strategies to increase drug exposure. Whether to adopt strategies to boost drug levels, such as adding ritonavir to the regimen, or select drugs without reduced sensitivity is a complex issue. One needs to consider a number of parameters including probability of achieving suppressive drug levels, potential for drug toxicity with increased drug exposure and overall long-term control of viraemia with this and subsequent regimens.

Another element of importance in our evaluations of drug potency is, of course, the pharmacokinetics of the agent under evaluation. Pharmacokinetics describes how the body handles a drug following administration.

Pharmacokinetic parameters are usually described using five parameters:

- Peak plasma concentration ($C_{max}$) – the highest observed plasma concentration following drug administration
- Time to reach $C_{max}$ ($T_{max}$) – the time taken to reach the highest observed plasma concentration
- Minimum (trough) plasma concentration ($C_{min}$) – the lowest observed plasma concentration following drug administration often simplified to the concentration of drug immediately prior to the next drug administration
- Area under the curve (AUC) – the total plasma exposure achieved during a specific time period
- Half-life ($T_{1/2}$) – the time taken for the plasma levels of drug to fall by 50%. Longer half-life offers the potential for less frequent dosing.

The difference between the concentration of drug that is minimally effective and the concentration of drug above which adverse events are unacceptable is known as the therapeutic window. It is important that $C_{min}$ and $C_{max}$ of an antiretroviral agent are within the therapeutic window so that loss of viral suppression or emergence of adverse events are avoided.

In order to understand PI pharmacokinetics better, it is important to remember the basics of drug metabolism. When a drug is administered, it typically dissolves in the stomach. As it travels through the gut, it is absorbed through the intestinal wall, where it may undergo metabolism. The absorbed fraction is then carried to the liver, where further metabolism may occur. The drug then travels around the body in the systemic circulation, after which the liver and kidneys typically play a major role in breaking down and clearing either the parent drug or drug metabolites. Metabolism that occurs before the drug enters the systemic circulation is called 'first-pass' metabolism. The bioavailability of a drug is the fraction of oral dose that survives first-pass metabolism and reaches the systemic circulation. Bioavailability, therefore, depends both on the degree of absorption and the extent of first-pass metabolism.

Effective drug levels depend on the characteristics of the virus infecting the patient. In some individuals who either have intrinsically low exposure to certain drugs or who are infected by virus with decreased sensitivity to one or more antiretrovirals it may be necessary to boost drug exposure. Currently, this is typically achieved by administering a low dose of ritonavir, which has been shown to boost the drug levels for a number of drugs, particularly the protease inhibitors[2,3].

Of course the use of ritonavir to alter the pharmacokinetic parameters of other PIs might be associated with benefits, as has been seen with saquinavir[4] and indinavir. However, any elevation of drug exposure to levels near $C_{max}$ for prolonged periods of time might be associated with increased adverse events. Therefore, great caution should be observed with boosting indinavir as the therapeutic window is more narrow than for other PIs. Patients in the BEST study receiving boosted indinavir therapy experienced a significant increase in the incidence of nephrolithiasis[5].

Once again, when looking at drug exposure as a parameter in evaluating drug potency, it is clear that a continuum exists and that exposure is a continuous variable, dependent on a variety of changeable factors.

In summary, it is necessary for us to initiate a new approach to the consideration of drug potency, drug exposure and drug resistance. We must not be satisfied that simplistic measurements of different parameters, viewed in isolation, will provide the necessary information required to effectively manage antiretroviral therapy in our patients. We must take the next important step forward and view this information as a continuum with variable constituent parameters that are inter-related. This is clearly a difficult task but one which we must address if we are to optimize therapy in the name of prolonged and improved lives of people living with HIV.

## References


1. Hill A, Craig C and Whittaker L. Prediction of drug potency from $C_{min}/IC_{50}$ or $C_{min}/IC_{95}$ ratio: false precision? *Antiviral Therapy* 2000; **5** (Suppl. 3):50-51
2. Kempf DJ, Marsh KC, Kumar G et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. *Antimicrobial Agents and Chemotherapy* 1997; **41**:654-660
3. Hsu A, Granneman GR, Cao G et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrobial Agents and Chemotherapy* 1998; **42**:2784-2791
4. Kirk O, Katzenstein TL, Gerstoft J *et al.* Combination therapy containing ritonavir plus saquinavir has superior short-term antiretroviral efficacy: a randomized trial. *AIDS* 1999;**13**:F9-16
5. Gatell JM, Lange J, Arnaiz JA *et al.* A randomized study comparing continued indinavir (800 mg tid) to indinavir/ritonavir (800/100 mg bid) in HIV patients having achieved viral load with indinavir plus 2 nucleoside analogues. The bid efficacy and safety trial (BEST). XIII International AIDS Conference, Durban, South Africa, 9-14 July 2000. Abstract WeOrB484




# Notes

# Clinical optimisation of protease inhibitor sequencing

**Andrew Zolopa MD**
*Assistant Professor of Medicine, Stanford University School of Medicine. Director, Stanford Positive Care Program. Chief, Division of AIDS Medicine, Santa Clara Medical Center, Stanford, California*

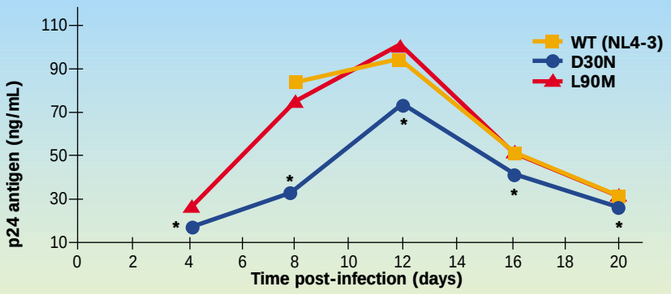
*Andrew Zolopa is Assistant Professor of Medicine at Stanford University School of Medicine where he directs the Stanford Positive Care Program and is Chief of AIDS Medicine Division at Santa Clara Valley Medical Center. The program consists of the Stanford Positive Care Clinic and the Positive PACE clinic at SCVMC. Dr Zolopa serves on the Institute of Medicine's Committee on HIV Prevention Strategies.*
*Dr Zolopa is the Principal Investigator for Stanford AIDS Clinical Trials Group subunit at Santa Clara County and is actively involved in HIV clinical trials research including evaluation of the role of HIV resistance testing in clinical practice. He is the PI for the Clinic-Based Investigator's Group (CBIG) and he maintains an active collaboration with researchers at San Francisco General Hospital Division of Epidemiology, evaluating effectiveness and resistance to HIV treatments in San Francisco's homeless population.*
*Dr Zolopa has published extensively in the field of HIV.*

The choice of initial antiretroviral regimen is critical to attaining the goal of successful management of HIV in the long term. The first-line regimen must not only provide potent and durable suppression of HIV replication (HIV RNA <50 copies/ml), but also be easy to take and well tolerated. However, perhaps the most important strategic requirement for the initial antiretroviral regimen is that it must also leave open subsequent therapy options to regain control of HIV replication in the event of viral load rebound.

Given the overlap in resistance profiles of many PIs, it is not surprising that many clinicians might be sceptical of the potential benefit of using subsequent PIs when patients fail on their first PI. However, there is now a growing body of evidence suggesting that if we evaluate the data and act strategically we can use PIs in a sequential fashion, to prolong the clinical benefits offered by this potent class of drugs.

