

Clinical issues

in **HIV/AIDS**

This series focuses on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

The ninth bulletin looks at the issue of therapeutic drug monitoring (TDM) and considers its potential

role in the management of HIV. There is also a website review looking at two sites providing the latest information and guidelines on HIV/AIDS.

Watch out for further update bulletins in the coming months.

In this issue ...

1 Commentary

Simon Barton BSc MD FRCOG

Consultant and Clinical Director
HIV/Genitourinary Medicine, Chelsea &
Westminster Hospital, London

David Hicks FRCOG MFFP DipVen

HIV/GUM Consultant Physician,
Department of Genitourinary Medicine,
Royal Hallamshire Hospital, Sheffield

3 Therapeutic drug monitoring

David J Back BSc PhD Professor,

Sara E Gibbons BSc MPhil Research

Associate and **Saye H Khoo** MD MRCP
Consultant Physician, Department of
Pharmacology and Therapeutics,
University of Liverpool

7 Website review

David Hicks FRCOG MFFP DipVen

HIV/GUM Consultant Physician,
Department of Genitourinary Medicine,
Royal Hallamshire Hospital, Sheffield

Commentary

Apart from the therapeutic advances in antiretroviral drugs, the management of HIV has evolved out of a series of laboratory-based advances. The recognition that AIDS was due to HIV was followed by its antibody detection, the recognition that CD4 count correlated to clinical status (a bedrock of management) was built upon when viral load measurement was developed, the clinical utility of resistance testing through genotyping and phenotyping provided further sophistication of management and virtual phenotyping may yet add more.

Continued over

Commentary continued

Therapeutic drug monitoring (TDM) has much attraction as the next step, particularly since we are familiar with its value in other therapeutic areas where control of disease can depend on drug titration. A framework to calculate an *in vivo* potency index for antiretroviral agents has been suggested,¹ and saliva has even been proposed as an alternative specimen to blood for TDM.²

Is TDM, however, just a theoretically appealing option or a practical proposition?

In this issue of *Clinical Issues in HIV/AIDS*, Professor Back and his team comment on this important issue.

The first prospective trial of TDM failed to demonstrate benefit in a treatment-experienced patient population.³

The second study^{4,5} was in treatment-naive subjects and showed good clinical benefits.

In the first study, 256 treatment-experienced patients failing their first-line antiretroviral therapy were randomised into control and TDM groups. The choice of regimen was modified by genotypic resistance testing in the control group and by genotypic resistance testing and protease inhibitor (PI) plasma trough levels at four weeks in the TDM group. Plasma HIV-1 RNA levels at Week 12 were the outcome measure.

Virologic outcome was comparable in both arms, and the study design was subsequently criticised at the time of presentation in an effort to explain this result.

The second trial is reported in its component findings for nelfinavir and indinavir in the article in this issue. The results seem to be a vindication of the TDM approach for PIs.

Some questions remain to be answered, however, particularly around adherence in the TDM and control groups, which multivariate analysis may help to explain.

The standard response of 'more research is needed' would appear to be the logical comment here, but it seems likely that TDM will find a place in the management of HIV. It may be that its use will be maximal in defined patient populations, or that better understanding of toxicity versus efficacy will permit a truly tailored approach for antiretroviral treatment.

References

1. Fletcher CV, Anderson PL, Kakuda TN *et al*. A novel approach to integrate pharmacologic and virologic characteristics: an *in vivo* potency (IVP) index for antiretroviral agents. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 2001 (Abstract 732).
2. Van Heeswyk R, Veldkamp AI, Mulder JW *et al*. Can saliva be used as an alternative specimen for therapeutic drug monitoring (TDM) of nevirapine (NVP) in HIV-1-infected patients? 13th International AIDS Conference, Durban, 2000 (Abstract WeOrB542).
3. Clevenbergh P, Durant J, Garraffo R *et al*. Usefulness of protease inhibitor therapeutic drug monitoring? PharmAdapt: a prospective multicentric randomized controlled trial: 12 weeks results. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 2001 (Abstract 260B).
4. Burger DM, Huguenin PWH, Droste J, Huitema ADR for the ATHENA study group. Therapeutic drug monitoring (TDM) of nelfinavir (NFV) 1250 mg BID in treatment-naive patients improves therapeutic outcome after 1 year: results from ATHENA. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, 2001 (Abstract 6.2b).
5. Burger DM, Huguenin PWH, Droste J, Huitema ADR for the ATHENA study group. Therapeutic Drug Monitoring (TDM) of indinavir (IDV) in treatment-naive patients improves therapeutic outcome after 1 year: results from ATHENA. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, 2001 (Abstract 6.2a).

