CONTENTS

For healthcare professionals only

This publication discusses experimental agents and the use of investigational dosing regimens for antiretroviral agents. Please consult the relevant prescribing information for each approved product. Prescribing information for approved Roche products is available at the Roche exhibition stand.
For information regarding drugs produced by other manufacturers please consult the prescribing information for these products or contact the relevant manufacturer.

Ceppie Merry

Dr Ceppie Merry is currently Consultant in Infectious Diseases at Trinity College, Dublin, Republic of Ireland, where she also holds a lectureship in pharmacology.

After graduating from Trinity College School of Medicine in 1991, Dr Merry undertook a PhD in the pharmacology of antiretroviral agents at the same institution, obtaining her doctorate in 1999. Additionally, she holds an MSc in HIV and Sexually Transmitted Diseases from the London School of Hygiene and Tropical Medicine, London, UK.

More recently, she was awarded a Clinical Infectious Diseases fellowship at the Northwestern Memorial Hospital, Chicago, US, where she worked until 2001.

In addition to her current role, Dr Merry acts as a Pharmacology Adviser to the International AIDS Society. She is also closely involved with the CARE trial, an ongoing study of antiretroviral therapy in resource-poor settings in Africa.

She has published numerous articles on the pharmacology of antiretroviral therapy, including such topics as drug-drug interactions, pharmacokinetics and therapeutic drug monitoring.

Anton Pozniak

Since 1998, Dr Anton Pozniak has held the post of Consultant Physician in the Directorate of HIV/Genitourinary Medicine at the Chelsea and Westminster Hospital, and Honorary Senior Lecturer at Imperial College, London, UK. He received his medical degree from Bristol University Medical School in 1979, and became involved in AIDS care in 1983. After spending two years at the University of Zimbabwe, he returned to London, where he became a senior lecturer and head of the HIV service at Kings College Hospital (1992 to 1998).

Dr Pozniak is a recognized authority on HIV and tuberculosis. He is also a member of the UK Adherence Strategy Group and the British HIV Association, and has been one of the co-ordinators of the UK guidelines on HIV treatment.

In addition, Dr Pozniak is Chair of the UK Providers of AIDS Care and Treatment Group, and sits on the UK government's Health Quality Board. He has been an investigator for many research studies in the field of HIV disease, and has presented at numerous national and international meetings. He is a member of the editorial board of both HIV Medicine *and* Sexually Transmitted Infections, *and has co-authored many original research reports, several reviews/book chapters on HIV, and numerous abstracts.*

INTRODUCTION

Welcome to Glasgow, to the *6th International Congress on Drug Therapy in HIV Infection,* and to Roche Pharmaceuticals' satellite symposium, 'Tailoring ART: Different People, Different Needs'. We hope you enjoy this opportunity to meet colleagues working in the field of HIV medicine, to share your knowledge and experiences with others, and to discuss new ideas that will improve the lives of people living with HIV or AIDS.

Now in its third decade, the global HIV/AIDS pandemic continues to evolve in ways that we could not have predicted when the disease was first recognized in the early 1980s. Highly active antiretroviral therapy (HAART) has dramatically improved the outlook for many people living with HIV infection; however, the emergence of new clinical dilemmas, changes in epidemiology and shifts in transmission patterns all mean that we must constantly monitor and update our prevention and treatment strategies.

To stay one step ahead of HIV, we must recognize that no two people with HIV infection are the same. Each individual has different treatment needs, based on factors such as their age, gender, lifestyle and personal circumstances – as well as the properties of the virus with which they are infected and the co-existence of other diseases or infections.

For these reasons, it is essential that we *tailor* antiretroviral therapy for each patient that we treat, rather than simply apply a 'one size fits all' approach to their management. A regimen that is perfect for one person might not be suitable for another. We are now in the fortunate position – at least when helping our patients choose their first- and second-line regimens – of having options that we did not have only a few years ago, options that continue to grow in number and widen the choices available to us. We are now beginning to realize that different patients have different treatment needs, and that we are in a position to select the option that best meets these needs.

This is the theme of our symposium today. Through a series of state-of-the-art presentations, we aim to highlight the need to tailor treatment for each person, and to examine in more detail how needs vary between different patient groups. Needless to say, there are always trade-offs – but, by considering fully each patient's lifestyle, personal circumstances and life goals, in addition to other factors such as their medical and treatment histories, gender, age, stage of disease and viral characteristics, we should be able to identify an optimal treatment regimen for each person.

The treatment of women with HIV infection and of patients who are co-infected with hepatitis C virus (HCV) presents particular challenges for physicians and other healthcare professionals. We are delighted to welcome Dr Sharon Walmsley to the symposium to discuss treatment issues relevant to each of these patient groups. The rising numbers of infections among women, and increasing recognition of the importance of liver disease as a cause of mortality in the HAART era, make these topics highly relevant to the management of HIV infection today.

Therapeutic approaches must be carefully considered by weighing risks versus benefits. The side effects of antiretroviral therapy are emerging as perhaps the most important reason for treatment failure or non-adherence among our patients – not, as we have tended to think, the number of pills that patients had to take or the need to take them twice a day. Additionally, fear of side effects is dissuading many patients from commencing therapy, even when it is clearly indicated. Adverse effects can therefore form an important barrier to effective therapy, and co-chair Dr Anton Pozniak will be discussing the role of both nelfinavir and of boosted saquinavir/low-dose ritonavir (saquinavir/r) in implementing effective regimens for HIV management that are tolerable for patients.

Boosted protease inhibitors have become a popular option in recent years for both treatment-naive and -experienced patients. However, until recently, we have had no data from well-designed clinical trials to help us decide between the available options. The MaxCmin trial series is set to change all that, and we are delighted that Dr David Cooper will be here to present the results of the MaxCmin1 study – the first ever head-to-head comparison of boosted protease inhibitors in patients with HIV infection.

As time goes on, more and more of our patients have already had three or more antiretroviral regimens, and tailoring effective therapy for them can be particularly challenging. Enfuvirtide (T-20) is the lead compound in a completely new class of antiretroviral agents with a novel mechanism of action – the fusion inhibitors. Enfuvirtide has already shown great promise in clinical trials that enrolled patients with limited treatment options. We are pleased to welcome Dr Manuel Battegay, who will be presenting the latest data from Phase III trials of this important developmental agent, and Ms Nicky Perry, who will be providing her insight and experience of enfuvirtide from a nursing perspective.

We trust that you will enjoy the presentations, and that you find the programme both informative and thought provoking.

Ceppie Merry
Anton Pozniak

A TAILORED FIT –
Viracept and the requirements of defined patient populations

Sharon Walmsley

Assistant Director, Immunodeficiency Clinic,
Toronto Hospital, University Health Network,
and Associate Professor of Medicine,
University of Toronto, Toronto, Ontario, Canada

Dr Sharon Walmsley is an Associate Professor in the Department of Medicine at the University of Toronto, and the Assistant Director of the Immunodeficiency Clinic at the Toronto Hospital, Ontario, Canada. She also heads the HIV clinical trials group in that institution. Dr Walmsley obtained her BSc in Microbiology and Immunology and her MD from the University of Western Ontario in London, Ontario. She has completed fellowships in Internal Medicine, Infectious Disease and Microbiology at the University of Toronto, and has also completed an MSc in Clinical Epidemiology.
Dr Walmsley has participated in numerous clinical trials in HIV medicine. She is the principal investigator of a Canadian Institute of Health Research–sponsored trial of structured treatment interruption in patients with virological failure. Additionally, she is participating in multiple studies evaluating risk factors for, and the incidence, prevalence and treatment of, lipodystrophy.
Dr Walmsley has a special interest in women and HIV, and is a co-investigator and member of the management committee of the Canadian Women's Study. Additionally, she was the co-chair for the Canadian Multidisciplinary Expert Panel that developed management guidelines for HIV-HCV co-infected patients.
Dr Walmsley is a member of many national and international AIDS committees. She is the Chair of the Protocol Development Team of the Canadian HIV Trials Network, and has served as a Secretary of the Canadian Association for HIV Research. She has received a five-year career scientist award from the Ontario HIV Treatment Network for further development of her expertise in HIV clinical management studies.

Introduction

Nelfinavir mesylate (Viracept) is an established therapy for the treatment of HIV infection that has shown potent and durable antiretroviral efficacy over at least 4 years of continuous treatment.[1] Additionally, nelfinavir preserves future treatment options, because virological failure on nelfinavir is not usually associated with cross-resistance to other protease inhibitors, and there is no evidence of any cross-resistance with non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Evidence is now accumulating that nelfinavir may be a particularly appropriate choice of antiretroviral therapy in specific groups of HIV-infected patients, such as women of child-bearing potential, and patients in whom liver function is a cause for concern. Recent trends suggest that physicians are increasingly likely to see these patients in their clinics, and need to be aware of their special treatment requirements in order to provide optimal, tailored care.

In previous years, many physicians attempted a 'one size fits all' approach to the treatment of HIV infection, using the same antiretroviral regimens for different patients without always taking into account whether important factors such as the patient's gender, personal circumstances, life goals, lifestyle or co-morbidities might impact on response rates or toxicity. Treatment decisions, both at the individual and policy-making levels, may have been based on extrapolations from the results of clinical trials performed in patient populations that differed significantly from the individual or population to whom the decision applied.

For example, recent epidemiological and surveillance data indicate that, worldwide, half of all HIV-infected adults aged 15 to 49 years are women (Figure 1).[2] In developed countries, this figure ranges between 20 and 40%.[2] Data from the Centers for Disease Control and Prevention (CDC) in the US indicate that the proportion of new domestic AIDS cases that are in women has increased almost every year since the mid-1980s, from <10% in 1986 to >25% in 2000.[3] Despite this, historically, women have not always been fully represented in major clinical trials of new antiretroviral therapies. In their systematic review, Bartlett and colleagues[4] found that the proportion of participants in major HIV clinical trials who were women was frequently <15%. Thus, there would appear to be a need for more data on the effects of antiretroviral therapy in women. Women represent a relatively large group of HIV-infected patients in whom, as discussed below, treatment needs may differ – and it remains unclear whether or not they are more susceptible to the adverse effects of antiretroviral drugs compared with men.[5]

Another issue that is rarely addressed in clinical trials is co-infection with hepatitis C virus (HCV). Epidemiological studies suggest that, depending on geographical location, between 30 and 50% of patients with HIV infection are also co-infected with HCV. This proportion may be as high as 80–90% among patients infected with HIV through intravenous drug use or receipt of contaminated blood products.[6] Co-infection with HCV may have a significant impact on the overall management of HIV infection, including the choice of antiretroviral agents, because of the need to prevent hepatic injury. However, few clinical trials have reported data on treatment outcomes – particularly with respect to safety – separately in patients with HIV-HCV co-infection. Furthermore, patients with co-infection or increased liver transaminases are specifically excluded from clinical trials. Consequently, it is not clear whether the results of many clinical trials are generalizable to patients who are co-infected with HCV – a significant problem, given the high prevalence of co-infection in many countries and populations.

Liver disease is becoming an important cause of morbidity and mortality in people with HIV infection receiving highly active antiretroviral therapy (HAART).[7] The high prevalence of HIV-HCV co-infection is, however, only one contributing factor. Other forms of viral hepatitis, alcohol and recreational drug use, and a history of drug-related hepatotoxicity (for example, due to antitubercular agents) may all place patients at risk of future hepatic injury. These patients, too, have special treatment needs that must be taken into account when choosing an effective – and safe – antiretroviral regimen.

Nelfinavir is an effective option for management of HIV infection

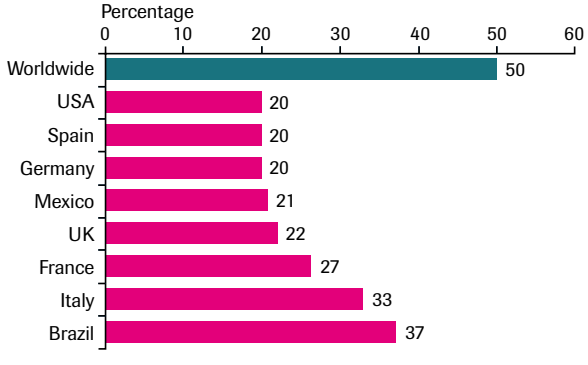
Nelfinavir is well established as a potent, durable option for patients with HIV infection who require antiretroviral therapy.[1,8–10] In addition, nelfinavir has a favourable tolerability and safety profile that is characterized by low rates of toxicity-related treatment discontinuations and a lack of major organ toxicities.[8]

In recent years, evidence has begun to emerge suggesting that, because of its favourable tolerability and safety profiles, nelfinavir may have additional utility in large sub-populations of patients with HIV infection. These include:

- women with HIV infection, including pregnant women and those of child-bearing potential
- patients with HIV-HCV co-infection and others in whom liver disease is of concern.

