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HIV-1 Resistance to First- and Second-Generation Non-nucleoside Reverse Transcriptase Inhibitors

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Abstract

Resistance to the first-generation non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz is characterized by rapid selection of viruses carrying one or several mutations in the reverse transcriptase gene, which immediately confer high-level resistance as well as cross-resistance to the two drugs. Such mutations have been detected close to the non-nucleoside reverse transcriptase inhibitor binding site and also in the connection domain of HIV reverse transcriptase. They lead to a loss of drug affinity without affecting viral fitness. As a single mutation is enough to confer high-level resistance, transmission of non-nucleoside reverse transcriptase inhibitor-resistant viruses (currently 2-7% of cases) is strongly associated with virologic failure of non-nucleoside reverse transcriptase inhibitor-based first-line regimens. The development of second-generation non-nucleoside reverse transcriptase inhibitors is a major challenge. The most promising compounds, etravirine and rilpivirine, are active on mutant viruses and possess a relatively high genetic barrier for resistance. Data on etravirine resistance in patients already exposed to first-generation non-nucleoside reverse transcriptase inhibitors show that, among 17 mutations in the reverse transcriptase gene, at least three must be present simultaneously in order to diminish etravirine activity. Recent studies of the prevalence of resistance in large databases of patients already exposed to nevirapine and efavirenz show that more than three-quarters of strains will still be sensitive to etravirine in both the southern and northern hemispheres. The first data on rilpivirine resistance are encouraging, but still too preliminary **(AIDS Rev. 2009;11:165-73)**

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Key words

HIV-1. Resistance. Second-generation NNRTI. Antiretroviral treatment. Etravirine. Rilpivirine.

Introduction

The HIV reverse transcriptase (RT) is targeted by two classes of antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Efavirenz, nevirapine, and delavirdine are so-called first-generation NNRTI. Since their market release in 1998, efavirenz and nevirapine have been a cornerstone of treatment for HIV-1 infection. However, their use is limited by their low genetic barrier to resistance and the marked cross-resistance between the two drugs (reviewed[1]). The development of second-generation NNRTI (etravirine and rilpivirine) took almost a decade.

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Mode of action of non-nucleoside reverse transcriptase inhibitors

The NNRTI differ from NRTI by the way in which they inhibit the RT enzyme. The NNRTI act as non-competitive inhibitors, binding RT with very high affinity within a small hydrophobic pocket close to the active site of the enzyme. The pocket is elastic, and its conformation

