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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.

Jonathan Schapiro

Stanford University
School of Medicine, Stanford,
California, USA

Jonathan M Schapiro is Director of the AIDS Service at the National Hemophilia Center, Tel-Hashomer, Israel and Clinical Assistant Professor in the Department of Medicine, Center for AIDS Research at Stanford University School of Medicine, California, USA.
In recent years, Dr Schapiro's research has largely focused on the study of resistance to and cross-resistance between protease inhibitors. He has also been involved in evaluating the clinical utility of resistance assays. Dr Schapiro has published widely and codirects the Stanford University HIV Medicine course. He is also a member of numerous International Expert Panels and Working Groups.

Patrick Yeni

Hôpital Bichat-Claude Bernard,
Paris, France

Guy-Patrick Yeni is the head of the Department of Infectious Diseases, CHU Bichat-Claude Bernard, Paris, and is also Professor of Infectious Diseases at the Xavier Bichat Medical School at the University of Paris. He gained an MD as a specialist in internal medicine and infectious diseases, and also has a PhD in immunology.
Dr Yeni is a member (formerly head) of the Clinical Trials group at the French Agency for AIDS Research (ANRS). His area of research interest lies in therapeutic trials in HIV disease.
Dr Yeni occupies numerous positions on regulatory and advisory panels. He is currently chair of the IAS-USA panel on antiretroviral therapy use in adult HIV infection, and is a member of the French panel for the treatment of HIV infection.

Introduction

Despite the proven efficacy of highly active antiretroviral therapy (HAART) many patients for whom HAART is indicated simply choose not to take it. Although this is their prerogative, physicians involved in caring for people with HIV/AIDS have a responsibility to ensure that patients are adequately informed in order that they might make the right choices for themselves. Physicians must therefore strive to understand both the rationale for each patient's actions and be aware of the medical interventions that might best marry clinical expediency with the patient's desires and perceptions of therapy.

From a clinician's perspective, durability, potency, safety and the ability to change to another effective regimen at failure are of vital importance. These are not, however, necessarily the same criteria by which those who are to take a proposed regimen will judge its acceptability.

Several studies suggest that the adverse effects of antiretroviral therapy - feared or actual - are the primary reason why patients either choose not to initiate HAART or decide to discontinue it. This in turn raises the issue of adverse events encouraging poor adherence despite high patient awareness of the need to maintain a good virological response. Sometimes physicians are inclined to afford less weight to drug toxicity than are their patients, attributing non-adherence to HAART to possibly more esoteric causes. Convenience and lack of lifestyle disruption are also of major importance to those being asked to initiate and maintain a lifetime course of therapy; as are a number of other factors which may be weighted quite differently by patients and their doctors.

How, then, are we to marry clinical strategy with patient concerns; and how do the current drugs and regimens measure against a hypothetical standard for an "ideal" antiretroviral treatment acceptable to both clinicians and patients alike?

To address these issues and stimulate thought about the ways in which medical necessities (like efficacy, durability and regimen sequencing) can be balanced against major patient requirements of safety, tolerability and convenience, we are very pleased to welcome Drs Mike Youle, Joseph Gathe, Sharon Walmsley and Anton Pozniak to speak at this symposium. Beginning with an overview of factors associated with the safety and efficacy of HAART by Dr Youle, three individual drugs will be evaluated from both the clinical and patient perspectives. Dr Gathe will discuss nelfinavir, Dr Walmsley saquinavir and Dr Pozniak the investigational fusion inhibitor enfuvirtide (T-20). Lastly, Co-Chair Dr Jonathan Schapiro will lead us through an interactive examination of how both clinical and patient needs come together in selecting new drugs for development.

We welcome you all to what promises to be an interesting examination of the ways in which the practice of HAART, both current and future, is being determined by the partnership between clinicians and their patients.

Jonathan Schapiro and
Patrick Yeni

Safety and long-term success of HAART

Mike Youle

Director of AIDS Research, Royal Free Hospital, London, UK

Dr Mike Youle is an associate specialist in HIV medicine at the Royal Free Hospital, London, and is also director of HIV clinical research at the same institution. He also holds honorary lectureships in medicine and public health at the Royal Free and University College Medical School, London. Dr Youle obtained a B. Med. Sci. from Sheffield Medical School before completing his MB there.

Dr Youle sits on numerous national and international AIDS committees. He currently sits on the Advisory Panel to the WHO-UNAIDS on global therapeutic guidelines, and on the British HIV Association Executive Committee, amongst other roles. He has also served as an editor for the Journal of Antimicrobial Chemotherapy, and on the editorial board for several other journals.

Introduction

The current consensus in HIV medicine is that the benefits of highly active antiretroviral therapy (HAART) are achieved only through continuous, life-long treatment. Sixteen different antiretroviral agents are now available, and these can be combined in numerous ways to form potent HAART regimens. Faced with the daunting task of choosing an optimal HAART regimen, what criteria should physicians and patients use in their decision making, and which of these should be given the greatest weighting?

For many, the first question to be answered is: "Will the regimen work?" A recent meta-analysis of 23 clinical trials (total n = 3257 enrolled) has indicated that triple-drug HAART regimens have comparable virological efficacy at either 24 or 48 weeks – regardless of their composition (Figure 1).[1]

Assuming that all triple-drug regimens have the potential to potently suppress viral replication, regimen choice should be based on other criteria, including durability, safety, tolerability, convenience, resistance, lifestyle factors and perhaps also economics. But which of these is the most important to patients and their caregivers?

Safety is the major driver of treatment success

Two large cohort studies have now demonstrated that tolerability is the key driver of treatment continuation in HIV infection.[2,3] In both of these studies, toxicity was the most important reason for changing or stopping a HAART regimen; virological failure and non-adherence, although important, were less commonly implicated. The ICONA study group,[2] for example, estimated that 58.3% of therapy discontinuations within the first year of treatment were related to unacceptable adverse effects; in contrast, virological failure accounted for only 14.1% of treatment withdrawals in the same study (Figure 2).

Two recent randomized clinical trials – the BID Efficacy and Safety Trial (BEST)[4] and MaxCmin1[5] – 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 lower rates of virological undetectability at 48 weeks (57% vs 74% by intent-to-treat analysis; limit of detectability 500 copies/ml; $P < 0.001$).

Adverse effects were overwhelmingly responsible for this observation: toxicity-related discontinuations numbered 18 in the indinavir group, compared with 48 in the boosted indinavir group. In contrast, only 1 and 3 patients in each group, respectively, withdrew because of virological failure.

The interim results of the MaxCmin1 trial confirm and extend these findings.[5] In MaxCmin1, patients were randomized to receive either saquinavir/r 1000/100 mg *bid* (12 pills per day; n = 148) or indinavir/r 800/100 mg *bid* (6 pills per day; n = 158) in addition to nucleoside analogue support. At 24 weeks, 31 (20%) indinavir/r recipients had permanently discontinued randomized treatment because of a clinical adverse effect, compared with 12 (8%) patients in the saquinavir/r arm. Consequently, the proportion of patients who had HIV RNA <400 copies/ml at 24 weeks was higher in the saquinavir/r group (76% vs 61% with indinavir/r). Only two patients in each arm discontinued randomized treatment because of virological failure.

The 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.

Figure 1

HAART regimens have comparable virological efficacy at either 24 or 48 weeks, irrespective of their composition.[1]

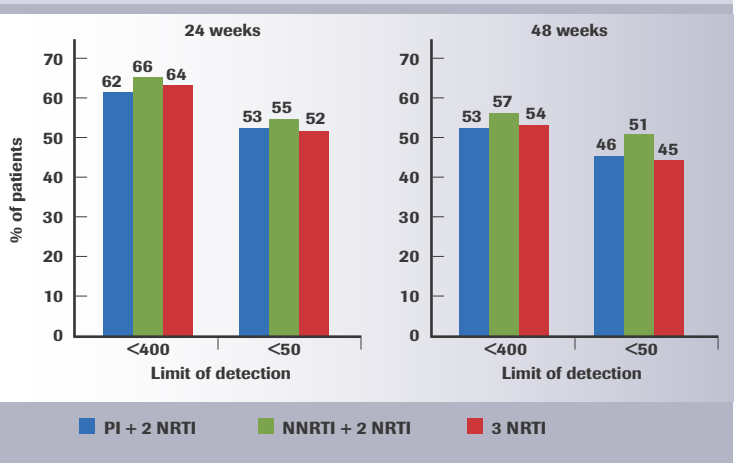
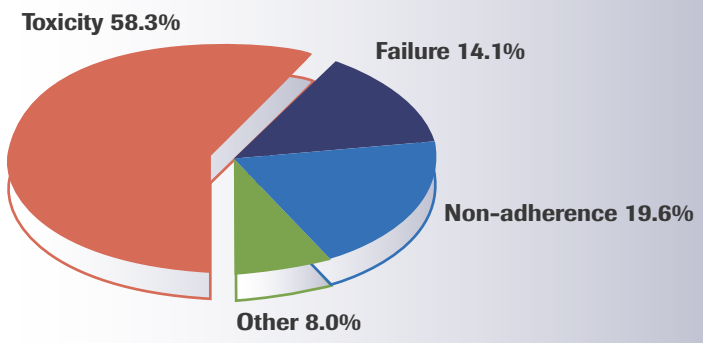


Figure 2

Reasons for treatment discontinuation at 45 weeks (from the Italian Cohort Antiretroviral Naïve [ICONA] Study Group).[2]



However, all drugs, including antiretrovirals, have adverse effects; our aim, therefore, should be to utilize those agents that we believe to have the best tolerability and safety profiles.