Simon E Barton BSc MD FRCOG Consultant and Clinical Director HIV/Genitourinary Medicine, Chelsea & Westminster Hospital, London

David Hicks FRCOG MFPP DipVen HIV/GUM Consultant Physician, Department of Genitourinary Medicine, Royal Hallamshire Hospital, Sheffield

Therapeutic drug monitoring

David J Back BSc PhD Professor, **Sara E Gibbons** BSc MPhil Research Associate and **Saye H Khoo** MD MRCP Consultant Physician, Department of Pharmacology & Therapeutics, University of Liverpool

Highly active antiretroviral therapy (HAART) can suppress viral replication and substantially prolong patient life. However, HAART can fail for a number of reasons, including poor adherence, insufficient drug potency, emergence of resistance, cellular factors and pharmacokinetic factors. Although many antiretroviral drugs are now available, the number of effective combinations for individual patients is still limited. Also, the durability of virologic response tends to decrease with each new treatment regimen until the patient is left with few or no therapeutic options. There is evidence that more than half of treatment-naïve patients will switch from their initial regimen within one year.¹ It is therefore imperative that we adopt strategies that will seek to optimise the available therapies, so as to achieve long-term viral suppression.

Monitoring the course of HIV infection has been an essential component of patient management. CD4 counts help track the immunological status of a patient, and viral load assays are used to monitor the potency and durability of a regimen and to guide treatment changes. Resistance assays are becoming a standard element of care despite issues around interpretation of results. With emerging evidence linking drug exposure and antiviral efficacy as well as toxicity, attention is now being focused on the role of monitoring plasma drug levels in patients receiving HAART. If inadequate drug levels – arising from poor adherence, inherent pharmacokinetic factors or drug interaction – are a major cause of treatment failure, then monitoring these levels and having an intervention strategy seems a logical approach to improve the success rate of therapy. Likewise, if high drug levels are present then this may relate to toxicity, either in the patient at that time or somewhere down the line. Monitoring drug levels with the intention of some kind of intervention strategy is known as therapeutic drug monitoring (TDM).

TDM is currently used in a number of clinical settings and is generally considered if:

- A well-defined relationship exists between the exposure to a drug and its efficacy/toxicity (PK-PD – pharmacokinetics-pharmacodynamics)
- There is a large inter-individual variability in exposure to a drug
- The drug has a relatively narrow therapeutic window.

Common examples of TDM include anticonvulsants, immunosuppressants and aminoglycoside antibiotics. In the setting of HIV management the role of TDM remains to be firmly established, although evidence is emerging that it may have a role in some regimens and in certain patient groups. However, there are issues that need to be resolved before we can consider TDM to be part of routine patient care.

A major confounder when considering TDM in a clinical setting is adherence. Patients who do not take their antiretroviral therapy on schedule or do not comply with food requirements would be expected to have low plasma drug concentrations and consequently a poor outcome. However, those patients may have apparently 'normal' plasma levels if they take the dose just before a hospital visit. Thus, a patient failing therapy for poor adherence would appear to have a normal drug level in any outcome analysis. Hence, a thorough assessment of adherence is essential to interpret a plasma drug level.

Nucleoside reverse transcriptase inhibitors (NRTIs)

All the licensed NRTIs have to be converted into their active triphosphate anabolite within cells and there is generally a very weak correlation between the parent drug concentration in plasma and the triphosphate concentration within the cell. Although significant relationships between intracellular triphosphates and outcome parameters for zidovudine and lamivudine have been shown,² the cost and complexity of determining triphosphate concentrations currently preclude consideration of monitoring (other than in trial settings).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

An argument raised against considering TDM of NNRTIs is that plasma concentrations of these drugs actually vary relatively little over a dosing interval, owing to their long half-life, and the fact that most patients will have adequate

concentrations. However, there are studies that give some evidence of a correlation between plasma drug level and response, and so open the door to consideration of a role for TDM in this class. A retrospective analysis of efavirenz treatment failure in Phase II clinical trials indicated a significant relationship between sub-optimal plasma concentrations and failure. This was three times as frequent (63% versus 21%) in patients with a minimum concentration (C_{\min}) $<3.5 \mu\text{M}$.³ More recently, increasing plasma efavirenz concentrations were associated with viral suppression and CNS-related toxicity.⁴ The authors of this study proceeded to define a possible therapeutic range (1,000–4,000 $\mu\text{g/l}$). However, numbers in the study were fairly small and more data are required to confirm the utility of using these cut-offs.