Figure 1

Proportion of the adult HIV/AIDS population accounted for by women, both globally and by country.[2]



Treatment of HIV infection may need to be different in women

Antiretroviral therapy may differ in women as compared with men for several reasons. Physiological and anatomical differences may give rise to divergent pharmacokinetics and pharmacodynamics; additionally, caregiving responsibilities and multiplicity of roles may act as barriers to adherence with therapy. There is some evidence to suggest that antiretroviral therapy is more likely to cause certain adverse effects in women than in men;[5] for example, severe nevirapine-associated rash has been shown to be several times more common in women.[11]

Furthermore, as persons with HIV are living longer and the effectiveness of HAART in preventing mother-to-child transmission (MTCT) is improving, increasing numbers of HIV-infected women are deciding to have children. This development, and the fact that many pregnancies are unplanned,[12] suggests that antiretroviral therapy in women of child-bearing potential must be chosen to be both effective and to have a high margin of safety in the event of pregnancy, whether accidental or intentional.

Nelfinavir is an appropriate choice for management of HIV infection in women…

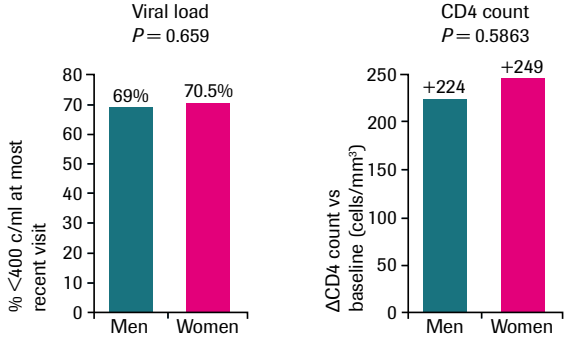
A growing body of evidence suggests that nelfinavir is as effective and well tolerated in women with HIV infection as it is in men. A recent study has suggested that the pharmacokinetics of nelfinavir do not differ significantly between HIV-infected men and women,[13] and several studies have provided evidence that nelfinavir reliably suppresses HIV replication irrespective of gender.[14–17]

In the Women First study,[14] 68 HAART-naive women received nelfinavir (750 mg *tid* or 1250 mg *bid*) as part of a four-drug antiretroviral regimen that also included saquinavir. After 48 weeks' treatment, >80% of women who remained on therapy had viral loads <400 copies/ml, and the authors concluded that nelfinavir durably suppressed viral replication in HIV-infected women. Nelfinavir was reported to be well tolerated in these patients, and rates of diarrhoea were lower than in previous trials that primarily enrolled men.

In addition, in their retrospective cohort analysis of patients (n = 1309) receiving nelfinavir plus two nucleoside analogues as first-ever HAART, Palella and co-workers found that women receiving this combination were as likely as men to have an undetectable viral load (<400 copies/ml) after at least 2 years of therapy, irrespective of baseline HIV RNA level.[17] Moreover, immunological responses were similar between the genders (Figure 2).

Figure 2

Virological and immunological responses to nelfinavir-based HAART in a cohort of men (n = 1001) and women (n = 308).[17]



Mean duration of treatment = 41 months.

…including pregnant women and those of child-bearing potential

As mentioned previously, more women with HIV infection are becoming pregnant. Current guidelines for the management of HIV infection indicate that pregnancy, in and of itself, is not a barrier to the use of HAART, and that pregnant women with a clinical indication for antiretroviral therapy should receive appropriate combination treatment.[18]

Recently, Morris and co-workers reported maternal and foetal outcomes in a series of 233 women who received protease inhibitors during pregnancy.[19] The vast majority of these women (n = 215; 92%) received nelfinavir. In this series:

- 56% of the women had HIV RNA <400 copies/ml at the last available visit (*vs* 20% at baseline)
- prematurity and low birth weight were not associated with the specific protease inhibitor used
- the rate of vertical transmission was <1%.

Smith *et al.* reported on the use of nelfinavir in 40 pregnant women with HIV infection.[20] All of the 36 infants for whom data were available were HIV-negative at birth; one subsequently seroconverted at 4 months.

In pregnancy, the potential impact of antiretroviral therapy on the developing foetus is a key consideration. A recent case report of teratogenicity, considered by the authors to be attributable to the first-trimester use of efavirenz,[21] has brought home to many clinicians just how important it is to consider the safety of anti-

retroviral therapy in pregnancy. These considerations should, moreover, apply to all women of child-bearing potential, since many pregnancies are unplanned.[12]

Unfortunately, as in many areas of medicine, data are lacking on the safety of drug treatment in pregnant women with HIV infection. The Antiretroviral Pregnancy Registry (www.apregistry.com) maintains a central database of pregnancy outcomes in women receiving antiretroviral therapy, and physicians are strongly encouraged to enrol their pregnant patients with the Registry as early as possible.

The latest Registry report details pregnancy outcomes data on 2416 live births that occurred between 1989 and 2001.[22] To date, nelfinavir is the only antiretroviral agent, other than the nucleoside analogues stavudine, lamivudine and zidovudine, for which sufficient data on first-trimester exposure exist to enable an assessment of teratogenic risk. No increased risk has been seen with nelfinavir: eight birth defects have been reported among 256 live births in women who received nelfinavir during the first trimester, representing a rate of 3.1 defects per 100 live births. This rate is exactly the same as that calculated by the CDC for the general population between 1991 and 1995.[22]

Additionally, in a recent analysis of seven clinical studies that included 2123 pregnant women,[23] Tuomala and co-workers found that the use of protease inhibitors during pregnancy was not associated with an increased risk of premature delivery or of low birth weight (<2500 g).

Unlike nevirapine, nelfinavir (and other protease inhibitors) does not cross the placenta to any appreciable extent, and does not achieve significant concentrations in cord blood.[24]

In summary, nelfinavir may represent an appropriate choice, as part of combination therapy, for the treatment of HIV infection in pregnant women. It appears to be both effective in maintaining viral suppression in the mother and in preventing MTCT, and, on the basis of currently available data, its use in the first trimester does not appear to be associated with an increased risk of birth defects. The current FDA classification of antiretroviral agents is shown in Table 1.

Although more data are required before specific recommendations for women are made, it appears that nelfinavir may be a suitable option for first-line treatment in this patient group, including patients who are pregnant or are of child-bearing potential.

Nelfinavir may be an appropriate choice for management of HIV infection in patients at risk of liver disease

Another 'defined patient population' in whom nelfinavir may have advantages over some other antiretroviral agents is in patients who are at increased risk of hepatotoxicity. As mentioned above, liver disease is becoming a major cause of mortality among HAART-treated patients with HIV infection.[7] At-risk patients include those with:

Current FDA classification of antiretroviral agents.[25]

Table 1

FDA category	Definition of classification[25]	Antiretrovirals[26–28]
B	Either (1) animal reproduction studies have not demonstrated a foetal risk, but there are no controlled studies in pregnant women; or (2) animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester, and there is no evidence of a risk in later trimesters.	Didanosine **Nelfinavir** Ritonavir Saquinavir Tenofovir
C	Either (1) studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal effects), and there are no controlled studies in women; or (2) studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.	Abacavir Amprenavir Efavirenz Indinavir Lamivudine Lopinavir/ritonavir Nevirapine Stavudine Zalcitabine Zidovudine

– HIV-HCV co-infection
– other forms of hepatitis
– alcoholism or alcohol misuse
– a past history of drug-induced hepatotoxicity, e.g. paracetamol (acetaminophen) overdosage, antitubercular therapy, and certain halogenated inhalational anaesthetics.

HCV co-infection is prevalent among patients with HIV infection, particularly among those who acquired HIV through intravenous drug use or the receipt of contaminated blood products.[6]

The clinical course and severity of HCV disease appear to be accelerated and worsened in the presence of HIV.[29] Moreover, co-infection with HCV appears to increase the risk of hepatotoxicity with at least some antiretrovirals, including efavirenz and nevirapine.[30] Indeed, some authors have called upon physicians to consider avoiding NNRTIs in patients with HIV-HCV co-infection.[31]

There are important differences between antiretroviral agents in their relative propensities to cause elevated levels of liver transaminases. Imperiale and co-workers recently presented data from the TARGET cohort (n = 2198),[32] in which risks of hepatotoxicity (ALT or AST >5 times the upper limit of normal) were assessed for a panel of widely used antiretroviral agents. As shown in Figure 3, nelfinavir was associated with the lowest risk of raised transaminases among the agents studied.

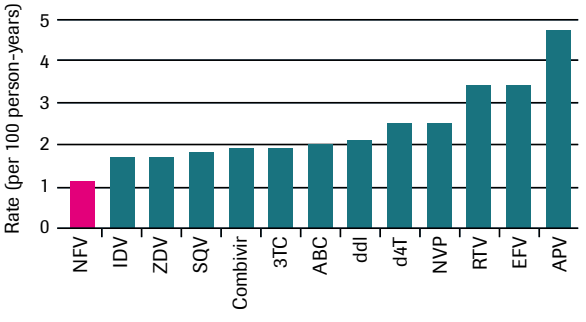
In another study, Dieterich and colleagues assessed the efficacy and safety of protease inhibitors in 1052 patients with HIV-HCV co-infection.[33] Four hundred and twenty-eight of the patients received nelfinavir. These authors found that nelfinavir was numerically less likely than other protease inhibitors to be associated with grade 3 or 4 elevations in AST and ALT over at least a 3-month period (Figure 4). They concluded that, among the protease inhibitors, nelfinavir may warrant further consideration for use in patients with HIV-HCV co-infection.

As noted above, full-dose ritonavir has been associated with relatively high rates of severe transaminase elevations. One hundred and seven patients in the study by Dieterich *et al.*[33] were receiving dual protease inhibitor therapy, and some may have been receiving higher dosages of ritonavir (e.g. 400 mg *bid*) than are now generally recommended. This may have contributed to the higher rates of transaminase elevation observed among patients receiving protease inhibitors other than nelfinavir.

In summary, there is increasing recognition that patients with HIV-HCV co-infection may have different treatment needs compared with non-HCV-infected

Figure 3

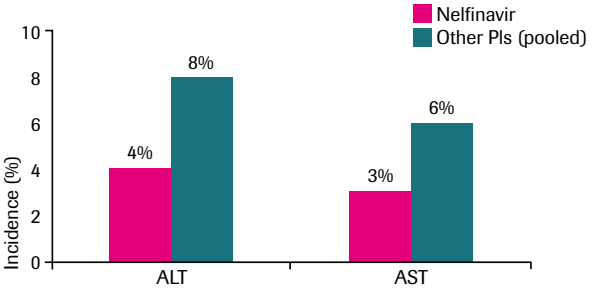
Nelfinavir (NFV) may be associated with a lower risk of severe increases in ALT or AST (>5 times upper limit of normal) compared with other antiretroviral agents.[32]



3TC = lamivudine; ABC = abacavir; APV = amprenavir; ddI = didanosine; d4T = stavudine; EFV = efavirenz; IDV = indinavir; NVP = nevirapine; RTV = ritonavir; SQV = saquinavir; ZDV = zidovudine.

Figure 4

Severe (grade 3 or 4) elevations in ALT or AST (versus other protease inhibitors [PIs]) among HIV-HCV co-infected patients (n = 1052) taking PI-based HAART.[33]



Mean time on PIs = 39.5 months.

patients, and that therapy should be individualized according to these needs. Nelfinavir appears to be associated with a very low risk of increases in liver transaminases, and may therefore be a suitable choice of treatment for these patients and, indeed, any patient in whom liver function is cause for concern. NNRTIs, in contrast, have been more frequently associated with severe hepatotoxicity, the risk of which appears to be increased in the presence of HCV infection.[30]

Summary

The HIV/AIDS population consists of numerous sub-populations, some of which may have distinct characteristics that influence treatment needs. Caution is necessary when applying the results of clinical trials to an individual or a group of individuals, particularly where there are significant differences between the clinical trial population and the individual or group being treated in clinical practice.

Women with HIV and patients at risk of liver injury – including those with HIV-HCV co-infection – are two of the largest of these 'defined patient populations'. Treatment needs differ in these populations, for physiological and pathophysiological reasons, and more research is needed to clarify which treatment strategies are optimal for these patients.

Emerging data suggest that, in addition to its proven track record in HIV infection generally, nelfinavir is an effective and well-tolerated option that has a high margin of safety in both women with HIV infection and patients with HIV-HCV co-infection.