Saquinavir/r 1000/100 mg bid may have best safety profile among boosted PIs

Among the boosted PIs, saquinavir/r 1000/100 mg *bid* appears to be very well tolerated. Currently, saquinavir/r is "strongly" recommended for use in the US Department of Health and Human Services' Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults & Adolescents.[6] Relatively few patients receiving saquinavir/r 1000/100 mg *bid* discontinue treatment because of clinical adverse effects, which are mostly gastrointestinal in nature.[5] Safety concerns with indinavir/r include nephrolithiasis, retinoid-like effects, and hyperlipidaemia; at a dosage of 800/100 mg *bid*, permanent discontinuations because of clinical adverse effects are relatively frequent.[4]

Figure 3

Incidence of hypercholesterolaemia and hypertriglyceridaemia associated with 60 weeks' treatment with either lopinavir/r (400/100 mg bid) or nelfinavir (750 mg tid) in study M98-863.[8]

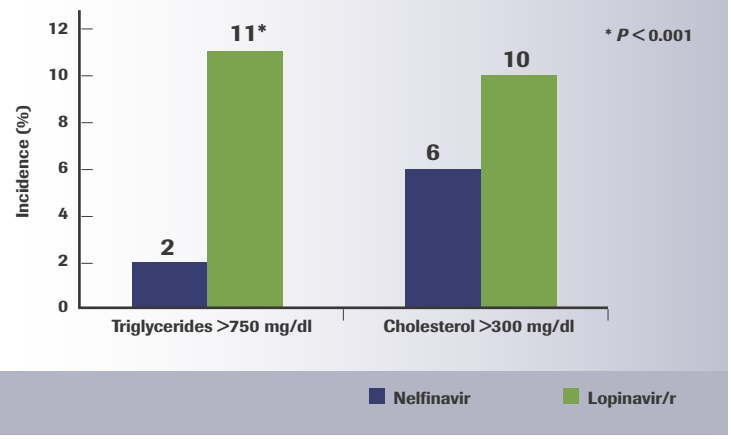
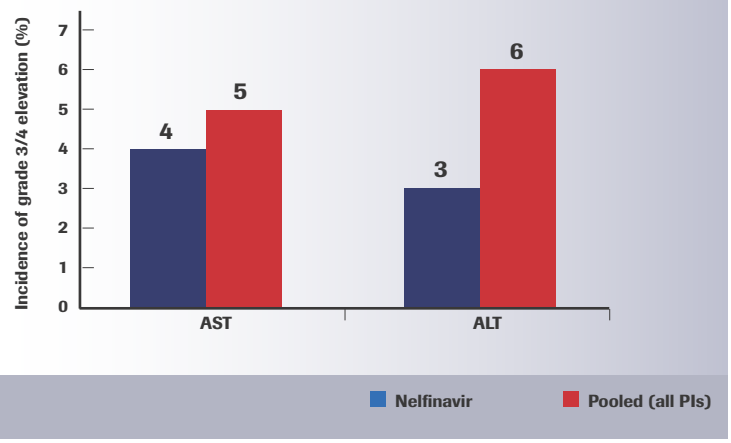


Figure 4

Incidence of hepatotoxicity in a cohort of HIV–HCV co-infected individuals treated with protease inhibitors.[18]



Few data from well-designed clinical trials are available on the tolerability of amprenavir/r 600/100 mg *bid*, compared either with amprenavir alone or with other boosted PIs. The principal adverse effects associated with amprenavir are gastrointestinal effects, dermatological reactions (including rare incidences of Stevens-Johnson syndrome) and paraesthesias.[7]

The principal adverse effects of lopinavir/r are diarrhoea and nausea. However, high incidences of hypercholesterolaemia (>300 mg/dl) and hypertriglyceridaemia (>750 mg/dl) have been noted in clinical trials,[8] particularly in patients with prior PI experience.[9]

Among the currently available boosted PIs, saquinavir/r 1000/100 mg *bid* may have the most favourable tolerability and long-term safety profiles.

Long-term safety: a growing concern in HIV

Concern is growing about the long-term safety of antiretroviral therapy, because of the increasing life expectancy of people with HIV infection. Hyperlipidaemia has long been associated with an increased risk of atherogenesis and coronary heart disease; additionally, cholesterol-lowering therapy has been proven to reduce cardiovascular events significantly in patients with elevated cholesterol levels.[10,11]

Both nelfinavir and saquinavir/r (1000/100 mg *bid*) appear to have minimal impact on plasma lipid levels. Study M98-863 found, at 60 weeks, grade 3 or 4 hypertriglyceridaemia in only 2% of patients taking nelfinavir, compared with 11% in lopinavir/r patients (Figure 3; $P < 0.001$).[8] As alluded to earlier, elevated triglyceride levels (grade 3 or 4) have been noted in up to 40% of multiple PI-experienced patients receiving lopinavir/r.[9] Additionally, a cross-sectional cohort study[12] has suggested that ritonavir-containing regimens are associated with slightly higher median triglyceride and cholesterol levels than regimens containing single PIs, such as nelfinavir.

However, the *impact* of ritonavir on serum lipid levels is clearly dose-related.[13] Several studies have now provided data suggesting that treatment with saquinavir plus low-dose ritonavir has *very* little effect on serum lipid levels, even in highly treatment-experienced patients.[14,15] Additionally, patients switching to saquinavir/r 1000/100 mg bid from regimens containing higher dosages of ritonavir may experience improvements in their serum lipid profiles.[16]

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

Preserving hepatic function in patients with HIV infection

In the HAART era, liver disease is emerging as the commonest cause of death among patients with HIV infection.[17] This may be attributable to the high prevalence of hepatitis C virus (HCV) co-infection in HIV-infected patients, but the hepatic adverse effects of antiretroviral therapy may also be a contributing factor. Minimizing the potential for antiretroviral therapy to cause hepatic injury should therefore be a priority for HIV physicians.

Compared with PIs as a whole, nelfinavir appears to be less likely to cause grade 3 or 4 elevations in hepatic transaminases among HIV-HCV co-infected patients (Figure 4).[18] Nevirapine, however, should probably be avoided or used with caution in patients with, or who may be predisposed to, liver disease.[19]

Summary and conclusion

Current HAART regimens are broadly comparable in terms of their virological and immunological efficacy. Data are emerging which indicate that safety is a key factor in determining ability to remain on therapy during the first year; in other words, the safety of a HAART regimen and its long-term success appear to be inextricably linked. Due consideration should therefore be given to the likely adverse effects of treatment and their acceptability to individual patients. Nelfinavir and saquinavir/r (1000/100 mg bid) have favourable tolerability and long-term safety profiles that make them valuable options in the treatment of HIV infection.

Notes

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Viracept:
Confidence of long-term control

Joseph Gathe
Medical Director, Donald R. Watkins Foundation,
Houston, Texas, USA

Joseph C. Gathe, Jr., M.D., received his medical degree from Baylor College of Medicine, Houston, Texas. He also attended the Washington University School of Medicine, St. Louis, Missouri. He completed his internship and residency at Baylor College of Medicine, St. Luke's Affiliated Hospital, Houston, Texas, where he was also Chief Resident. Dr. Gathe completed a fellowship in Infectious Diseases at Baylor College of Medicine, and the Methodist Hospital. During this time he received the Alpha Omega Honor Society Henri J. Kaiser Merit Scholar Award and the Henry O. McIntosh Award for Outstanding Resident in Internal Medicine. Dr. Gathe is a diplomat of the American Board of Internal Medicine, and subspecialty Infectious Disease.
Dr. Gathe is a clinical instructor, Department of Internal Medicine, Baylor College of Medicine. He is president of Therapeutic Concepts, P.A. and also serves as president of Donald R. Watkins Memorial Foundation, a non profit organization providing primary healthcare to indigent populations; Director, Scientific Advisory Board, Houston Clinical Research Network; and Chief of Staff of Infectious Diseases, Park Plaza Hospital, all in Houston, Texas. In addition, he is on the Advisory Board of the Diocesan AIDS Ministry in Houston.
Dr. Gathe is associated with the HIV Research-Houston Clinical Research Network, a Division of Montrose Clinic. He is also a fellow of the American College of Physicians and of the Infectious Diseases Society of America.
Dr. Gathe has been Principal or Co-Investigator for over 83 protocols focused on HIV/AIDS and the use of antiretrovirals, NRTI's, and protease inhibitors in treatment of these diseases. He has published extensively on these topics in such professional journals as AIDS, The Journal of Infectious Diseases, Annals of Internal Medicine, Journal of Acquired Immune Deficiency Syndromes Diseases, American Journal of Medicine and other professional publications.
Dr. Gathe is a member of many medical and scientific societies and was recognized by the African-American Health Care Trailblazers Hall of Fame in both 1998 and 1999.

Introduction

As a direct result of highly active antiretroviral therapy (HAART), patients with HIV infection are living longer, healthier lives than ever before. However, while progress has been made in controlling HIV, issues such as the challenges of long term compliance with therapy, long-term adverse events and the development of HIV drug resistance have created new challenges for people living with HIV and their care providers.

HIV readily develops mutations that confer resistance to one or more drugs in any HAART regimen, and some of these mutations will also confer resistance to other drugs in the same class. This phenomenon, called cross-resistance, can limit the number of treatment options that are open to patients in the future, making it extremely difficult to control HIV infection in later years. For example, significant cross-resistance is known to occur between the protease inhibitors (PIs) indinavir and ritonavir. Cross-resistance is also seen in other classes, such as the NNRTIs, where it is extensive.

