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Sunday 13th July 15.45 – 17.45

Amphithéâtre Bleu, Level 2,
Le Palais des Congrès

2nd IAS Conference on HIV
Pathogenesis and Treatment, Paris

MASTERS of ART

Satellite Symposium

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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.

Introduction

Françoise Brun-Vézinet
Head, Department of Virology, Bichat-Claude Bernard Hospital, Paris, France

Professor Françoise Brun-Vézinet is currently Professor of Microbiology at University of Medicine Paris, and Head of the Department of Virology at Bichat-Claude Bernard Hospital, Paris. After earning her degree in medicine from the University of Paris, she completed her postdoctoral fellowship in virology in 1988. She was involved in initial research on infection with HIV-1 and HIV-2, and continues to work in that specialty. Her research efforts are currently focused on the variability of HIV and resistance to antiretroviral drugs.

Anton Pozniak
Consultant, 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 HIV Medicine, *and has co-authored many original research reports, several reviews/book chapters on HIV, and numerous abstracts.*

Welcome to Paris, to the 2nd IAS Conference on HIV Pathogenesis and Treatment, and to the Roche satellite symposium, "Masters of ART". We hope that you will benefit from this opportunity to interact with colleagues from around the world.

This year marks the 20th anniversary of the discovery of HIV-1 – 20 years in which new challenges have emerged as quickly as our knowledge of the virus and its pathogenesis has grown. In that time, the introduction of highly active antiretroviral therapy (HAART) has greatly extended the lives of HIV-infected individuals, but has created the new challenges of long-term toxicity and extensive cross-resistance. If we are to make the goal of life-long suppression of HIV achievable for all HIV-infected individuals, then we must not only increase the number of effective treatment options, but also learn how to adapt treatment strategies to get the best out of the drugs available to us.

In today's symposium, we aim to examine the current state of the art of HIV therapy. In some ways, the successful treatment of HIV-infected individuals is a marriage between science and art. Choosing an active combination of antiretrovirals that will effectively tackle the virus, while maintaining quality of life, is an art that requires the application of scientific principles and clinical knowledge to a set of unique, patient-specific circumstances. It is therefore fitting that our symposium takes place in Paris, a city that has a long association with the arts, social progress and scientific research.

Toxicity and lack of adherence are the most common reasons for treatment failure among HIV-infected patients. Indeed, anxiety about side effects may even prevent patients from initiating or continuing therapy where there is a clear clinical need. Two of today's speakers, Dr Calvin Cohen and co-chair Dr Anton Pozniak, will show us some of the strategies that can be used to advance protease inhibitor (PI) treatment to meet the changing needs of our patients.

Boosting with low doses of ritonavir significantly increases the plasma concentrations of co-administered PIs, resulting in improved convenience and, possibly, enhanced efficacy against drug-resistant HIV. This strategy has now become a standard of care. However, few studies have provided the data we need to decide which boosted PI regimen to use. The results of the MaxCmin1 trial, and preliminary data from the MaxCmin2 trial, will be presented by Dr Cohen. These two head-to-head trials are providing valuable insights into the comparative safety and tolerability of different boosted PI regimens.

PI boosting is an established strategy; however, there are circumstances in which it may be necessary to use two boosted PIs together. Such an approach can provide added potency to overcome PI resistance, and might also form the basis of an effective nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen for patients who are unable to take these drugs because of resistance or toxicity. Dr Cohen and Dr Pozniak will present data on the use of saquinavir in combination with lopinavir/ritonavir both with and without NRTIs.

The requirement for chronic HIV therapy is a burden for those infected with HIV, and one that may compromise therapeutic benefit. We must therefore strive to enhance the convenience and tolerability of existing agents, thereby encouraging good adherence with treatment and, hopefully, improving its efficacy. Dr Pozniak's talk will include a summary of recently presented data on the new Roche 625 mg formulation of nelfinavir, which will reduce the pill count from ten tablets per day to four tablets per day.

The growing prevalence of drug-resistant virus in the community means that there is an urgent need for drugs that are active against resistant HIV strains. Roche has recently developed enfuvirtide, the first of a new class of antiretrovirals with a completely novel mode of action, the fusion inhibitors. Because it acts at a different mechanistic site, enfuvirtide is active against virus that is resistant to other antiretroviral agents. We are delighted to welcome Professor Joep Lange to present some of the latest data from the on-going Phase III trials of enfuvirtide, and Dr James Witek, who will be describing how to achieve the maximum benefit from treatment with this important new compound.

With the increasing importance of liver disease as a cause of mortality in the HAART era, preserving hepatic function has become an important goal in the overall management of HIV infection. Dr Douglas Dieterich will discuss the antiretroviral treatment of HIV–HCV co-infected patients, focusing on the place in therapy of nelfinavir.

We very much hope that you will enjoy the meeting and that you will find these presentations both informative and stimulating.

Françoise Brun-Vézinet
Anton Pozniak

Neo-classical ART:
the role of nelfinavir in HIV-HCV co-infected patients

Douglas Dieterich
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Douglas T. Dieterich, MD, is a Professor of Medicine, Vice Chair, and Chief Medical Officer of the Department of Medicine at Mount Sinai School of Medicine, New York City. He has a triple appointment in the Divisions of Liver Disease, Gastroenterology, and Infectious Diseases.

After graduating from Yale University, New Haven, CT, Dr Dieterich received his medical degree from New York University School of Medicine. He completed his internship and residency in internal medicine at the Bellevue Hospital Center in New York City, where he was also a fellow in the Division of Gastroenterology.

Dr Dieterich is a member of many professional societies, and is a fellow of both the American College of Physicians and the American College of Gastroenterology. He has served on several committees of the AIDS Clinical Trials Group, National Institutes of Health (NIH), including the Steering Committee of the Opportunistic Infections Core Committee and the Cytomegalovirus (CMV) Committee, and was Chair and Co-chair, respectively, of the Enteric Parasites Committee and Protozoan Committee. He also served on the NIH Study Sections for CMV and cryptosporidiosis.

Dr Dieterich is an investigator for several ongoing studies evaluating the safety and efficacy of various antiviral treatment regimens for HIV and chronic hepatitis. He is the author of numerous journal articles, abstracts, and book chapters on viral hepatitis and AIDS-associated infections of the gastrointestinal tract and liver, and their treatment.

Nelfinavir is among the least hepatotoxic of all antiretroviral agents

The high incidence of hepatitis C virus (HCV) co-infection in HIV-infected individuals (around 30%), coupled with increased survival and antiretroviral hepatotoxicity, has led to the emergence of liver disease as a major cause of mortality in HIV populations with access to highly active antiretroviral therapy (HAART; Figure 1).[1-4]

Preserving hepatic function has therefore become an important goal in the overall management of HIV infection. All antiretrovirals are potentially hepatotoxic, but there may be important differences between agents: nevirapine and ritonavir (at therapeutic dosages) appear to be the most likely among available antiretrovirals to cause liver enzyme elevations,[5] while nelfinavir appears to be associated with a low overall risk of liver enzyme elevations.[6]

The hepatic safety of nelfinavir has been confirmed in several clinical studies. For example, the TARGET cohort study[7] assessed liver function in 2,198 HIV-infected patients (23% hepatitis B and/or C co-infected) treated with HAART between 1997 and 2001. In this study, the lowest rates of severe liver enzyme elevations among 13 antiretroviral agents were seen with nelfinavir (Figure 2).

Moreover, Sulkowski *et al.*[8] showed that addition of nelfinavir to a dual nucleoside-based regimen was not associated with any increase in the risk of grade 3 or 4 liver enzyme elevations. In contrast, the use of therapeutic-dose ritonavir in this group of patients was associated with a relative risk of severe liver enzyme elevations of 4.8 versus dual nucleosides alone. Moreover, in two retrospective studies in 1,052[9] and 740[10] HIV–HCV co-infected patients receiving protease inhibitor (PI) therapy for ≥ 3 months, nelfinavir was associated with lower rates of severe liver enzyme elevations compared with other PIs (Figure 3).

Nelfinavir-based HAART has been clinically proven to provide potent and durable suppression of HIV replication over at least 4 years of continuous treatment,[11] and has shown comparable efficacy to agents such as atazanavir and ritonavir-boosted fosamprenavir in randomized clinical trials.[12-14]

In comparison with other antiretroviral agents, few patients discontinue nelfinavir because of adverse events. In addition, since nelfinavir selects for the unique D30N resistance-associated mutation that does not reduce viral sensitivity to any of the other currently available PIs, continued successful treatment with PIs may be possible after failure of first-line nelfinavir-based combinations, as shown in practice by a body of clinical evidence.[15-17]

In conclusion, the available data show that nelfinavir is an effective antiretroviral agent with a superior safety and tolerability profile that may have an important role to play in the treatment of patients with HIV–HCV co-infection. As with other antiretroviral agents, however, it is important to monitor liver function at regular intervals in all patients receiving nelfinavir.

Nelfinavir appears to have a favourable safety profile in HIV–HCV co-infected patients

References

1. Bica I, McGovern B, Dhar R, *et al. Clin Infect Dis* 2001; **32**:492–497.
2. Puoti M, Spinetti A, Ghezzi A, *et al. J Acquir Immune Defic Syndr* 2000; **24**:211–217.
3. Soriano V, Garcia-Samaniego J, Valencia E, *et al. Eur J Epidemiol* 1999; **15**:1–4.
4. Martin-Carbonero L, Soriano V, Valencia E, *et al. AIDS Res Human Retrovirus* 2001; **17**:1467–1471.
5. Wit FW, Weverling GJ, Weel J, *et al. J Infect Dis* 2002; **186**:23–31.
6. Prescribing information for Viracept, 2002. Available at www.viracept.com.
7. Imperiale S, Lanes SF, Stern JO, *et al. 6th International Congress on Drug Therapy in HIV Infection (HIV6)*, 2002; poster 150.
8. Sulkowski MS, Thomas DL, Chaisson RE, *et al. JAMA* 2002; **283**:74–80.
9. Dieterich D, Fischl M, Sepulveda G. *42nd Interscience Conference on Antimicrobial Agents and Chemotherapy*, 2002; poster H-1729.
10. Aceti A, Pasquazzi C, Zechini B, *et al. J Acquir Immune Defic Syndr* 2002; **29**:41–48.
11. Gathe J, Chu A, Yuen N, *et al. 8th European Conference on Clinical Aspects and Therapy of HIV Infection*, 2001; poster LB10.
12. Schürmann D, Gathe G, Sanne I, *et al. 6th International Congress on Drug Therapy in HIV Infection (HIV6)*, 2002; poster PL14.4.
13. Konopnicki D, De Wit S, Pol B, *et al. 6th International Congress on Drug Therapy in HIV Infection (HIV6)*, 2002; poster P16.
14. Sanne I, Cahn P, Percival L, *et al. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy*, 2001; abstract I-667.
15. Tebas P, Patick AK, Kane EM, *et al. AIDS* 1999; **13**:F23–F28.
16. Zolopa AR, Tebas P, Gallant J, *et al. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 2000; abstract 2065.
17. Zolopa AR, Shafer RW, Warford A, *et al. Ann Intern Med* 1999; **131**:813–821.