With nevirapine, results of the INCAS trial suggest the potential for TDM. In this study, higher nevirapine exposure was associated with greater initial clearance of HIV RNA and a higher probability of achieving undetectable levels of plasma HIV RNA.⁵

Protease inhibitors (PIs)

It is with the PIs that there is the greatest weight of evidence supporting the potential role of TDM in patient management. Tables 1 and 2 focus on studies that highlight the PK-PD relationship for nelfinavir and indinavir. In addition, data relating to these drugs have recently emerged from the ATHENA trial.

ATHENA is a nationwide cohort study of HIV-infected patients in the Netherlands. Within a focus group of 600 patients, subjects were

Table 1. Pharmacokinetic-pharmacodynamic relationship for nelfinavir

Study findings

Patients using quadruple therapy including nelfinavir 750 mg three times daily had more rapid clearance of HIV-1 RNA when the concentration ratio was higher.⁶

Two-hour post-dose nelfinavir concentration was an independent predictor of response in Phase III trials with nelfinavir 750 mg three times daily.⁷

VIRACEPT – baseline viral load and plasma nelfinavir concentrations were predictors of virological response in subjects on nelfinavir.⁸

Nelfinavir C_{\min} is an independent factor associated with virological success in both three times daily and twice daily regimens.⁹

PACTG 382 – children with highest AUC of nelfinavir or efavirenz at Week 2 had most rapid fall in HIV RNA between Weeks 2–4.¹⁰

Table 2. Pharmacokinetic-pharmacodynamic relationship for indinavir

PK parameters	Patients	PD parameters	Time
<i>Efficacy studies</i>			
AUC, C_{\min}	ART experienced	Δ HIV-1 RNA	24 weeks ¹¹
Concentration ratio	ART experienced and naive	Δ HIV-1 RNA	24 weeks ¹²
C_{\min}	ART experienced	Δ HIV-1 RNA	24 weeks ¹³
AUC, C_{\min} , C_{\max}	NNRTI/PI naive	Δ HIV-1 RNA	36 days ¹⁴
AUC, C_{8h}	PI naive	HIV-1 RNA	OS ¹⁵
<i>Toxicity studies</i>			
Concentration ratio	ART experienced	Urological complaints	OS ¹⁶

PK, pharmacokinetics; PD, pharmacodynamics; AUC, area under the drug concentration-time curve; C_{\min} , minimum concentration; C_{\max} , maximum concentration; ART, antiretroviral therapy; PI, protease inhibitor; OS, outpatient study; Δ , change

randomised to a group in which TDM results were reported to their treating physician (including advice as to yes/no modification of dosages) or to a blinded group who did not receive TDM results. Initial analysis was limited to treatment-naive patients who started a regimen containing either nelfinavir (1,250 mg BID) or indinavir with or without ritonavir. Plasma HIV RNA and PI plasma levels were obtained at regular visits. For nelfinavir, the TDM group showed a higher proportion of patients with a viral load below 500 copies after six (95.1% versus 82.4%; $p=0.06$) and 12 (80.5% versus 58.8%; $p=0.03$) months of treatment. The authors conclude that TDM of nelfinavir in this group of patients improved treatment outcome and should become 'standard of care'.¹⁷ For indinavir, the TDM group showed a higher proportion of patients with a viral load below 500 copies after six (92.9% versus 74.1%; $p=0.06$) and 12 (75.0% versus 48.1%; $p=0.04$) months of treatment. Again the conclusion was that TDM of non-boosted and boosted indinavir in treatment-naive patients improves treatment outcome, predominantly by allowing better management of indinavir toxicity.¹⁸

PI boosting and TDM

As ritonavir increases the plasma concentrations of other PIs, the utility of TDM in HIV management has been called into question. However, it should be noted that inter-individual variability of plasma concentrations remains high even with ritonavir enhancement (this also applies to lopinavir/ritonavir) and that there may be situations in which PI concentrations are considered sub-inhibitory (for example, once daily dosing). It is possible that for once daily dosing, area under the plasma concentration-time curve or maximum concentration may be the key pharmacokinetic parameter. There is still much that we do not understand about the concentration-effect relationship of antiretrovirals (and this includes issues of protein binding and intracellular concentrations).

Conclusions

There are a number of challenges facing TDM:

- What is the target concentration? Is a single trough sample adequate and how many times in excess of the minimum effective concentration (MEC) should the C_{min} be? Setting a target MEC based on wild type (WT) HIV is likely to be totally inappropriate for patients on salvage therapy.

- In order to more accurately reflect the relationship between drug concentration and a patient's individual isolate, the concept of inhibitory quotients (IQ) or virtual IQ has been proposed.¹⁹ However, there is much more work needed to validate these ideas.
- It is possible that TDM may have greater utility in relation to toxicity than efficacy, but again we need more data.