This potential for cross-resistance means that we must use antiretroviral therapy very carefully from the moment that the decision to start treatment is taken. It is possible to plan treatment from the start to minimize the risk that cross-resistance will occur. Choosing antiretroviral drugs for initial use that have a low potential for cross-resistance, and which allow the future use of other drugs in the event of virological failure, is an important part of such a plan.

The PI nelfinavir has now shown consistent, long-term efficacy in randomized clinical trials. There is also a wealth of data to suggest that nelfinavir is not usually associated with cross-resistance to other PIs.

Virological failure on a nelfinavir-containing regimen is not usually associated with mutations in the HIV protease enzyme. Furthermore, those who do have a mutation in protease following the failure of a nelfinavir-based regimen usually have a mutation known as D30N. Because D30N is unique to nelfinavir, it is not usually associated with significant cross-resistance to other PIs. What these findings mean is that patients who are no longer responding to nelfinavir-based treatment might be expected to respond well to treatment with another PI.

Studies, both in the laboratory and in patients, have confirmed this. Samples of HIV from patients no longer responding to nelfinavir have been shown to retain susceptibility to a range of other PIs. Additionally, a majority of patients no longer responding to nelfinavir have been found to do well on subsequent saquinavir/ritonavir-based therapy.

In summary, nelfinavir appears to allow the future use of other PIs – as well as NNRTIs – in the event that patients stop responding to nelfinavir. These facts make nelfinavir an important and powerful option for the first-line treatment of HIV infection.

Nelfinavir: consistently and reliably effective in HIV infection

Many studies have now confirmed the potent, durable efficacy of nelfinavir in the treatment of HIV infection. One of these was study 511 (AG511), a randomized clinical trial comparing nelfinavir 500 or 750 mg *tid* with placebo, plus dual nucleoside analogues, in antiretroviral-naïve patients (n = 297).[1] At the 12-month time-point, patients from the nelfinavir 750 mg arm who had a viral load <5000 copies/ml (n = 56) voluntarily entered an open-label long-term extension of the trial, designated AG511-LTE,[2] which lasted for a further 3 years.

Analysis of data from AG511-LTE illustrates the sustained, reliable effect of nelfinavir-containing treatment on HIV infection. After a total of 4 years of treatment, 94% and 86% of patients had HIV RNA levels <400 and <50 copies/ml, respectively. These impressive results were accompanied by sustained increases in CD4 count. At the end of the study extension period, CD4 counts had increased, on average, by 403 cells/mm^3 versus baseline, building on the mean increase of 198 cells/mm^3 that was seen in the 12-month study AG511.

For long-term therapeutic management, there are other key factors that must be considered in addition to efficacy and durability. One very important consideration is the risk of viral resistance, and the impact that this might have on the future ability of HAART to control the virus in an individual patient.

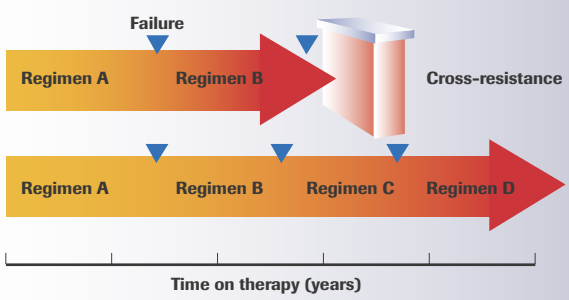
Cross-resistance is an important determinant of long-term treatment success

The emergence of viral resistance is one of the major reasons why patients stop or change their HAART regimen. Even in the presence of effective drug therapy, HIV can develop mutations that confer resistance to one of the drugs in a HAART regimen. When this happens, viral replication may increase to such an extent that the patient's viral load again becomes detectable. At this point, virological failure is considered to have occurred, and a new regimen is started.

However, some of the mutations that HIV develops can confer resistance to antiretroviral drugs *other than the ones that the patient is currently taking*. This phenomenon, called cross-resistance, can significantly reduce the number of new regimens that can be started in a patient experiencing virological failure (Figure 1). Additionally, a growing body of clinical evidence shows that response to treatment diminishes with increasing experience of antiretrovirals; this is partly due to accumulating drug resistance. For example, in study ACTG 398, only 16% of patients who had previously taken antiretroviral agents from all three

Figure 1

The development of cross-resistance between antiretroviral agents in the same class can limit the number of future treatment options that a patient has.



classes achieved HIV RNA levels <400 copies/ml, compared with 43% of double-class experienced patients.[3] Thus, cross-resistance gradually exhausts the range of available treatment options.

Fortunately, by planning treatment before the first HAART regimen is started, we can minimize the risk of cross-resistance developing and limit its impact. Such planning is essential to make sure that each individual patient can benefit from as many agents as possible within each class of antiretrovirals.

Most patients with detectable HIV RNA on nelfinavir do not have protease mutations

How can nelfinavir help to minimize the risk of cross-resistance? Analysis of HIV from 189 patients, from four clinical studies and two observational cohorts, reveals that the *HIV protease enzyme from >60% of patients with detectable plasma HIV RNA on nelfinavir contains no mutations* (Figure 2).[4] These patients are unlikely to have significant resistance to any PI, making the likelihood of response to treatment with a second-line PI very high. Additionally, in the same analysis, among patients who *did* have a mutation in the protease enzyme, most had the D30N mutation. As shown in Figure 3, the D30N mutation is not selected by any other currently available PI.[5]

Patients who do develop a primary mutation in protease during nelfinavir therapy are hence most likely to have D30N, which does not appear to affect the inhibitory activity of other PIs.

PI cross-resistance is therefore avoided in most patients who experience viral rebound while on nelfinavir. Overall, around 90% of patients with rebound (or non-response) on nelfinavir have a good chance of success with another PI.

The SWATCH study[6] has provided further evidence that nelfinavir is potent, and that virological failure on nelfinavir is not usually associated with protease mutations. In this study, patients were randomized to receive either nelfinavir (+ zidovudine + lamivudine) or efavirenz (+ didanosine + stavudine), and a third group alternated between these two regimens every three months.

Virological efficacy was similar in the efavirenz and nelfinavir arms at 48 weeks. Seven of 54 patients in the nelfinavir-based arm of the study experienced virological rebound during the study period. Genotypic (i.e. resistance mutation) data were available for six of these patients; no patient developed either D30N or L90M, the other primary resistance mutation that occasionally arises in patients receiving nelfinavir. Phenotypic (i.e. *in vitro* drug susceptibility) data were available for five of the seven patients; 30-fold resistance to lamivudine was found in two patients, while no patients had significant phenotypic resistance to nelfinavir.

These data suggest that failure on a nelfinavir-based regimen is probably attributable to resistance to another drug in the regimen, or to factors other than drug resistance (e.g. sub-therapeutic drug concentrations relating to poor adherence).

Figure 2

Genotypic analysis of HIV from patients (n = 189) experiencing either viral rebound or non-response after between 16 weeks and 2 years of nelfinavir-based antiretroviral therapy.[4]

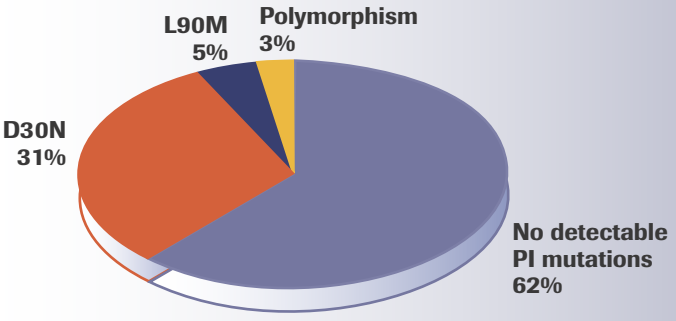
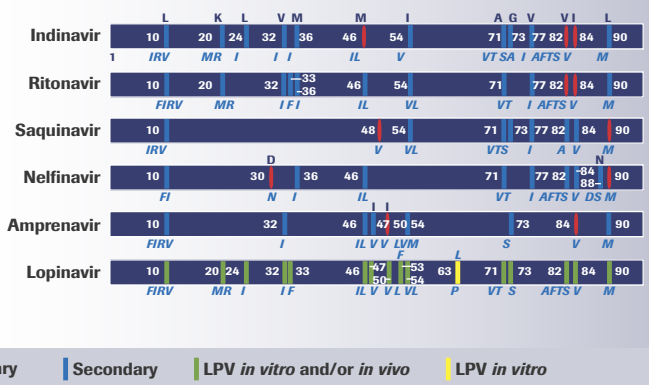


Figure 3

Comparison of the resistance profile of protease inhibitors. D30N is unique to nelfinavir.[5]



Nelfinavir allows the future use of PIs and NNRTIs: the clinical evidence

In summary:

• When treatment with nelfinavir fails, few patients have mutant viral protease.

• Of those who do, most are likely to have D30N, which does not confer cross-resistance to the available PIs.

Theoretically, therefore, it should be possible to use other PIs when treatment with nelfinavir fails. But is there any proof that this is true?

Many studies have now provided evidence that, after virological rebound on nelfinavir, there is a good chance that future PI- or NNRTI-containing regimens will achieve potent suppression of HIV replication.

Genotypic resistance testing in the Genotype-Assisted Antiretroviral Therapy (GART; CPCRA 046) study,[8] for example, found that the presence of the D30N mutation had a beneficial effect on short-term virological

response to the next HAART regimen administered. The 152 patients recruited to the study had experienced viral rebound after at least 16 weeks of PI-based antiretroviral therapy. The D30N mutation was associated with an average decrease in viral load of 0.41 $\log_{10}$ copies/ml during the first 2 months of the subsequent regimen.

Additionally, phenotypic analyses in two studies – CCTG 575[9] and VIRA3001[10] – have demonstrated that patients with virological failure during therapy with nelfinavir have HIV that remains susceptible to a range of other PIs. In contrast, prior therapy with, or baseline phenotypic resistance to, PIs other than nelfinavir was in many cases associated with significant cross-resistance.

Genotypic and phenotypic studies are only part of the picture. What happens *in the clinic* when patients rebounding on nelfinavir are changed onto other PIs? Now, clinical research has provided evidence of the sustained efficacy of PI regimens following rebound on nelfinavir therapy.

Tebas *et al.*, for example, found that most patients who had previously received nelfinavir subsequently responded to saquinavir/ritonavir-containing regimens.[11] As shown in Figure 4, a viral load of <500 copies/ml was rapidly achieved and sustained in most patients following 24 weeks of saquinavir/ritonavir-based treatment.

The C-BIG study[12] also showed that other PIs can form the basis for a viable treatment plan following nelfinavir rebound. Eighty-eight patients who had experienced virological failure on a nelfinavir-containing regimen were subsequently treated with saquinavir/ritonavir plus one or more previously unused NRTIs or an NNRTI. After 24 weeks of therapy, 85% of patients receiving saquinavir/ritonavir/NNRTI had achieved a viral load of <400 copies/ml.

Similar results were found in a retrospective clinical cohort study of 54 patients who switched to saquinavir/ritonavir-based therapy after virological rebound on a range of treatment regimens.[13] Individuals who had taken nelfinavir and developed the D30N mutation responded well to the new regimen: all achieved HIV RNA levels <500 copies/ml after 12 weeks of treatment (Figure 5).

In summary, nelfinavir allows the future use of other PIs; the evidence to support this comes from clinical studies as well as genotypic and phenotypic analyses.

Nelfinavir plasma concentrations are optimized by co-administration with food

Much attention has focused recently on how to optimize treatment with existing antiretroviral agents; for example, through the use of low-dose ritonavir as a "boosting" agent. Nelfinavir, in contrast to some other PIs, does not require the addition of ritonavir to attain adequate plasma concentrations; rather, administering nelfinavir with food improves its absorption from the gastrointestinal tract, increasing plasma concentrations by two- to three-fold. Moreover, a light snack appears to be sufficient to optimize nelfinavir concentrations.[14]

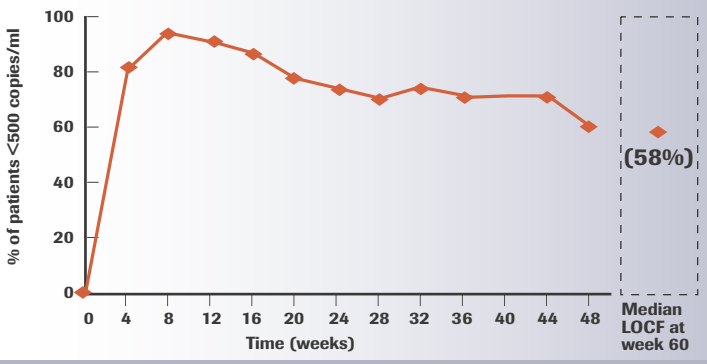
The benefits of administering nelfinavir with food have been illustrated by the ATHENA study of therapeutic drug monitoring (TDM).[15] In this study, treatment-naïve patients receiving nelfinavir (plus supportive nucleoside analogue therapy; n = 92) were randomized to receive nelfinavir treatment guided by TDM, or the current standard of care (i.e. no TDM). Patients found to have sub-optimal nelfinavir concentrations were advised to take the drug with food, and their plasma concentrations re-measured at a later date. This simple advice was sufficient to optimize plasma nelfinavir concentrations in approximately half of these patients, and undoubtedly contributed to the difference in virological efficacy observed at 48 weeks between the TDM and no-TDM groups (percent <500 copies: 81% vs 59%, respectively; $P < 0.03$).[15,16]

Nelfinavir: the confidence of long-term control

Nelfinavir is an effective agent in HIV infection.[1,2] In addition, the knowledge that other antiretrovirals – either PIs or NNRTIs – can be used successfully after nelfinavir

Figure 4

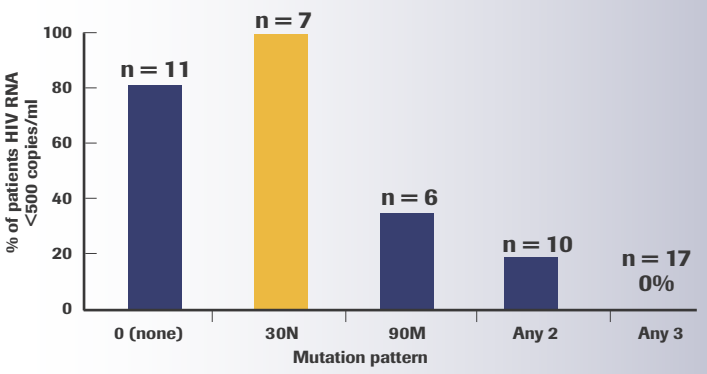
Virological response (percentage of patients with HIV RNA <500 copies/ml) of nelfinavir-rebound patients to a subsequent regimen based on saquinavir/ritonavir. [11]



LOCF = last observation carried forward.

Figure 5

Response to a saquinavir/ritonavir-containing regimen among patients with virological failure on various prior regimens, stratified by baseline mutation.[13]



Two out of three patients with mutations at 46, 82, or 84 achieved viral loads <500 copies/ml

means that physicians can prescribe, and patients can take, nelfinavir with a high degree of confidence.

Patients receiving nelfinavir may be less likely, compared with patients taking other antiretroviral agents, to stop or change their treatment regimen. In a study of risk factors for treatment discontinuation or modification,[17] nelfinavir was the only antiretroviral agent that was associated with a decreased relative risk of these outcomes.

Additionally, a recent study showed that patients switched onto nelfinavir from an NNRTI, because of toxicity, virological failure or another reason, remained on nelfinavir for a median time that was twice as long as they had stayed on their NNRTI.[18]

Taken together, all of this evidence suggests that nelfinavir works well, allows the future use of other antiretroviral agents, and that many patients are able to continue taking it long term.

Nelfinavir: a valuable option for first-line treatment of HIV infection

In summary, nelfinavir is an important option for the first-line treatment of HIV infection, not only because it has shown consistent, long-lasting efficacy in antiretroviral-naive patients, and is well tolerated, but also because it has low potential to cause cross-resistance to other PIs. Most patients who have taken nelfinavir first-line should be able to switch successfully to an alternative PI-containing regimen (or, indeed, to an NNRTI-containing regimen). Clinical evidence for this is supported by genotypic and phenotypic analyses of HIV.

As an agent that allows the future use of PIs and NNRTIs, nelfinavir should be considered as a component of first-line treatment for HIV infection. Nelfinavir is a useful part of any planned strategy for the long-term, potent suppression of the virus.

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Notes

Fortovase:
maximizing power, improving safety

Sharon Walmsley
Associate 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. Recently, she has participated in the Fortovase Once-Daily Canada USA (FOCUS) trial and the MaxCmin2 trial. 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, and she has a special clinical interest in the topic of women in HIV.
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. She 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

We now have over six years' clinical experience with saquinavir, the first protease inhibitor (PI) to become available for the treatment of HIV infection. In that time, saquinavir has proven to be a potent and very well tolerated agent in both antiretroviral-experienced and -naïve patients.

Co-administration of low doses of ritonavir ("r"; 100 mg bid) with saquinavir (1000 mg bid) boosts saquinavir plasma drug concentrations by around 10-fold. In recent years, boosted PIs such as saquinavir/r 1000/100 mg bid have become an important option in the treatment of HIV infection. However, to date, only one randomized clinical trial – the MaxCmin1 trial – has compared the efficacy and safety of different boosted PIs. The interim results of this trial suggest that saquinavir/r 1000/100 mg bid is at least as effective as, and has superior tolerability to, indinavir/r 800/100 mg bid. Additionally, preliminary data from several clinical trials and cohort studies have suggested consistently that saquinavir/r 1000/100 mg bid may have little or no effect on serum lipid levels over at least one year of therapy.

In 1995, saquinavir (Fortovase) became the first PI to be licensed worldwide for the treatment of HIV infection. The combination of saquinavir, and of other PIs that were launched subsequently, with other antiretroviral agents has revolutionized the treatment of HIV/AIDS.

In the ensuing six years, we have learned a great deal about saquinavir and how best to use it to maximize its potency and improve its convenience profile. A key development has been the use of low doses of ritonavir ("r"; 100 mg *bid*) in combination with saquinavir to augment its pharmacokinetics, facilitating increased potency and reductions in pill burden and dosage frequency. Pharmacokinetic[1] and clinical studies[2-4] have demonstrated that the ideal dosage, for most patients, is saquinavir/r 1000/100 mg *bid*. This dosage offers patients an attractive combination of potent, durable antiretroviral activity and favourable tolerability and safety profiles. Significantly, saquinavir/r appears to be a valuable treatment option in both treatment-naive and -experienced patients.[2-4]

MaxCmin1: the first head-to-head trial of boosted protease inhibitors

Recently, the interim results of the MaxCmin1 study[2] – the first randomized, head-to-head comparison of boosted PIs – have been reported. Patients recruited to MaxCmin1 (n = 306) included antiretroviral- and PI-naive individuals, those who had previously experienced intolerance to PIs, and patients with virological failure on a PI-based regimen (Figure 1). The median viral load at baseline was 4 $\log_{10}$ copies/ml, and the mean CD4 count was 277 cells/mm^3. Patients were randomized to receive either saquinavir/r 1000/100 mg *bid* (12 pills per day) or indinavir/r 800/100 mg *bid* (6 pills/day), with supportive nucleoside analogue therapy.