Figure 1

**Replication kinetics of PI-resistant HIV mutants in parallel cultures: D30N vs L90M vs WT****




* p<0.05; Mann-Whitney U test, MOI= multiplicity of infection
** 1,000 TCID50 of each virus was used per 106 PHA-prestimulated PBMCs (MOI=0.001)
Martinez-Picado, *J Virol*, 1999

Nelfinavir has demonstrated a number of characteristics that warrant consideration as the PI of choice in an initial antiretroviral regimen, as it has been shown clearly that this drug allows the subsequent use of intra-class drug sequencing:

1. Virus with the nelfinavir-selected D30N primary resistance mutation does not replicate as well as (is less fit than) wild-type or other PI-selected mutants
2. Nelfinavir has a unique resistance profile with infrequent cross resistance to other PIs
3. Nelfinavir is highly potent in combination with NRTIs in antiretroviral-naïve individuals and is well tolerated in a convenient bid regimen.

I will address each of these points in order.

## Viral fitness

It has been shown that most primary drug-resistance mutations impair viral fitness to some degree. With nelfinavir, the most commonly occurring mutant, D30N, is associated with a significant decrease in viral replication rates compared with L90M mutants or wild-type strains, possibly requiring more compensatory mutations than initial mutants selected by other PIs[1,2] (see figure 1).

If the D30N mutant is less fit than wild-type strains, this may allow for a response to a second protease inhibitor-based regimen. A less fit virus with a lower rate of replication may produce a lower level of viremia and decrease the rate at which new drug resistance mutations arise. Both of these features could in turn, result in a better response to subsequent PI-based regimens.

On the basis of the current data relating to viral fitness, we should question whether there is a role for fitness phenotype testing to complement existing genotype and phenotype drug susceptibility testing.

## Unique resistance profile of nelfinavir

The D30N mutation is unique to nelfinavir and data have shown that patients entering a trial with D30N at baseline have virologic response rates similar to those entering with no primary resistance mutations – 100% and 82% achieving HIV RNA levels <500 copies/ml respectively[3] (see figure 2).

This observation is complemented and extended by data from the GART study showing that patients with the D30N mutation had better virological re-

Figure 2

**Pr mutation pattern and virologic response to RTV + SQV therapy**

| | Median baseline values (range) | | | | | | |
|---|---|---|---|---|---|---|---|
| Mutation Patterns | Patients n | Additional mutations Pr | RT | CD4 | HIV RNA | Follow-up n(%) <500 | <50 |
| 0 (none) | 11 | 5 (1-7) | 10 (0-17) | 240 | 4.7 | 9 (82) | 6 (55) |
| 30N | 7 | 4 (3-9) | 11 (9-14) | 500 | 3.6 | 7 (100) | 3 (43) |
| 90M | 6 | 6 (4-7) | 10 (8-19) | 345 | 4.6 | 2 (33) | 0 |
| Any2 | 10 | 7 (0-10) | 12 (4-16) | 140 | 5.0 | 2 (20) | 0 |
| Any≥3 | 17 | 7 (2-10) | 14 (7-24) | 170 | 5.0 | 0 | 0 |

Zolopa, *Annal Int Med*, 1999

Figure 3

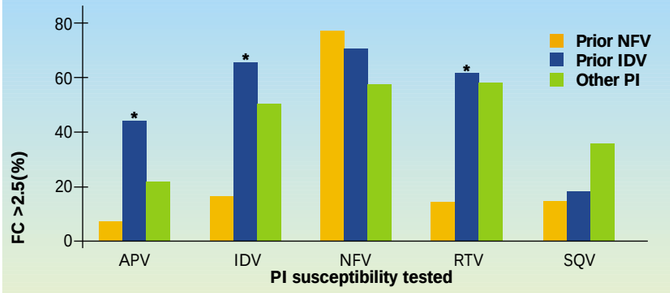
**GART**
**Virologic impact of Pr resistance mutations**

| | Unadjusted for Prior PI treatment | | Adjusted for Prior PI treatment | |
|---|---|---|---|---|
| Pr mutation | HIV RNAΔ* | p value | HIV RNAΔ* | p value |
| 30N | -0.41 | 0.04 | -0.47 | 0.06 |
| 46I/L | -0.03 | 0.84 | -0.01 | 0.93 |
| 82A/F/T | 0.11 | 0.48 | 0.15 | 0.36 |
| 84V | -0.22 | 0.39 | -0.22 | 0.40 |
| 90M | 0.31 | 0.04 | 0.25 | 0.13 |

* Average of weeks 4 and 8
Mayers, *Antiviral Ther*, 1999

Figure 4

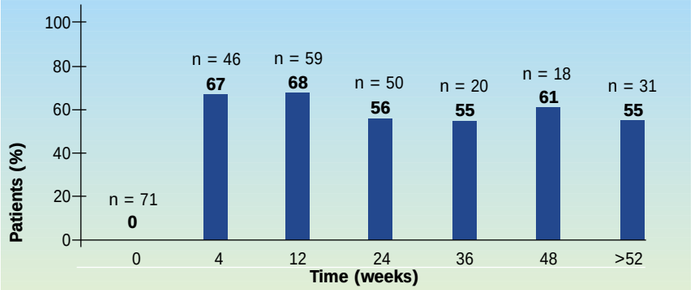
**CCTG 575: Reduced PI phenotype susceptibility by prior PI**




* p<0.001 for comparison of 3 groups of prior therapy
Haubrich and the CCTG, ICAAC, 1999

Figure 5

**Response to RTV + SQV after initial NFV-based ART**
Patients with HIV RNA ≤500 (AT)




Zolopa, ICAAC, 1999

sponse rates than those with other primary PI mutations[4] (see figure 3).

The observed lack of genotypic cross-resistance between nelfinavir and other PIs[5] is supported by phenotypic evidence of a lack of cross resistance in study CCTG 575[6], where patients with high-level nelfinavir resistance had significantly lower cross-resistance to other PIs (see figure 4).

This lack of cross-resistance seen with nelfinavir-resistant strains, has also been observed in the VIRA 3001 study where patients entering the trial with nelfinavir resistance, had relatively low levels of resistance to other PIs[7]. In contrast, patients with IDV resistant strains had higher levels of resistance to nelfinavir, amprenavir and saquinavir. In addition, clinical data from one study of ritonavir-boosted saquinavir after failure of nelfinavir-containing antiretroviral therapy showed impressive virological response, with nearly 60% of patients (OT data) maintaining viral levels below 500 copies/ml at 48 weeks[8] (see figure 5)

## Nelfinavir is effective and well tolerated

As a final point in consideration of selecting and sequencing PIs in combination therapy, it should be noted that nelfinavir is also a highly potent PI that provides durable viral suppression in antiretroviral-naïve patients[9]. Treatment with nelfinavir (1250 mg twice-daily) in combination with stavudine (d4T) and lamivudine (3TC) sustained HIV RNA levels below 50 copies/ml up to 96 weeks in approximately 65% of patients using an on-treatment analysis (approximately 45% by intention-to-treat) in preliminary results from a subset of patients[10].

It is of significant relevance that, in contrast to PIs, NNRTIs have significant overlap of primary resistance mutations, suggesting that sequencing of these would be almost impossible. This has been borne out in clinical trials[11,12].

In conclusion, strategic use of antiretroviral therapy will require consideration of resistance and cross-resistance patterns from day 1 of therapy. Use of resistance testing should help in making best use of antiretrovirals over time. The D30N mutation appears to be unique to nelfinavir, with little or no cross- resistance to other PIs. There is growing evidence that dual PI therapy can provide a good response in patients who have failed nelfinavir-based regimens.

## References


1. Martinez-Picado J, Savara AV, Sutton L and D'Aquila RT. Replicative fitness of protease inhibitor-resistant mutants of human immunodeficiency virus type 1. *Journal of Virology* 1999; **73**:3744-3752
2. Gamarnik A, Wrin T, Ziermann R *et al.* Drug resistance is associated with impaired protease and reverse transcriptase function and reduced replication capacity: characterization of recombinant viruses derived from 200 HIV-1-infected patients. *Antiviral Therapy* 2000; **5** (Suppl. 3); 92-93
3. Zolopa AR, Shafer RW, Warford A *et al.* HIV-1 genotypic resistance patterns predict response to saquinavir-ritonavir therapy in patients in whom previous protease inhibitor therapy had failed. *Annals of Internal Medicine* 1999; **131**:813-821
4. Mayers DL, Baxter JD, Wentworth DN *et al.* The impact of drug resistance mutations in plasma virus of patients failing protease inhibitor-containing HAART regimens on subsequent virological response to the next HAART regimen: results of CPCRA 046 (GART). *Antiviral Therapy* 1999; **4** (Suppl. 1):51
5. Hirsch MS, Brun-Vezinet F, D'Aquila RT *et al.* Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel. J*ournal of the American Medical Association* 2000; **283**:2417-2426
6. Haubrich R, Kemper C, Witt M *et al.* Differences in protease inhibitor (PI) phenotypic susceptibility after failure of the first PI-containing regimen. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, USA, 26-29 September 1999. Abstract 1167
7. Cohen C, Kessler H, Hunt S *et al.* Phenotypic resistance testing significantly improves response to therapy: final analysis of a randomized trial (VIRA3001). *Antiviral Therapy* 2000; **5** (Suppl. 3):67
8. Tebas P, Patick AK, Kane EM *et al.* Virologic responses to a ritonavir/saquinavir-containing regimen in patients who had previously failed nelfinavir. *AIDS* 1999; **13**:F23-F28
9. Gathe J, Chu A, Kass C *et al.* Three year experience with nelfinavir combination therapy. The XIII International AIDS Conference, Durban, South Africa, 9-14 July 2000. Abstract TuPeB3236
10. Petersen A, Antunes F, Arasteh KN *et al.* A comparison of the long-term antiviral efficacy of bid and tid dosing of nelfinavir in combination with stavudine (d4T) and lamivudine (3TC) beyond 48 weeks. Seventh European Conference on Clinical Aspects and Treatment of HIV-infection, Lisbon, Portugal, 23-27 October 1999. Abstract 205
11. MacArthur RD, Kosmyna JM, Crane LR *et al.* Sequencing of non-nucleoside reverse transcriptase inhibitors based on specific mutational patterns fails to lower plasma HIV-RNA levels in persons extensively pre-treated with antiretrovirals who are failing virologically on nevirapine-containing antiretroviral regimens. Seventh European Conference on Clinical Aspects and Treatment of HIV-infection, Lisbon, Portugal, 23-27 October 1999. Abstract 208
12. Shulman N, Zolopa A, Murlidharan U *et al.* Efavirenz (EFV) and adefovir (ADV)-based salvage in antiretroviral experienced HIV+ patients. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, USA, 26-29 September 1999. Abstract 2201




# Notes

# Clinical optimisation of protease inhibitor pharmacokinetics

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*Dr Montaner received his MD with Honors in 1979 at the University of Buenos Aires, Argentina. In 1981, he joined the University of British Columbia as a post-doctoral fellow. He then completed a residency in Internal Medicine and Respiratory Medicine at UBC. He was Chief Resident for the Department of Medicine in 1986/1987.*

*In 1988 Dr Montaner joined the Faculty at St. Paul's Hospital/University of British Columbia as the Director of the AIDS Research Program and the Infectious Disease Clinic. He is the Director, Clinical Activities of the BC Centre for Excellence in HIV/AIDS and a founding co-Director of the Canadian HIV Trials Network. He held a National Health Research Scholar of Health Canada (NHRDP) for a period of 10 years starting in 1988. In 1996 he successfully competed for the Endowed Chair on AIDS at SPH/UBC. In 1997, he was appointed Professor of Medicine at UBC.*

*Dr Montaner has published extensively with regard to respiratory complications of AIDS and antiretroviral therapy for HIV infection. Of note, he pioneered the use of adjunctive corticosteroids for AIDS-related* Pneumocystis carinii *pneumonia. Later on, his work played a significant role in establishing the relationship between the development of HIV resistance to nucleoside analogues and clinical progression of the disease. Over the last couple of years, Dr Montaner was involved in several important international studies including the AVANTI Trials, CAESAR and INCAS. Also, he evaluated several alternative therapeutic approaches, such as Acemannan, Hydroxyurea and GP160. More recently, Dr Montaner has focussed on simplification of antiretroviral therapy and the management of multiple drug resistant HIV. He has also initiated a new effort to characterize the long term safety of antiretroviral therapies.*

*Dr Montaner is the Editor of the BC Centre Therapeutic Guidelines. Also, he is responsible for several aspects of the Drug Distribution Program for the BC Centre for Excellence in HIV/AIDS.*

*Dr Montaner is a member of the Scientific Committees for the bi-annual International Conference on HIV Therapy. He is the co-chair of the Annual International Workshop on Salvage Therapy. He was the co-Chair of the Scientific Program and a member of the Organizing Committee for the XIth International Conference on AIDS, which attracted 15,000 participants to Vancouver in the summer of 1996. He is the Track B co-Chair for the 2001 IAS Conference on AIDS Therapeutics. He is a member of the International AIDS Society (USA) Expert Panel on Antiretroviral Therapies. He is the Treasurer of the Canadian Association for HIV Research and an elected member of the Council of the International AIDS Society.*

## Introduction

Clinical pharmacology is rapidly emerging as a major issue for optimal HIV management, as exemplified by the observation that knowing the resistance profile of a drug without knowing its plasma level can be likened to having viral load data in the absence of a CD4 count. Despite proven efficacy of protease inhibitor (PI)-based therapy, the pharmacological profiles of some PI drugs can complicate therapy in several ways: a short half-life ($T_{1/2}$) may necessitate frequent and inconvenient dosing; rapid clearance requires the use of high doses and the subsequent high plasma peak ($C_{max}$) levels can reduce the tolerability of the regimen; low plasma trough ($C_{min}$) levels can lead to an intermittent loss of viral suppression that promotes the evolution of drug resistance. The use of a dual-PI regimen in which pharmacokinetic interactions between the two drugs raise $C_{min}$ may strengthen the regimen by preventing the emergence of drug resistance. Supporting evidence for this conjecture can be found in the demonstrated association between PI $C_{min}$ and both the rate of development of resistance mutations[1] and the extent of virological suppression over time. Inter-patient variability in PI metabolism and therefore drug exposure – itself associated with *in vivo* virological response[2] – is another factor that may respond favourably to the use of a dual-PI regimen with improved pharmacokinetics. Thus, pharmacokinetic (PK) boosting should result in enhanced antiviral potency – including potency against drug-resistant strains – while simultaneously reducing the pill burden, dosing schedules, and possibly cost.



## Mechanisms of PK boosting

The co-administration of small doses of ritonavir (RTV) significantly improves the pharmacokinetics of other PIs. The potent inhibitory action of RTV on cytochrome P450 (CYP) 3A4 in the gut reduces first-pass PI metabolism and so prolongs $C_{max}$, while inhibition of CYP 3A4 in the liver reduces systemic drug metabolism and so prolongs $T_{1/2}$. RTV boosting, however, does not follow the same pattern for all PI drugs. For saquinavir (SQV) and lopinavir (ABT-378), the predominant effect of RTV is to elevate $C_{max}$, while for indinavir (IDV), nelfinavir and amprenavir, RTV boosting primarily extends $T_{1/2}$[3,4]. In the case of nelfinavir, boosting with RTV results in a substantial increase in the plasma levels of its active metabolite, M8, and this may prove to be of clinical relevance, therefore warranting further investigation[5]. Saquinavir is one of the most widely studied of the PIs with respect to RTV boosting, and its *in vivo* $C_{max}$ and $C_{min}$ under boosting are in good agreement with predicted estimates across a wide range of SQV dosages. The ratio of observed SQV $C_{min}$ to the *in vivo* 95% inhibitory concentration ($EC_{95}$) for HIV replication is high for all twice-daily (*bid*) SQV/RTV combinations studied. However, it should be stressed that while $C_{min}$/EC ratios are often used as a predictor of antiviral potency for RTV-boosted regimens, the procedures for determining its components are not standardized and estimates of the ratio will vary considerably depending on how each factor is assessed[6]. Hence, the only effective means of evaluating a boosted regimen is by direct, head-to-head clinical trials.