References

1. Gathe J, Chu A, Yuen N, *et al.* Durability of nelfinavir combination therapy after 4 years: 3-year extension data from Agouron Study 511. *8th European Conference on Clinical Aspects and Treatment of HIV Infection.* Athens, Greece, 2001; poster LB/P10.
2. Report on the global AIDS epidemic 2002. Geneva: UNAIDS, 2002. Available at: www.unaids.org [Accessed 5 September 2002].
3. HIV/AIDS surveillance in women. L264 slide series (through 2000). Atlanta: Centers for Disease Control and Prevention, 2002. Available at: http://www.cdc.gov/hiv/graphics/women.htm [Accessed 5 September 2002].
4. Bartlett JA, DeMasi R, Quinn J, *et al.* Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS* 2001; **15:**1369–1377.
5. Zorrilla CD. Antiretroviral combination therapy in HIV-1 infected women and men: are their responses different? *Int J Fertil* 2000; **45:**195–199.
6. Spengler U, Rockstroh JK. Hepatitis C in the patient with human immunodeficiency virus infection. *J Hepatol* 1998; **29:**1023–1030.
7. Bica I, McGovern B, Dhar R, *et al.* Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001; **32:**492–497.
8. Saag MS, Tebas P, Sension M, *et al.* Randomized, double-blind comparison of two nelfinavir doses plus nucleosides in HIV-infected patients (Agouron study 511). *AIDS* 2001; **15:**1971–1978.
9. Burger DM, Hugen PWH, Droste J, *et al.* Therapeutic drug monitoring (TDM) of nelfinavir (NFV) 1250mg bid in treatment-naive patients improves therapeutic outcome after 1 year: results from ATHENA. *2nd International Workshop on the Clinical Pharmacology of HIV Therapy.* Noordwijk, The Netherlands, 2001; abstract 6.2b and oral presentation.
10. Negredo E, Martinez-Picado J, Ruiz L, *et al.* SWATCH study: a multicenter trial of proactive treatment switching. Results at 48 weeks of follow-up. *41st Interscience Conference on Antimicrobial Agents and Chemotherapy.* Chicago, USA, 2001; abstract I-672 and oral presentation.
11. Bersoff-Matcha SJ, Miller WC, Aberg JA, *et al.* Sex differences in nevirapine rash. *Clin Infect Dis* 2001; **32:**124–129.
12. Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect* 1998; **30:**24–29,46.
13. Sharma R, Bellantone B, Singh D, *et al.* A comparison of the pharmacokinetics of nelfinavir in African-American women versus men with HIV infection. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster WePeB5970.
14. Squires K, Currier J, Clark R, *et al.* Final 48-week results of a Phase II, randomized study of the safety, efficacy, and pharmacokinetics of BID vs TID nelfinavir and saquinavir in combination with lamivudine and stavudine in HIV-positive women (Women First Trial). *8th Conference on Retroviruses and Opportunistic Infections.* Chicago, USA, 2001; abstract 330.
15. Greiger-Zanlungo P, Alpert P, Smith C, *et al.* Prolonged successful therapy with nelfinavir in inner-city women. *XIV International AIDS Conference.* Barcelona, Spain, 2002; abstract B10506.
16. Keiser P, Nassar N, Koen G, *et al.* Comparison of virologic response in a cohort of women and men treated with nelfinavir containing HAART regimens. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster WePeB5962.
17. Palella F, Gathe J, Brutus A, *et al.* Gender comparisons in long term responses among patients receiving nelfinavir (NFV) and dual NRTIs as first ever HAART. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster WePeB5967.
18. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. 30 August 2002. Available at: www.hivatis.org [Accessed 5 September 2002].
19. Morris AB, Rua Dobles A, Zorrilla C, *et al.* An update of protease inhibitor (PI) use in 233 pregnancies. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster WePeB5917.
20. Smith MU, Katner AD, Buchanan AD, *et al.* Prevention of vertical transmission of HIV-1 with nelfinavir (NLF) based highly active antiretroviral therapy (HAART). *XIV International AIDS Conference.* Barcelona, Spain, 2002; abstract MoPeD3684.
21. Fundaro C, Genovese O, Rendeli C, *et al.* Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* 2002; **16:**299–300.
22. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989 through 31 January 2002. Wilmington, NC: Registry Coordinating Center, 2002.
23. Tuomala RE, Shapiro DE, Mofenson LM, *et al.* Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med* 2002; **346:**1863–1870.
24. Marzolini C, Rudin C, Decosterd LA, *et al.* Transplacental passage of protease inhibitors at delivery. *AIDS* 2002; **16:**889–893.
25. Millstein LG. FDA's 'pregnancy categories'. *N Engl J Med* 1980; **303:**706.
26. Newell M-L, Rogers M. Pregnancy and HIV infection: a European consensus on management. *AIDS* 2002; **16** (Suppl. 2):S1–S18.
27. Prescribing information for Viread. Available at: www.viread.com [Accessed 24 September 2002].
28. Prescribing information for Kaletra. Available at: www.kaletra.com [Accessed 24 September 2002].
29. Soto B, Sanchez-Quijano A, Rodrijo L, *et al.* Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997; **26:**1–5.
30. Sulkowski MS, Thomas DL, Mehta SH, *et al.* Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002; **35:**182–189.
31. Bartlett JG. The 2002 abbreviated guide to medical management of HIV infection. Baltimore, MD: Johns-Hopkins University School of Medicine, 2002. Available at: http://www.hopkins-aids.org/publications/abbrevgd/abbrevgd.pdf [Accessed 6 September 2002].
32. Imperiale SM, Lanes SF, Stern JO, *et al.* TARGET: incidence of elevated ALT/AST with HAART in a large observational cohort. *4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.* San Diego, USA, 2002; poster 89.
33. Dieterich DT, Fischl M, Sepulveda G. The safety/efficacy of protease inhibitors (PIs) in hepatitis C (HCV) co-infected patients. *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Diego, USA, 2002; abstract H–1729.

NOTES

MEASURING UP –
Clinical performance of boosted saquinavir in diverse treatment groups

David Cooper

Director and Professor of Medicine, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia

David Cooper, Professor of Medicine at the University of New South Wales, is Director of the National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia. The National Centre conducts research into the HIV/AIDS epidemic in Australia, with the ultimate aim of reducing the burden of the HIV/AIDS in that country.

The major responsibilities of the National Centre are the epidemiology and surveillance of HIV/AIDS in Australia, including research aspects, and the co-ordination and conduct of clinical trials of innovative therapies and vaccines for HIV disease. The National Centre has an active clinical research program, with particular emphasis on primary HIV infection. Professor Cooper is also Head of the Immunology/HIV/Infectious Diseases Clinical Service Unit at St Vincent's Hospital, Sydney, one of the largest inpatient and outpatient facilities for the treatment of HIV disease in Australia. He also directs the New South Wales State Reference Laboratory for AIDS within the Centre for Immunology at St Vincent's Hospital. Professor Cooper is recognized internationally as a leading HIV clinician and clinical investigator. He is a member of the UNAIDS Management Committee for the PETRA study of interruption of perinatal transmission by antiretroviral therapy in Africa. He is also a Director of HIVNAT, a clinical research and trials collaboration based at the Thai Red Cross AIDS Research Centre at the Chulalongkorn University Hospital in Bangkok, Thailand. He is a former president of the International AIDS Society and serves on the editorial boards of several international journals, including Journal of Acquired Immune Deficiency Syndromes, AIDS *and* Sexually Transmitted Diseases.

Introduction

Boosted protease inhibitors (PIs) are now an established mode of treatment for patients with HIV or AIDS. Boosting with minidose ritonavir (100 mg *bid*; 'r') results in high and sustained plasma concentrations of co-administered PIs, with significant improvements in efficacy. Three boosted PIs have now been licensed for use in Europe — saquinavir/r 1000/100 mg *bid* (both as Invirase/r and Fortovase/r), lopinavir/r 400/100 mg *bid* and amprenavir/r 600/100 mg *bid* or 1200/200 mg *qd*. However, while boosting PIs has the potential to improve performance, there is some doubt as to whether all boosted PIs will be the same in terms of efficacy or their propensity to cause adverse effects. As many HIV patients are now living longer due to highly active antiretroviral therapy (HAART), it is even more important to consider both the short- and long-term safety of treatment.

Selecting the most appropriate antiretroviral therapy can be compared to choosing a special new outfit. Not only do we consider whether it is the correct size and that the style and colour suits us, we also want to ensure that the outfit is 'timeless' and will still be in vogue in a few years' time. Similarly, when selecting a boosted PI, we need to ensure that, in addition to being effective, it also has a good safety and tolerability profile to minimize the risk of toxicity in the long term. So how do different boosted PIs measure up against each other in terms of efficacy and long-term safety?

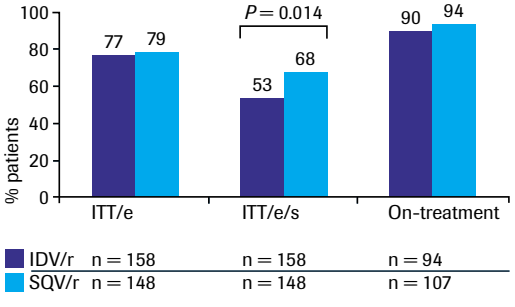
The MaxCmin1 study — comparing the safety and efficacy of indinavir/r 800/100 mg *bid* and saquinavir/r 1000/100 mg *bid* — is the first-ever randomized, head-to-head comparison of boosted PIs. The study has shown that, while indinavir/r and saquinavir/r are both highly potent PIs, the superior tolerability of saquinavir/r over indinavir/r means that fewer patients need to discontinue or switch treatment, allowing more patients on saquinavir/r to maintain viral load suppression out to 48 weeks.

MaxCmin1 has been followed by the ongoing MaxCmin2 study, in which the efficacy and safety of lopinavir/r 400/100 mg *bid* and saquinavir/r 1000/100 mg *bid* are being compared. The preliminary 24-week results of MaxCmin2 are scheduled to be presented during this conference.

While most people can fit into standard-sized clothing, there are a few individuals who, despite trying many different outfits, may not be able to find one that fits. These people require their outfit to be 'made to measure'. Similarly, with antiretroviral therapy, some patients are extremely limited in their treatment options because of resistance or toxicity. In such cases, it is particularly important to tailor treatment to the patient. A few studies have investigated the use of the double-boosted PI regimen saquinavir/lopinavir/r 1000/400/100 mg *bid*, both with and without nucleoside reverse transcriptase inhibitors (NRTIs), in highly treatment-experienced patients, and have shown promising results.

Figure 1

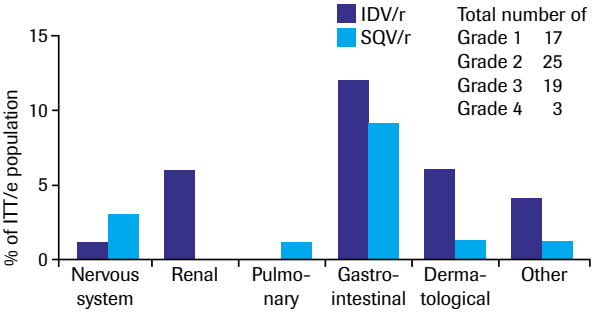
MaxCmin1 study: percentage of patients with HIV RNA <400 copies/ml at 48 weeks.[1]



ITT/e = intent-to-treat, exposed, switch included; ITT/e/s = intent-to-treat, exposed, switch = failure.

Figure 2

MaxCmin1 study: clinical non-fatal adverse events leading to permanent discontinuation of randomized treatment.[1]



P-value for the difference among those who permanently switched from randomized treatment: 0.02 (Fisher's exact)

Not all PIs demonstrate the same adverse event profile

HAART has substantially improved the health and longevity of patients with HIV infection. This means that patients are living longer, making the long-term safety and tolerability of antiretroviral therapy even more important. The adverse events of PIs have been well described, but it is important to note that not all PIs have the same adverse event profile, or the same impact on laboratory parameters such as lipid levels. This has been demonstrated recently in the first-ever randomized, head-to-head comparison of boosted PIs – MaxCmin1.[1]

MaxCmin1: the first head-to-head comparison of boosted PIs

MaxCmin1 compared indinavir/r 800/100 mg *bid* with saquinavir/r 1000/100 mg *bid*, in combination with dual NRTI therapy, in HIV-infected patients.[1] The study included a heterogeneous group of 306 patients, of whom 25% were antiretroviral-naive, 60% were PI-experienced and 30% were in CDC category C (AIDS) at baseline.

After 48 weeks, both treatments produced an improvement in the CD4 count and showed similarly high potency, with 90% of indinavir/r patients and 94% of saquinavir/r patients still on therapy having HIV RNA levels <400 copies/ml (Figure 1). However, analysis of the intent-to-treat/exposed/switch = failure (ITT/e/s) population, in which a switch from the randomized treatment was considered a failure, highlighted quite different results. This analysis demonstrated that significantly more patients on saquinavir/r (68%) than indinavir/r had viral loads <400 copies/ml ($P = 0.014$; Figure 1). This disparity between the treatment arms was primarily due to the larger number of switches (or discontinuations) due to adverse events within the indinavir/r arm of the study.

This was confirmed by analysis of the tolerability of the two boosted PIs, This indicated that indinavir/r was less well tolerated than saquinavir/r, primarily because of its renal and dermatological adverse effects. Patients taking indinavir/r experienced significantly more grade 3 or 4 adverse events than patients taking saquinavir/r (104 *vs* 60; $P = 0.04$), which led to significantly more treatment switches (28% *vs* 15%; $P = 0.006$; Figure 2).

Elevated lipid levels are associated with increased rates of cardiovascular disease and pancreatitis, and are one long-term safety parameter that can be assessed in current studies. The use of antiretrovirals that do not significantly increase lipid levels is therefore desirable. PIs appear to have a varying propensity to affect lipid metabolism, and, therefore, fasting lipid levels were monitored in MaxCmin1.

Within the first 4 weeks of the MaxCmin1 study, saquinavir/r was associated with a significantly lower percentage increase from baseline in total cholesterol (8% *vs* 17%; $P < 0.01$), low-density lipoprotein (LDL)-cholesterol (6% *vs* 21%; $P < 0.01$) and triglycerides (12.5% *vs* 28.5%; $P < 0.05$) than indinavir/r. At 48 weeks, the percentage change in lipid levels remained similar to that seen at 4 weeks. The investigators from the MaxCmin1 study concluded that: *'saquinavir/r has a more favourable toxicity profile and comparable antiviral effects to indinavir/r in the doses studied. More patients in the saquinavir/r arm remained virologically suppressed on the study drug at week 48 – probably because of a better toxicity profile.'*

MaxCmin2: the second head-to-head comparison of boosted PIs

The MaxCmin2 trial was initiated in January 2002 to compare the efficacy, safety and tolerability of saquinavir/r 1000/100 mg *bid* and lopinavir/r 400/100 mg *bid*. The eagerly awaited preliminary 24-week results are scheduled to be presented at this congress.

Double PI boosting

Patients who have received extensive antiretroviral therapy and who have a high viral load may benefit from double PI boosting, in which minidose ritonavir is used to boost two other PIs simultaneously. A number of small studies have investigated the use of the double PI boosting regimen saquinavir/lopinavir/r 1000/400/100 mg *bid* with NRTIs. These studies have shown promising results in highly treatment-experienced patients with treatment failure on their current regimens. For example, one study[2] reported a decrease in viral load of 0.8 $\log_{10}$ copies/ml at 4 weeks in approximately 60% of patients, while three studies[3–5] demonstrated that 36–42% of patients maintained viral suppression after 24–48 weeks' treatment (Table 1).

Double PI boosting – without NRTIs

The adverse effect profile of NRTIs is well described. Mitochondrial toxicity is commonly associated with NRTI treatment, and interference with the metabolism of these organelles can lead to lactic acidosis. Similarly, changes affecting the adipose tissue may promote body composition changes. Peripheral neuropathy is another commonly experienced event with some NRTIs.

In some patients, the use of NRTIs may be precluded by previous experience of significant adverse effects. In still others, accumulating drug resistance may mean that treatment-experienced patients have HIV that is no longer susceptible to any currently available NRTI.

Staszewski *et al.*[6] therefore evaluated the efficacy of an NRTI-sparing, double boosted PI regimen. In this ongoing study, 42 patients with limited NRTI options due to resistance or toxicity were treated with saquinavir/lopinavir/r 1000/400/100 mg *bid* alone. The results, to date, are promising, showing an almost two-fold elevation in CD4 count and a reduction of 3.5 $\log_{10}$ copies/ml, maintained out to 24 weeks (Figure 3). These preliminary data indicate that PI double boosting may represent a potential NRTI-sparing strategy, and suggest that further study may be warranted.

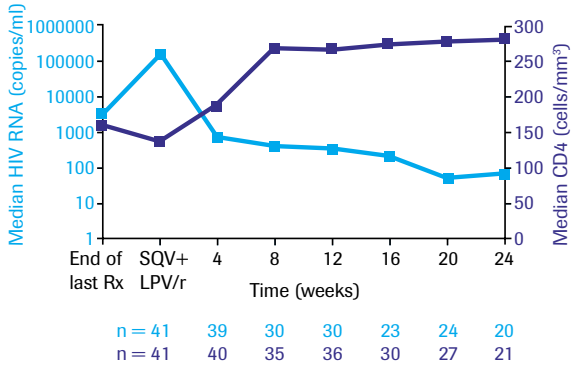
Table 1

Trials of saquinavir/lopinavir/r 1000/400/100 mg *bid* + NRTIs.

Study author	n	Efficacy
Smith *et al.*[2]	36	61% > –0.8 log at week 4
Ruiz *et al.*[3]	24	36% < 80 copies/ml at 24 weeks
Hellinger *et al.*[4]	28	42% < 50 copies/ml at 24 weeks
Zala *et al.*[5]	23	40% < 500 copies/ml at 48 weeks

Figure 3

Treatment of patients with limited nucleoside analogue options using saquinavir/lopinavir/r 1000/400/100 mg *bid*.[6]



Summary and conclusion

Improvements in the overall treatment of patients with HIV and AIDS have highlighted the need for drugs with better long-term safety and tolerability profiles. While boosted PIs provide an effective treatment for HIV infection, they are not all equally well tolerated. The MaxCmin1 study showed clearly that good tolerability is key to effective treatment, and that, regardless of its efficacy, patients will discontinue a boosted PI if it causes excessive toxicity.

Saquinavir/r 1000/100 mg *bid* was clearly a 'good fit' for many patients in MaxCmin1. While saquinavir/r and indinavir/r were both highly potent, head-to-head comparison showed that saquinavir/r was better tolerated at the dosages studied. Fewer patients on saquinavir/r switched or discontinued treatment, allowing more patients to remain on therapy and to achieve and maintain undetectable viral loads.

Tailoring treatment to the patient is important in those with limited options due to resistance or toxicity. In such cases, double PI boosting with saquinavir/lopinavir/r 1000/400/100 mg *bid* appears to be an effective option.

Additional head-to-head comparisons of boosted PIs will further clarify the differences between PIs in terms of their tolerability and safety profiles. The results of the most recent head-to-head study, MaxCmin2, are awaited with interest.

References

1. Cahn P, Dragsted UB, Pedersen C, *et al.* Safety and efficacy evaluation of a phase IV randomised, open-label, multicentre trial of indinavir/ritonavir (800/100 mg bid) vs. saquinavir/ritonavir (1000/100 mg bid) in adult HIV-1 infection: the MaxCmin1 trial. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster WeOrB1265.
2. Smith GHR, Klein MB, Murphy T, *et al.* Double, boosted salvage therapy with lopinavir/ritonavir and saquinavir-sgc in HIV-1 infected patients having failed 3 classes of antiretrovirals. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster TuPeB4547.
3. Ruiz L, Ribera E, Bonjoch A, *et al.* Virological and immunological benefit of a salvage therapy that includes Kaletra plus Fortovase preceded or not by antiretroviral therapy interruption (TI) in advanced HIV-infected patients (6-month-follow-up). *9th Conference on Retroviruses and Opportunistic Infections.* Seattle, USA, 2002; poster 421–W.
4. Hellinger J, Morris AB, Piscitelli S, *et al.* Pilot study of saquinavir-SGC (Fortovase, SQV) 1000 mg twice daily and lopinavir/ritonavir (Kaletra, LPV/r) in protease inhibitor-experienced HIV+ individuals: dose escalation and combined normalized inhibitory quotient (cNIQ). *9th Conference on Retroviruses and Opportunistic Infections.* Seattle, USA, 2002; poster 451–W.
5. Zala C, Patterson P, Coll P, *et al.* Early antiviral response and safety of a dual boosted protease inhibitor regimen including lopinavir/r (LPV) plus amprenavir (AMP) or Fortovase (FTV) in heavily pre-treated HIV infected patients. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster TuPeB4492.
6. Staszewski S, Dauer B, Stephan C, *et al.* A new strategy: boosted double protease inhibitor (PI) regimen lopinavir/r plus saquinavir (LPVr/SQV) without reverse transcriptase inhibitors (RTI). *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Diego, USA, 2002; poster V9.

NOTES

WILL IT SUIT ME?

The importance of safety and patient acceptance to long-term success

Anton Pozniak

Consultant Physician, Chelsea and Westminster Hospital, London, UK

Since 1998, Dr Anton Pozniak has held the post of Consultant Physician in the Directorate of HIV/Genitourinary Medicine at the Chelsea and Westminster Hospital, and Honorary Senior Lecturer at Imperial College, London, UK. He received his medical degree from Bristol University Medical School in 1979, and became involved in AIDS care in 1983. After spending two years at the University of Zimbabwe, he returned to London, where he became a senior lecturer and head of the HIV service at Kings College Hospital (1992 to 1998).

Dr Pozniak is a recognized authority on HIV and tuberculosis. He is also a member of the UK Adherence Strategy Group and the British HIV Association, and has been one of the co-ordinators of the UK guidelines on HIV treatment.

In addition, Dr Pozniak is Chair of the UK Providers of AIDS Care and Treatment Group, and sits on the UK government's Health Quality Board. He has been an investigator for many research studies in the field of HIV disease, and has presented at numerous national and international meetings. He is a member of the editorial board of both HIV Medicine *and* Sexually Transmitted Infections, *and has co-authored many original research reports, several reviews/book chapters on HIV, and numerous abstracts.*

Introduction

Only 10 years ago, patients with HIV infection and their physicians had little choice when it came to selecting antiretroviral therapy — only three agents were available, and they all belonged to the same drug class. Since then, the number of antiretroviral compounds available has increased rapidly, so that we now have around 16 individual agents in three different drug classes that we can combine in numerous ways to form highly active antiretroviral therapy (HAART).

We now face a dilemma of an entirely different kind: with so many different options, how do we choose the best regimen for our patients? What criteria should we base our decisions on, and which of these should receive the greatest weighting?

A key point is tailoring antiretroviral therapy that is acceptable to patients — and again, what is acceptable to one patient is unlikely to be acceptable to all patients. In antiretroviral therapy, one size does not fit all.

Drug safety is emerging as a key factor that determines patient acceptability and hence long-term success of anti-HIV therapy. Better tolerated antiretroviral agents with few long-term adverse effects — including, among the protease inhibitors (PIs), nelfinavir and saquinavir/ritonavir (saquinavir/r; 1000/100 mg *bid*) — have a good chance of success over many months and years, primarily because they are less likely to cause the debilitating adverse effects or major organ toxicities seen with many other agents.

Although HAART has proved extremely successful in reducing the morbidity and mortality associated with HIV infection,[1] many patients still have major reservations about starting therapy, and a substantial proportion choose to defer treatment to a later date. Those who do begin treatment may experience difficulties adhering to their regimen, and many will stop or change to a different regimen within a year. Why?

Data from the Swiss HIV Cohort Study[2] and other studies[3–6] have provided some clues. Fear of adverse effects appears to be a major reason — and, in some studies, the most important reason — why patients refuse HAART when it is recommended to them by their physician.[2,3] Similarly, the frequency and severity of adverse effects have been identified as a major barrier to adherence with HAART.[4,5] In addition, the ICONA study group[6] estimated that nearly 60% of therapy discontinuations at 45 weeks of treatment were related to unacceptable adverse effects; in contrast, therapy failure accounted for <15% of treatment withdrawals in the same study (Figure 1). Thus, adverse effects are major barriers to effective antiretroviral treatment.

Safety is a major driver of treatment success

Two recent randomized clinical trials — the BID Efficacy and Safety Trial (BEST)[7] and MaxCmin1[8] — strongly support these findings. In BEST, patients already receiving indinavir 800 mg *tid* plus nucleoside support (n = 323) were randomized to either continue this regimen (n = 162) or to switch to boosted indinavir (indinavir 800 mg *bid* plus ritonavir ['r'] 100 mg *bid*; n = 161). Despite its more convenient twice-daily administration schedule, indinavir/r was associated with significantly fewer patients achieving virological undetectability (<500 or <20 copies/ml) at 48 weeks (Table 1).

Discontinuation due to adverse effects was the main reason for this difference: toxicity-related discontinuations numbered 18 in the indinavir group, compared with 48 in the boosted indinavir group. In contrast, only one and three patients in each group, respectively, withdrew because of virological failure.

The 48-week results of the MaxCmin1 trial confirm and extend these findings.[8] In MaxCmin1, patients were randomized to receive either saquinavir/r 1000/100 mg *bid* (12 pills per day; n = 148 treated) or indinavir/r 800/100 mg *bid* (6 pills per day; n = 158 treated) in addition to nucleoside analogue support. At 48 weeks, 41% of indinavir/r recipients had permanently discontinued randomized treatment because of a clinical adverse effect, compared with 28% of patients in the saquinavir/r arm ($P = 0.025$ saquinavir/r *vs* indinavir/r). Consequently, the proportion of patients who had HIV RNA <400 copies/ml at 48 weeks was higher in the saquinavir/r group (68% *vs* 53% with indinavir/r) by intent-to-treat (switch = failure) analysis. This difference was statistically significant ($P = 0.014$). Interestingly, only five patients discontinued treatment because of virological failure.

One message is therefore clear. Within their first year of treatment, patients appear to be at risk of discontinuing their HAART regimen — regardless of its pill count or frequency of dosage — if it is not well tolerated. However, all drugs, including antiretrovirals,

Figure 1

Reasons for treatment discontinuation at 45 weeks (from the Italian Cohort Antiretroviral Naive [ICONA] Study Group).[6]

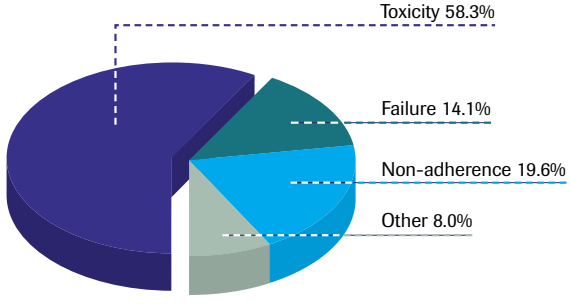


Table 1

Percentage of patients with undetectable viral loads after 48 weeks' treatment with either indinavir or indinavir/r (plus nucleoside analogues) in the BEST trial (intent-to-treat analysis).[7]

Outcome measure	Indinavir *tid* (n = 162)	Indinavir/ritonavir *bid* (n = 161)	*P*-value
HIV RNA <500 copies/ml	74%	57%	<0.001
HIV RNA <20 copies/ml	63%	51%	<0.001

Table 2

Some signature adverse effects of protease and non-nucleoside reverse transcriptase inhibitors.

Drug	Signature adverse effects
Amprenavir	Rash; hyperlipidaemia; gastrointestinal adverse effects
Atazanavir	Jaundice
Efavirenz	CNS adverse effects e.g. anxiety, insomnia; rash; hepatotoxicity
Indinavir	Nephrolithiasis
Lopinavir/ritonavir	Hyperlipidaemia, diarrhoea
Nelfinavir	Diarrhoea
Nevirapine	Hepatotoxicity; dermatological adverse effects (sometimes severe)
Ritonavir	Gastrointestinal adverse effects; hepatotoxicity; hyperlipidaemia
Saquinavir	Gastrointestinal adverse effects

'Signature' adverse effects are those that are often cited as adverse effects of each drug. The inclusion of an adverse effect in this table is not to be taken as a statement of its frequency or severity in association with that agent.

Table 3

Incidence of adverse events (% of patients) as reported from the European summary of product characteristics (indinavir, saquinavir, nelfinavir, ritonavir)[9] or the US product labelling (lopinavir/r).[10]

Adverse event	Indinavir[a]	Saquinavir-SGC[b]	Nelfinavir[b]	Ritonavir[a]	Lopinavir/r[c]
Nausea	35.3	10.6	4.5	47.5	6.7
Vomiting	11	2.9		23.6	2.5
Diarrhoea	24.6	19.9	25.9	44.9	15.6
Dyspepsia	10.7	8.4		Frequently	2.1
Taste perversion	19.1	>2		11.4	
Abdominal pain	14.6	2.3		11.6	4.0
Acid regurgitation	6.5				
Headache	25.2	5.0		15.5	2.5
Rash	19.1		3.0	Frequently	0.6
Fatigue/asthenia	24.3	4.7		22.3	4.0
Renal calculi	4.0				
Dry skin	16.2				
Flatulence	7.8	5.7	2.5	Occasionally	
Insomnia	7.4			Occasionally	1.5
Pruritus	7.4				
Hyperaesthesia	7.1			Frequently	
Dry mouth	6.8			Occasionally	
Dysuria	6.5				
Paraesthesia	5.2			Peripheral 15.4 Perioral 26.6	
Myalgia	5.2	>2		Occasionally	
Dizziness	10.7			Frequently	
Vasodilation				Frequently	

a Assessed as at least possibly related to drug therapy.
b Adverse effect of moderate or severe intensity, considered possibly related to drug therapy.
c Adverse effect of moderate or severe intensity, with probable, possible or unknown relationship to study drug.
SGC = soft-gelatin capsule.

have adverse effects; 'signature' adverse effects of PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are shown in Table 2. Our aim, therefore, should be to utilize those agents that we believe to have the best tolerability and safety profiles.

As Table 2 shows, there are important differences between antiretroviral agents in terms of the types of adverse effects that they cause, their severity, and their potential impact on quality of life.

Nelfinavir and saquinavir/r have superior tolerability compared with many other antiretrovirals

A recent comparative safety review (Table 3) indicates that, among the PIs, nelfinavir and saquinavir have favourable tolerability profiles.[9] The adverse effects of nelfinavir and saquinavir are mostly gastrointestinal in nature, and extensive clinical experience suggests that patients receiving either drug are unlikely to experience major organ toxicities or to discontinue therapy because of adverse effects.

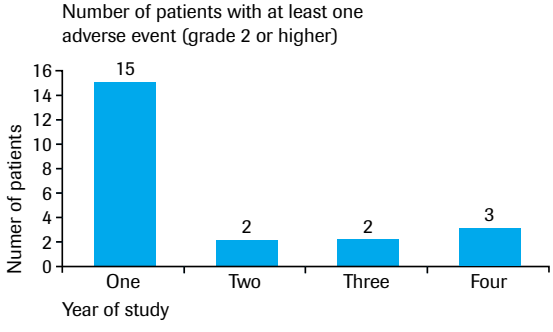
In their study of 556 patients receiving HAART at a single UK treatment centre, Mocroft *et al.* found that the risk of treatment modification or discontinuation during a median follow-up period of 14.2 months was reduced for older patients, those who were treatment-naive, and those who were receiving nelfinavir.[11] The investigators commented that these results appeared to be consistent with reports of the favourable tolerability profile of nelfinavir.

The ability of patients to remain on a therapy appears to be closely linked to its tolerability and safety. This is further illustrated by the long-term results of Study AG511.[12] In this study, 94.4% (34/36) and 86.1% (31/36) of patients remaining on nelfinavir-based HAART after 4 years had a viral load <400 and <50 copies/ml, respectively. Safety analysis revealed that most patients did not experience adverse effects (above grade 1 in severity) on nelfinavir-based therapy. Of those who did, the vast majority occurred during the first year of therapy, with very few adverse effects in later years (Figure 2): only two patients reported diarrhoea after the end of the first year.

As mentioned above, diarrhoea is considered by many physicians to be the 'signature' adverse effect of nelfinavir; however, evidence from clinical trials suggests that, in fact, diarrhoea is a class effect of PIs that occurs with similar frequency irrespective of the specific agent used (Table 3). In study M98-863, for example, diarrhoea occurred with similar frequency among patients receiving either nelfinavir- or lopinavir/r-based HAART for 48 weeks (17.1 vs 15.6%, respectively).[13] Studies suggest that most patients with nelfinavir-associated diarrhoea experience improvement or complete resolution of their symptoms when treated with calcium carbonate 500 mg *bid* or loperamide 2 mg three times weekly, in addition to dietary advice.[14]

Figure 2

Distribution of adverse events over time in study 511.[12]



HAART to heart: avoiding long-term toxicities

Tolerability – that is, the propensity of a drug or regimen to cause adverse effects that affect day-to-day quality of life – is therefore very important to patients. As discussed above, poor tolerability is the most common reason for treatment discontinuation, and is frequently implicated when patients do not adhere well to therapy or decide not to begin HAART when it is offered to them.

HIV infection is currently managed as a chronic infection – with treatment considered to be life-long. Evidence is emerging that our HAART-treated patients are no longer dying of HIV-related causes, but are succumbing to other illnesses that are exacerbated or unmasked by antiretroviral therapy. Heart disease is increasing in frequency as a cause of death among HIV-infected people;[15] there may be several factors driving this change:

- older age is a known risk factor for cardiovascular disease; the success of HAART in preventing AIDS-related death has meant that more patients are living to an age where they are at increased risk for myocardial infarction, angina and other types of cardiovascular disease
- there may be relatively high rates of pre-existing cardiovascular risk factors among the HIV-infected population. For example, 54% of a sample of >200

Figure 3

Nelfinavir (750 mg *tid*): less lipid toxicity than lopinavir/r (400/100 mg *bid*) in study M98-863 at week 48.[13] These results were confirmed at week 60 (data not shown).[17]

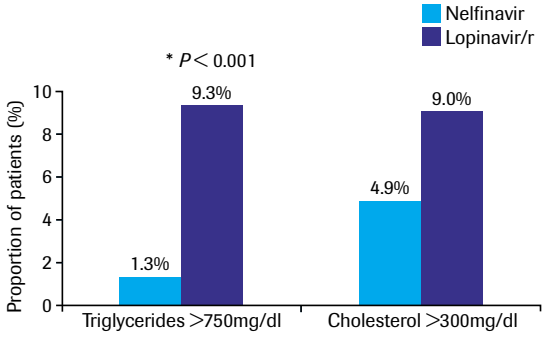
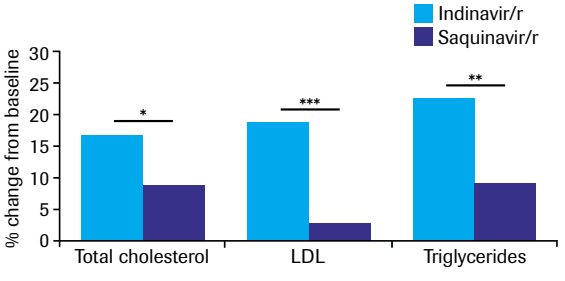


Figure 4

Percentage changes in total cholesterol, low density lipoprotein cholesterol (LDL) and triglyceride levels, between baseline and 48 weeks, among patients receiving either indinavir/r 800/100 mg *bid* or saquinavir/r 1000/100 mg *bid* in the MaxCmin1 trial.[8]



Significance: * $P < 0.01$; ** $P < 0.05$; *** $P = 0.06$ for comparison between indinavir/r and saquinavir/r.

HIV-infected patients from San Francisco, USA, indicated that they smoked cigarettes,[16] a figure that is well above the national average

– antiretroviral therapy has been associated with pro-atherogenic changes in plasma lipid levels, and these changes may increase the risk of future cardiovascular morbidity.

When selecting treatment regimens for our patients, we must therefore pay more attention to preventing *all-cause* morbidity and mortality rather than focusing only on opportunistic infections and malignancies. To do this, we need to select therapies that have a lower potential to cause adverse effects with long-term consequences – for example, hyperlipidaemia.

Nelfinavir and saquinavir/r 1000/100 mg *bid* have less effect on plasma lipid levels than some other PIs

There are important differences between individual PIs in terms of their relative abilities to cause hyperlipidaemia: for example, nelfinavir and saquinavir/r (1000/100 mg *bid*) appear to have comparatively little effect on plasma lipid levels. Study M98-863 found, at 48 weeks, grade 3 or 4 hypertriglyceridaemia in only 1.3% of patients taking nelfinavir, compared with >9% in lopinavir/r patients (Figure 3; $P < 0.001$).[13] Interestingly, the risk of severe hypertriglyceridaemia with lopinavir/r appears to increase with the degree of previous exposure to PIs;[18–20] up to 40% of multiple PI-experienced patients receiving lopinavir/r 400/100 or 533/133 mg *bid* may have triglyceride levels >750 mg/dl (>8.5 mmol/L).

Not all ritonavir-boosted PIs appear to cause significant lipid toxicity, however. Several studies have now provided data suggesting that treatment with saquinavir plus low-dose ritonavir (100 mg *bid*) has very little effect on serum lipid levels, even in highly treatment-experienced patients.[8,21]

In the MaxCmin1 trial (see above for details), total cholesterol, triglyceride and low density lipoprotein (LDL)-cholesterol levels were measured at baseline and 48 weeks after starting either indinavir/r 800/100 mg *bid* or saquinavir/r 1000/100 mg *bid* in all patients. Between baseline and 48 weeks, only minor increases (<10%) in each parameter were observed in the saquinavir/r group. Importantly, saquinavir/r was associated with minimal changes (+2.5%) in LDL-cholesterol levels. In contrast, indinavir/r was associated with much larger changes in lipid levels, and the difference between the groups in the magnitude of change at 48 weeks was statistically significant for both cholesterol and triglycerides (Figure 4).

Traditionally, hyperlipidaemia has been ascribed to the use of PIs, but evidence is emerging that drugs in other classes may play an important role.[22–24] In a recent study of antiretroviral-naive patients with HIV infection,[23] changes in mean LDL-cholesterol, total cholesterol and triglyceride levels between baseline and week 48 were higher for patients receiving stavudine-based HAART (n = 83) than for those receiving zidovudine-based HAART (n = 89). Similarly, the 48-week results of study 903, in which the effects of two PI-sparing regimens (efavirenz plus lamivudine plus either tenofovir or stavudine) were compared in antiretroviral-naive patients, showed that stavudine was associated with significantly ($P < 0.001$) greater mean increases in triglyceride and total cholesterol levels compared with tenofovir.[24]

Recently, Haubrich and colleagues presented the results of a study suggesting that there was little difference between nelfinavir and efavirenz in terms of their effects on fasting lipid levels over 24 weeks.[25]

Additionally, O'Brien and co-workers have shown that patients switching to saquinavir/r 1000/100 mg *bid* from regimens containing higher dosages of ritonavir (400 mg *bid*) may experience improvements in their serum lipid profiles.[26]

Taken together, these data suggest that nelfinavir and saquinavir/r may be associated with lower long-term risks of cardiovascular disease, and a potentially reduced need for adjunctive lipid-lowering therapy, than some other PIs.

Summary and conclusion

Data are emerging which indicate that tolerability and safety are key factors in determining the acceptability of HAART to patients. Not only do adverse effects, or the fear of them, deter patients from commencing HAART — even when it is clinically indicated — but they can also act as a significant barrier to adherence and a major reason for early treatment discontinuation or modification. We must, therefore, *tailor* antiretroviral therapy to avoid toxicities that are likely to lead patients to miss doses, or to want to change or stop their treatment too early. Individualization is the key, because there will be important differences between patients in their abilities to tolerate different adverse effects.

Among PIs, nelfinavir (1250 mg *bid*) and saquinavir/r (1000/100 mg *bid*) appear to have favourable tolerability and long-term safety profiles that make them valuable options in the treatment of HIV infection. Their adverse effects are mainly gastrointestinal in nature, and data on nelfinavir suggest that its adverse effects do not usually lead to treatment modification or discontinuation.[11] Diarrhoea, the most frequently cited adverse effect of nelfinavir, has been shown to be mainly mild or moderate in severity, and can be easily controlled using calcium carbonate or loperamide.[14]

Hyperlipidaemia is an adverse effect that is often ascribed to the use of PIs; however, it is becoming clear that there are important differences between individual PIs in this regard, and that agents in other drug classes may also be involved. Large, randomized clinical trials[8,13] have indicated that nelfinavir, and saquinavir/r 1000/100 mg *bid*, may be less likely than some other PIs to cause hypertriglyceridaemia or hypercholesterolaemia. Other studies show that reductions in cholesterol and triglyceride levels can be achieved when patients with hyperlipidaemia are switched to saquinavir/r 1000/100 mg *bid*[26] or to nelfinavir.[27]

Whether a particular antiretroviral regimen will suit an individual patient is dependent on many factors; however, we know that safety is central to patient acceptance of therapy. Choosing therapy that is tolerable for patients is, therefore, an important step in maximizing the probability of long-term success.

References

1. Palella Jr FJ, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; **338:** 853–860.
2. Bassetti S, Battegay M, Furrer H, *et al.* Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? *J Acquir Immune Defic Syndr* 1999; **21:**114–119.
3. Maisels L, Steinberg J, Tobias C. An investigation of why eligible patients do not receive HAART. *AIDS Patient Care STDs* 2001; **15:**185–191.
4. Proctor VE, Tesfa A, Tompkins DC. Barriers to adherence to highly active antiretroviral therapy as expressed by people living with HIV/AIDS. *AIDS Patient Care STDs* 1999; **13:**535–542.
5. Ammassari A, Murri R, Pezzotti P, *et al.* Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr* 2001; **28:**445–449.
6. D'Arminio Monforte A, Lepri AC, Rezza G, *et al.* Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral-naive patients. ICONA Study Group. Italian Cohort of Antiretroviral Naive Patients. *AIDS* 2000; **14:**499–507.
7. Cahn P, Casiró A, Puentes T, *et al.* Continued indinavir (800 mg TID) versus switching to indinavir+ritonavir (800/100 mg BID) in HIV patients having achieved viral load suppression. A randomized study: the BID Efficacy and Safety Trial. *1st IAS Conference on HIV Pathogenesis and Treatment.* Buenos Aires, Argentina, 2001; poster 60.
8. Cahn P, Dragsted UB, Pedersen C, *et al.* Safety and efficacy evaluation of a phase IV randomised, open-label, multicentre trial of indinavir/ritonavir (800/100 mg bid) vs. saquinavir/ritonavir (1000/100 mg bid) in adult HIV-1 infection: the MaxCmin1 trial. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster WeOrB1265 and oral presentation.
9. Moyle GJ, Gazzard GJ. A risk-benefit assessment of HIV protease inhibitors. *Drug Saf* 1999; **20:**299–321.
10. Prescribing information for Kaletra™. Abbott Laboratories, 2002 Jan. Available at: www.kaletra.com [Accessed 11 October 2002].
11. Mocroft A, Youle M, Moore A, *et al.* Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS* 2001; **15:**185–194.
12. Gathe Jr J, Chu A, Yuen N, *et al.* Durability of nelfinavir combination therapy after 4 years: 3-year extension data from Agouron Study 511. *8th European Conference on Clinical Aspects and Therapy in HIV Infection.* Athens, Greece, 2001; poster LB10.
13. Walmsley S, Bernstein B, King M, *et al.* Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med* 2002; **346:**2039–2046.
14. Negredo E, Sirera G, Puig J, *et al.* Management of nelfinavir-associated diarrhoea. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster TuPeB4526.
15. Selik RM, Byers Jr RH, Dworkin MS. Trends in diseases reported on U.S. death certificates that mentioned HIV infection, 1987–1999. *J Acquir Immune Defic Syndr* 2002; **29:**378–387.
16. Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. *AIDS Patient Care STDs* 2002; **16:**39–42.
17. Ruane P, Mendonca J, Timerman A, *et al.* Kaletra™ vs. nelfinavir in antiretroviral-naive subjects: week 60 comparison in a Phase III, blinded, randomized clinical trial. *1st IAS Conference on HIV Pathogenesis and Treatment.* Buenos Aires, Argentina, 2001; poster 6.
18. Rockstroh J, Brun S, Bertz R, *et al.* Kaletra ABT-378/ritonavir and efavirenz: 48-week safety/efficacy evaluation in multiple PI experienced patients. *5th International Congress on Drug Therapy in HIV Infection.* Glasgow, UK, 2000; poster P43.
19. Feinberg J, Brun S, Marsh T, *et al.* Durable suppression of HIV+ RNA after two years of Kaletra (ABT-378/ritonavir) therapy in single protease inhibitor experienced patients. *5th International Congress on Drug Therapy in HIV Infection.* Glasgow, UK, 2000; poster P101.
20. Stryker R, Brun S, King M, *et al.* Kaletra (ABT-378/ritonavir) in antiretroviral-naïve HIV+ patients: follow-up beyond two years and viral load suppression below 3 copies/mL. *5th International Congress on Drug Therapy in HIV Infection.* Glasgow, UK, 2000; poster P46.
21. Piketty C, Gonzalez-Canali G, Castiel P, *et al.* Limited hyperlipidaemia in patients receiving a five drug combination including ritonavir, saquinavir and efavirenz. *1st IAS Conference on HIV Pathogenesis and Treatment.* Buenos Aires, Argentina, 2001; poster 508.
22. Garcia-Benayas T, Blanco F, Gomez JM, *et al.* HAART-related lipid disturbances: possible role of non-nucleosides. *1st IAS Conference on HIV Pathogenesis and Treatment.* Buenos Aires, Argentina, 2001; abstract 490.
23. Kumar P, Rodriguez-French A, Thompson M, *et al.* Prospective study of hyperlipidemia in ART-naïve subjects taking Combivir/abacavir (COM/ABC), COM/nelfinavir (NFV), or stavudine (d4T)/lamivudine (3TC)/NFV (ESS40002). *9th Conference on Retroviruses and Opportunistic Infections.* Seattle, USA, 2002; abstract 33.
24. Gallant J, Staszewski S, Pozniak A, *et al.* Favorable lipid and mitochondrial (mt) DNA profile for tenofovir disoproxil fumarate (TDF) compared to stavudine (d4T) in combination with lamivudine (3TC) and efavirenz (EFV) in antiretroviral therapy (ART) naïve patients: a 48-week interim analysis. *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Diego, USA, 2002; abstract LB-2.
25. Haubrich R, Miller C, Gathe J, *et al.* The effect of NFV versus EFV on fasting lipid levels: interim analysis from a prospective randomized study in treatment naive patients (AG1127). *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy.* San Diego, USA, 2002; abstract H-1914.
26. O'Brien WA, Acosta E, Felizarta F, *et al.* Switch of saquinavir 400mg/ritonavir 400mg to saquinavir 1000mg/ritonavir 100mg during BID four drug antiretroviral therapy. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster WeOrB1263.
27. Duncombe C. Reversal of hyperlipidemia and lipodystrophy in patients switching therapy to nelfinavir. *J Acquir Immune Defic Syndr* 2000; **24:**78–79.

NOTES

NEW THREADS –
Therapeutic profile of enfuvirtide in treatment-experienced patients

Manuel Battegay

Professor of Infectious Diseases and Internal Medicine, Division of Infectious Diseases, Department of Internal Medicine, University Hospital, Basel, Switzerland

Manuel Battegay is Head of the Clinical HIV/AIDS Unit at the University Hospital Basel, Basel, Switzerland. He is also Professor of Medicine and Head of the Division of Infectious Diseases at the same university.
He has been involved in HIV-related clinical research since 1988, and has a particular interest in the pathophysiological aspects of HIV infection.
He is also actively involved in clinical trials of antiretroviral therapy and in studies relating to the clinical aspects of HIV infection in general.
He is one of the investigators of the Swiss HIV Cohort Study, of which he was Chairman of the Scientific Board until this year.
Manuel Battegay has authored or co-authored many scientific articles on HIV infection that have been published in international medical journals.

Introduction

In the mid-1990s, HIV therapy moved to a new level with the introduction of protease inhibitors (PIs) – an advance that heralded the arrival of highly active antiretroviral therapy (HAART). PIs revolutionized the management of HIV infection and brought with it a dramatic decline in morbidity and mortality. HAART has become the basis of our therapeutic strategy, but its long-term use, particularly in patients who are highly treatment-experienced, may be associated with extensive drug resistance. Many patients now have limited treatment options. It is perhaps this group of patients for whom there is currently the greatest need for therapeutic innovation in the field of HIV medicine.

It is therefore encouraging that, once again, we are anticipating new HIV treatment strategies that may help patients who are most in need. Enfuvirtide (T-20) is the most advanced compound in an entirely new class of antiretroviral agents with a unique mechanism of action – the fusion inhibitors. The recently presented results of Phase III clinical trials showed that enfuvirtide, in combination with individualized background therapy, produces clinically meaningful and statistically significant therapeutic benefit, offering renewed hope for many patients with advanced infection, multidrug-resistant virus and limited treatment options. Data from these studies also suggest that enfuvirtide has a good safety profile and, perhaps surprisingly, patient acceptance of its subcutaneous mode of administration is high. Taken together, these results suggest that enfuvirtide is set to become an important new thread in the fabric of HAART.

A new class offering new hope

Currently available antiretrovirals act intracellularly, after HIV has entered the host CD4 cell and begun to replicate. Targets for intracellular HIV inhibition include the reverse transcriptase and protease enzymes, which play pivotal roles in the transcription of viral genetic material and the production of new viral components, respectively. Unlike conventional antiretrovirals, fusion inhibitors — a new class of drugs – block HIV before it can enter CD4 cells. This extracellular mode of action is unique, and underpins the performance of the first fusion inhibitor to be developed — enfuvirtide (T-20). Now being tested in Phase III clinical trials, enfuvirtide is the most clinically advanced fusion inhibitor that is currently undergoing evaluation.

Its extracellular mode of action also provides a theoretical basis for clinical observations that have been made thus far, including its efficacy in patients with multidrug-resistant virus, its apparent lack of drug interactions, and its encouraging safety profile. Indeed, if, as it appears, enfuvirtide does not substantially enter CD4 or other cells, then the potential for interaction with cellular metabolic processes will be minimal. This may reduce its potential to cause systemic toxicities, which is important because tolerability is one of the key factors that affects treatment adherence.[1]

How exactly does enfuvirtide exert its extracellular inhibitory effects? First, we need to re-cap on the process of viral entry. This is thought to proceed via three different but co-operative steps, known as:

- attachment
- co-receptor binding
- fusion.

Attachment occurs through interaction between the gp120 molecules on the surface of the virus and the CD4 receptor molecules on the surface of CD4 cells. A conformational change then takes place that allows gp120 to interact with co-receptors (CXCR4 or CCR5), which are also located on the CD4 cell surface (Figure 1). It is thought that there is then a further conformational change that allows the viral gp41 molecule to be inserted into the cell membrane, rather like a harpoon piercing the skin. An interaction then occurs in which coiled regions of gp41 (HR1 and HR2) form a bundle; gp41 then contracts, or 'zips', bringing the viral and cell surfaces together. This allows fusion of the viral envelope and host cell membrane to take place (Figure 2).

By binding to the HR1 region, enfuvirtide prevents the contraction or 'zipping' action of gp41, thereby preventing fusion of the virus with the cell (Figure 3).

What is the exact nature of enfuvirtide? Enfuvirtide is a peptide molecule — much larger than conventional antiretroviral agents such as saquinavir or zidovudine (Figure 4). Its size and physicochemical properties make it a most complex molecule: its synthesis alone consists of 106 separate steps. As a peptide, enfuvirtide would be rapidly digested in the gastrointestinal tract. Consequently, it must be administered by subcutaneous injection. While this might have been expected to be a significant barrier to the successful use of enfuvirtide, patient surveys performed as part of clinical trials have suggested that this is not generally the case.[2]

Addressing a current unmet need in HIV infection

Since the advent of HAART, the significant increase observed in life expectancy and quality of life for people living with HIV has been dramatic. However, in the absence of complete viral suppression, viral replication and mutation continues, and the emergence of resistance and subsequent (virological) treatment failure inevitably follows. We have already seen significant evidence to show that not only is there an increasing number of treatment-experienced patients with multidrug-resistant forms of HIV (Figure 5),[3] but that there is an increase in the number of newly diagnosed people who have resistant viral strains.[4] The net result of these trends is that there is a large and growing number of patients with limited, or reduced, treatment options. Therefore, we clearly need new antiretroviral agents that are active against HIV strains with resistance to conventional antiretroviral drugs.

Efficacy of enfuvirtide (T-20)

Phase II trials of enfuvirtide provided strong data to support its further clinical development. Despite the fact that patients recruited to trial T20-205 (n = 70) were heavily treatment-experienced, adding enfuvirtide to conventional oral antiretrovirals was associated with a rapid and, in many patients, durable reduction in mean viral load from baseline, of 1.4 $\log_{10}$ copies/ml over 48 weeks (on-treatment analysis).[5] Similarly, in the T20-206 trial,[6] treatment-experienced patients with viral loads >400 copies/ml at baseline were randomized to receive either a fixed oral antiretroviral regimen, or the same fixed regimen plus enfuvirtide (at one of three different dosages). Patients in this study were PI- and nucleoside analogue-experienced, but non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive. At 48 weeks, 47% of patients receiving any dose of enfuvirtide plus oral antiretrovirals had achieved a viral load <50 copies/ml, compared with 37% of those who received oral antiretrovirals only (intent-to-treat, missing = failure analysis).

Figure 1

HIV gains entry to CD4 cells via a process that involves three steps. This figure shows the first two of these: attachment of the viral envelope glycoprotein gp120 to the CD4 receptor on the host cell, and subsequent binding to the cell-surface co-receptors (CXCR4 or CCR5). The latter step is brought about by conformational change in gp120.

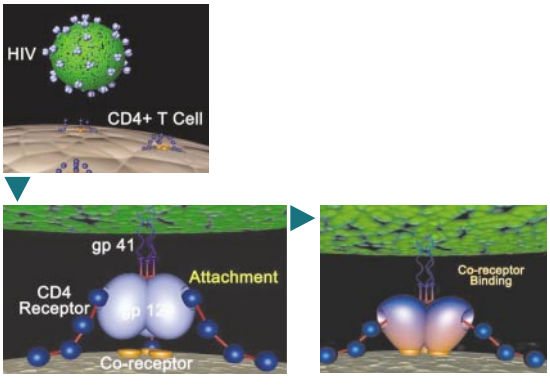


Figure 2

Co-receptor binding (see Figure 1) induces a further conformational change in gp120, which exposes the gp41 envelope protein. This protein has two heptad repeat (HR) regions, HR1 and HR2, which 'zip' together, pulling the viral envelope closer to the surface of the CD4 cell until they are close enough to fuse. This process is called 'fusion'.

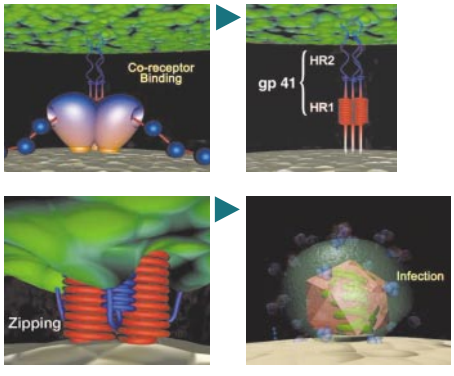
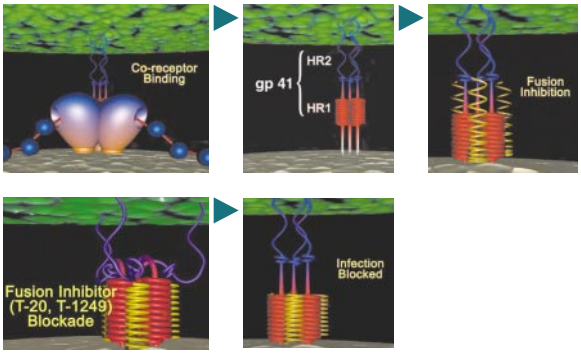


Figure 3

Enfuvirtide, shown here as a yellow coil, blocks the process by which HIV fuses with the CD4 cell by binding to the viral envelope glycoprotein gp41 and preventing its two regions, HR1 and HR2, from 'zipping' together.



Following on from these early results, the primary 24-week analyses of Phase III studies of enfuvirtide have been presented.[7,8] These trials, designated TORO 1 and TORO 2, enrolled HIV-1-infected patients who were triple class-experienced and/or had documented resistance to each of the three classes of conventional antiretroviral agents. Prior to randomization, an optimized background (OB) regimen consisting of three to five approved (including up to two experimental) antiretroviral agents was selected for each patient, based on their prior treatment history and HIV genotype and/or phenotype.

Patients were randomized 2:1 to receive enfuvirtide (90 mg *bid*) plus OB, or OB alone (control arm). In the TORO 1 and TORO 2 studies, respectively, 491 and 504 HIV-1-infected patients were randomized, received at least one dose of study drug and provided at least one on-treatment assessment. In the TORO 1 study (conducted in North America and Brazil),[7] patients who received enfuvirtide as part of their combination regimen achieved a median reduction in HIV RNA levels of 1.70 $\log_{10}$ copies/ml, compared with a reduction of 0.76 $\log_{10}$ copies/ml for those randomized to the control arm. The difference in the magnitude of decrease in viral load between the two arms was 0.93 $\log_{10}$ copies/ml and was statistically significant ($P < 0.0001$).

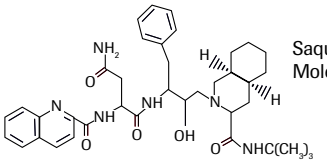
In the TORO 2 study (conducted in Europe and Australia),[8] patients who received enfuvirtide as part of their combination regimen achieved a median reduction in HIV RNA levels of 1.43 $\log_{10}$ copies/ml, compared with a reduction of 0.65 $\log_{10}$ copies/ml for those who were randomized to the control arm (Figure 6). The difference in the magnitude of decrease in HIV RNA between the two arms was 0.78 $\log_{10}$ copies/ml and was statistically significant ($P < 0.0001$).[8]

In addition, secondary analyses also showed that, in both studies, patients receiving enfuvirtide were around twice as likely to achieve an undetectable viral load as those who did not receive enfuvirtide. Furthermore, time to virological failure was significantly longer among enfuvirtide recipients compared with patients in the control arm.[7,8]

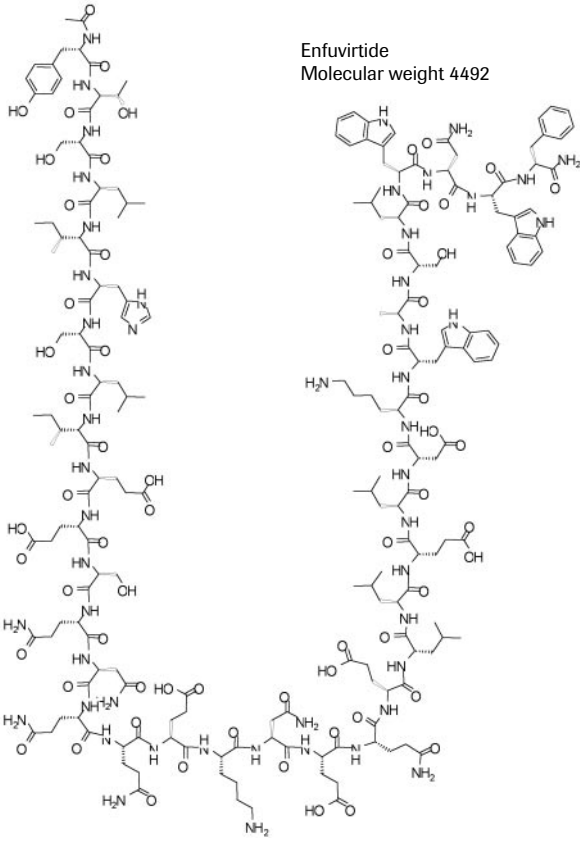
It should also be noted that the benefits of enfuvirtide were not restricted to viral suppression. Enfuvirtide therapy was also associated with significantly greater changes in CD4 count at 24 weeks (versus baseline) in both TORO 1 and TORO 2, compared with control (+76 *vs* +32 cells/mm^3 in TORO 1; $P = 0.0001$; +65 *vs* +38 cells/mm^3 in TORO 2; $P = 0.0236$ for enfuvirtide *vs* control). To observe such increases in CD4 count in such advanced patients is important, given that these patients are at high risk of opportunistic infection.

Figure 4

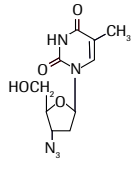
Structural formulae and molecular weights of saquinavir, enfuvirtide and zidovudine. Enfuvirtide is the largest and most complex peptide ever manufactured on a large scale for therapeutic use.



Saquinavir mesylate
Molecular weight 767



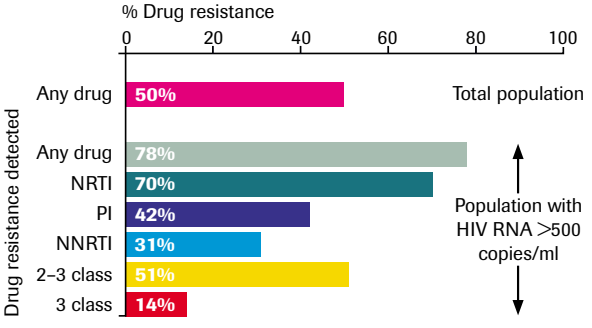
Enfuvirtide
Molecular weight 4492



Zidovudine
Molecular weight 267

Figure 5

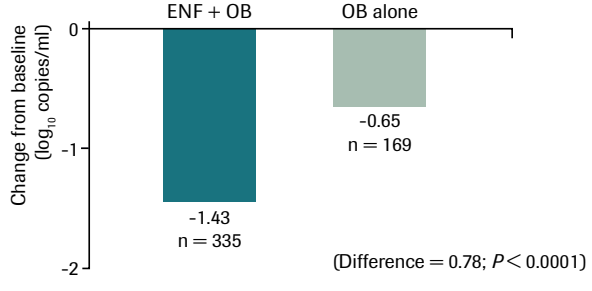
Prevalence of resistance to currently available antiretroviral drugs among people with HIV infection (n = 1080) who were tested in 1999 in the US.[3]



Results are weighted to represent the >130,000 patients in the US who were receiving care in 1996, who survived until 1999 and who had a viral load >500 copies/ml.

Figure 6

Changes in log_{10} HIV viral load (least squared means; intent-to-treat last observation carried forward) among treatment-experienced patients who received either enfuvirtide (ENF; 90 mg *bid*) plus optimized background (OB) therapy, or OB therapy alone, for 24 weeks in study TORO 2.[8]



Safety and tolerability of enfuvirtide

Many toxicities associated with conventional antiretroviral agents that work inside the cell might be expected to result from interference with intracellular physiological processes or interactions with cellular receptors. Because enfuvirtide does not appear to accumulate inside cells, and interacts specifically with HIV-1 gp41 extracellularly, the potential for this agent to cause intracellular toxicity is reduced.

In addition, enfuvirtide is less likely to exacerbate the adverse effects observed with conventional antiretroviral agents. Phase II and III studies showed that enfuvirtide is well tolerated and does not appear to be commonly associated with major systemic toxicities. In the TORO trials, adverse events in the enfuvirtide + OB arms were similar to those seen in the control arms, with the exception of injection site reactions (ISRs; see below).[7,8] ISRs aside, the events most frequently reported in patients taking enfuvirtide plus OB in TORO 2 were diarrhoea (19.9%, compared with 20.1% in the control group) and nausea (11.3% compared with 14.8% in the control group).[8] It is also promising to note that most patients had little or no change in the toxicity grade of laboratory parameters.