Saquinavir/r 1000/100 mg *bid* has a superior safety profile

After 24 weeks' treatment:

• 83% of patients in the saquinavir/r arm remained on randomized treatment, compared with 73% of patients in the indinavir/r group.

• More patients discontinued indinavir/r than saquinavir/r due to adverse events (42 patients vs 25 patients). This was primarily driven by the higher incidence of renal adverse events in the indinavir/r group.

Additionally, a wider spectrum of adverse events leading to discontinuation was observed in the indinavir/r group compared with the saquinavir/r group (Figure 2). Patients receiving indinavir/r reported a total of 75 grade 3 or 4 adverse events, while those receiving saquinavir/r reported 45.

These results suggest that good tolerability is the main driver of treatment continuation in HIV therapy.

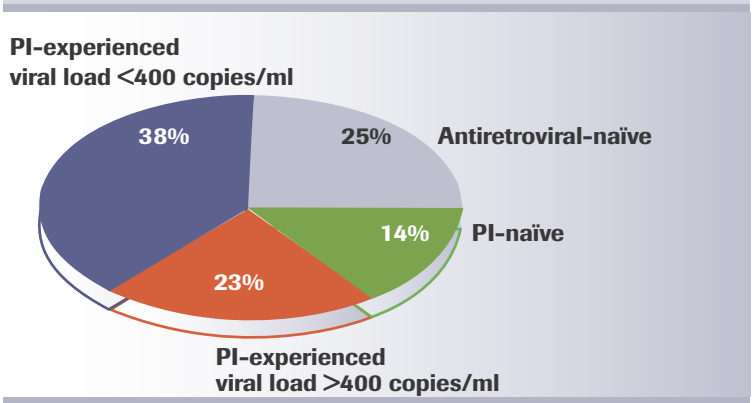
Saquinavir/r 1000/100 mg bid is highly efficacious

In terms of efficacy, both saquinavir/r and indinavir/r treatment were very potent; only two patients (1%) in each treatment group experienced virological rebound requiring discontinuation of the study drug.

However, when analysed in terms of 24-week HIV RNA levels, more patients who were exposed

Figure 1

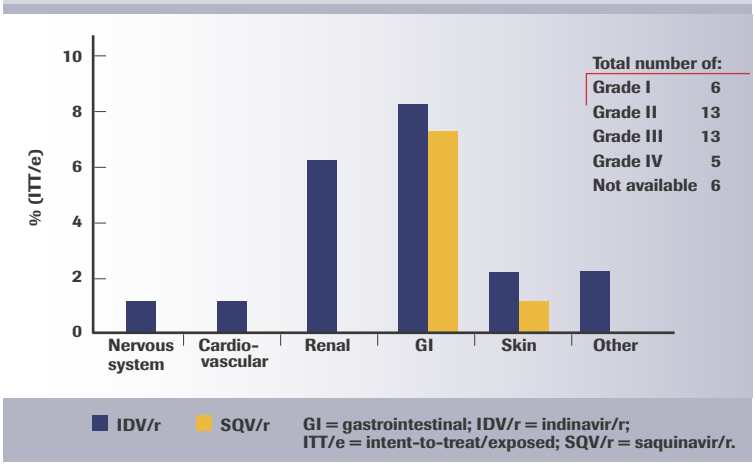
Baseline level of treatment experience among patients enrolled in the MaxCmin1 trial.[2]



PI = protease inhibitor

Figure 2

Clinical non-fatal adverse events leading to treatment discontinuation in the MaxCmin1 trial.[2]



GI = gastrointestinal; IDV/r = indinavir/r; ITT/e = intent-to-treat/exposed; SQV/r = saquinavir/r.

Figure 3

Percentages of patients achieving viral load <400 copies/ml at 24 weeks in the MaxCmin1 trial (by intent-to-treat analysis).[2]

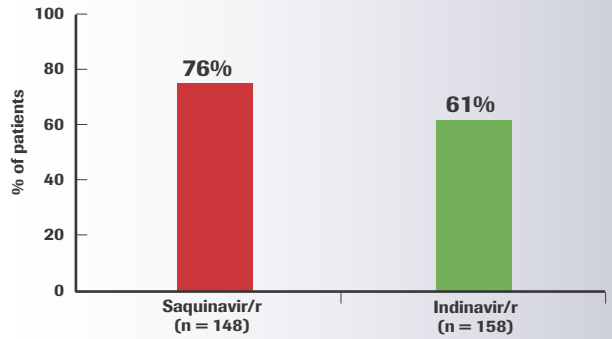
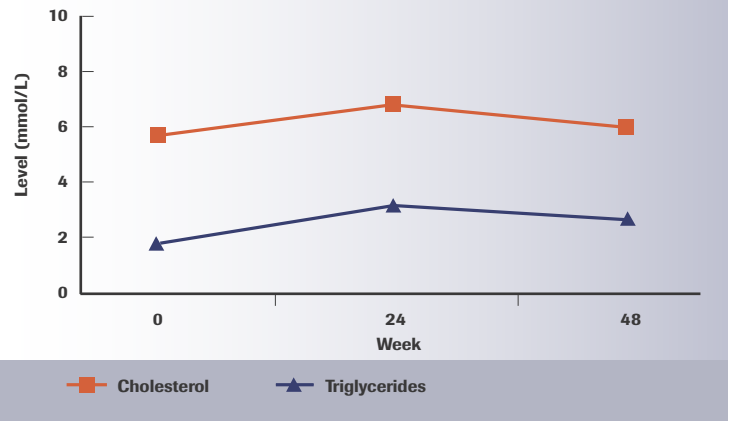


Figure 4

Changes in serum triglyceride and cholesterol levels over 48 weeks in treatment-experienced patients receiving saquinavir/r 1000/100 mg bid plus supportive antiretroviral therapy.[9]



to treatment with saquinavir/r had undetectable viral loads, when compared with the indinavir/r group. Using intent-to-treat analysis, where switch to another antiretroviral regimen was recorded as failure, more patients receiving saquinavir/r achieved HIV RNA levels <400 copies/ml (Figure 3). Including patients who discontinued the originally randomized treatment, 79% and 72% of patients originally randomized to saquinavir/r or indinavir/r, respectively, had HIV RNA <400 copies/ml at 24 weeks. Similar trends were seen at a limit of quantification of 100 copies/ml; additionally, analysis of changes in CD4 count at 24 weeks favoured saquinavir/r.

Saquinavir/r 1000/100 mg *bid* maximizes efficacy — and improves safety

The interim results of the MaxCmin1 study indicate that saquinavir/r 1000/100 mg bid is highly efficacious. The trends towards higher rates of virological suppression in the saquinavir/r arm appear to be driven by the better tolerability profile of this agent; this supports the argument that safety and tolerability have the greatest impact on the success of highly active antiretroviral therapy (HAART).

The final 48-week results of the MaxCmin1 trial will be presented at the 14th International AIDS Conference (Barcelona, 2002), and are eagerly awaited. A second trial in this series, MaxCmin2, is under way. In this trial, patients have been randomized to receive either saquinavir/r 1000/100 mg bid or lopinavir/r 400/100 mg bid in addition to supportive nucleoside therapy. Preliminary results are expected in late 2002.

Powerful antiviral activity in treatment-experienced patients

MaxCmin1 and other studies have shown that saquinavir/r 1000/100 mg bid appears to be very well tolerated in treatment-experienced patients. As with other boosted PIs, gastrointestinal adverse effects are experienced by some individuals, although these are usually mild and seldom lead to treatment interruption. Concern has been raised about the tolerability and safety of boosted PIs: boosting indinavir may increase the risk of nephrolithiasis and other adverse effects,[2,5] while lopinavir/r has been associated with elevated serum lipid levels,[6] particularly in PI-experienced patients.[7] The MaxCmin 1 and 2 studies will provide important comparative data on the incidence of adverse events with two boosted PIs in the randomized trial setting.

Saquinavir/r 1000/100 mg bid appears to be associated with few clinical adverse effects other than mild-to-moderate gastrointestinal events, and preliminary data suggest that it has little impact on serum levels of triglycerides and cholesterol (Figure 4).[2,8,9] In addition, patients switching to saquinavir/r 1000/100 mg bid from regimens containing higher dosages of ritonavir may experience reductions in their cholesterol and triglyceride levels.[4] Taken together, these initial findings suggest that **patients receiving saquinavir/r 1000/100 mg bid may be less likely to:**

- discontinue treatment
- require lipid-lowering therapy, or
- be exposed to an excess risk of future cardiovascular morbidity because of lipid abnormalities.

Double protease inhibitor boosting: a promising option in treatment-experienced patients

As we leave 1996 further and further behind, an increasing proportion of our patients can be considered treatment-experienced or highly treatment-experienced. Effective, durable control of HIV replication in this group of patients is difficult to achieve, not least because of accumulating drug resistance and prior experience of adverse events. Double PI boosting, in which low doses of ritonavir are used to boost concentrations of two PIs simultaneously, is a promising new approach to treatment in this patient group.

Three different combinations of PIs are currently undergoing evaluation:

- saquinavir/lopinavir/r 1000/400/100 mg bid
- saquinavir/amprenavir/r 1000/600/100 mg bid
- amprenavir/lopinavir/r 600–750/400/100 mg bid.