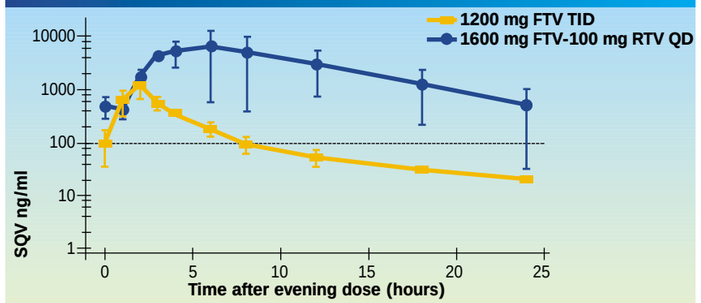
Regardless of how it is evaluated, the goals of any boosted regimen are the same: to improve PI pharmacokinetics in terms of potency, durability and activity against drug-resistant virus; to reduce pill burden and frequency of dosing; to reduce or abolish dietary or other restrictions; and to improve regimen tolerability and cut the cost of therapy by reducing the amount of PI to be taken.

## Twice-daily dosing

A *bid* regimen of 400 mg SQV plus 400 mg RTV is already well-established in HIV therapy[7,8]. More recent data on the development of *bid* dosing of IDV/RTV combinations from the Protocol 078 study show improved 12-hour pharmacokinetics for 800 mg IDV plus 100 mg RTV *bid*. However, increased hydration is required while on IDV/RTV to offset the well-known nephrolithiasis associated with the use of IDV. Clinical data from the bid Efficacy and Safety Trial (BEST) for RTV-boosted *bid* IDV compared with unboosted three-times-daily (*tid*) IDV showed similar overall efficacy, but incidence of kidney stones was higher on the boosted regimen (10% versus 4%)[9].

Figure 1

**Pharmacokinetics of FTV/RTV QD vs FTV TID**




Saag *et al*, ICAAC, 1999

Figure 2

**SQV-SGC (Fortovase®) tolerability alone and in combination with Ritonavir (Norvir)**

| Group | Dose FTV (mg) | Dose RTV (mg) | No of Subjects* | Total No of Events | Most Common Events (number of subjects reporting event) |
|---|---|---|---|---|---|
| A | 1200 | - - - | 8 | 39 | Bloated(4), Fatigue(6), Flatulence(5), |
| B | 1600 | 100 | 10 | 49 | Bloated(1), Diarrhea(4), Fatigue(3), Flatulence(5), Headache(5), Irritable(3), Light Headed(2), Nausea(5), Sleepy(2), Vomiting(2),Headache(4), Irritable(2), Nausea(5). |
| C | 1200 | 100 | 8 | 52 | Bloated (2), Diarrhea (3), Fatigue (7), Flatulence (4), Headache (4), Irritable(2), Nausea (5). |
| D | 1800 | 100 | 9 | 55 | Bloated(2), Constipation(3), Diarrhea(4), Dry Mouth(2), Fatigue(3), Flatulence(3), Headache(4), Mouth Numbness(1), Nausea(6), Sleepy(1), Stomach Cramps(1), Taste Disturbance(1). |
| E | 1200 | 200 | 9 | 57 | Bloated(5), Diarrhea(4), Fatigue(5), Flatulence(5), Headache(4), Hot Flushes(2), Nausea(5). |

*Total numbers available for safety may be greater than the number available for PK

## Once-daily (*qd*) dosing

The possibility of *qd* dosing for RTV-boosted SQV and IDV is currently under investigation, and Fortovase® (FTV; SQV soft gel capsules) has shown early promise as a *qd* agent[10]. The addition of 100 mg RTV to 1600 mg FTV given once daily yields an enhanced 24 hour pharmacokinetic profile that is unaffected by the administration of the nucleoside analogue ddI in healthy volunteers. The mean 24-hour $C_{min}$ for this combination is well above the

$EC_{95}$, and the 24-hour area under the FTV concentration-time curve (the $AUC_{24}$) is 300-700% greater than in the absence of RTV (see figure 1).

IDV has also been studied as a *qd* alternative in normal volunteers. The most effective combination studied (IDV 800 mg/RTV 200 mg *qd*) showed a higher $C_{max}$ (9.1 versus 6.7 µg/ml) than the 800/100 *bid* regimen, which explains the increase in adverse events noted. In particular, this is expected to further increase the higher rate of kidney stones seen previously in the BEST study with the 800/100 regimen.

In summary, based on these data, our centre currently recommends the use of RTV-boosted PI regimens, specifically Fortovase® and indinavir based *bid* therapy as well as *qd* SQV 1600/1200 mg with 100 mg RTV.

## References


1. Molla A, Korneyeva M, Gao Q et al. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nature Medicine* 1996; **2**:760-766
2. Gieschke R, Fotteler B, Buss N and Steimer JL. Relationships between exposure to saquinavir monotherapy and antiviral response in HIV-positive patients. *Clinical Pharmacokinetics* 1999; **37**:75-86
3. Kempf DJ, Marsh KC, Kumar G et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. Antimicrobial *Agents and Chemotherapy* 1997; **41**:654-660
4. Hsu A, Granneman GR, Cao G et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrobial Agents and Chemotherapy* 1998; **42**:2784-2791
5. Kurowski M, Kaeser B, Mroziekiewicz A *et al.* The influence of low doses of ritonavir on the pharmacokinetics of nelfinavir 1250 mg bid. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, 17-20 September 2000.
6. Hill A, Craig C and Whittaker L. Prediction of drug potency from $C_{min}/IC_{50}$ or $C_{min}/IC_{95}$ ratio: false precision? *Antiviral Therapy* 2000; **5** (Suppl. 3):50-51
7. Kirk O, Katzenstein TL, Gerstoft J *et al.* Combination therapy containing ritonavir plus saquinavir has superior short-term antiretroviral efficacy: a randomized trial. *AIDS* 1999;**13**:F9-16
8. Department of Health and Human Services and Henry J Kaiser Family Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available at: http://hivatis.org. January 28 2000.
9. Gatell JM, Lange J, Arnaiz JA *et al.* A randomized study comparing continued indinavir (800 mg tid) to indinavir/ritonavir (800/100 mg bid) in HIV patients having achieved viral load with indinavir plus 2 nucleoside analogues. The bid efficacy and safety trial (BEST). The XIII International AIDS Conference, Durban, South Africa, 9-14 July 2000. Abstract WeOrB484
10. Saag MS, Kilby M, Ehrensing E et al. Saquinavir systemic exposure and safety of once daily administration of Fortovase® (saquinavir) soft gel capsule (FTV) in combination with low-dose ritonavir (RTV). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, USA, 26-29 September 1999. Abstract 330




# Notes

# Strategic development of novel antiretroviral therapies

*New options for therapy experienced patients*

**Joep Lange MD, PhD**
*Academic Medical Centre, Amsterdam, The Netherlands*

*Dr Joep Lange began his career at the University of Amsterdam, specialising in Internal Medicine with a special interest in infectious diseases. In 1984, he became involved in the Amsterdam Cohort Study on HIV-infection and AIDS and in laboratory research on HIV infection at the University of Amsterdam, which led to the first full description of the serological antibody response pattern to HIV infection (thesis 'Serological markers in HIV infection', 1987).*