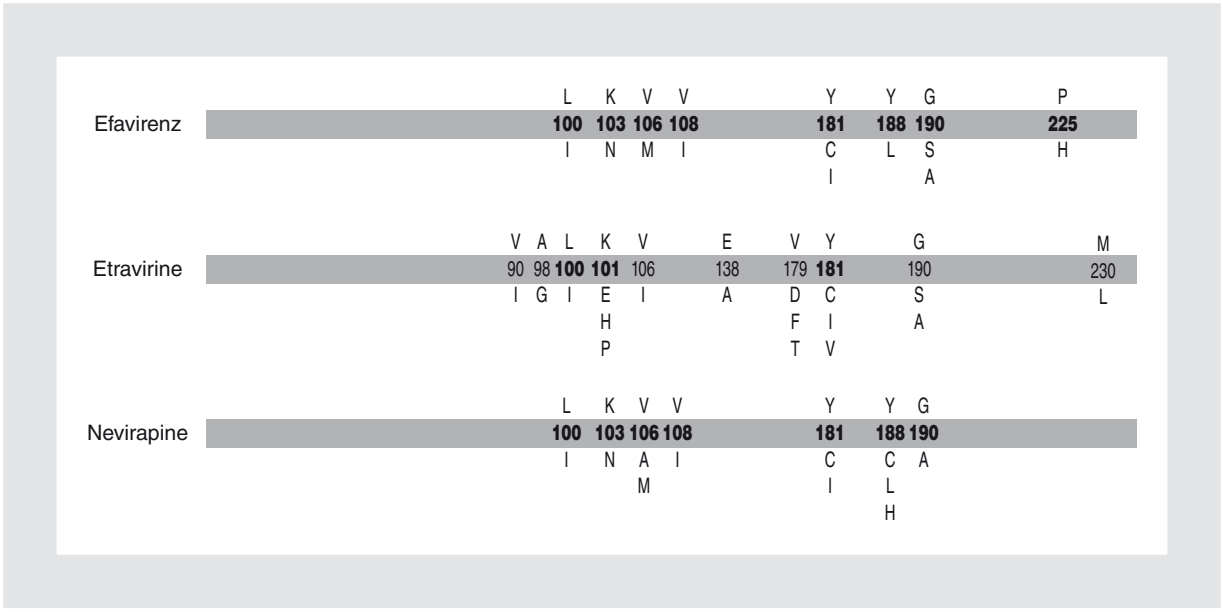

Figure 1. *Resistance mutations selected by NNRTI (IAS List, December 2008). Major mutations are shown in bold type. This slide summarizes non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance patterns. There is a clustering of mutations between codons 100 and 106 and codons 181 and 190, with several others occurring in the low 200s. There is broad cross-resistance in these patterns, although subtle differences can be seen*[1] (Johnson, et al. Topics HIV Med. 2008. [www.iasusa.org]).

depends on the size and chemical structure of the inhibitor, as well as on its binding mode. The NNRTI are small molecules with a variety of chemical structures, capable of inhibiting the RT activity of HIV-1, but not of HIV-1 group O and HIV-2. Contrary to NRTI, NNRTI do not need to be phosphorylated and do not integrate growing DNA strands. First-generation NNRTI fix within the pocket, binding amino acids Y181, Y188, and W229 on the one hand, and K103, V106, and V179 on the other hand. Nevirapine and efavirenz show marked cross-resistance, despite their very different structures. The need emerged for new NNRTI effective on resistant strains. Diarylpyrimidines were developed with two major objectives: (i) to bind conserved amino acids crucial for RT activity (W229 plays an important role in the positioning of viral DNA during polymerization), and (ii) to obtain a far more flexible chemical structure than that of first-generation NNRTI, thereby permitting several possible conformations within the pocket and allowing efficient binding to take place despite the presence of mutations[2]. The new commercial compounds are etravirine (TMC125, Intelence™) and rilpivirine (TMC278), marketed by Tibotec.

Etravirine (TMC125, Intelence™)

In vitro, etravirine is very active on wild-type HIV-1 group M strains (50% effective concentration EC_{50} 1.4-4.8 nM) and also seems to be active on HIV-1 group O and HIV-2 (EC_{50} 3.5 μM)[3]. However, etravirine cannot be used at these concentrations in HIV-2-infected patients. Single-agent etravirine therapy of naive patients at a dose of 900 mg twice daily for seven days led to a viral load reduction of 1.9 $\log_{10}$ copies/ml[4]. The initial reduction in viral load during etravirine monotherapy was similar to that obtained with a combination of five antiretroviral drugs belonging to three different classes (zidovudine, lamivudine, abacavir, indinavir, and nevirapine)[4].

Rilpivirine (TMC278)

In vitro, rilpivirine has an EC_{50} of 0.5 nM for wild-type viruses and is active on viruses resistant to first-generation NNRTI[5]. In phase II trials of rilpivirine monotherapy at doses of 25, 50, 100, or 150 mg once a day for seven days, viral load fell by 1.2 $\log_{10}$ on average, whatever the dose[6]. The phase III trials in antiretroviral naive-patients are on-going.

Non-nucleoside reverse transcriptase inhibitor resistance mutations (Fig. 1)

Figure 1 shows NNRTI resistance mutations included on the list of the International AIDS Society (www.iasusa.org).

First-generation non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine)

Resistance mutations can be subdivided into three distinct "clusters". The first includes L100I, K103N, V106A, and V108I; the second Y181C, Y188L/C/H, and G190A/S; and the third the less frequent mutations P225H, M230L, and P236L. The first two clusters represent the two opposite sides of the NNRTI binding pocket in the RT molecule, located on the main subunit (p66). The third cluster is located on the second subunit p51. Recently, mutation I132M was implicated in NNRTI resistance (phenotypic resistance index increased > 10-fold for nevirapine and two- to threefold for efavirenz), along with mutation I135A/M (twofold increase in the phenotypic resistance index of efavirenz and nevirapine)[7].

It should be noted that mutations conferring resistance to a single NNRTI can provoke high-level resistance through a loss of affinity. Given the massive selective advantage conferred by these mutations, resistance to NNRTI emerges very rapidly from the outset of viral escape during NNRTI-containing treatment regimens. Similarly, viral rebound occurs systematically and very rapidly during NNRTI monotherapy, and the escaping virus appears to be fully resistant.

Second-generation non-nucleoside reverse transcriptase inhibitors (etravirine and rilpivirine)

An *in vitro* study of a panel of viral isolates showed that nearly 90% of those with resistance mutations to first-generation NNRTI were sensitive to etravirine[3]. At least two mutations are required to reduce etravirine sensitivity, and selection of a resistant virus requires multiple mutations, indicating that the genetic barrier is far higher than with other members of this therapeutic class[3]. The positions most frequently involved are those classically observed with other NNRTI (L100I, Y181C/I, G190E, M230L), as well as other rarely described mutations (V179I/F, Y318F).

Few data are available on the mutations selected by rilpivirine. No mutations were selected by rilpivirine concentrations above 40 nM after several passages *in vitro*. Lower concentrations (10 nM) can select the L100L/I, V106V/I, Y181Y/C, and M230M/I mutations, leading to sevenfold and fourfold increases in the phenotypic resistance index for efavirenz and rilpivirine[8], respectively. In a study of treatment-naive patients, no mutations were detected after eight days of rilpivirine monotherapy[9].

Relative to first-generation NNRTI, these two compounds therefore have a far more robust genetic barrier and remain active on strains harboring certain mutations that confer resistance to first-generation NNRTI.

Cross-resistance among non-nucleoside reverse transcriptase inhibitors

Only some mutations confer strong cross-resistance to all first-generation NNRTI. This is the case of K103N and Y188L, the mutations most frequently selected by efavirenz. The strongest cross-resistance is seen with viruses bearing more than one NNRTI resistance mutation, including L100I, G190A, or V106A. In contrast, Y181C, the mutation selected most rapidly and most frequently by nevirapine, only confers limited cross-resistance to efavirenz. Nevertheless, in patients whose viral population has acquired the Y181C mutation after nevirapine failure, the switch to efavirenz is almost always followed by rapid failure and frequent appearance of the K103N mutation[10].

Second-generation NNRTI therefore remain active in patients in whom first-generation NNRTI have failed. Etravirine resistance was studied in the DUET trials, testing the boosted darunavir/etravirine combination in treatment-experienced patients[11,12]. Mutations affecting the response to etravirine were studied in a subgroup of patients who received recycled enfuvirtide. The analysis focused on 57 mutations, including the NNRTI resistance mutations included in the XVII International HIV Drug Resistance Workshop 2008 list[16], plus other mutations previously reported to reduce sensitivity to NNRTI. 17 of these mutations affected the response to etravirine (V90I, A98G, L100I, K101E, K101P, K101H, V106I, E138A, V179D, V179F, V179T, Y181C, Y181I, Y181V, G190A, G190S, M230L). The impact of the mutations was higher when a large number of mutations were already present before treatment, with a probable threshold of more than three mutations (Fig. 2)[11,13]. The 2008 French Agence Nationale de Recherches sur le Sida (ANRS) resistance algorithm for etravirine is based on these data; resistance is "possible" when three mutations are present and "probable" when four or more mutations are present (www.hivfrenchresistance.org). The phenotypic and clinical cutoffs for etravirine were recently determined (a first for this drug class), as follows: 0-3 for sensitive isolates, 3-13 for isolates with intermediate sensitivity, and > 13 for resistant isolates[14]. Moreover,