Of these combinations, saquinavir/lopinavir/r is, perhaps, the one for which there is greatest pharmacokinetic and clinical support.

In comparison to other double boosting combinations, saquinavir/lopinavir/r does not appear to be associated with an increase in adverse drug interactions over that seen for each individual drug.[10] Additionally, four clinical trials of saquinavir/lopinavir/r 1000/400/100 mg bid in antiretroviral-experienced patients have now provided evidence that this combination is effective and well tolerated.[10-13] In one study, saquinavir/lopinavir/r produced a reduction in viral load of approximately 1.5 $\log_{10}$ copies/ml that was sustained for at least 20 weeks.[13] Importantly, Staszewski and colleagues[10] have recently demonstrated that saquinavir/lopinavir/r 1000/400/100 mg bid can be used successfully without nucleoside analogues, in patients who cannot tolerate or have significant resistance to these drugs. In their study, 24 weeks' double boosted PI treatment was associated with a median decrease in HIV RNA of 2.7 $\log_{10}$ copies/ml.

Summary and conclusions

- The interim results of the MaxCmin1 study indicate that saquinavir/ritonavir 1000/100 mg twice daily is a highly efficacious and well-tolerated option for patients who require boosted PI therapy.
- In comparison with some other boosted PIs, saquinavir/r has a superior safety profile; additionally, preliminary data suggest that it may have minimal impact on serum lipid levels. This becomes more and more important as antiretroviral therapy continues to evolve and life expectancy among patients with HIV infection continues to increase.
- Among the available boosted PIs, saquinavir/r offers patients the confidence of potent, durable efficacy, coupled with superior tolerability and a favourable safety profile.
- The double boosting regimen saquinavir + lopinavir/r offers a new, interesting treatment option for heavily pretreated patients or patients who cannot tolerate nucleoside reverse transcriptase inhibitors.

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Notes

Notes

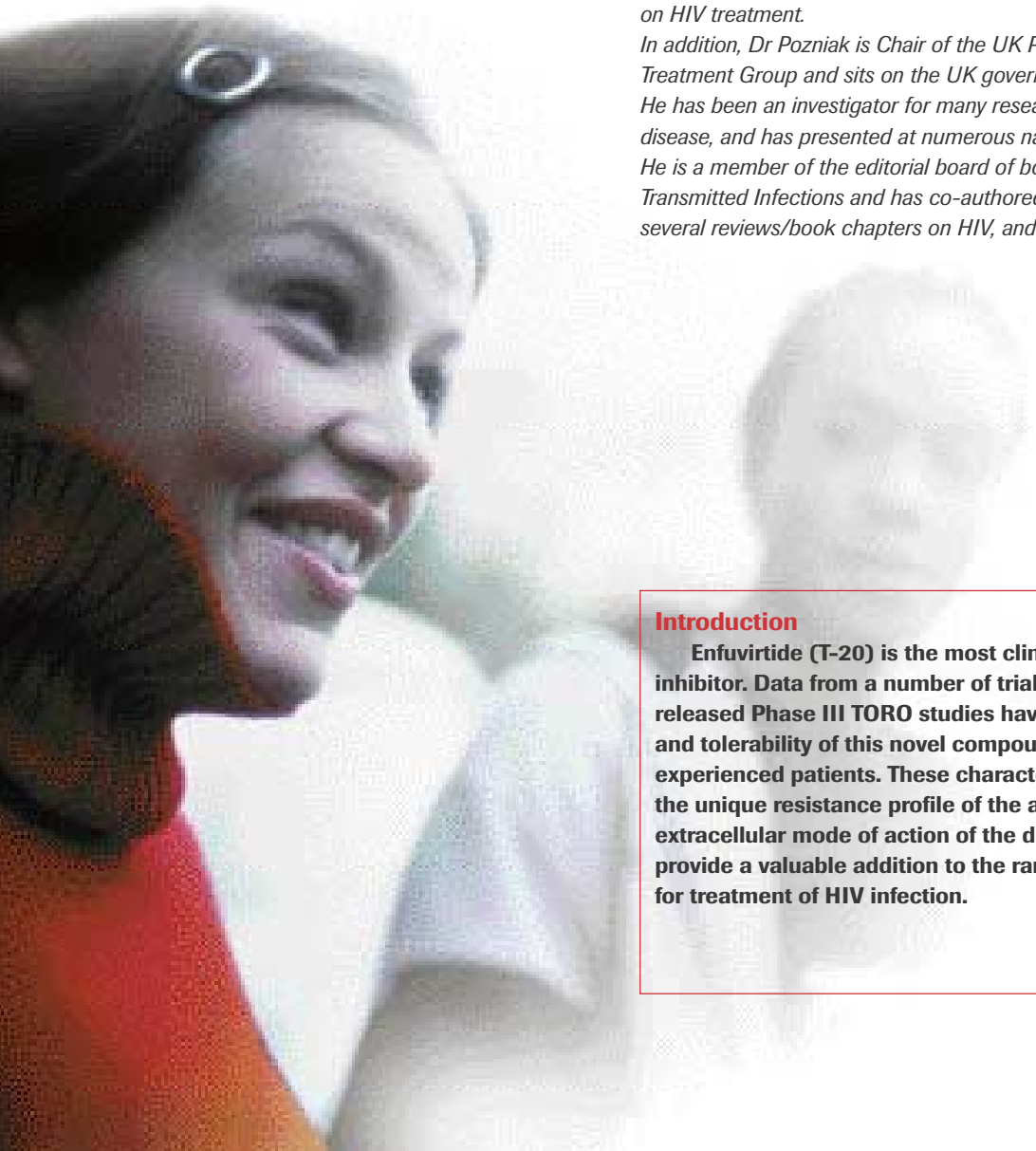
Enfuvirtide (T-20):
Fighting fusion, inspiring hope

Anton L. 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 recognised 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

Enfuvirtide (T-20) is the most clinically advanced fusion inhibitor. Data from a number of trials, including recently released Phase III TORO studies have demonstrated the potency and tolerability of this novel compound in heavily treatment-experienced patients. These characteristics, along with the unique resistance profile of the agent, stem from the extracellular mode of action of the drug. Enfuvirtide is set to provide a valuable addition to the range of therapies available for treatment of HIV infection.

An unmet need

Since the advent of highly active antiretroviral therapy (HAART) for the treatment of HIV infection, the number of patients living with the disease long-term has increased. Treatment failure due to the emergence of resistance is a problem that continues to limit the potential benefits of therapy and the number of patients living with multidrug resistant forms of HIV continues to increase. Consequently, as shown in Figure 1, the number of individuals initially infected with drug-resistant HIV is also increasing.[1] This population of patients who have severely limited treatment options therefore presents a group with a desperate need for new antiretroviral agents that are active against HIV strains resistant to conventional antiretrovirals.

Enfuvirtide: a new mode of action

Enfuvirtide is the most clinically advanced drug in a new class of antiretroviral agents, the fusion inhibitors. There is a growing body of data to support the efficacy of this new agent, a peptide that mimics a key section of the gp41 HIV viral protein. By interacting with gp41, enfuvirtide blocks HIV from fusing with and entering CD4 cells: this new mode of action is likely to drive the efficacy, safety and resistance characteristics of this new agent. The currently available antiretrovirals disrupt the HIV replication cycle once the virus is inside the cell.

Recent studies have indicated that the toxicity profile of an antiretroviral agent is one of the main drivers of adherence to medication.[2] Importantly, the extracellular mode of action of enfuvirtide also reduces the potential for systemic adverse events, as the build up of the drug inside cells is limited. The drug therefore offers enormous potential for the treatment of HIV infection.

Enfuvirtide: antiviral activity

Phase II trials, T20-205 for example, provided a wealth of activity data to support the further development of enfuvirtide, and Phase III trials have now reached their primary 24 week endpoints. In spite of the heavily treatment-experienced background of patients recruited to T20-205, a rapid and durable change in viral load from baseline of 1.5 log copies/ml was achieved over 48 weeks in many patients when enfuvirtide was added to conventional oral antiretrovirals.[3] Similarly, in the T20-206 trial in patients PI and NRTI experienced but NNRTI naïve, nearly 50% of patients (ITT population; combined enfuvirtide arms) achieved HIV RNA < 50 copies/ml at 48 weeks when enfuvirtide (T-20) was added to background therapy.[4]

In the pivotal TORO 1 and TORO 2 enfuvirtide Phase III studies HIV-1 infected patients, who were treatment-experienced and/or had documented resistance to each of the three classes of currently available antiretrovirals were eligible to be screened for the study. Prior to randomisation an optimised background (OB) of 3-5 approved or experimental antiretrovirals were selected for each patient based on prior treatment history and HIV genotype and phenotype. Patients were then randomised 2:1 to enfuvirtide plus OB or OB alone (control arm). The primary endpoint of the study was the difference in viral load in the two arms at 24 weeks based on an intent to treat (ITT) analysis using the last observation carried forward (LOCF) approach for missing data. In the TORO 1 and TORO 2 studies respectively 491 and 504 HIV-1 infected patients were randomised and 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) patients who received enfuvirtide as part of their combination regimen achieved a reduction in HIV levels of 1.697 $\log_{10}$ copies/ml compared to 0.763 $\log_{10}$ copies/ml for those who were randomized to the control arm. (Figure 2). The difference in the magnitude of decrease in HIV between the two arms, was 0.934 $\log_{10}$ copies/ml and was statistically significant ($p<0.0001$).[5] In the TORO 2 study (conducted in Europe and Australia) patients who received enfuvirtide as part of their combination regimen achieved a reduction in HIV levels of 1.43 $\log_{10}$ copies/ml