*Dr Lange was appointed Director of the newly founded National AIDS Therapy Evaluation Centre (NATEC), in 1990. NATEC is a government-sponsored body, responsible for the initiation and co-ordination of clinical trials in the field of HIV infection and its secondary complications, in the Netherlands.*

*Prior to his return to the University of Amsterdam as Professor of Internal Medicine in 1995, he was Chief, Clinical Research and Drug Development (later Clinical Research and Product Development), Global Programme on AIDS, World Health Organization, Geneva, Switzerland.*

*Dr Lange has been principal investigator of more than 10 trials on antiretroviral therapy, the first of which was a pilot dose-efficacy study of zidovudine + acyclovir in asymptomatic HIV-infected subjects at high risk for disease progression, which started in April 1987 (the first trial in which zidovudine was administered to asymptomatic HIV-infected subjects).*

*He serves or has served on the Editorial Boards of 'Genitourinary Medicine', 'AIDS', and 'Clinical Trials and Meta-Analysis' and has been Section Editor for the Clinical Treatment Section of the 'AIDS' 1991 and 1992/1993 Annual Supplements. He is also Editor-in-Chief of the newly founded journal 'Antiviral Therapy'. He was also co-chairman of the Clinical Care track of the VIII International Conference on AIDS, which was held in Amsterdam in July 1992.*

*Dr Lange serves or has served on several advisory groups on antivirals to pharmaceutical companies, on several Data and Safety Monitoring Boards of international antiviral drug trials, on several NIH review panels, is a member of the ACTG International Virology Committee, and was a member of the Executive Committee that drafted the US Public Health Service Task Force Recommendations on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus.*

*Dr Lange has published more than 100 papers on the serology, natural history and treatment of HIV infection.*

Currently available antiretroviral agents can be classed according to the target viral enzyme that they inhibit. Nucleoside analogues (zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir) and non-nucleoside analogues (efavirenz, delavirdine, nevirapine) inhibit the enzyme responsible for viral RNA transcription, reverse transcriptase. Protease inhibitors (nelfinavir, saquinavir, indinavir, ritonavir, amprenavir and lopinavir) prevent the action of the protease enzyme, which is responsible for the cleavage of polyproteins into constituent proteins of a mature virion. Drugs within these two classes comprise the constituent elements of combination therapy regimens that are widely used today. The fact that they work at different stages in the viral life cycle has led many to believe that divergent therapy (using drugs effective against different viral targets) provides the optimal approach to combat the virus. However, there is, in contrast, a theoretical benefit to convergent therapy (using drugs from the same class that target a single viral protein). Such an aggressive selection pressure against one target in the viral life cycle might force the virus to mutate into a non-viable strain. However, there is little evidence to suggest that this is what happens in the clinical setting.

In therapy-experienced patients, virus may be resistant to one or more agents in a particular drug class as well as being resistant to more than one drug class. Cross-resistance limits therapeutic benefit from subsequent therapy, even when multiple agents are used from the various available drug classes. It is clear, therefore, that there is a pressing need to develop inhibitors of new viral targets, particularly those which are active against strains resistant to conventional targets.

Potential new targets identified for such new drug classes include:

- Viral integrase enzyme (responsible for the integration of viral DNA into the cellular DNA)
- Viral regulatory enzymes (responsible for the transcription of proviral DNA into RNA)
- Viral zinc finger nucleocapsid proteins (responsible for the formation of the nucleocapsid)
- Viral entry into host cell (initial attachment of virus into cell, chemokine receptor interactions and subsequent fusion events) (See figure 1).

Neuraminidase inhibitors for treatment of influenza have provided a strong precedent to support the consideration of the development of agents targeted at viral/cell associations. Agents developed in this group include zanamivir (Relenza®), oseltamivir (Tamiflu®) and an investigational compound, RWJ-270201. Looking at the replication cycle of the influenza virus, we can see that it follows the typical pattern of viral replication: fusion; loss of outer membrane; replication of genetic material; translation into constituent proteins; and finally, assembly and budding. Like protease inhibitors, neuraminidase agents inhibit the final stages of the viral life cycle, but they differ in that neuraminidase inhibitors block viral shedding from the host cell while protease inhibitors block the construction of the constituent proteins required for a mature virion. The successful development of agents which block viral/cell associations has been an important advance and provides encouraging results for those involved in the search for new viral targets.

Looking in more detail at viral/cell associations in the HIV field, it is clear that in the last decade a considerable amount has been learned about the process of HIV attachment and fusion to host cells. The process is characterised by a number of distinct stages. Firstly, the external viral envelope glycoprotein, gp120, interacts with a domain on the primary cellular receptor, CD4, on the surface of T-helper cells or macrophages.

After this, the conformation of gp120 is altered, revealing a hitherto concealed area that is able to bind to the receptors known as CXCR-4 or CCR-5. These are chemokine co-receptors. After gp120 interacts with CD4 and these co-receptors, these molecules fall away allowing the 'spring-loaded' gp41 molecule to spring open and inject into the fusion domain of the target cell, revealing the intermediate structure known as a pre-hairpin intermediate.

The N- and C-terminal domains of this intermediate fold back onto each other in an anti-parallel fashion, bringing the viral and cellular membranes together. Fusion then occurs, a process which requires further elucidation (see figure 2).

Figure 1

**Potential new targets**
The life-cycle of HIV, showing potential targets for intervention

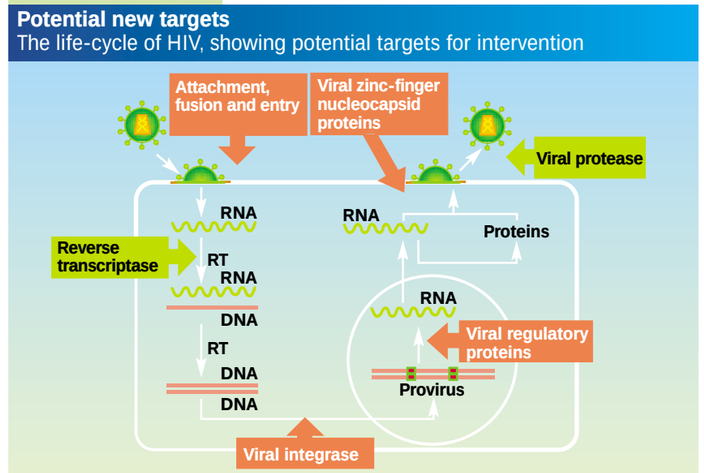
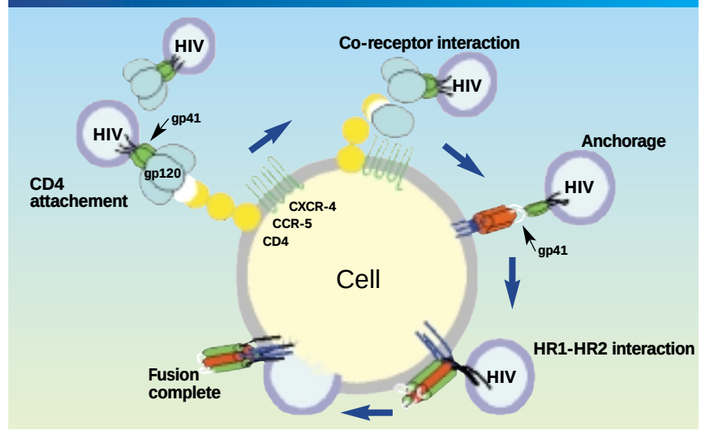



Figure 2

**HIV interaction with CD4 cell**




Potential inhibitors of viral entry can be divided into three mechanistically distinct classes: *attachment inhibitors*, *co-receptor inhibitors*, and *fusion inhibitors*.

Looking first at attachment inhibitors, over the past 15 years attempts to block viral attachment to target cells have not been clinically successful, including the use of soluble CD4, which did however show promising *in vitro* activity[1]. More recently a novel protein, PRO 542, has been associated with more successful results. PRO 542 (CD4-IgG2) consists of the N-terminal domains of human CD4 fused to the constant heavy and light chain regions of human IgG2. *In vitro*, PRO 542 has successfully neutralized a broad range of HIV variants and shown activity in SCID-Hu models with primary isolates. In a small, single-injection, dose-ranging trial, in subjects with HIV RNA >3000 copies/ml and CD4 counts >50 cells/mm$^3$, PRO 542 was well toler-

ated, non-immunogenic and displayed linear pharmacokinetics. In the highest dose group (10 mg/kg) the maximum mean decrease in viral load (0.36 $log_{10}$ decrease) occurred 4 hours after the single dose[2]. In a phase I/II paediatric trial, four of six subjects treated with PRO 542 at a dose of 10 mg/kg experienced a >0.7 $log_{10}$ decrease in HIV RNA, which at day 14 was sustained in three of the four subjects. Again, the trial showed that PRO 542 was well tolerated[3].

Moving on to consider chemokine receptor inhibitors, these can be divided into two classes according to the chemokine receptor that they inhibit (CXCR-4 or CCR-5). There are currently at least two inhibitors in early development against CCR-5. PRO 140 is a murine anti-CCR-5 monoclonal antibody, whereas SCH-C is a small molecule with a pharmacokinetic profile that may support oral administration. AMD-3100 is an inhibitor of CXCR-4 that has been studied when administered by continuous IV infusion.

Focusing on fusion inhibitors, the synthetic C peptides, T-20 and T-1249, have been developed to mimic the C-terminal region of gp41 and prevent the fold-back process through binding to the N-terminal region. T-20 is a 36 amino-acid peptide, which has shown activity against NSI and SI viruses, as well as synergy with other entry inhibitors and also with reverse transcriptase and protease inhibitors. T-1249 is a 39 amino-acid peptide in earlier clinical development with more potent *in vitro* activity and the potential for once daily administration.

Despite the need for parenteral administration, the potential advantages of T-20 and T-1249 fusion inhibitors are significant and include:

- Potency
- Safety
- Lack of drug interactions
- Lack of cross resistance to conventional agents (should work against resistant strains).

It is promising that *in vitro* synergy has already been demonstrated between T-20 and an attachment inhibitor (PRO-542), a CXCR-4 inhibitor (AMD 3100) and a CCR-5 inhibitor (TAK779).

In summary, the current situation is promising and it is anticipated that a new class of inhibitors will be developed to block viral entry. It is also anticipated that these drugs, which would work outside of the cell, will make a significant contribution to the existing therapeutic arsenal.

## References


1. Schooley RT, Merigan TC, Gaut P *et al.* Recombinant soluble CD4 therapy in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. A phase I-II escalating dosage trial. *Annals of Internal Medicine* 1990; **112**:247-253
2. Jacobson JM, Lowy I, Fletcher CV *et al.* Single-dose safety, pharmacology, and antiviral activity of the human immunodeficiency virus (HIV) type 1 entry inhibitor PRO 542 in HIV-infected adults. *Journal of Infectious Diseases* 2000; **182**:326-329
3. Shearer W and Israel R. rCD4-IgG2 in HIV-1-infected children: phase I/II study. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, USA, 30 January - 2 February 2000. Abstract 701




# Notes

# Clinical directions with novel targets

**Anton Pozniak MD, FRCP**
*Consultant Physician and Honorary Senior Lecturer, Chelsea and Westminster Hospital, London, UK*

*Dr Anton Pozniak studied medicine at the University of Bristol. He became involved in AIDS in 1983 at the Middlesex Hospital, London. Dr Pozniak worked as Lecturer and Honorary Consultant at the Department of Medicine at the University of Zimbabwe in the early 1990's. He returned to the UK to join the Academic Department of Genito-urinary Medicine at the Middlesex, then moving as Senior Lecturer and Honorary Consultant at King's Healthcare NHS Trust in 1992. In 1998 Dr Pozniak moved to his current position as Consultant Physician and Honorary Senior Lecturer, Chelsea and Westminster Hospital.*
*Dr Pozniak has published widely on HIV and AIDS. He is a member of various medical organisations including the British HIV Association and the Medical Society for the study of Venereal Diseases and chairman of PACT (Providers of AIDS, Care and Treatment).*

As previously discussed by Dr Lange, several new targets are under development for antiretroviral therapy in HIV disease. Three of these targets – initial binding of virus, co-receptor interactions and fusion events – relate to HIV entry into host cells. It is not inconceivable, given the number of different ways in which cellular infection can be blocked, that in the future entire regimens focusing on HIV entry may be possible, just as viral reverse transcription is currently targeted by triple nucleoside and NRTI/NNRTI regimens. While there is obviously much work to be done before this possibility is realised, progress is being made with the introduction of entry inhibitor drugs – in particular the experimental agent T-20, currently in clinical trials. This drug is a 36 amino-acid peptide inhibiting gp41-mediated fusion. It acts by adhering to the N terminal of gp41, preventing the C terminal folding back in an anti-parallel fashion, thereby preventing subsequent viral-cell fusion (see figure 1).

T-20 has demonstrated activity in T-cell lines at nanomolar concentrations. *In vitro* it is active against NSI and SI viruses and is synergistic with other experimental entry inhibitors as well as with RTIs and PIs. Due to the size of the molecule and the fact that this drug is a peptide, oral administration is not possible hence T-20 is administered by twice-daily subcutaneous injections. It is currently entering Phase III clinical trials.

Trials of T-20 started with a small Phase I, proof-of-concept trial, moving on to dosage and formulation studies. Ongoing, Phase II development has involved a paediatric study, chronic safety study, dose comparison study and a formulation improvements study. Collectively, these trials have provided a strong body of evidence that T-20 is active and generally well tolerated.

The initial Phase I, proof-of-concept trial involved four doses (3 mg, 10 mg, 30 mg and 100 mg) of IV monotherapy T-20, given bid over an 18-day period. Significant decreases in viral load were observed with the 100 mg dose group, achieving a median decrease of 1.96 $\log_{10}$ copies/ml[1] (see figure 2).

Given these very promising data, study TRI-003 was established. This was a multicentre, randomized, Phase II, dose-ranging trial in heavily pretreated patients. Seventy-eight patients were randomised to one of six different regimens:

- Continuous subcutaneous infusion (CSI) daily
  - 12.5 mg
  - 25 mg
  - 50 mg
  - 100 mg
- bid subcutaneous injection (SC)
  - 50 mg
  - 100 mg

Treatment was administered for 28 days against a background of stable antiretroviral therapy or no therapy. Median baseline HIV RNA was 100,000 copies/ml and median CD4 count was 96 cells/mm$^3$. The greatest decreases in HIV RNA levels were seen in patients receiving the bid subcutaneous injections rather than the continuous infusion. In this group, those receiving 50 mg bid SC achieved decreases of approximately 1.2 $\log_{10}$ copies/ml from baseline, while those receiving 100 mg bid SC achieved decreases of 1.5 $\log_{10}$ copies/ml (median nadir over 28-day study period). These results are particularly significant when one considers that these patients were heavily antiretroviral-experienced and did not initiate T-20 therapy with a new background regimen. Intent-to-treat analysis also showed significant decreases in viral load over the 28-day study period, with the greatest decreases observed in the 100 mg bid SC group.

Following these results, the T20-205 safety study was initiated. This multicentre, open-label, single-arm, 48-week study involved a rollover protocol from prior short-term T-20 studies. The study allowed for individualized therapy based on drug history and genotype. A dose of 50 mg bid SC was selected for the study. At baseline, mean HIV RNA levels were 5.0 $\log_{10}$ copies/ml and median CD4 count was 90 cells/mm$^3$. 97% of patients were PI-experienced while 79% were NRTI-, NNRTI- and PI-experienced. The median number of prior antiretrovirals was nine and the median number of concomitant therapies in the study was five[2,3].

At 16 weeks, intent-to-treat analysis revealed that approximately 54% of patients (60% by an on-treatment analysis) had achieved plasma viral loads <400 copies/ml or had at least a one log reduction in viral load. The data also highlighted two important facts:

Figure 1

**T-20 Mechanism of action**

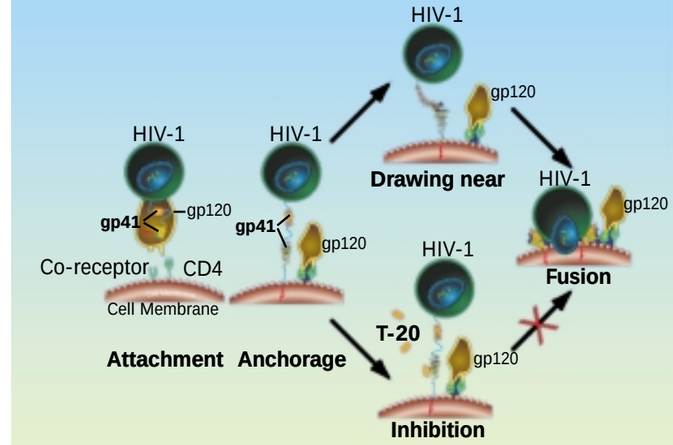
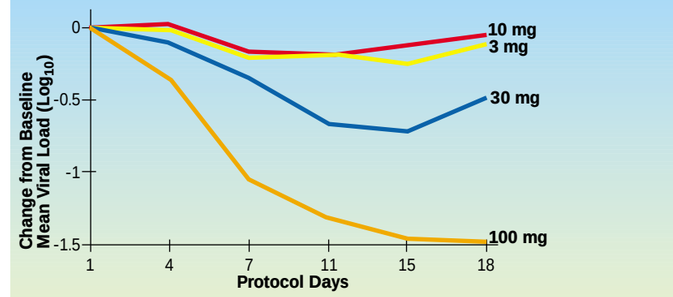



Figure 2

**TRI-001: T-20 IV monotherapy HIV-RNA results**




Kilby, Hopkins, Venetta *et al.* Nature Medicine Nov 1998, Vol 4 (11)

- 60% of patients who had been exposed to all three classes of approved ARVs (NRTIs, NNRTIs and PIs), achieved overall viral loads <400 copies/ml or had at least a one log reduction in viral load
- 53% of patients, resistant at baseline to drugs in all three drug classes, responded to therapy while 30% achieved plasma viral loads <400 copies/ml

At week 48, using an intent-to-treat analysis, 33% of these extensively pre-treated individuals (56% by an on-treatment analysis) had achieved plasma viral loads <400 copies/ml or experienced more than a tenfold reduction in viral load from baseline levels.

These results were particularly encouraging as they demonstrate that T-20 containing combination regimens are effective in patients who are heavily pre-treated and harbour multi-drug resistant viral strains.

As previously discussed, due to the size of the T-20 molecule, it cannot be administered orally, hence

parenteral administration is necessary. Given the potential impact of this on long-term patient acceptance, a T20-205 Activities of Daily Living (ADL) survey was conducted, which required patients to complete written questionnaires at baseline and at week 48 of the 205 study. Measures included activities of daily living and assessment of the ease of T-20 preparation, storage and disposal.

Fifty-four of 71 surveys were received and results clearly indicated that the majority of patients (64%) did not consider that T-20 injections limited their daily activities. Perhaps, unsurprisingly, the activity most negatively affected by daily T-20 injections was 'travel', however, this view was held by only 53% of patients. Furthermore, 87% of patients indicated that ease of injection was 'not bad, easy or very easy'. A similarly positive response was recorded for patient experience with preparation, storage and disposal. On a scale of one to five, where one is very difficult and five is very easy, patients indicated that disposal was easy (4.4), refrigeration was easy (3.8) and dissolving was not bad (3.4).

A randomized, controlled, open-label, dose comparison study, T20-206, has also been initiated to evaluate the addition of T-20 to a background antiretroviral regimen compared to background therapy alone. Three doses of T-20 are being evaluated (50 mg, 75 mg and 100 mg bid) and background therapy includes abacavir, amprenavir, ritonavir and efavirenz.

Preliminary analysis of study T20-208 data has revealed comparable PK profiles between a single injection formulation (100 mg T-20) and that of the original drug regimen comprising 2x50 mg injections. It is hoped that this more convenient regimen will benefit the patient since the number of daily injections has been reduced from four to two.

As a final point, it is pertinent to balance the positive results seen to date with T-20 against the challenges that face the future development of this drug. The most obvious challenge is that of patient acceptance of parenteral administration, but early survey results have indicated that no patients regard injection as a 'very difficult' procedure and only 13% find it a 'somewhat difficult' procedure. The potential for T-20 to elicit an antibody response has been raised as a potential issue, but available data to date have indicated that pre-existing antibodies to gp41 that cross react to T-20 do not appear to impact on safety, pharmacokinetics or antiviral activity. Furthermore, development of antibodies reacting to T-20 in patients not previously antibody positive seems to be minimal and with apparently no clinically relevant consequences. As with all antiretroviral agents, the development of resistance is a potential issue and mutations in the gp41 that map to the binding region for T-20 have been observed. Ongoing studies will allow the resistance profile of T-20 to be better defined. Lastly, the issue of complex synthetic manufacture is already being addressed such that large-scale manufacturing is currently being scaled up to meet future potential demand.

In summary, T-20 shows significant promise for treatment of HIV infection, and importantly, is active in patients with extensive prior exposure to antiretroviral therapies. Promisingly, T-20 has also demonstrated synergy with existing agents and with other entry inhibitors. There is no doubt that T-20 represents a potentially important new addition to HIV therapeutic management tools and further data are eagerly awaited.

## References


1. Kilby JM, Hopkins S, Venetta TM *et al.* Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. *Nature Medicine* 1998; **4**:1302-1307
2. Lalezari J, Eron J, Carlson M et al. Sixteen week analysis of heavily pre-treated patients receiving T-20 as a component of multi-drug salvage therapy. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, USA, 26-29 September 1999. Abstract LB-18
3. Cohen C, Lalezari J, Eron J *et al.* Forty-eight week analysis of patients receiving T-20 as a component of multi-drug salvage therapy. The XIII International AIDS Conference, Durban, South Africa, July 9-14 2000. Late Breaker Abstract.




# Notes

# Summary and closing remarks


**Margaret Johnson MD, FRCP**
*Clinical Director of HIV Services at the Royal Free Hospital, London.*


*Dr Johnson is currently Consultant Physician in General Medicine, HIV/AIDS, Thoracic Medicine at the Royal Free Hospital NHS Trust, London and Honorary Senior Lecturer in Virology, Royal Free Hospital School of Medicine, University of London and Clinical Director HIV/AIDS , Royal Free NHS Trust.*

*Since her appointment to the Consultant Staff of the Royal Free Hospital, Dr Johnson has developed the Royal Free HIV/AIDS Service. This has become one of the major treatment centres for HIV patients in the UK and at present, looks after 1,500 HIV positive patients, approximately 400 of whom have AIDS. She has set up the first and largest open access testing clinic in the UK, which now sees more than 3 000 people annually for HIV testing. She also started the first specific clinic for women with HIV infection and now looks after a very large population of women with HIV from all over the UK. With the help of management, Dr Johnson has succeeded in securing funding for this service on the basis of it being one of the major treatment centres, thus securing its future. She also has a major interest in antiviral therapy and takes part in the majority of large European trials of new antiviral strategies, thus enabling patients to have a wide choice in therapy.*

*As well as co-ordinating a large number of research projects, Dr Johnson is involved in 25 ongoing clinical trials of antiviral therapies and treatments for opportunistic infections.*

*Dr Johnson has served or is serving on numerous national and international committees, has served on organising and scientific committees for national and international conferences including the World AIDS Conference (Geneva and Durban) and the 5th International Congress in Glasgow, and has published over 150 papers in the field of HIV and AIDS.*

At the risk of reiterating the obvious, the most pressing need in HIV clinical care at present is the optimization of therapy and the introduction of novel agents. As has been clearly demonstrated by the preceding expert presentations, such approaches are required not only to improve the benefits of HAART for a substantial proportion of those currently on therapy, but also to extend those benefits into a situation of decades-long chronic disease management.