The lack of data from prospective studies focusing on the clinical utility of TDM makes it difficult to provide definite recommendations on the use of TDM in the clinical situation. However, note that we have recently incorporated recommendations into the British HIV Association (BHIVA) guidelines for the treatment of HIV-infected patients.²⁰

BHIVA guidelines²⁰ – summary

- Guidelines for the treatment and management of HIV infection have been produced in a number of countries in Europe, as well as in Australia and the USA.
- The BHIVA guidelines have been extensively revised and now include a detailed discussion of their recommendations. They attempt to provide consensus across a range of healthcare workers, including physicians, virologists, people living with HIV and special interest voluntary organisations.
- The BHIVA guidelines have a number of important roles, which are:
 - To promote a uniformly high standard of care in all HIV treatment centres in the UK.
 - To set out the strengths, weaknesses and relevance of recent research findings.
 - To assist in discussions between purchasers and providers regarding funding for HIV/AIDS diagnostic testing, care and treatments.
 - To act as a basis for clinical audit within clinical governance.
 - To act as a source of reference on AIDS treatments for those physicians caring for patients infected with HIV.
- It is inevitable that, as HIV/AIDS is a rapidly evolving medical field, new data will change therapeutic choices and preferences. Consequently, complete updates of the guidelines are planned at least annually.

References

1. Wit FWNM, van Leeuwen R, Weverling GJ *et al.* Outcome and predictors of failure of highly active antiretroviral therapy: one-year follow-up of a cohort of human immunodeficiency virus type 1-infected persons. *J Infect Dis* 1999; **179**: 790–798.
2. Fletcher CV, Kawle SP, Kakuda TN *et al.* Zidovudine triphosphate and lamivudine triphosphate concentration-response relationships in HIV-infected persons. *AIDS* 2000; **14**: 2137–2144.
3. Joshi AS, Barrett JS, Fiske WD *et al.* Population pharmacokinetics of efavirenz in phase II studies and relationship with efficacy. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 1999 (Abstract 1201).
4. Marzolini C, Telenti A, Decosterd LA *et al.* Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001; **15**: 71–75.
5. Veldkamp AI, Weverling GJ, Lange JMA *et al.* High exposure to nevirapine in plasma is associated with an improved virological response in HIV-1-infected individuals. *AIDS* 2001; **15**: 1089–1095.
6. Hoetelmans RMW, Reijers MHE, Weverling GJ *et al.* The effect of plasma drug concentrations on HIV-1 clearance rate during quadruple therapy. *AIDS* 1998; **12**: F111–F115.
7. Powderly WG, Saag MS, Chapman S *et al.* Predictors of optimal virological response to potent antiretroviral therapy. *AIDS* 1999; **13**: 1873–1880.
8. Kerr B, Pithavala Y, Zhang M *et al.* Virologic response – plasma drug concentration relationship in Phase III study of nelfinavir mesylate (VIRACEPT). 12th World AIDS Conference, Geneva, 1998 (Abstract 12304).
9. Pellegrin JL, Breilh D, Garrugue I *et al.* Virological response to nelfinavir-containing regimens: analysis of individual pharmacokinetic (PK) parameters and drug resistance mutations. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, 2001 (Abstract 5.5).
10. Fletcher CV, Fenton T, Powell C *et al.* Pharmacologic characteristics of efavirenz and nelfinavir associated with virological response in HIV-infected children. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 2001 (Abstract 259).
11. Stein DS, Fish DG, Bilello JA *et al.* A 24-week open-label Phase I/II evaluation of the HIV protease inhibitor MK-639 (indinavir). *AIDS* 1996; **10**: 485–492.
12. Burger DM, Hoetelmans RMW, Hugen PWH *et al.* Low plasma concentrations of indinavir are related to virological treatment failure in HIV-1-infected patients on indinavir-containing triple therapy. *Antivir Ther* 1998; **3**: 215–220.
13. Fletcher CV, Brundage RC, Rimmel RP *et al.* Pharmacologic characteristics of indinavir, didanosine and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother* 2000; **44**: 1029–1034.
14. Murphy RL, Sommadossi JP, Lamson M *et al.* Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1. *J Infect Dis* 1999; **179**: 1116–1123.
15. Acosta EP, Henry K, Baken L *et al.* Indinavir concentrations and antiviral effect. *Pharmacotherapy* 1999; **19**: 708–712.
16. Dieleman JP, Gyssens IC, van der Ende ME *et al.* Urological complaints in relation to indinavir plasma concentrations in HIV-infected patients. *AIDS* 1999; **13**: 473–478.
17. Burger DM, Hugen PWH, Droste J, Huitema ADR for the ATHENA study group. Therapeutic drug monitoring (TDM) of nelfinavir (NFV) 1250 mg BID in treatment-naive patients improves therapeutic outcome after 1 year: results from ATHENA. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, 2001 (Abstract 6.2b).
18. Burger DM, Hugen PWH, Droste J, Huitema ADR for the ATHENA study group. Therapeutic drug monitoring (TDM) of indinavir (IDV) in treatment-naive patients improves therapeutic outcome after 1 year: results from ATHENA. 2nd International Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, 2001 (Abstract 6.2a).
19. Kempf D, Hsu A, Jiang P *et al.* Response to ritonavir (RTV) intensification in indinavir (IDV) recipients is highly correlated with virtual inhibitory quotient. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 2001 (Abstract 523).
20. www.bhiva.org/guidelines.htm