Figure 1

The incidence of strains of HIV with >10 fold phenotypic resistance to antiretroviral agents in untreated, recently infected patients (n = 389) in North America.[1]

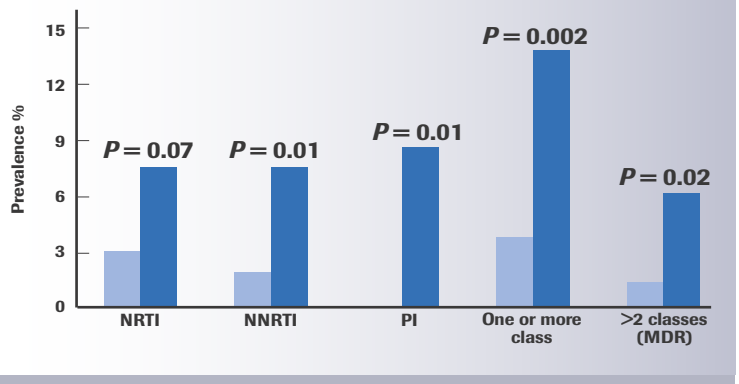
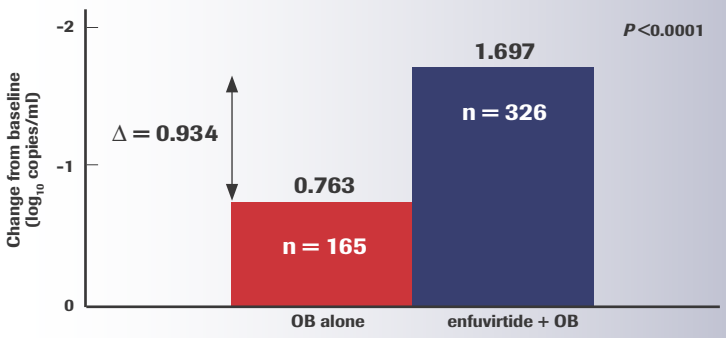


Figure 2

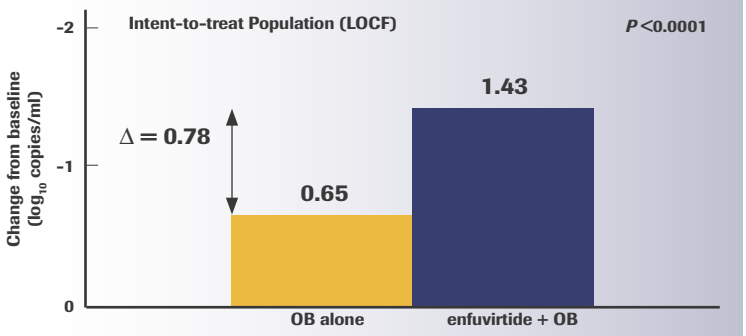
TORO 1 study, change in viral load from baseline, in highly treatment-experienced patients, receiving optimized background therapy alone or optimized background therapy plus enfuvirtide (T-20), over 24 weeks (Intent-to-treat analysis – last observation carried forward).



OB = optimized background

Figure 3

TORO 2 study, change in viral load from baseline, in highly treatment-experienced patients, receiving optimized background therapy alone or optimized background therapy plus enfuvirtide (T-20), over 24 weeks (Intent-to-treat analysis – last observation carried forward).



OB = optimized background

Figure 4

Percentage of patients remaining on enfuvirtide (T-20) after 48 weeks of treatment in three different clinical trials.

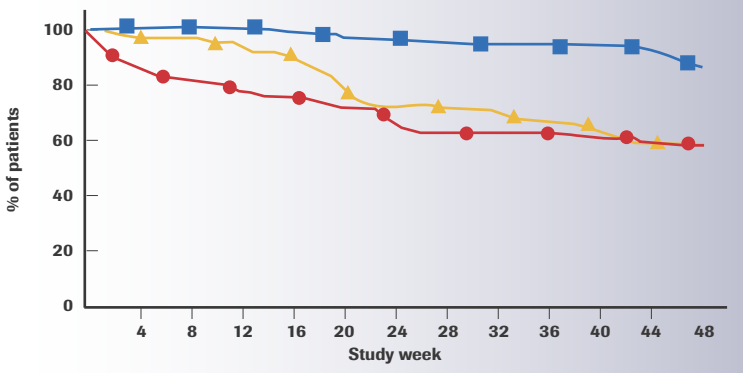
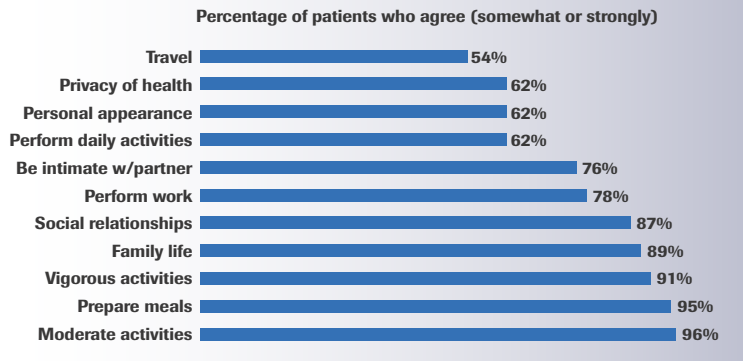


Figure 5

Responses of T20-205 patients to a survey monitoring the effect of enfuvirtide (T-20) on various activities of daily living.

"…relative to my other HIV/AIDS drugs, injections have not limited or altered my ability to…"



compared to 0.65 $\log_{10}$ copies/ml for those who were randomized to the control arm (Figure 3). The difference in the magnitude of decrease in HIV between the two arms, was 0.78 $\log_{10}$ copies/ml and was statistically significant ($p<0.0001$).[6]

Enfuvirtide: adherence and tolerability

The majority of toxicities associated with antiretroviral agents result from interference with intracellular physiological processes, or interactions with cellular receptors. As indicated above, because enfuvirtide does not accumulate inside the cell, and interacts specifically with HIV-1 gp41, the potential for this agent to cause intracellular toxicity is reduced. In addition, the agent is less likely to exacerbate the adverse events observed with current antiretroviral agents. Accordingly, the T20-205 safety evaluation attributed no therapy discontinuations to enfuvirtide.[3]

The pharmacokinetics of enfuvirtide support administration as a single 90 mg subcutaneous injection, twice daily. The main adverse event associated with enfuvirtide is a generally mild to moderate injection site reaction. This reaction is rarely treatment-limiting: testament to the fact that this is an adverse event that patients can generally tolerate. Long-term studies show that the majority of patients remain on enfuvirtide after 48 weeks of treatment (Figure 4).[3,4,7] Ongoing Phase III trials have been designed to further assess the safety and tolerability of enfuvirtide. Initial data from the Phase III TORO 1 and TORO 2 trials have suggested that the safety profile of the enfuvirtide containing regimen was generally similar to the control arm and similar to earlier Phase II studies. [6,7]

To assess the impact of enfuvirtide treatment on quality of life, patients taking part in the enfuvirtide T20-205 study were asked to gauge the effect of treatment on a number of different activities. The results of this survey are shown in Figure 5, which indicates that in most patients enfuvirtide treatment did not limit activities of daily living.[8] Additionally, the majority of patients did not find the subcutaneous administration of enfuvirtide difficult.

The place of enfuvirtide in HAART

Evidence from *in vitro* phenotypic and genotypic analyses that enfuvirtide has a unique resistance profile is now being validated by data from clinical trials. As with other antiretroviral agents, to maintain durability of response enfuvirtide must be used in combination with other active drugs. Information such as patient history should be used in conjunction with genotypic and/or phenotypic testing to construct a combination of effective agents as a firm background for enfuvirtide treatment.

Enfuvirtide has not been shown to be a substrate, inducer or inhibitor of cytochrome P450. It is therefore unlikely that enfuvirtide will interact with other antiretrovirals. Furthermore, the stepwise nature of the fusion process offers great potential for synergy of enfuvirtide with other entry inhibitors that might subsequently be developed to target different stages of the HIV entry process.

Notes

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Power to the people

Jonathan M. Schapiro
Clinical Assistant Professor, Center for AIDS Research, Stanford University School of Medicine, Stanford, California, USA

Jonathan M Schapiro is Director of the AIDS Service at the National Hemophilia Center, Tel-Hashomer, Israel and Clinical Assistant Professor in the Department of Medicine, Center for AIDS Research at Stanford University School of Medicine, California, USA.
Dr Schapiro attended the Ben-Gurion University School of Medicine in Beer Sheva, Israel, where he received the Harry Peristowsky Award to the Outstanding Graduating Student.
During his Fellowship in the Stanford Center for AIDS Research, Dr Schapiro's research demonstrated the importance of drug resistance mutations, adherence and drug levels to protease inhibitor failure. Subsequently, he received the Timothy L Beckett Jr Award for Excellence in Clinical Teaching and the Jack Remington award for Clinical Excellence in Infectious Diseases.
In recent years, Dr Schapiro's research has largely focused on the study of resistance to and cross-resistance between protease inhibitors. He has also been involved in evaluating the clinical utility of resistance assays and the development of advanced interpretation systems for these assays. Dr Schapiro has published several articles in leading journals, such as the Annals of Internal Medicine and The Lancet.
Dr Schapiro is also a highly active contributor to educational initiatives, co-directing the Stanford University HIV Medicine course and being involved in several CME programs for AIDS-treating physicians. He is also a member of numerous International Expert Panels and Working Groups.