Figure 1

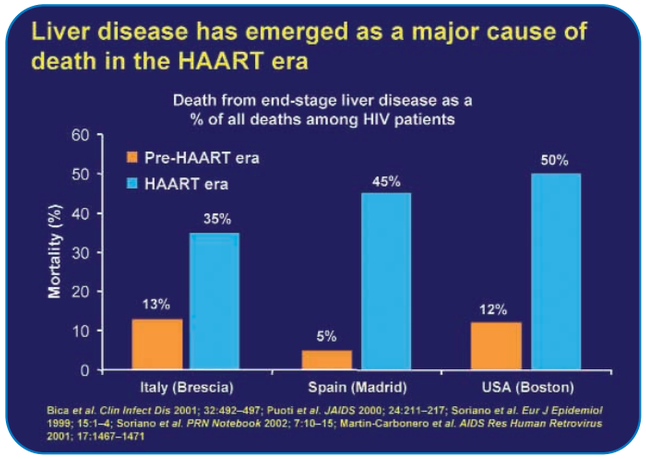
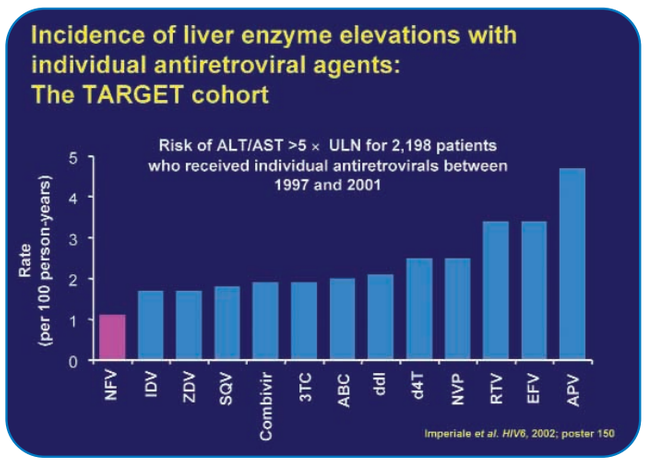


Figure 2



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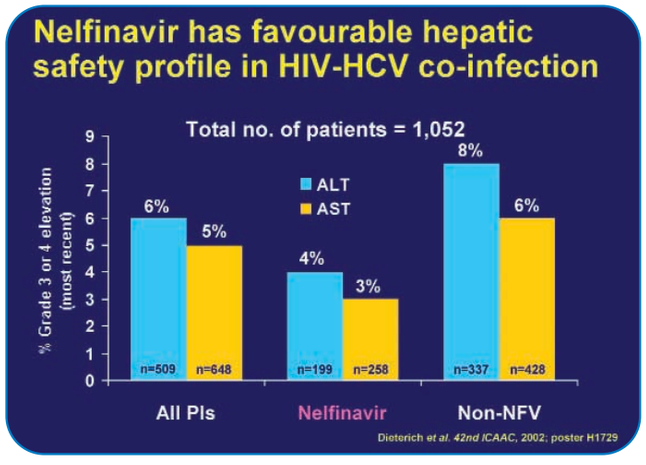


Notes

Renaissance ART:

novel treatment strategies using boosted saquinavir

Calvin Cohen
Research Director, Community Research Initiative New England, and Research Director, Harvard Vanguard Medical Associates, Boston, MA, USA

Calvin J. Cohen, MD, MSc, is a Clinical Instructor at Harvard Medical School in Boston, MA, a Staff Physician at Bngham and Women's Hospital, and Research Director of Harvard Vanguard Medical Associates and the Community Research Initiative of New England.

Dr Cohen earned his BA at Cornell University in Ithaca, NY, his MD at the Albert Einstein College of Medicine in New York City, and his MSc at the Harvard School of Public Health in Boston, MA. After graduating, he completed his internship and residency in medicine at Beth Israel Hospital in Boston. He was also Chief Medical Resident at the Veterans Administration Hospital in Brockton, MA, under the auspices of Harvard Medical School. His fellowship in general internal medicine was conducted at Harvard Medical School.

Dr Cohen has served as co-chair of the Scientific Advisory Committee AmFAR Community-Based Clinical Trial Network, and was a co-investigator of the Harvard/BCH AIDS Clinical Trial Unit. In addition to his clinical and research role, he is currently a co-principal investigator of the New England AIDS Education and Training Center, and is a member of the Science Planning Council for the Community Program for Clinical Research on AIDS (CPCRA), a network of clinician-researchers supported by the National Institutes of Health.

Dr Cohen's research interests are focused on the antiviral treatment of HIV and related topics. He has authored and co-authored numerous articles published in Annals of Internal Medicine, New England Journal of Medicine, *and* The Lancet. *Dr Cohen is the recipient of the Outstanding Physician's Award for his work at Harvard Vanguard Medical Associates; The Harvard Pilgrim Health Care Robert H. Ebert Teaching Award and the Champions of the Search Award; the AIDS Action Committee Community Recognition Award; the AECOM Distinction for Research in Cardiology; and the Upjohn Award for Excellence in Medical Training.*

Boosting protease inhibitors (PIs) with low doses of ritonavir ("r"; usually ≤ 200 mg/day) significantly increases the plasma concentrations of the co-administered PI, resulting in improved convenience and possibly enhanced efficacy against drug-resistant HIV. This strategy has now become a standard of care and has made a big difference in the treatment of PI-experienced patients. However, a potential problem with this approach is the increased toxicity that may occur with higher drug levels. Saquinavir/r, at a dosage of 1000/100 mg twice daily, has demonstrated good efficacy, and has safety and tolerability profiles that compare favourably with those of other boosted PIs.

In the MaxCmin1 study, the first ever head-to-head comparison of boosted PIs, the efficacy of saquinavir/r 1000/100 mg twice daily (n = 148) was comparable to that of indinavir/r 800/100 mg twice daily (n =158).[1] However, in an intent-to-treat analysis in which discontinuation of randomized treatment was considered as failure, saquinavir/r resulted in a higher proportion of patients with < 400 plasma HIV-1 RNA copies/ml than indinavir/r ($P = 0.014$, Figure 1). This is a consequence of the higher rate of discontinuations due to clinical non-fatal adverse events in the indinavir/r arm than in the saquinavir/r arm (18% *vs* 10%, $P = 0.006$). In particular, patients in the saquinavir/r arm were less likely to experience treatment-limiting gastrointestinal, renal or dermatological adverse events than those in the indinavir/r arm. In addition, saquinavir/r was associated with much lower changes from baseline in fasting lipid levels compared with indinavir/r at weeks 4 and 48.

Saquinavir/r 1000/100 mg *bid* provides potent efficacy while avoiding some of the adverse effects of other PIs

In the next study in this series, MaxCmin2, saquinavir/r 1000/100 mg twice daily (n = 163) was compared with lopinavir/r 400/100 mg twice daily (n = 163). The results of a preliminary week-24 analysis show that both regimens appear to be highly effective (Figure 2) and well tolerated in the treatment of HIV infection, although results have not been presented for each arm separately.[2] These data are awaited with interest.

The favourable tolerability and safety profiles of saquinavir/r 1000/100 mg twice daily make this one of the few good first boosted PI options. In addition, it is especially suitable for patients at risk of cardiovascular disease or experiencing adverse effects with other boosted PIs.

Patients with extensive treatment experience and a high viral load may benefit from the added potency of double boosted PI treatment (two PIs in combination with low-dose ritonavir). The choice of PI combination is important, because pharmacokinetic interactions and cross-resistance can reduce the efficacy of double boosted PI regimens. The combination of saquinavir with lopinavir/r is highly promising due to favourable pharmacokinetics,[3] potential synergy between saquinavir and lopinavir,[4] and a lower level of phenotypic cross-resistance between lopinavir and saquinavir than between lopinavir and other currently available PIs.[5]

In the PIE study,[6] a pilot investigation in 28 PI-experienced HIV-infected individuals with a high baseline incidence of PI resistance, 24 weeks of treatment with saquinavir/lopinavir/r (1000/400/100 mg twice daily) resulted in 42% of patients achieving a viral load of < 50 HIV-1 RNA copies/ml. There were few withdrawals due to tolerability problems (3/28) or virological failure (1/28), and only a modest impact was seen on plasma lipid levels.

A number of other studies investigating the safety and efficacy of saquinavir/lopinavir/r in combination with nucleoside reverse transcriptase inhibitors have also shown promising results (Figure 3).[7–9]

Double PI boosting is a promising new option for heavily pre-treated patients

In conclusion, saquinavir/r 1000/100 mg twice daily has demonstrated high efficacy with a very good safety and tolerability profile. Double boosted PIs such as saquinavir/lopinavir/r can be highly effective as part of an individualized therapeutic regimen, and may be of particular importance in heavily pretreated patients.

References

1. Cahn P, Dragsted UB, Pedersen C, *et al. XIV International AIDS Conference*, 2002; poster WeOrB1265.
2. Dragsted UB, Gerstoft J, Youle M, *et al. 6th International Congress on Drug Therapy in HIV Infection (HIV6)*, 2002; poster PL14.5.
3. Stephan CJ, Lutz T, Kurowski M, *et al. XIV International AIDS Conference*, 2002; poster TuPeB4561.
4. Molla A, Mo H, Vasavanonda S, *et al. Antimicrob Agents Chemother* 2002; **46**:2249–2253.
5. Parkin NT, Chappey C, Maranta M, *et al. 5th International Workshop on HIV Drug Resistance and Treatment Strategies*, 2001; poster 065.
6. Hellinger J, Cohen CJ, Morris AB, *et al. 9th Conference on Retroviruses and Opportunistic Infections*, 2002; poster 451-W.
7. Ruiz L, Ribera E, Bonjoch A, *et al. 9th Conference on Retroviruses and Opportunistic Infections*, 2002; poster 421-W.
8. Smith GHR, Klein MB, Murphy T, *et al. XIV International AIDS Conference*, 2002; poster TuPeB4547.
9. Zala C, Patterson P, Coll P, *et al. XIV International AIDS Conference*, 2002; poster TuPeB4492.

Figure 1

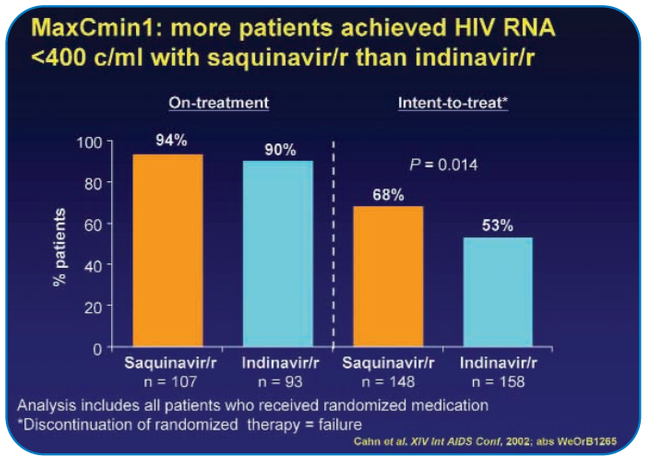


Figure 2

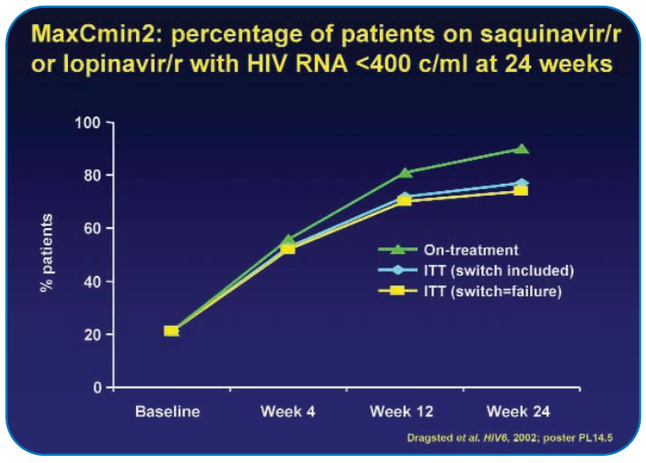
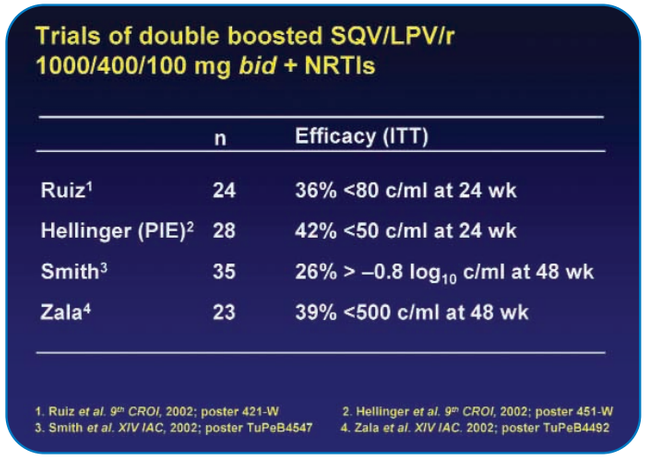


Figure 3



Notes

Contemporary ART: advancing protease inhibitor treatment to meet changing patient needs

Anton Pozniak
Consultant, 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 HIV Medicine*, and has co-authored many original research reports, several reviews/book chapters on HIV, and numerous abstracts.*

The introduction of highly active antiretroviral therapy (HAART) has greatly extended the lives of HIV-infected individuals, but has created the new challenges of long-term toxicity and extensive cross-resistance. There are several different techniques that can be used to help overcome these problems.

Use of existing drugs in new ways

Nucleoside reverse transcriptase inhibitors (NRTIs) are considered the standard supportive therapy for protease inhibitor (PI)-based antiretroviral combination therapy. However, prolonged use of NRTIs can lead to the shortening of mitochondrial DNA, and this has been implicated in causing a range of potentially serious toxicities including symptomatic hyperlactataemia, lactic acidosis, hepatosteatosis, lipoatrophy and haematological abnormalities.

Nucleoside-sparing therapy may be useful in patients with progressive toxicity or resistance to these agents

These conditions can be distressing for the patient and may also lead to changes in body shape and appearance (lipodystrophy). There are also other important drug-specific toxicities within the nucleoside class, such as abacavir-associated hypersensitivity and zidovudine-related anaemia. In the light of these toxicity problems, there is little to be gained from continuing NRTI treatment in patients with NRTI-resistant virus.

In such cases, the use of low-dose ritonavir ("r") to boost, simultaneously, two PIs may be an effective NRTI-sparing treatment option. Staszewski's group has investigated the use of saquinavir/lopinavir/r (1000/400/100 mg *bid*) in patients from the Frankfurt Cohort who had NRTI-associated toxicities or extensive resistance to NRTIs.[1] Data from 42 patients who have reached 24 weeks of therapy show a median decrease in viral load of 3.5 $\log_{10}$ copies/ml and a median increase in CD4 cell count of 146 cells/mm^3 (Figure 1). This response is particularly impressive considering the extensive treatment experience (median 6.5 years' prior antiretroviral treatment, 91% PI-experienced) and advanced disease stage (median CD4 cell count 131 cells/mm^3) of these patients.

Refinement of existing drugs to improve performance

A second strategy for advancing PI treatment is to improve the performance of an existing drug. For example, the PI nelfinavir, an established drug that is one of the most widely used PIs, has been reformulated to reduce the number of pills that patients need to take (from ten down to four pills daily).

Pharmacokinetic studies[2] have shown that the new formulation is bioequivalent to the existing formulation when both are taken with food (Figure 2). In addition, data from two studies[3,4] suggest that the new formulation may be associated with a clinically significant improvement in diarrhoea (Figure 3). A Marketing Authorisation Application has been submitted to the EU for this formulation.

Reformulating antiretrovirals can improve their convenience and/or tolerability

Development of new drugs

There is a growing need for drugs with activity against PI-resistant virus. Research in this area is proceeding; several promising new PIs have been identified and are currently in development. Another strategy is to develop antiretrovirals with novel modes of action that can be used in combination with existing PIs to provide potent combinations; an example is the new fusion inhibitor, enfuvirtide.

References

1. Staszewski S, Dauer B, Stephan C, *et al. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy*, 2002; poster H176.
2. Charoin JE, Oxley P, Gerber M, *et al. 4th International Workshop on Clinical Pharmacology of HIV Therapy*, 2003; poster 6.5.
3. Kaeser B, Akintola D-J, Saifulanwar A, *et al. 4th International Workshop on Clinical Pharmacology of HIV Therapy*, 2003; poster 6.4.
4. Nieto-Cisneros L, Johnson M, Horban A, *et al. 4th International Workshop on Clinical Pharmacology of HIV Therapy*, 2003; poster 6.6.

Figure 1

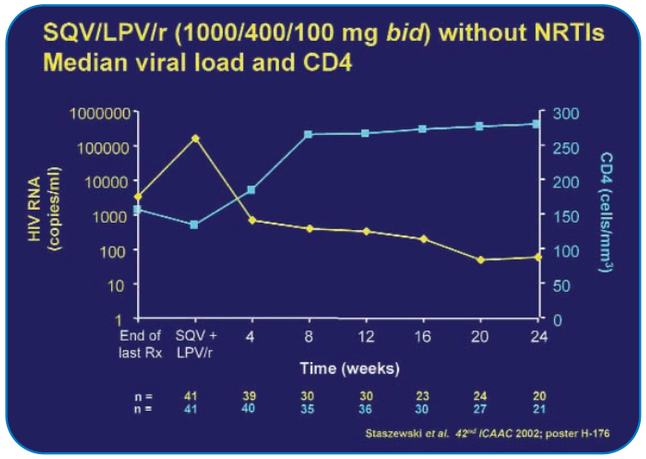
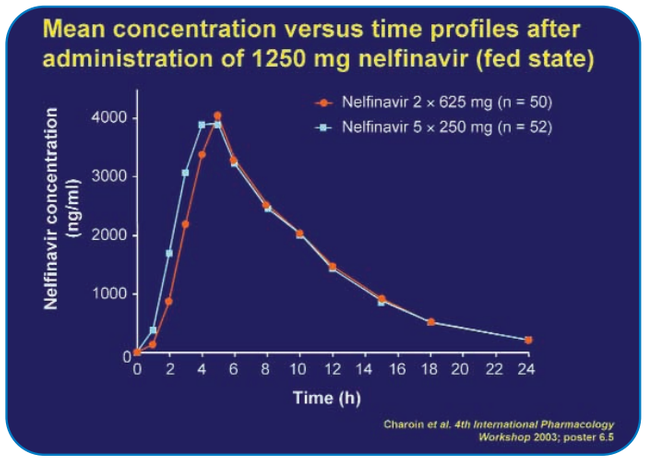


Figure 2



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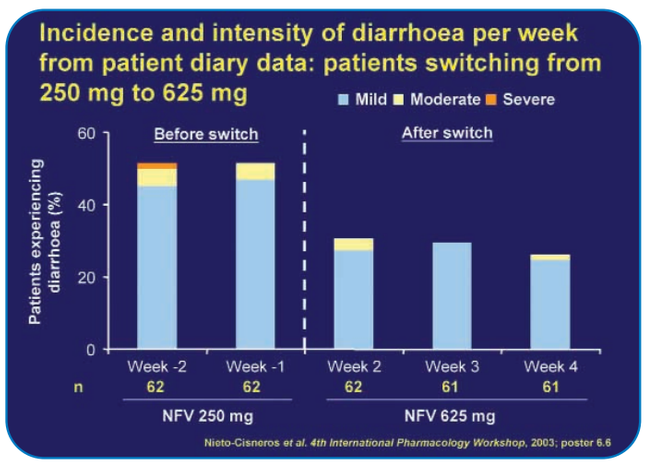


Notes

ART nouveau: new analyses to further define the clinical profile of enfuvirtide

Joep Lange
Professor of Medicine, University of Amsterdam, Academic Medical Centre, Amsterdam, The Netherlands

Joep Lange, MD, PhD, is currently President of the International AIDS Society. He is Professor of Internal Medicine at the Academic Medical Centre of the University of Amsterdam, The Netherlands. He is also Director of that country's National AIDS Therapy Evaluation Centre (NATEC) and Chief Scientific Adviser of the International Antiviral Therapy Evaluation Centre (IATEC), one of the leading organizations for clinical research into the prevention and treatment of HIV and other viral infections.

Professor Lange graduated in medicine from the University of Amsterdam, and went on to obtain a PhD for his work on serological markers in HIV infection.

Professor Lange has an active interest in removing barriers to anti-HIV treatment in resource-poor countries, and is the chairman of the PharmAccess International Foundation and Chair of the Steering Committee of the International HIV Treatment Access Coalition (ITAC). He is also a member of numerous medical societies, including the American Association for the Advancement of Science and the American Society for Microbiology.

Professor Lange has been involved in HIV research for 20 years, and has published more than 200 research articles and several book chapters. He has also been a principal investigator for over 30 clinical trials on antiretroviral therapy.

Enfuvirtide works best when combined with at least two other active antiretrovirals

Enfuvirtide (ENF; formerly T-20) is the first of a completely new class of anti-HIV drugs, the fusion inhibitors. Substantial efficacy and safety data have already been obtained for enfuvirtide from over 1,000 patient-years of experience in Phase I, II and III clinical trials.

Efficacy and durability of enfuvirtide

The two pivotal Phase III trials of enfuvirtide, TORO 1 and TORO 2, were conducted in highly difficult-to-treat patients with HIV-1 infection.[1,2] The 24-week integrated analysis of these studies[3] showed that the response to enfuvirtide (which is administered subcutaneously) added to an optimized background (OB) regimen of oral anti-retrovirals was significantly greater than the response to OB therapy alone, in terms of:

- additional reduction in plasma viral load (least squares mean difference –0.85 $\log_{10}$ HIV-1 RNA copies/ml, $P < 0.0001$)
- additional increase in CD4 cell count (least squares mean difference 37 cells/mm^3, $P < 0.0001$)
- proportion of responders (Figure 1)
- virological failure (45.5% enfuvirtide + OB *vs* 70.7% OB alone) and time to virological failure (76.5 days for OB alone; could not be estimated for enfuvirtide + OB).

The durability of this response has now been demonstrated by the recent analysis of 48-week data. The proportion of responders remained significantly higher in the enfuvirtide + OB group than in the OB alone group, and the majority of week-24 responders in both treatment groups maintained their response at week 48.[4]

In sub-group analyses, the response to treatment with enfuvirtide + OB was greater than the response to treatment with OB alone in all sub-groups (based on demographic and baseline characteristics, on prior antiretroviral use and on the number of active antiretrovirals used in the OB regimen).[3] Some trends in the extent of the response were seen. Patients with at least two active antiretrovirals in the OB regimen (i.e. a baseline genotypic sensitivity score [GSS] of ≥ 2, Figure 2) and patients with ≥ 100 CD4 cells/mm^3 were more likely to benefit from treatment with enfuvirtide.

A multiple regression analysis of predictors of the week-24 response confirmed that baseline CD4 cell counts and baseline GSS or phenotypic sensitivity score (PSS) were strongly predictive of the virological response. These results emphasize the importance of initiating treatment with any new class of antiretroviral in combination with other drugs to which the patient's virus remains sensitive, and before CD4 cell counts fall to low levels.

Safety profile of enfuvirtide

The safety analysis at week 24 showed injection site reactions (ISRs), most of which were of mild to moderate intensity, to be the most common adverse event (Figure 3). However, there was no evidence of an increasing severity of ISRs over time, and the rate of discontinuations due to ISRs was 3%. Apart from ISRs, the most common adverse events at week 24 were diarrhoea (enfuvirtide + OB, 27%; OB, 34%), nausea (enfuvirtide + OB, 20%; OB, 24%), and fatigue (enfuvirtide + OB, 16%; OB, 17%).[3] An additional safety update was completed with longer exposure to study drug. This analysis identified that the rate of pneumonia, primarily bacterial, was higher on enfuvirtide + OB than on OB alone.[3]

In Phase III trials of enfuvirtide, most week-24 responders maintained their response at week 48

In summary, enfuvirtide in combination with OB therapy has demonstrated efficacy and safety over 24 weeks of treatment in patients with extensive prior experience of anti-retroviral therapy. Sub-group and predictor analyses suggest that the patient population most likely to benefit from enfuvirtide will be treatment-experienced individuals who still have remaining therapeutic options. Careful selection of the background regimen to include at least two active agents will result in an improved response.

References

1. Lalezari JP, Henry K, O'Hearn M, *et al. N Engl J Med* 2003; **348**:2175–2185.
2. Lazzarin A, Clotet B, Cooper D, *et al. N Engl J Med* 2003; **348**:2186–2195.
3. Delfraissy J-F, Montaner J, Eron J, *et al. 10th Conference on Retroviruses and Opportunistic Infections*, 2003; poster 568.
4. Roche Pharmaceuticals press release 20th March 2003. Available at www.roche-hiv.com.

Figure 1

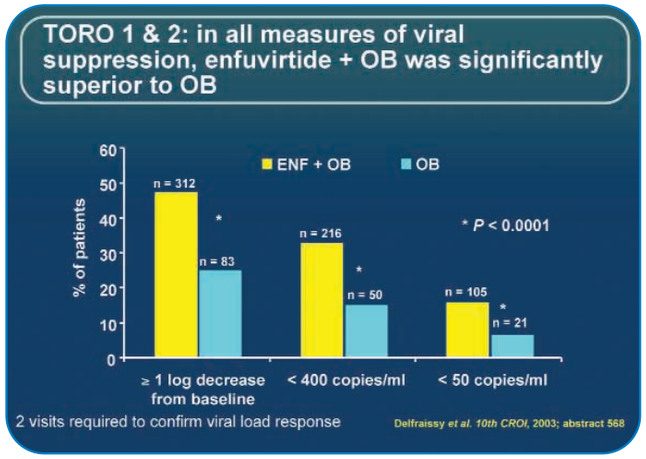


Figure 2

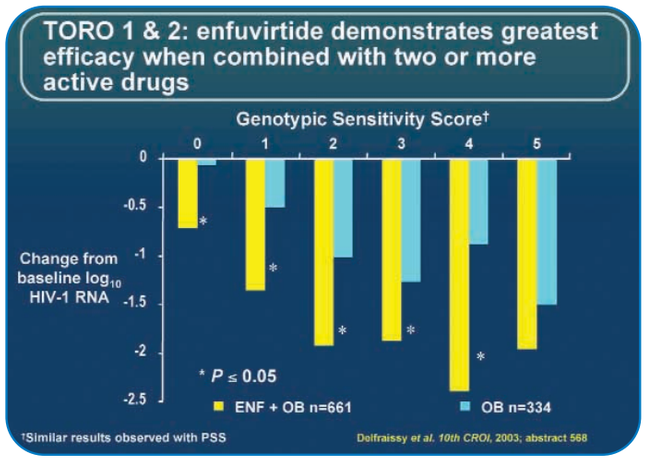
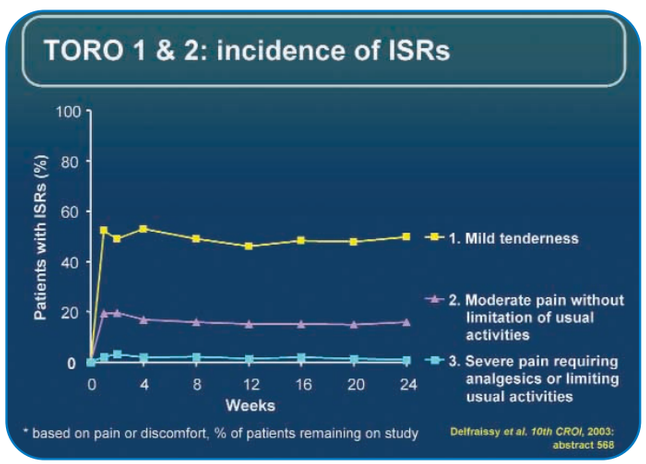


Figure 3



Notes

Fine ART:

achieving optimal patient outcome with enfuvirtide

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James Witek, MD, FACP, has over 13 years' experience as an HIV physician, researcher and educator. He is currently an Assistant Professor of Medicine and the Chief of HIV/AIDS Medicine at Drexel University College of Medicine in Philadelphia, PA. He serves as the Medical Director of the Partnership Comprehensive Care Practice, one of the largest HIV practices in the state of Pennsylvania with over 1,300 patients.

Dr Witek attended the Medical College of Ohio in Toledo, OH, and completed his internal medicine residency at Thomas Jefferson University Hospital in Philadelphia. He is a member of several national and international societies, including the International AIDS Society and the International Association of Physicians in AIDS Care, and is a fellow of the American College of Physicians.

Dr Witek is the author of numerous journal articles, abstracts, and book chapters on the clinical management of HIV infection. He has served as principal investigator on many HIV clinical trials, including the recent TORO 1 trial of enfuvirtide.

His most rewarding professional moments occur when providing direct care to his patients.

Treatment-experienced patients are a fast-growing segment of the HIV-infected population. They often have high viral loads, extensive drug resistance and problems with toxicity that make adherence to complex regimens difficult. To extend the options available to these patients, there is a need for new antiretrovirals that are active against resistant virus.

Week 24 data from the two Phase III clinical trials, TORO 1[1] and TORO 2,[2] clearly demonstrate the efficacy of the novel HIV fusion inhibitor enfuvirtide (ENF; formerly T-20) in treatment-experienced patients with highly resistant virus. These studies have also shown that enfuvirtide generally lacks systemic toxicities associated with conventional antiretroviral treatments.

Enfuvirtide generally lacks the systemic toxicities associated with conventional antiretroviral treatments

The design of the TORO studies delineates a clear approach to antiretroviral selection in the treatment-experienced patient. If similar results are to be achieved in clinical practice, this approach should be replicated.

In the TORO studies, antiretroviral treatment history and phenotypic/genotypic resistance assays were used to select an optimized background regimen to pair with enfuvirtide. Additionally, patients were highly motivated and continuously supported, and were encouraged to attain exceptional adherence (Figure 1).