Of all the emerging data arguing for such optimization, and providing ways in which it can be approached, perhaps the most well-known and convincing example is the 48-week data from the Viradapt trial of genotype-assisted therapy, and its 24-week pharmacological sub-study (see figures 1–3).

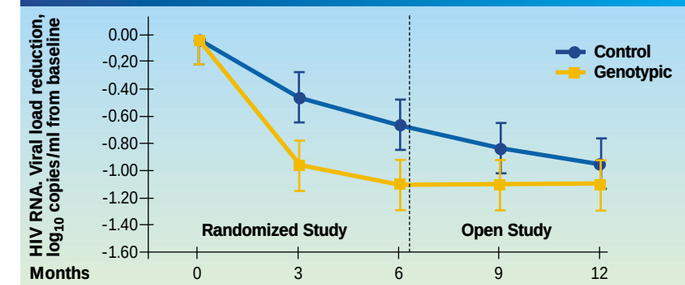
In this set of 108 individuals with viral loads >10,000 after at least 3 months of PI-based therapy, those 65 whose next regimen was individually selected on the basis of genotype testing experienced almost twice the reduction in viral load at 6 months than the 43 whose next regimen was based on standard of care alone. The introduction of open-label testing at month 6 extended this improvement to the control arm and resulted in a similar response at month 12 – a benefit that also extended to the percentage of participants below the 200 RNA copies/ml detection limit of the study (see figures 1–3).

Clearly, choosing drugs based on the careful assessment of pre-existing resistance and cross-resistance leads to significantly improved clinical benefit. The speed with which resistance testing is becoming incorporated into standard of care is a testament to the utility of this method of optimizing treatment. But the pharmacological data from this key study teach us an equally important lesson (see figure 3).

Those in the genotyped arm who did not exhibit more than a single monthly plasma PI measurement below the wild-type $IC_{50}$ ('Optimal Concentrations' group) had markedly better viral load reductions over 6 months than those from the same arm who showed two or more PI measurements below this level ('Sub-Optimal Concentrations' group). In fact, the genotyped sub-optimal concentration group showed a very similar reduction to the control opti-

Figure 1

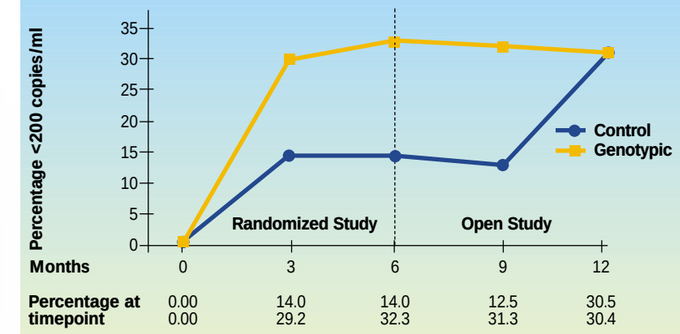
**Mean changes in plasma HIV-RNA from baseline throughout 12 months in control and genotypic arms of the Viradapt study**




Adapted from Clevenbergh *et al. Antiviral Tharapy* 2000; 5:65–70

Figure 2

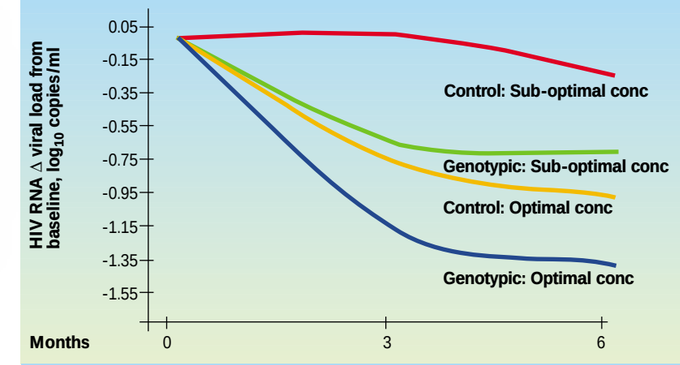
**Percentage of patients with plasma HIV-RNA below the limit of detection (200 copies/ml) in control and genotypic arms of the Viradapt study**




Adapted from Clevenbergh *et al. Antiviral Tharapy* 2000; 5:65–70

Figure 3

**Efficacy analysis based on drug levels and randomization arm in the Viradapt study**




Adapted from Graffo *et al. Antiviral Tharapy* 1999; 4 (Suppl 1):75–76

Figure 4

**'It was the opinion of the Ad Hoc group that it might be appropriate to allow a shortened initial development programme and, hence, faster approval, for new drugs which possess activity against virus which is resistant to one or more approved agents and/or have pharmacokinetic properties which might favour their use in the failing patient population.'**

**Committee for Proprietary Medicinal Products (CPMP)**
Draft Points To Consider In The Assessment Of An Anti-HIV Medicinal Product
July 2000

Figure 5

**Specific points to consider with respect to accelerated approval based on medium-term data in heavily pretreated patients:**

**Resistance Profile:**

- **Low or no cross-resistance with existing agents in the same class**
- **Unique resistance profile if the mechanism of action differs from the available classes**

**If there is no attractive resistance profile, then...**

**Pharmacokinetic profile:**

- **High-level plasma and/or intracellular concentrations expected to give useful activity against strains resistant to one or more drug classes**

CPMP July 2000

member of the first new class of antiretroviral drug since the licensing of nevirapine introduced the non-nucleoside RT inhibitors. The incorporation of this and other new drugs into a framework of optimized strategies for continuing therapy can be expected to prolong significantly the wellbeing of those on HAART.

The importance of all these approaches to therapeutic optimization is reflected in the acknowledgement by the European Committee for Proprietary Medicinal Products that new agents and formulations addressing this need – such as formulations displaying improved pharmacokinetics and candidate drugs with activity against resistant virus – should be considered for expedited approval (see figures 4 & 5). The incorporation of the fundamental tenets of optimized therapy into the approvals procedure will assuredly lay the foundation for an extended and improved approach to HIV management that encompasses both the use of the current agents and of those yet to come.

mal concentration group. The implications of this are as sobering as they are surprising: that without adequate drug exposure there is no benefit to resistance testing beyond what can be obtained without it.

The Viradapt data demonstrate the importance of assessing cross-resistance and optimizing pharmacological exposure for maintaining and extending therapeutic efficacy. Moreover it emphasizes the importance of taking an integrated approach in which neither of these two factors, nor any other strategic element, is considered independently.

While resistance testing and pharmacological enhancement are two promising ways of preserving current therapy, a truly long-term solution to HIV management will require the introduction of entirely new drugs and drug classes against novel targets. Effective integrase inhibitors are still some way off despite ongoing pre-clinical research. Tat inhibitors are even further away. However, HIV entry inhibitors, both binding- and fusion-directed, are much closer to becoming a part of the antiretroviral armamentarium. Of these inhibitors, the most promising and furthest along the path of clinical development is T-20. As described by Drs Lange and Pozniak, T-20 has shown potent antiviral activity in its clinical trials and looks set to become the first



# Notes