Introduction

The treatment of HIV infection has evolved significantly from the early antiretroviral monotherapy regimens, most notably with the introduction of highly active antiretroviral therapy (HAART) following the development of the protease inhibitor (PI) class of agents. The introduction of further new agents and new classes, such as the non-nucleoside reverse transcriptase inhibitors (NNRTIs) resulted in an ever-increasing number of options for combination therapy. With many of the current combinations effectively suppressing viral replication if taken appropriately, patients and their physicians have increasingly looked at other 'differentiating factors' to help them select their first- and second-line therapies. Important among these factors is the day-to-day convenience of the dosage regimen — with once- or twice-daily dosage emerging as popular selection criteria for treatment-naive patients.

It is also important that we do not lose sight of the needs of treatment-experienced patients. What we are now seeing in the clinical setting is significant growth in the numbers of patients who have received prolonged treatment with two or more different HAART regimens and who are presenting with multi-drug-resistant virus and few remaining treatment options. It is these treatment-experienced patients, who may now comprise almost one-third or more of the patients that physicians see in their clinics, and who require new treatment options that are effective in the face of extensive drug resistance.

Along with this need to extend the period of effective therapy, through the introduction of new agents, comes an important consideration – that of long-term safety. Treatment-experienced patients who have received prolonged combination therapy must be monitored for any evidence of long-term toxicities, which may not have become apparent in original clinical trials or, indeed, during the first few years of therapy. Given the urgent medical need for new treatments that are effective for treatment-experienced patients, how should the scientific community and pharmaceutical industry identify the most important criteria for developing future antiretroviral agents? The idea that HIV is becoming a more manageable, often chronic disease, prompts a systematic assessment of the priorities of treatment, to ensure that the characteristics of new drugs under development will have maximum benefit in filling current unmet needs of patients.

The changing nature of antiretroviral therapy

At the end of 2001, UNAIDS/WHO estimated that 40 million people were living with HIV/AIDS worldwide. Over the next decade, this figure is regrettably going to increase, mostly as a result of new infections and increasing rates of diagnosis, but also because of the impact of antiretroviral therapy on life expectancy. Hopefully a mounting number of patients will have access to potent drugs to combat HIV: and as a direct result the life expectancy of individuals with HIV infection will continue to lengthen significantly. Figure 1 illustrates that the introduction of HAART regimens in the mid-1990s coincided with a precipitous drop in the number of deaths from HIV in the USA, while the overall prevalence of AIDS continues to increase steadily.

What are the main achievements that have resulted in the successful evolution of therapy?

• *Efficacy*

Before the introduction of the first protease inhibitor (PI) in 1995, the key unmet medical need was efficacy, making potency the major driver of antiretroviral drug development. Dual nucleoside analogue regimens failed after a limited period of time because the potency of these combinations was not sufficient to suppress viral replication below the level necessary to prevent the emergence of resistant virus. In addition, the development of mutations that confer cross-resistance to other agents in the same class of antiretrovirals limited the potency of subsequent regimens. With the PIs came a novel mode of action and unique resistance profiles, which, together with the potency of these agents, resulted in effective suppression of HIV when used diligently in triple drug combinations.

The introduction of HAART regimens was accompanied by a shift in the perception of the disease. The prevention and treatment of HIV-associated opportunistic infections became a secondary issue to the antiretroviral management of HIV/AIDS as a chronic infectious disease.

• *Convenience, toxicity and safety*

With this advance came new treatment issues, however. Increased potency was accompanied by increased complexity, with treatment strategies involving a greater number of pills that had to be taken at regular intervals throughout the day often with dietary restrictions such as fasting. Concerns that patients found it difficult to adhere to regimens that contained high numbers of pills and regular doses resulted in a new search for improved formulations of certain agents, and the development of regimens that contained two or more drugs in the same pill.

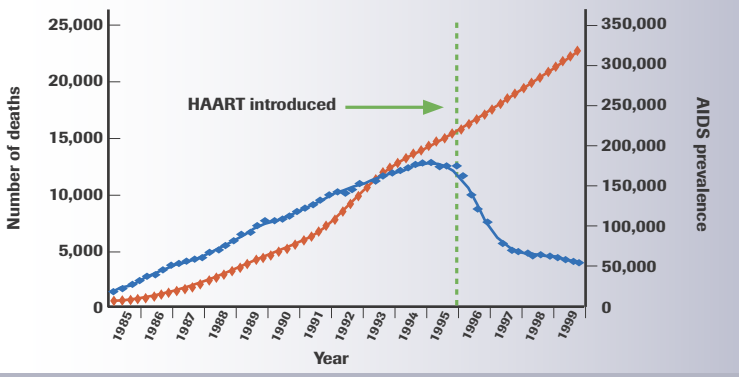
While concentrating on issues of patient convenience, of great importance was recognition that the adverse effects and long-term safety issues associated with antiretroviral agents were an important consideration. Two recent cohort studies have confirmed that toxicity of antiretroviral agents is a key driver of ability to remain on therapy,[1,2] and may have a greater impact on overall treatment success than pill count. Additionally, patient surveys designed to assess the reasons why people do not adhere to HAART have revealed that the frequency and severity of adverse effects is a key driver of non-adherence.[3]

The current unmet need

The treatment options for antiretroviral-naïve patients are improving with first-line regimens with good efficacy and improved convenience and safety.

Figure 1

Estimated number of deaths from AIDS, and prevalence of the disease in the USA 1985–1999.



But for the growing number of patients with multiple HAART failures, options are often limited and entail complex regimens with increasing adverse events. The needs of these patients need urgently to be met.

• *Multiple drug resistance*

In the absence of a treatment that completely eradicates HIV from an infected individual, there is the continuing danger that the virus will eventually mutate and rebound even when potent antiretroviral drugs are being used. Consequently, there is an increasing number of patients who have experienced, and developed resistance to, a range of drugs from each class of antiretrovirals, and have almost exhausted the available treatment options. For example, in a representative study of more than 200,000 US patients receiving care between 1996 and 1999, 50% of individuals were found to harbour HIV that was phenotypically resistant to at least one antiretroviral drug.[4] Moreover, 51% of the patients whose viral load was >500 copies/ml were infected with strains of HIV resistant to 2 or 3 classes of antiretrovirals (Figure 2). In addition, a population of individuals initially infected with drug resistant forms of the virus is emerging.[5]

The focus is therefore to develop new antiretrovirals with unique resistance profiles. The fusion inhibitor, enfuvirtide (T-20), is the first of a new class of HIV drugs that will hopefully go a long way in fulfilling the needs of this growing population. Enfuvirtide (T-20) T-20 has demonstrated efficacy in difficult-to-treat patients with resistance to multiple drug classes and it does not confer cross-resistance to NRTIs, NNRTIs or PIs. Experience has shown that durable suppression of HIV replication can be achieved only when combinations of agents are taken together. This means that, for the durable suppression of HIV in treatment-experienced patients, the development of additional agents with novel resistance profiles is vital.

• *Long-term safety*

The increased life expectancy of HIV-infected patients now afforded by HAART has also led to a major shift in the common causes of death, towards non-HIV causes of morbidity and mortality. For example, hepatitis B or C co-infection is prevalent among HIV-infected individuals, and liver disease is emerging as a common cause of death. The long-term safety profile of antiretroviral agents is therefore coming under closer scrutiny, to avoid exacerbation of existing illnesses (such as liver disease), or the creation of new problems for patients in the future (like cardiovascular disease). The development of additional antiretroviral agents with favourable, non-overlapping, long-term safety profiles is a priority.

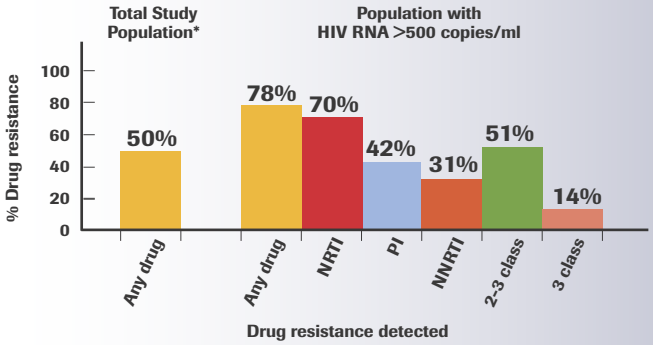
Making decisions for the future

At present, therefore, much of the focus of treatment research is on the area of urgent medical need, concentrating on the development of agents with unique resistance profiles and activity against multiple-drug-resistant virus. How then, do we reconcile this focus, with the pivotal physician selection criteria of drug potency?

Consider, for example, the development of two hypothetical antiretroviral agents, only one of which can be selected for further development. One agent might have pharmacokinetic properties that support once-daily administration, while the other must be taken three times daily. The second agent has a good tolerability profile, and is not associated with any serious adverse events; the first, however, has been linked to a potentially hazardous long-term side effect in a minority of patients. Which drug should be chosen? How should we balance safety against convenience? What about a new drug from an existing class of antiretrovirals that has an established mechanism of action, but for which resistance data indicate an overlap with another agent in that class, versus an agent with a novel, but unproven, mechanism of action? These questions and considerations need to be addressed in an open forum, to ensure that new drug development and physician treatment implementation is optimised for the ultimate benefit of those living with HIV. With continual attention to the needs of HIV-infected patients, treatment options tailored to meet the different requirements of heterogeneous groups of patients should become an achievable goal.

Figure 2

Prevalence of drug resistance in HIV isolates from 209,000 patients in medical care in the USA.[4]



* 63% had viral load >500 copies/ml

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Notes

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