There are five key steps for selecting patients who are most likely to benefit from enfuvirtide treatment and ensuring that they achieve the best possible response (Figure 2).

The selection of an active, individualized antiretroviral combination to use alongside enfuvirtide treatment is of paramount importance. In the TORO trials, patients with at least two active agents in the background regimen benefited most from enfuvirtide treatment: an increased number of active agents in the background regimen correlated with a greater reduction in viral load at 24 weeks.[3]

This suggests that enfuvirtide should be used when there are still potent agents with which it can be paired. Inactive compounds in an antiretroviral regimen only add complexity, drug interactions, cost and toxicity. Resistance testing can greatly assist in the identification of potentially active agents. Expert advice and a complete treatment and tolerance history for the patient can further refine which agents to use in combination with enfuvirtide.

Several studies have shown that poor patient adherence correlates with virological failure.[4,5] Since enfuvirtide is administered subcutaneously by self-injection, particular concerns might be raised about adherence to this treatment.

However, results from surveys of patients in a Phase II trial (T20-205) and from TORO 1 and 2 have shown that most patients were able to adequately incorporate enfuvirtide into their lives.[6,7] Success is dependent on patient motivation, adequate training, ongoing monitoring and support, and the development of a therapeutic partnership between patient, nurse and physician.

In summary, careful selection of patients with documented resistance or intolerance to antiretrovirals, and evidence of two or more active antiretroviral options for background therapy, combined with adequate training and support, maximizes the probability of patients responding to an enfuvirtide-based regimen.

Achieving success would be expected to lead to the continued motivation of patient and physician (Figure 3). Conversely, the use of enfuvirtide as a "deep salvage" option in HIV patients with extensive antiretroviral resistance and less than two remaining active oral antiretrovirals may be associated with some benefit, but is likely to result in a more transient response and disappointment for both patient and physician.

Careful selection of patients, optimizing background therapy, and training/support maximize the probability of patients responding to an enfuvirtide-based regimen

References

1. Lalezari JP, Henry K, O'Hearn M, *et al. N Engl J Med* 2003; **348**:2175–2185.
2. Lazzarin A, Clotet B, Cooper D, *et al. N Engl J Med* 2003; **348**:2186–2195.
3. Delfraissy J-F, Montaner J, Eron J, *et al. 10th Conference on Retroviruses and Opportunistic Infections*, 2003; poster 568.
4. Bartlett JA, DeMasi R, Quinn J, *et al. AIDS* 2001; **15**:1369–1377.
5. Paterson DL, Swindells S, Mohr J, *et al. Ann Intern Med* 2000; **133**:21–30.
6. Cohen CJ, Dusek A, Green J, *et al. AIDS Patient Care STDs* 2002; **16**:327–335.
7. Green J, Wintfield N. *6th International Congress on Drug Therapy in HIV Infection*, 2002; poster P48.

Figure 1

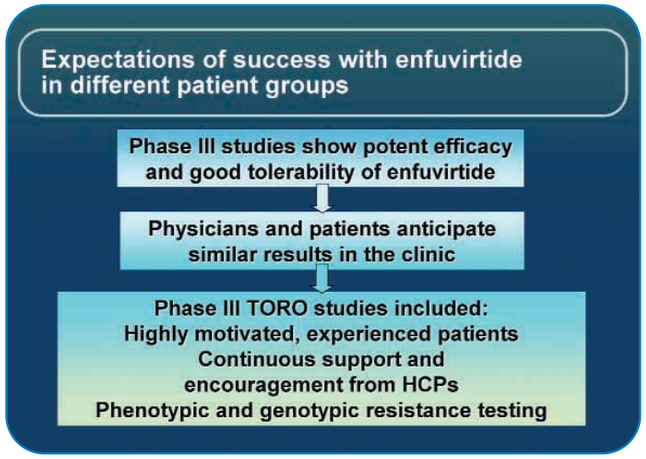


Figure 2

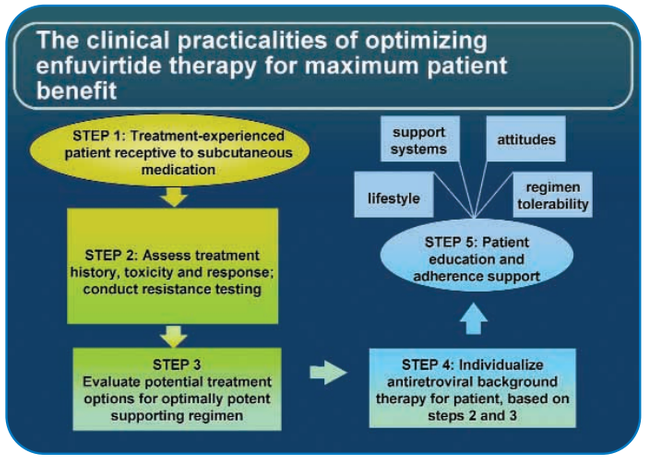
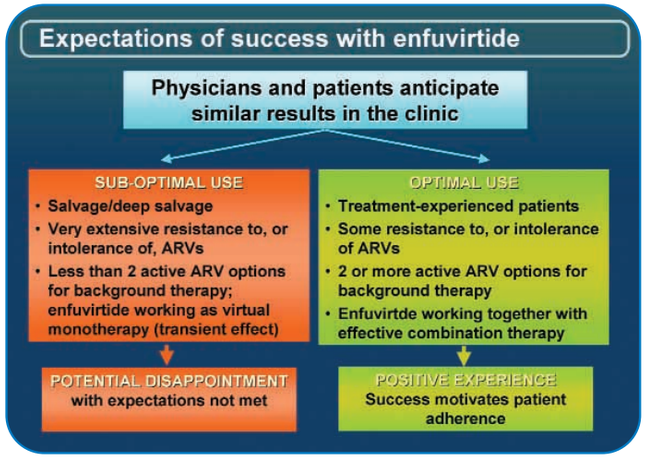


Figure 3



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