The most frequent adverse events associated with enfuvirtide in clinical trials have been localized ISRs. These occur in almost all patients and are generally mild to moderate in severity; importantly, they are rarely treatment-limiting. In trials TORO 1 and TORO 2,[7,8] approximately 3% of patients over 24 weeks discontinued enfuvirtide therapy because of ISRs, which suggests that most patients are able to tolerate them.

Clearly, with enfuvirtide being administered as a subcutaneous injection twice daily, consideration has to be given to the potential impact of this drug on patients' quality of life and ability to perform activities of daily living. To date, two analyses have been conducted with this in mind – the Subcutaneous Injection Survey (SIS),[9] which assessed 547 patients from both Phase III TORO trials at 8 weeks, and the activities of daily living survey from the T20-205 trial, with assessment at 48 weeks.[2]

Both of these surveys showed that the storage and preparation of enfuvirtide are generally easy for patients and, importantly, that self-injection of enfuvirtide is simple to perform for most patients. In the SIS, 66% of patients said that they found self-injection of enfuvirtide to be 'easy' or 'very easy'.[9] The surveys also showed that, generally, enfuvirtide has little or no impact on patients' abilities to perform activities of daily living (Figure 7).[2]

Summary

Enfuvirtide is the first agent in a new class of antiretroviral drugs. It is a fusion inhibitor, which means that it blocks HIV before it can enter CD4 cells. This extracellular mode of action is unique and provides the theoretical basis for the observed efficacy and safety of enfuvirtide in patients with multidrug-resistant virus, its lack of cross-resistance, and its lack of drug interactions in clinical trials.

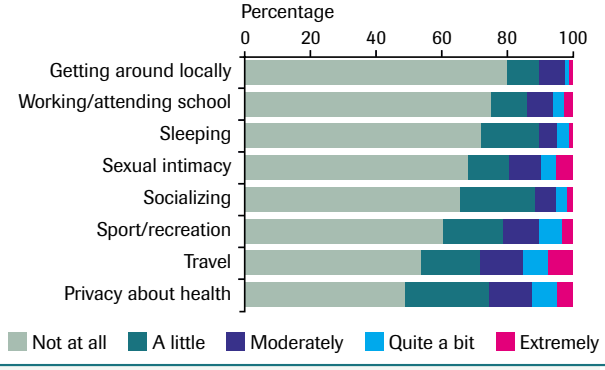
Enfuvirtide has demonstrated clinically meaningful and statistically significant therapeutic benefit in heavily treatment-experienced patients. In Phase III trials, patients who received enfuvirtide plus OB therapy were twice as likely to achieve an undetectable viral load than patients who received OB only.[7,8] Similarly, patients who received enfuvirtide had approximately twice the increase from baseline in CD4 count over 24 weeks than patients who did not. These are important benefits of enfuvirtide in a patient population that is difficult to treat.

Enfuvirtide appears to be well tolerated and does not seem to be associated with systemic toxicities. The most commonly observed adverse effect of enfuvirtide is localized injection site reactions, which are usually mild to moderate in severity and, in clinical trials, have resulted in only 3% of patients choosing to discontinue their therapy. In surveys, most patients have shown acceptance of twice-daily enfuvirtide injections, and, promisingly, the impact of enfuvirtide on patients' abilities to perform activities of daily living appears to be minimal.

In summary, enfuvirtide represents an important new thread in the fabric of HAART, and it offers new hope for treatment-experienced patients who have limited treatment options.

Figure 7

Impact of enfuvirtide on activities of daily living, as assessed in 547 patients enrolled in Phase III trials of enfuvirtide.[9] Patients were asked: 'How much have injections limited your ability to perform the following daily activities?'



References

1. Ammassari A, Murri R, Pezzotti P, *et al.* Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr* 2001; **28:**445–449.
2. Cohen CJ, Dusek A, Green J, *et al.* Long-term treatment with subcutaneous T-20, a fusion inhibitor, in HIV-infected patients: patient satisfaction and impact on activities of daily living. *AIDS Patient Care STDs* 2002; **16:**327–335.
3. Richman DD, Bozzette S, Morton S, *et al.* The prevalence of antiretroviral drug resistance in the US. *41st Interscience Conference on Antimicrobial Agents and Chemotherapy.* Chicago, US, 2001; abstract LB-17.
4. d'Arminio Monforte A, Lepri AC, Rezza G, *et al.* Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral-naive patients. ICONA Study Group. Italian Cohort of Antiretroviral Naive Patients. *AIDS* 2000; **14:**499–507.
5. Lalezari J, Cohen C, Eron J, *et al.* Forty-eight week analysis of patients receiving T-20 as a component of multi-drug salvage therapy. *XIII International AIDS Conference.* Durban, South Africa, 2000; abstract LbPp116.
6. Lalezari J, DeJesus E, Northfelt D, *et al.* A week 48 assessment of a randomized, controlled open-label Phase II trial (T20-206) evaluating three doses of T-20 in PI-experienced, NNRTI-naive patients infected with HIV-1. *9th Conference on Retroviruses and Opportunistic Infections.* Seattle, US, 2002; poster 418-W.
7. Henry K, Lalezari J, O'Hearn M, *et al.* Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals (ARVs) in North America and Brazil. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster LbOr19B.
8. Clotet B, Lazzarin A, Cooper D, *et al.* Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals (ARV) in Europe and Australia. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster LbOr19A.
9. Green J, Salgo MP, Delehanty J. Patient survey on injection on enfuvirtide (T-20): ease of use and impact on activities. *XIV International AIDS Conference.* Barcelona, Spain, 2002; poster TuPeB4480.

NOTES

NOTES

NEW THREADS –
Weaving enfuvirtide into patients' lives

Nicky Perry

Research Manager, Department of HIV and Genitourinary Medicine, Brighton & Sussex University Hospital NHS Trust, Brighton, UK

Nicky Perry has been in the nursing profession for the past 21 years and has worked in the HIV/AIDS field since 1988. Initially, she worked at St Stephen's Hospital (now the Chelsea & Westminster Hospital) in London, UK, and, after 2 years, was appointed to the position of Research Nurse at the Kobler Centre, also in London.
Subsequently, Ms Perry moved to Australia, where she was Clinical Trials Co-ordinator at the Community HIV Research Network in Sydney. On her return to the UK, she took up her current post as Research Manager for HIV and Genitourinary Medicine at Brighton General Hospital, Brighton. Ms Perry is currently Chair of the National HIV Nurses Association (NHIVNA) and is also a co-opted member of the British HIV Association (BHIVA) Executive Committee. She has recently completed an MSc in Evidence Based Health Care at Oxford University, Oxford, UK.

Introduction

Until now, antiretroviral agents have been available for oral administration; enfuvirtide is the first antiretroviral agent that is given by subcutaneous injection. Nurses, therefore have a key role in assessing, training, motivating and supporting patients as they attempt to weave enfuvirtide therapy into their daily lives.

Before therapy begins

The involvement of a specialist HIV nurse could have a profound impact on patients' use and acceptance of enfuvirtide. From the outset, the patient needs to be well informed, motivated and both willing and able to take the drug on a regular basis. Even before enfuvirtide is started, nurses can provide an assessment of patients' suitability for therapy. First, a prior knowledge of the patient and their history of compliance with other medications is useful to enable nurses to assess factors such as their home life and the availability of support from family or friends. Time spent with patients before commencing therapy is crucial in ensuring long-term adherence to therapy.

Key areas that need to be assessed before therapy begins are:

- What is the patient's home life like? What are their personal circumstances? Are these compatible with enfuvirtide therapy?
- What is the patient's lifestyle like? For example, do they work irregular hours and, if so, might this interfere with their ability to adhere to therapy? Do they have to travel frequently because of work?
- Does the patient live alone, or do they live with someone who might be able to help with injections?
- Do they have any physical problems or disabilities than might make it difficult to reconstitute enfuvirtide, use aseptic technique or administer the injection?
- Are they afraid of injections?
- Does the patient have difficulties adhering to conventional antiretrovirals? Might this suggest a predisposition to poor adherence to enfuvirtide?

By reviewing these types of issues together, the nurse and patient can put together a dosage schedule, ensure appropriate referrals and involvement of the multidisciplinary team, so that enfuvirtide fits into that particular patient's lifestyle.

An important point for all healthcare professionals working with patients who are receiving enfuvirtide is the important role they can play in 'normalizing' therapy. Many patients may feel apprehensive about having to inject themselves twice daily; a useful analogy to use in this case is that of insulin use by patients with diabetes mellitus. Reinforcing that patients with diabetes mellitus can live normal lives, and that injecting insulin simply becomes a part of their normal daily routine, may improve patients' acceptance of therapy.

Moving forward

Once the decision to commence therapy has been taken, nurses have an enormously important role in training the patient and ensuring he or she fully understands their new treatment. Patients prescribed enfuvirtide should not attempt to self-inject before completing a training session with a nurse or other healthcare professional involved in training. In addition to reviewing procedures for reconstitution, sterile preparation and administration, the time spent with a patient before therapy commences can also be used to go over information provided by the physician and to allay any fears they may have.

Areas with which nurses can help include:

- ensuring the patient understands what enfuvirtide is for, how it works, and the need to take it in addition to their other, oral, medications
- making sure the patient knows how and where to store their supplies to ensure the stability of the drug, and how to dispose of their used needles and syringes safely
- training the patient in sterile reconstitution and subcutaneous administration techniques
- reviewing acceptable sites of administration (abdomen, outer thigh and upper arm), and emphasizing the need to rotate injection sites
- providing an accessible point of contact for patients when they have questions or problems with their treatment.

Enfuvirtide may be stored at room temperature prior to reconstitution; however, once reconstituted, if not used immediately, it should be refrigerated. When refrigerated, enfuvirtide solution must be used within 24 hours. If patients do choose to store *unreconstituted* enfuvirtide in their refrigerator, they should be made aware that both the powder for reconstitution and the diluent (sterile water) should be brought to room temperature before use.

Importance of the nurse–patient relationship to adherence

As with all other antiretroviral drugs, adherence is paramount to successful therapy with enfuvirtide, and patients must fully understand the implications of non-adherence before they begin. Nurses can help patients to incorporate enfuvirtide into their everyday lives by discussing ways to minimize the impact on their time.

The most time-consuming aspect of the process is the time it takes to completely dissolve the vial of enfuvirtide with sterile water. This generally takes 15 minutes, but can take up to 45 minutes. Patients,

therefore, should be advised to begin the process of reconstituting their enfuvirtide as soon as they awake (assuming that their supplies are already at room temperature), before having a shower and dressing for the day. This means that the drug can be dissolving while they are doing other things, minimizing any impact on patients' time in the morning.

Because stability studies indicate that enfuvirtide solution is stable for up to 24 hours if stored in a refrigerator (data on file, Roche Pharmaceuticals Ltd), patients can also be told to prepare their morning and evening doses together. The unused vial is simply refrigerated until it is time for the next dose. Establishing a daily routine in which patients inject enfuvirtide at the same time each day, at a specific location, may also encourage high levels of adherence.

The most common adverse effect of subcutaneous enfuvirtide administration is injection site reactions (ISRs), and, as with all adverse effects, these may have the potential to interfere with adherence. Although most patients are able to cope with ISRs, there are some tips and other pieces of advice that, it has been reported by both patients and nurses, can help minimize their impact. These are:

- use a different injection site each time you administer enfuvirtide. Ask your partner or a family member to inject in difficult-to-reach places
- inject enfuvirtide slowly, avoiding intramuscular administration
- after administration, gently massage the site to disperse the drug throughout the subcutaneous tissues.

It should be noted, however, that these interventions are not yet backed by clinical evidence.

Figure 1

Injection kit for enfuvirtide.

The importance of ongoing support

Once the nurse–patient relationship is established, the nurse could become the initial point of enquiry for patients who have questions about the practical aspects of their therapy. In turn, the nurse should have support from clinical specialist nurses and other members of the multidisciplinary healthcare team in order to better support the patient. Ongoing assessment of the patient's reconstitution technique is useful and, by involving community nurse specialists, can be done in the home rather than in a clinical setting. Involving the patient's partner, family or friends, and teaching them how to administer enfuvirtide, could enable the patient to have a break from self-injecting.

Other initiatives that may help patients include 'buddy' systems, where patients who have just begun enfuvirtide therapy are paired with another patient who is also on enfuvirtide, and the use of a help-line or pager number that patients can call when they have specific questions about their treatment.

By encouraging close collaboration between patient, nurse, physician and other members of the healthcare team, together with educational and support programmes, it should be possible to fully realize the potential of this exciting new therapy for patients with HIV infection.

NOTES

NOTES

NOTES

NOTES