Website review

The website of the Canadian AIDS Treatment Information Exchange can be found at **www.thebody.com/catie/catiepage.html**

This is a national, non-profit organisation committed to improving the health and quality of life of Canadians living with HIV/AIDS. It does this by providing treatment information for patients and carers through its comprehensive website, two electronic mailing lists, publications and a toll-free phone service (available only in Canada). As you may expect, it is bilingual (English and French), and a highly readable site using plain but non-patronising language.

Apart from the free phone service, users can access a range of free print publications which are relevant to all communities of people with HIV/AIDS, as well as electronic mailing lists for news 'as it happens'. There is the usual electronic forum for discussion and debate.

The 'Ask the Experts' section allows you to access information about topics as diverse as hepatitis and oral health, and offers spiritual support from a rabbi.

I clicked on the section 'Women and HIV' and was given a selection of recently asked questions, which included HIV in the menopause and a query about Native American women. If these don't provide an answer, then you can ask an expert by leaving an email. The response is impressively swift.

The answers in the Women's Health Forum were organised by category. Accessing information on birth control, hormones and menstruation, women and side-effects and women and HIV treatment takes you to a variety of recent questions and answers around each topic.

This is a very attractive site and one which provides an excellent common-sense, readable service. Its glossy appearance is not surprising when the number of large pharmaceuticals and organisations supporting it is realised.

The number of web links to other organisations is huge and can take you from the AIDS Vaccine Advocacy Coalition to the United Synagogue of Conservative Judaism. I was disappointed, however, to find that the Pet Owners with HIV/AIDS Resource Service, which was the first and only complete pet care service in New York City for people living with HIV and AIDS, has suspended all operations, although its guidelines still exist.

For guidelines about humans affected by HIV/AIDS, go to **www.hivguidelines.org** This is the site of the New York State Department of Health AIDS Institute supported by Johns Hopkins University, so you know that it will be comprehensive, considered and up-to-date. A complete set of clinical guidelines takes an age to download, but it's worth it. Guidelines on adult, paediatric and adolescent HIV, perinatal HIV transmission and prevention guidelines and mental health guidelines will be joined by HIV and oral health guidelines later this year.

Interestingly, the guideline process is described through formulation, development, publication and dissemination, descriptions of committee meetings, consensus and external peer review.

You will need Adobe Acrobat™ to access the information, but it is 'state of the art'.

The section on clinical education contains a variety of HIV clinical information and includes sets of teaching slides and multimedia presentations.

A question and answer sheet on the subject of the window period for HIV infection is illuminating and well referenced.

I entered 'therapeutic drug monitoring' in the search facility but there was no result.

David Hicks FRCOG MFFP DipVen HIV/GUM Consultant Physician, Department of Genitourinary Medicine, Royal Hallamshire Hospital, Sheffield

The data, opinions and statements appearing in the articles herein are those of the contributor(s) concerned; they are not necessarily endorsed by the sponsor or publisher. Accordingly, the sponsor and publisher, and their respective employees, officers and agents, accept no liability for the consequences of any such inaccurate or misleading data, opinion or statement.

Published by Hayward Medical Communications, a division of Hayward Group plc, Rosemary House, Lanwades Park, Kentford, Newmarket CB8 7PW. Tel: 01638 751515. Fax: 01638 751517. email: admin@haywardmedical.co.uk

Design & Editorial Office Hayward Medical Communications, 8-10 Dryden Street, Covent Garden, London WC2E 9NA. Tel: 020 7240 4493. Fax: 020 7240 4479. email: edit@hayward.co.uk

Copyright © 2001 Hayward Group plc. All rights reserved.

Sponsored by an educational grant from



Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU