AIDS Rev. 2010;12:52-9

Simplification of Antiretroviral Therapy with Etravirine

Esteban Martínez[1] and Mark Nelson[2]
[1]Infectious Diseases Unit, Hospital Clínic, University of Barcelona-IDIBAPS, Barcelona, Spain; [2]Chelsea and Westminster Hospital, London, UK

Abstract

Etravirine is the first representative of a new generation of nonnucleoside reverse transcriptase inhibitors and demonstrates potent antiviral activity against HIV strains resistant to other available nonnucleoside reverse transcriptase inhibitors. The drug demonstrates efficacy when added to an optimized background regimen in patients who experience virologic failure with multiple drug classes including nonnucleoside reverse transcriptase inhibitors. Although the pill burden (four pills) is currently higher than that for nevirapine and efavirenz, etravirine can be taken once daily and may also be dispersed in water. It appears to be a safe and tolerable option. Due to its lack of significant interactions, its efficacy, and tolerability, it can be considered a suitable option for antiretroviral therapy, even in patients with prior exposure to nonnucleoside reverse transcriptase inhibitors. Long-term trials are necessary to confirm the role of etravirine in simplification strategies, but preliminary clinical data is reassuring. **(AIDS Rev. 2010;12:52-9)**

Corresponding author: Esteban Martínez, esteban@fundsoriano.es

Key words

Etravirine. Antiretroviral therapy. HIV. Switch studies. Simplification strategy.

Introduction

Specific guidelines incorporating the latest information on the use of antiretroviral agents have been issued by several organizations, both national and international, and have become routinely used to guide antiretroviral therapy initiation and change[1,2]. The increase in the number and effectivity of antiretroviral agents, combined with an improved knowledge of the pathogenesis of HIV infection, has substantially refined the use of antiretroviral therapy. In contrast to other infections in which specific therapy is initiated as soon as the diagnosis is established, therapy for HIV infection is usually deferred until a certain level of immunological decline, although this differs between guidelines, or the presence of specific clinical manifestations. This conservative attitude is due to several reasons. HIV infection has been elusive to eradication despite the promising incorporation of newer antiretroviral class agents into regimens containing more than three standard drugs[3]. In addition, intermittent antiretroviral therapy has proved to be associated with a higher morbidity and mortality due to HIV- and non-HIV-related causes[4]. Therefore, even in the best case scenario, antiretroviral therapy will be required indefinitely in order to be successful in the long term. In addition, high levels of adherence to antiretroviral therapy will be also required for long-term success to be achieved[5]. Adherence is clearly highly dependant upon the patient, but is also associated with the convenience and tolerability of therapy of the individual therapeutic agents prescribed. In the early days of HAART, the number of effective therapeutic agents was limited and many of them had dose restrictions and were also associated with numerous immediate and long-term toxicities. The availability of better tolerated and more convenient drugs, coupled with improvements in formulations of antiretroviral agents, has made therapy simpler, encouraging a higher proportion of patients to receive therapy, with the majority able to achieve sustained inhibition of HIV

Correspondence to:
Esteban Martínez
Unidad de Enfermedades Infecciosas
Hospital Clínic
Universidad de Barcelona-IDIBAPS
08036 Barcelona, España
E-mail: esteban@fundsoriano.es

replication. This, together with the increasing recognition of the deleterious impact of uncontrolled HIV replication on general health[6,7], has led to the recommendation that earlier initiation of antiretroviral therapy be considered, particularly in those with preexisting comorbidities.

The role of the HIV physician has evolved over time. Initially, care principally addressed the management of opportunistic infections and tumors and HIV drug resistance secondary to regimen failure. The majority of individuals are now able to achieve long-term viral suppression, and physicians now principally need to consider the management of comorbidities, toxicities of antiretroviral agents, and the issues of an ageing HIV population[8,9]. We herein review the concept of therapy simplification in the light of current antiretroviral therapy and the promising characteristics of etravirine, a new nonnucleoside reverse transcriptase inhibitor (NNRTI), for therapy simplification.

Limitations of currently recommended antiretroviral agents

Protease inhibitors

The development of HAART regimens containing protease inhibitors changed HIV infection from a fatal disease into one which, although chronic, is in most cases a manageable condition[10]. Protease inhibitors have steadily remained, in most guidelines, recommended agents for both antiretroviral-naive and antiretroviral-experienced patients[1,2]. Protease inhibitor-based regimens have demonstrated virologic potency and durability, and, when boosted with ritonavir, have a high barrier to the development of viral resistance. In clinical trials, individuals who experience virologic failure during their first protease inhibitor-based regimen rarely develop protease inhibitor-associated mutations, which, although rare in clinical practice, are more commonly reported. This is due to the potent inhibitory effect of ritonavir on the cytochrome P450 3A4 isoenzyme, which allows pharmacokinetic boosting to increase drug exposure and prolong plasma half-lives of the active protease inhibitor[11]. This also permits reduced dosing frequency and/or pill burden, which may improve adherence to the regimen. The increased trough concentration (C_{min}) is associated with an improvement of the antiretroviral activity of the active protease inhibitor, which is beneficial in individuals harboring HIV strains with reduced susceptibility to protease inhibitors.

The major drawback associated with ritonavir boosting is the potential for an increased risk of metabolic abnormalities and a greater potential for drug-drug interactions[12-14]. Protease inhibitor-based therapy is associated with the development of hypertriglyceridemia and an increase in low-density lipoprotein, with dyslipidemia reported to occur in 25% of patients after one year of treatment[15,16]. However, there is heterogeneity among the available agents within the protease inhibitor class in terms of their lipid effects[17]. The effect of ritonavir on lipids is characterized by an increase in triglycerides and very low-density lipoprotein and a reduction in high-density lipoprotein in healthy volunteers after only two weeks of exposure[18]. Ritonavir boosting often results in an increased frequency of protease inhibitor-associated adverse events because of increased drug exposure. Indinavir-associated nephrotoxicity[19] and atazanavir-induced jaundice[20] are both increased with ritonavir boosting. Other adverse events associated with ritonavir include asthenia, headache, gastrointestinal effects (including nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion), and neurologic disturbances (e.g. circumoral and peripheral paresthesia)[21]. Most ritonavir-related adverse events are related to plasma drug levels, but they are often mild due to the low doses of ritonavir needed for effective drug boosting, although they may remain clinically unacceptable for a proportion of patients.

Since all protease inhibitors are metabolized by, and are inhibitors of, CYP3A4, and since ritonavir is a particularly potent inhibitor, numerous potential drug interactions have been reported with the protease inhibitors, which are important not only for other agents used to treat HIV and its complications, but also for medication that may be increasingly needed to treat the complications of ageing, which are being increasingly reported in the HIV-infected population[22]. Ritonavir can affect the metabolism of agents through other enzyme systems including CYP2D6 and CYP1A2, so coadministration of drugs that interact with these isoenzymes may also result in altered drug activity.

Nonnucleoside reverse transcriptase inhibitors

Regimens containing NNRTI have demonstrated virologic potency and durability[23]. The major disadvantage of first-generation NNRTI is the comparatively low genetic barrier for development of resistance. Both efavirenz and nevirapine require only a single mutation to confer resistance, and cross resistance between both drugs is the norm. Efavirenz and nevirapine are both metabolized by cytochrome P450 (CYP) enzyme

systems, primarily by CYP2B6, with lesser involvement of CYP3A4[24,25]. In contrast to protease inhibitors that inhibit the metabolism of other drugs through cytochrome P450, giving rise to an increased risk of toxicity from the metabolically inhibited drugs, efavirenz and nevirapine are inducers of the metabolism of other drugs and their concomitant administration may lead to a reduction in efficacy of the effective agent. This situation may be clinically relevant with methadone.

Although nevirapine is well tolerated in the long term, there is increasing recognition that efavirenz may continue to be associated with neuropsychological effects in some individual patients[26]. These effects may frequently be mild and are often not recognized by the patient, although they may be evident to the treating physician, family, and friends. Efavirenz also has the disadvantage of being teratogenic and is contraindicated in women who are pregnant or who are wishing to become so[27].

Nucleoside reverse transcriptase inhibitors

A combination of two nucleoside reverse transcriptase inhibitors (NRTI) remains the cornerstone of antiretroviral therapy[1,2]. However, there is increasing recognition of toxicities associated with this class of drugs. The NRTI are particularly associated with mitochondrial-associated toxicity, with hyperlactatemia and lipoatrophy being recognized as the most characteristic acute and chronic toxicities, respectively[28,29].

The once-daily fixed-dose combinations of tenofovir/emtricitabine and abacavir/lamivudine are the NRTI most widely used in the therapy of naive patients[1,2]. However, abacavir has been associated with a higher risk of cardiovascular disease in some studies, although the mechanism of this toxicity remains unclear[30,31], and tenofovir has been associated with kidney and bone toxicity that, although usually mild, may be of increased relevance in those with established kidney and bone abnormalities, particularly as the HIV population ages[32,33]. Although tenofovir/emtricitabine and abacavir/lamivudine have shown less potential for mitochondrial toxicity than other NRTI, they still have the potential to be associated with mitochondrial toxicity[34,35]. Due to the increasing recognition of toxicities associated with agents within this class, there is an increasing interest in the potential for use of nucleoside-sparing antiretroviral regimens.

Simplification of antiretroviral therapy

Simplification of antiretroviral therapy consists of a change in a therapeutic regimen that has achieved sustained inhibition of HIV replication by an equally effective, simpler regimen with the objective of improving adherence or quality of life, preventing or reversing specific toxicities, or preserving treatment options[1,2]. Simplification of therapy has been achieved through the replacement of a drug with problems of convenience, tolerability, or potential pharmacologic interactions by another potentially effective drug not associated with these issues. An additional form of simplification (not discussed in this review) has consisted of reducing the number of pills by improvement in formulation, the development of fixed-dose combinations, or reducing the number of agents in a regimen, e.g. protease inhibitor monotherapy. Simplification may also be achieved with the advent of new pharmacokinetic information, allowing the frequency of dosing to be reduced.

However, there may be disadvantages with simplification[36]. When simplifying antiretroviral therapy, the first goal is maintenance of viral suppression. One important factor in maintaining viral suppression is the genetic barrier of the replacing drug. This is particularly important in individuals who harbor resistant HIV, as has been demonstrated in a number of clinical trials.

The first simplification strategy introduced widely was that of replacing a protease inhibitor with an NRTI or a NNRTI. In the NEFA study[26], adult patients who were virologically suppressed (HIV-1 RNA < 200 copies/ml) on a regimen of two NRTI and at least one protease inhibitor (mostly unboosted) for at least six months were randomized to replace the protease inhibitor with either nevirapine, efavirenz, or abacavir. After 48 weeks of follow-up, there was a clear trend toward a higher rate of virologic failure among patients in the abacavir arm. Most of the patients experiencing virologic failure in the NEFA study had experienced previous suboptimal therapy with NRTI. Indeed, rates of virologic failure were similar between treatment arms in patients who had not previously received suboptimal antiretroviral therapy: 5% for nevirapine, 4% for efavirenz, and 6% for abacavir. However, when patients had a treatment history consistent with suboptimal antiretroviral therapy, the risk of virologic failure in individuals receiving abacavir (29%) was more than double that observed for those receiving efavirenz (10%) or nevirapine (13%). The NEFA results provide a clear example of the importance of not decreasing the overall genetic barrier to resistance after switching to a new regimen in patients with documented antiretroviral resistance. Those individuals who had received previous mono or dual therapy with NRTI likely had recorded mutations, yet had achieved virologic suppression at baseline because

of the residual activity of two NRTI plus the full activity of the protease inhibitor. When the protease inhibitor was switched to abacavir, the overall genetic barrier of the regimen was decreased due to cross resistance between abacavir and the recorded resistance to NRTI. In contrast, when the protease inhibitor was switched to efavirenz or nevirapine, the full activity of these new drugs could be anticipated since there is no cross resistance between NNRTI and NRTI. Nevertheless, among patients who switched to nevirapine or efavirenz, those with prior suboptimal therapy were at higher risk of virologic rebound than those without. This reflects the fact that first-generation NNRTI have a low genetic barrier to resistance and must be supported by an active background regimen rather than one that may be already weakened by the presence of resistance to NRTI.

In the recent SWITCHMRK 032 and 033 studies[37] similar results were obtained with a switch from protease inhibitors to raltegravir. Virologically suppressed patients who were receiving a lopinavir/ritonavir-based antiretroviral therapy with at least two NRTI were randomized to continue lopinavir/ritonavir or switch to the integrase inhibitor raltegravir. Both studies were prematurely stopped at 24 weeks as raltegravir failed to meet the protocol-defined criteria for non-inferiority in the proportion of patients with sustained HIV-1 RNA < 50 copies/ml. There were 32 (9%) confirmed virologic failures (HIV-1 RNA > 50 copies/ml) in the pooled raltegravir arms vs. 17 (5%) in the lopinavir/ritonavir arms. Of note, 84% of patients with confirmed virologic failure in the raltegravir arms reported that they were not receiving their first antiretroviral regimen at study entry, and 66% reported a history of virologic failures on previous regimens. Of the 12 patients with confirmed virologic failure (HIV-1 RNA > 400 copies/ml), eight (75%) had emergent raltegravir resistance mutations. The SWITCHMRK studies are a clear example of the risks of replacing a drug with a high genetic barrier to resistance with an alternative agent with a lower genetic barrier to resistance in patients with recorded resistance mutations.

Potential of etravirine for antiretroviral simplification

Pharmacokinetic characteristics

Etravirine, formerly known as TMC125, is a novel diarylpyrimidine NNRTI developed to inhibit HIV-1 with resistance to currently available NNRTI (Fig. 1). The spectrum of activity of etravirine is attributed to its ability to bind HIV reverse transcriptase in more than one distinct mode. The torsional flexibility of the molecule permits access to numerous conformational variants, and its compact structure allows repositioning and reorientation when mutations in the binding pocket are present. Significant *in vitro* activity and a high genetic barrier of resistance to etravirine was demonstrated against a panel of viruses with single or double mutations conferring resistance to NNRTI, including viruses harboring K103N with K101E or Y181C. Unlike efavirenz or nevirapine, resistance to etravirine only develops following multiple mutations in reverse transcriptase[38,39].

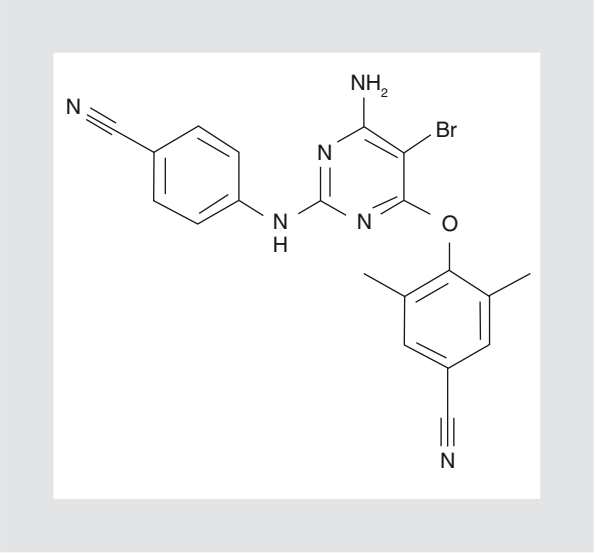

Figure 1. *Etravirine molecular structure.*

Etravirine was approved for clinical use at a dosage of 200 mg twice daily in the USA and Europe in January and August 2008, respectively. It is recommended to administer etravirine following a meal to achieve optimal bioavailability, although no clinical relevance has been attributed to the differences in pharmacokinetics when etravirine is taken following meals of different composition. Etravirine can be dispersed in water where it is tasteless and odorless and remains stable for up to six hours. Of note, liquids other than water have not been evaluated and therefore are not recommended for the preparation of etravirine dispersion. A drug-interaction study with a single dose of etravirine given with steady state ranitidine or omeprazole showed no clinically relevant effect when etravirine was coadministered with these acid-suppressing agents, suggesting that alterations in pH do not affect the bioavailability of etravirine. Based on the relatively long elimination half-life (30-40 hours), once-daily dosing was a plausible option for etravirine administration,

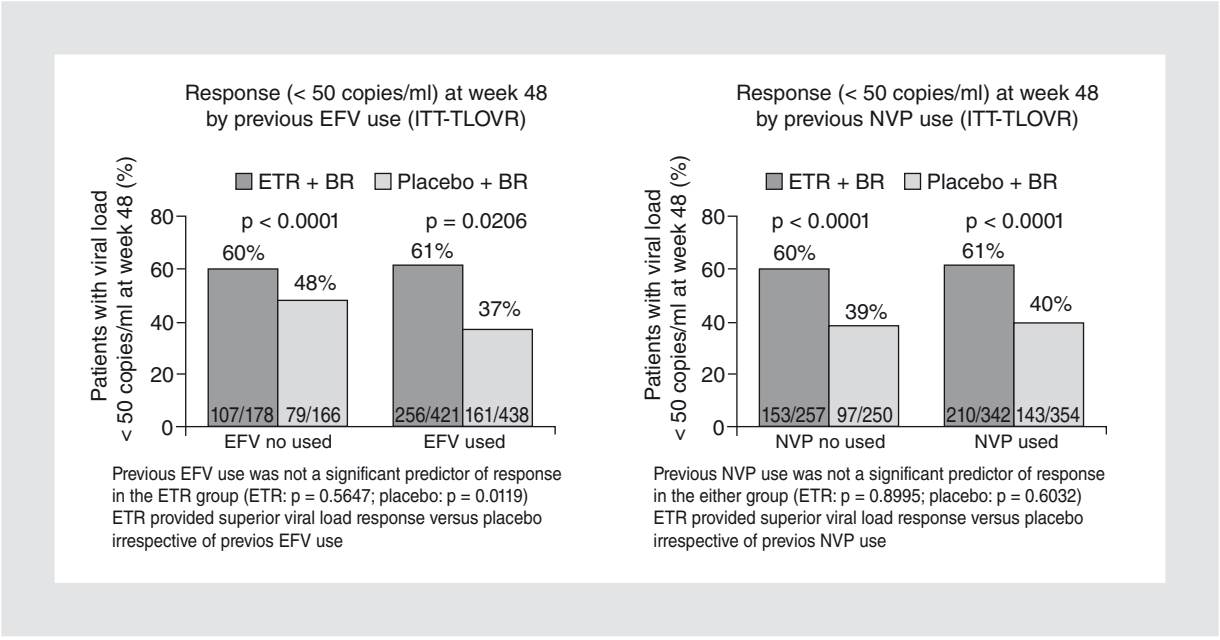

Figure 2. *Efficacy of etravirine in the DUET 1 and 2 studies by prior use of efavirenz or nevirapine. Similar efficacy results were observed in both cases. Note: p value from logistic regression model. EFV: efavirenz; NVP: nevirapine; ITT: intent to treat; TLOVR: time to loss of virologic response; ETR: etravirine; BR: background regimen.*

although the pill burden of initial formulations precluded the use of once-daily dosing and ultimately led to the maintenance of twice-daily regimens throughout the entire development program[40]. There is currently an ongoing trial comparing etravirine 400 mg taken once daily with efavirenz in antiretroviral-naive patients (ClinicalTrials.gov Identifier: NCT00903682).

The drug is highly protein bound, and its distribution to compartments other than plasma has not been evaluated. Drug metabolism is primarily performed by cytochrome P450 isoenzymes (CYP3A4, CYP2C9, CYP2C19). The major metabolic pathway of etravirine is methyl hydroxylation, although glucuronidation may also exist. Etravirine is not recommended in combination with tipranavir/ritonavir, carbamazepine, phenobarbital, phenytoin, rifampin, or products containing St John's wort because all are potent inducers of CYP450 enzymes and would likely reduce etravirine levels. Use of an alternative to clarithromycin is suggested when treating *M. avium* complex. Dose adjustments may be required for fosamprenavir and sildenafil, and the concomitant use of atazanavir is recommended only in the presence of low-dose ritonavir. Etravirine can be combined with many antiretrovirals without dose adjustment, such as atazanavir/r, darunavir/r, didanosine, enfuvirtide, lopinavir/r, raltegravir, saquinavir/r, and tenofovir[40]. No clinically relevant interactions were demonstrated in the pharmacokinetics of rifabutin, paroxetine, oral contraceptives, digoxin, or methadone when coadministered with etravirine.

Efficacy

Studies with etravirine in antiretroviral-naive patients are currently ongoing. The most complete data on the efficacy of etravirine in antiretroviral-experienced patients come from two large, randomized, double-blind, placebo-controlled phase III studies with identical design: DUET-1 and DUET-2[41-44]. Patients with a viral load > 5,000 copies/ml with a virus harboring > 3 (primary) and > 1 resistance mutations to protease inhibitors and NNRTI, respectively, were randomized to receive etravirine 200 mg or placebo plus an optimized background regimen that included darunavir/ritonavir and the optional use of enfuvirtide. At 48 weeks, the proportion of patients with a viral load < 50 copies/ml was 60 and 61% in the etravirine arms of DUET-1 and DUET-2, respectively, compared with 39 and 41% in the placebo arms ($p < 0.001$, for both analyses). In DUET-1 and DUET-2, the efficacy of etravirine after prior use of either nevirapine or efavirenz was similar[45] (Fig. 2).

Tolerability and safety

The most common, significant adverse effects associated with the first-generation NNRTI, nevirapine

and efavirenz, are cutaneous reactions (including Stevens-Johnson syndrome), hepatotoxicity with nevirapine, and neuropsychiatric effects with efavirenz[46,47]. Etravirine has been well tolerated in clinical studies, with low rates of discontinuation attributable to adverse effects. The discontinuation rates in the DUET studies were similar to those for placebo (approximately 5%)[41,42]. Patients receiving etravirine did not have a higher frequency of hepatotoxicity or central nervous system (CNS) adverse effects compared with those receiving placebo[41,42,48-50].

The primary adverse effect observed with etravirine has been rash. Rash occurred at a higher rate among patients receiving etravirine (17%) than among patients receiving placebo (9%) in the DUET studies[41,42]. Most episodes of rash were mild-to-moderate in severity, and only 2% of patients discontinued etravirine because of rash. The rash typically occurred early during therapy (median time of onset, 11 and 14 days in DUET-1 and DUET-2, respectively)[51]. Patients with rash generally noticed that the rash resolved with continued therapy (median time of resolution, 12 and 16 days in DUET-1 and DUET-2, respectively). Stevens-Johnson syndrome and other severe life-threatening reactions occurred in < 0.1% of all etravirine recipients, a frequency lower than that reported with efavirenz[52]. In patients who experience a severe rash, etravirine should be discontinued permanently. Patients with or without a history of rash associated with nevirapine or efavirenz did not have an increased risk of this complication when receiving etravirine (22 and 19%, respectively)[51].

Etravirine is a pregnancy category B drug. Preliminary data in pregnant HIV-infected women suggest that no etravirine dose adjustment is needed during the third trimester, and that etravirine does not have an effect on fetal or neonatal toxicity[53]. Because of the limited knowledge of its safety profile in infants, women should be instructed to not breastfeed while receiving etravirine. Although 4 mg/kg of etravirine provided comparable exposure to the adult dosage in children aged 6-17 years[54], etravirine is not approved for use in children. No renal dosage adjustment is required. Although there is no dosage adjustment for mild or moderate hepatic impairment (Child-Pugh class A or B), there are no data regarding patients with severe hepatic impairment (Child-Pugh class C)[55]. However, there is available data in coinfected patients, suggesting that etravirine with a background regimen of darunavir/ritonavir does not appear to increase adverse effects[56].

Resistance

Etravirine demonstrated activity against 1,049 (97%) of 1,081 viral isolates that were resistant to first-generation NNRTI[57]. A sequential passage experiment including both wild-type and NNRTI-resistant isolates was performed to identify mutations selected by etravirine *in vitro*[58]. The development of resistance was dependent on the presence of multiple coexisting mutations, demonstrating the high genetic barrier of etravirine. Mutations selected by etravirine included well-known resistance mutations to NNRTI (L100I, Y181C, G190S, M230L, and Y318F), as well as newly recognized mutations (V179L and V179F). The presence of ≥ 3 resistance mutations to NNRTI (including V90I, A98G, L100I, K101E/H/P, V106I, E138A, V179D/F/T, Y181C/I/V, and G190A/S) at baseline resulted in a significant reduction in achievement of virologic response with etravirine[59]. It is reassuring that the prevalence of ≥ 3 of these mutations among viral isolates from patients experiencing treatment failure to NNRTI has been < 10%[60-63]. Virologic failure with efavirenz is usually associated with the K103N mutation, in contrast to virologic failure with nevirapine that is usually associated with the Y181C mutation. Therefore, efavirenz use may be less likely to lead to etravirine resistance than nevirapine[60]. Anyway, etravirine can be successfully used after virologic failure to either nevirapine or efavirenz.

Clinical experience with etravirine in antiretroviral therapy simplification

Etravirine has been widely used in treatment-experienced patients with virologic failure in clinical carriage. Due to its relatively low rates of toxicity, there has also been an increase in its use in treatment-experienced individuals who require a change in therapy due to the development of toxicity. In one report, 44 individuals switched therapy to etravirine with a viral load of less than 50 copies/ml, 18 switched from efavirenz, 16 from a ritonavir-boosted protease inhibitor, two from nevirapine, and eight from an NRTI. All individuals received etravirine at a dose of 200 mg twice daily and 31 received therapy with two NRTI and etravirine alone. At 48 weeks, 94% by intent to treat and 100% by on-treatment analyses continued to suppress viral replication to below 50 copies/ml. Two patients ceased therapy and in both cases this was not related to the drug[64].

Due to increased recognition of the long-term CNS toxicity of efavirenz, and the wide use of this agent as

first-line therapy, coupled with the relative safety of newer agents such as etravirine, raltegravir, and maraviroc, there has been increased interest in the use of these agents when CNS toxicity is prolonged. Clinical trials of substitution of raltegravir are planned and the increased use and improvements of genotype to phenotype testing to establish CCR5 tropism in virologically suppressed patients potentially may permit the use of maraviroc in this setting.

One issue with efavirenz to etravirine switch is whether there may be a need for altered dosing of etravirine when switch occurs due to the possibility of a drug-drug interaction between the two agents. A pharmacokinetic study has been reported exploring this issue in healthy volunteers, and although there were reductions in area under the curve, C_{max}, and C_{min}, these were not felt to be of pharmacokinetic importance with etravirine at doses of either 200 mg twice daily or 400 mg once daily[65].

A study of switching individuals on an efavirenz-based therapy with continuing CNS toxicity to this agent to etravirine has recently completed (SSAT 029). The SSAT 029 study recruited individuals who had received efavirenz for at least 12 weeks and who had continuing CNS toxicity attributable to efavirenz. All individuals were required to have a screening viral load < 50 copies/ml. Twenty-four individuals were enrolled and randomized to an immediate switch to etravirine or to switch at 12 weeks to this drug. All patients were followed for 24 weeks. The primary endpoint of the study was the proportion change in CNS adverse events at week 12. Secondary endpoints included the proportion change in CNS adverse events at week 24, scales of depression, anxiety, and adherence and changes from baseline in laboratory parameters (ClinicalTrials.gov Identifier: NCT00792324).

Conclusions

Etravirine is the first representative of a new generation of NNRTI and demonstrates potent antiviral activity against HIV strains resistant to other available NNRTI. The drug demonstrates efficacy when added to an optimized background regimen in patients who experience virologic failure with multiple drug classes, including to NNRTI. There are also ongoing studies in antiretroviral-naive patients that are expected to confirm the role of etravirine in the initiation of antiretroviral therapy. Although the pill burden (four pills) is currently higher than that for nevirapine and efavirenz, etravirine can be taken once daily and may also be dispersed in water. It appears to be a safe and tolerable option. Due to its lack of significant interactions, its efficacy, and tolerability, it can be considered a suitable option of antiretroviral therapy, even in patients with prior exposure to nevirapine or efavirenz. Long-term trials are necessary to confirm the role of etravirine in simplification strategies, but preliminary clinical data is reassuring.

References

1. Expert Panel of Gesida and Plan Nacional sobre el SIDA. Consensus document from Gesida/Plan Nacional sobre el SIDA regarding the antiretroviral treatment in adults infected with HIV: updated January 2010. Available at: http://www.gesida.seimc.org/pcientifica/fuentes/DcyRc/gesidadcyrc2010_DocconsensoTARGESIDA-PNS-verpc.pdf
2. Clumeck N, Dedes N, Pozniak A: the EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults in Europe. Available at: http://www.europeanaidsclinicalsociety.org/guidelinespdf/EACS-EuroGuidelines2009FullVersion.pdf
3. Dahl V, Josefsson L, Palmer S. HIV reservoirs, latency, and reactivation: prospects for eradication. Antivir Res. 2010;85:286-94.
4. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count–guided interruption of antiretroviral treatment. N Engl J Med. 2006;355:2283-96.
5. Pham P. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. AIDS Patient Care STDS. 2009; 23:803-7.
6. Hunt P, Martin J, Sinclair E, et al. T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. J Infect Dis. 2003;187:1534-43.
7. Kuller L, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008;5:e203.
8. Gebo K. HIV and aging: implications for patient management. Drugs Aging. 2006;23:897-913.
9. Guaraldi G, Baraboutis I. Evolving perspectives on HIV-associated lipodystrophy syndrome: moving from lipodystrophy to non-infectious HIV co-morbidities. J Antimicrob Chemother. 2009;64:437-40.
10. Palella F, Delaney K, Moorman A, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med. 1998;338:853-60.
11. Zeldin R, Petruschke R. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. J Antimicrob Chemother. 2004;53:4-9.
12. Calza L, Manfredi R, Chiodo F. Hyperlipidaemia in patients with HIV-1 infection receiving highly active antiretroviral therapy: epidemiology, pathogenesis, clinical course and management. Int J Antimicrob Agents. 2003;22:89-99.
13. Noor M. The role of protease inhibitors in the pathogenesis of HIV-associated insulin resistance: cellular mechanisms and clinical implications. Curr HIV/AIDS Rep. 2007;4:126-34.
14. Moyle G. Metabolic issues associated with protease inhibitors, J Acquir Immune Defic Syndr. 2007;45(Suppl 1):S19-26.
15. Calza L, Manfredi R, Farneti B, Chiodo F. Incidence of hyperlipidaemia in a cohort of 212 HIV-infected patients receiving a protease inhibitor-based antiretroviral therapy. Int J Antimicrob Agents. 2003;22:54-9.
16. Montes M, Pulido F, Barros C, et al. Lipid disorders in antiretroviral-naïve patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors. J Antimicrob Chemother. 2005;55:800-4.
17. Currier J. Update on cardiovascular complications in HIV infection. Top HIV Med. 2009;17:98-103.
18. Shafran S, Mashiter L, Roberts S. The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. HIV Med. 2005;6:421-5.
19. Arnaiz J, Mallolas J, Podzamczer D, et al. Continued indinavir versus switching to indinavir/ritonavir in HIV-infected patients with suppressed viral load. AIDS. 2003;17:831-40.
20. Squires K, et al. Similar efficacy and tolerability of atazanavir compared to atazanavir/ritonavir, each in combination with abacavir/lamivudine, after initial suppression with abacavir/lamivudine and atazanavir/ritonavir in HIV-1 infected patients: 84 week results of the ARIES trial. 5th IAS Conference on HIV Treatment, Pathogenesis and Prevention, Cape Town, 2009 [abstract WeLBB103].

21. Kaul D, Cinti S, Carver P, Kazanjian P. HIV protease inhibitors: advances in therapy and adverse reactions, including metabolic complications. Pharmacotherapy. 1999;19:281-98.
22. Dresser G, Spence J, Bailey D. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet. 2000;38:41-57.
23. Waters L, John L, Nelson M. Non-nucleoside reverse transcriptase inhibitors: a review. Int J Clin Pract. 2007;61:105-18.
24. Riska P, Lamson M, MacGregor T, et al. Disposition and biotransformation of the antiretroviral drug nevirapine in humans. Drug Metab Dispos. 1999;27:895-901.
25. Ward B, Gorski J, Jones D, Hall S, Flockhart D, Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther. 2003;306:287-300.
26. Martínez E, Arnaiz J, Podzamczer D, et al. Three-year follow-up of protease inhibitor-based regimen simplification in HIV-infected patients. AIDS. 2007;21:367-9.
27. Watts D. Teratogenicity risk of antiretroviral therapy in pregnancy. Curr HIV/AIDS Rep. 2007;4:135-40.
28. Brinkman K, Smeitink J, Romijn J, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. Lancet. 1999;354:1112-15.
29. Vrouenraets S, Treskes M, Regez R, et al. Hyperlactataemia in HIV-infected patients: the role of NRTI-treatment. Antivir Ther. 2002;7:239-44.
30. Martínez E, Larrousse M, Gatell J. Cardiovascular disease and HIV infection: host, virus, or drugs? Curr Opin Infect Dis. 2009;22:28-34.
31. Martínez E, Larrousse M, Podzamczer D, et al. Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction. AIDS. 2010;24:F1-9.
32. Nelson M, Katlama C, Montaner J, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. AIDS. 2007;21:1273-81.
33. Labarga P, Barreiro P, Martin-Carbonero L, et al. Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. AIDS. 2009;23:689-96.
34. Venhoff N, Setzer B, Melkaoui K, Walker U. Mitochondrial toxicity of tenofovir, emtricitabine and abacavir alone and in combination with additional nucleoside reverse transcriptase inhibitors. Antivir Ther. 2007;12:1075-85.
35. Kohler J, Hosseini S, Hoying-Brandt A, et al. Tenofovir renal toxicity targets mitochondria of renal proximal tubules. Lab Invest. 2009;89:513-39.
36. Negredo E, Bonjoch A, Clotet B. Benefits and concerns of simplification strategies in HIV-infected patients. J Antimicrob Chemother. 2006;58: 235-42.
37. Eron J, Young B, Cooper D, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet. 2010;375:396-407.
38. Andries K, Azijn H, Thielemans T, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. Antimicrob Agents Chemother. 2004;48: 4680-6.
39. Vingerhoets J, Azijn, Fransen E, et al. TMC125 displays a high genetic barrier to the development of resistance: evidence from in vitro selection experiments. J Virol. 2005;79:12773-82.
40. Schöller-Gyüre M, Kakuda T, Raoof A, DeSmedt G, Hoetelmans R. Clinical pharmacokinetics and pharmacodynamics of etravirine. Clin Pharmacokinet. 2009;48:561-74.
41. Madruga J, Cahn P, Grinsztejn B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomized, double-blind, placebo-controlled trial. Lancet. 2007;370:29-38.
42. Lazzarin A, Campbell T, Clotet B, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomized, double-blind, placebo-controlled trial. Lancet. 2007;370:39-48.
43. Haubrich R, Cahn P, Grinsztejn B, et al. DUET-1: week-48 results of a phase III randomized double-blind trial to evaluate the efficacy and safety of TMC125 vs placebo in 612 treatment-experienced HIV-1-infected patients. Program and abstracts 15th CROI, Boston, 2008 [abstract 790].
44. Johnson M, Campbell T, Clotet B, et al. DUET-2: week-48 results of a phase III randomized double-blind trial to evaluate the efficacy and safety of TMC125 vs placebo in 591 treatment-experienced HIV-1-infected patients. Program and abstracts 15th CROI, Boston, 2008 [abstract 791].
45. Cahn P, Molina J, Towner W, et al. 48-week pooled analysis of DUET-1 and DUET-2: the impact of baseline characteristics on virologic response to etravirine. XVIIth IAC, Mexico, 2008 [abstract TUPE0047].
46. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens containing nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomized open-label trial, the 2NN study. Lancet. 2004;363:1253-63.
47. Treisman G, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. AIDS. 2002;16:1201-15.
48. Gruzdev B, Rakhmanova Z, Doubovskaya E, et al. A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naïve, HIV-1 infected subjects. AIDS. 2003;17:2487-94.
49. Gazzard B, Pozniak A, Rosenbaum W, et al. An open-label assessment of TMC125 –a new, next-generation NNRTI, for 7 days in HIV-1 infected individuals with NNRTI resistance. AIDS. 2003;17:F49-54.
50. Ruxrungtham K, Pedro RJ, latiff G, et al. Impact of reverse transcriptase resistance on the efficacy of TMC125 (etravirine) with two nucleoside reverse transcriptase inhibitors in protease inhibitor-naïve, nonnucleoside reverse transcriptase inhibitor-experienced patients: study TMC125-C227. HIV Med. 2008;9:883-96.
51. Mills A, Grinsztejn B, Katlama C, et al. The incidence of rash observed with the NNRTI etravirine in the phase III DUET trials using pooled 48-week data. Program and abstracts XVIIth IAC, Mexico, 2008 [abstract TUPE0059].
52. Borras-Blasco J, Navarro-Ruiz A, Borras C, Castera E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J Antimicrob Chemother. 2008;62:879-88.
53. Izurieta P, Kakuda T, Clark T, et al. Safety and pharmacokinetics of etravirine in pregnant HIV-infected women. 12th European AIDS Conference, Germany, 2009: [abstract PE4.1/6].
54. Kakuda T, Konigs C, Feiterna-Sperling C, et al. Pharmacokinetics of the next-generation NNRTI TMC125 in HIV-infected children between 6 and 17 years of age. Program and abstracts 15th CROI, Boston, 2008: [abstract 578].
55. Scholler-Gyure M, Kakuda T, Dsmedt, et al. Pharmacokinetics of TMC125 in HIV-negative volunteers with mild and moderate hepatic impairment. Program and abstracts 47th ICAAC, Chicago. American Society for Microbiology, 2007 [abstract A-1428].
56. Clotet B, Katlama C, Clumeck N, Nijs S, Witek J. Etravirine demonstrates a favourable safety and tolerability profile versus placebo irrespective of hepatitis co-infection: Week 96 analysis from the DUET trials. 12th European AIDS Conference, Germany, 2009 [abstract PE7.3/9].
57. Schapiro JM, Vingerhoets J, Nijs S, et al. Combined PI and NNRTI resistance analysis of the pooled DUET trial: towards a regimen-based resistance interpretation. Abstracts of the 6th European HIV Drug Resistance Workshop, Budapest, 2008: [abstract 46].
58. Vingerhoets J, Buelens A, Peeters M, et al. Impact of baseline mutations on the virological response to TMC125 in the phase III clinical trials DUET-1 and DUET-2. Abstracts of the 16th International HIV Drug Resistance Workshop, Barbados, 2007. Antivir Ther. 2007;12:S34.
59. Vingerhoets J, Tambuyzer L, Azijn H, et al. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled phase III clinical studies. AIDS. 2010 [Epub ahead of print].
60. Scott C, Grover D, Nelson M. Is there a role for etravirine in patients with nonnucleoside reverse transcriptase inhibitor resistance? AIDS. 2008; 22:989-90.
61. Bacheler L, Van der Borght K, Van Craenenbroeck E, Winters B, Lecocq P. Exploring etravirine resistance among recent routine clinical samples submitted for resistance testing. Program and abstracts of the XVII International HIV Drug Resistance Workshop, Spain, 2008. Antivir Ther. 2008;13(Suppl 3):A120.
62. Stevens W, Wallis C, Sanne I, Venter F. Will etravirine work in patients failing nonnucleoside reverse transcriptase inhibitor-based treatment in Southern Africa? J Acquir Immune Defic Syndr. 2009;52:655-66.
63. Llibre J, Santos J, Puig T, et al. Prevalence of etravirine-associated mutations in clinical samples with resistance to nevirapine and efavirenz. J Antimicrob Chemother. 2008;62:909-13.
64. Scott C, Khatib N, Bower M, Gazzard B, Nelson M. Etravirine use in clinical practice: 48-week data from a single centre cohort. 9th International Congress on Drug Therapy in HIV Infection, Glasgow. J Int AIDS Soc. 2008;11(Suppl 1):49.
65. Boffito M, Jackson A, Lamorde M, et al. Pharmacokinetics and safety of etravirine administered once or twice daily after 2 weeks treatment with efavirenz in healthy volunteers. J Acquir Immune Defic Syndr. 2009; 52:222-7.