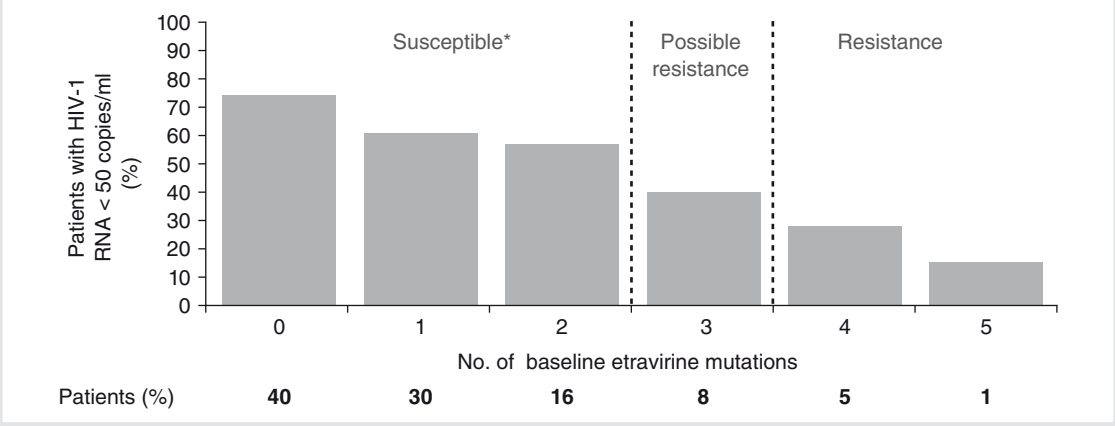

Figure 2. *Virologic efficacy according to number of baseline etravirine resistance mutations. Mutations conferring resistance to etravirine: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S. *2008 ANRS algorithm* (Lazzarin, et al. Lancet 2007; Rimsky, et al. IHDRW 2007; www.hivfrenchresistance.org).

genotypic/phenotypic (Monogram® data[15]) and genotypic/clinical correlations (data from the DUET trials[16]) allowed etravirine resistance mutations to be weighted, most weight being given to mutations Y181I, Y181V, K101P, and L100I.

The weighted ETR mutation scores are shown in the following table:

Table 1. Individual mutation weight to etravirine

1	1.5	2.5	3
V90I	V106I	L100I	Y161L
A98G	E138A	K101P	Y161V
K101E	V179F	Y181C	
K101H	G190S	M230L	
V179D			
V179T			
G190A			

However, the correlation between the weighted mutation score and clinical efficacy is not linear. Two studies from others groups have reported data on resistance to etravirine. Poveda, et al. reported the phenotypic impact of the Y181C mutation in combination with at least one etravirine resistance-associated mutation (12.6-fold reduced susceptibility) and described two novel changes, K101H and E399D, that significantly diminished etravirine susceptibility[17]. Marcelin, et al. have investigated the factors associated with response to etravirine-containing regimens in 243 experienced patients and have reported that mutation K103N was associated with success, and mutations Y181V and E138A were independently associated with poor response, whereas no effect on response was observed with Y181C[18].

The resulting score assigned to each mutation a value as a function of their weight (Value 4: L100I, K101P, Y181C/I/V; value 3: E138A/G, V179E, G190Q, K238T,K101P, V106A, E138K, 179L, Y188L; and value 1: V90I, K101H, V106M, E138Q, V179D/F/M, Y181F, Y189I, G190E/T, H221Y, P225H, K238T) and, in accordance with the presented mutations, a result from the score is obtained.

Three categories are defined according to the ETR response rates: 0-2 (highest response), 2.5-3.5 (intermediate response) and ≥ 4 (progressive reduced response). If the result is less than 4, ETR has a 90% probability to be effective (fold change < 2.9) (Fig. 3).

Interactions with nucleoside reverse transcriptase inhibitor resistance mutations

There is growing evidence that mutations associated with resistance to the two classes of RT inhibitors interact. Paolucci, et al. reported that mutation of codon 190 induces high-level *in vitro* resistance to nevirapine and moderate resistance to the thymidine analogs zidovudine and stavudine[19]. The simultaneous presence of G190S and T215Y facilitates the emergence of resistance to both NNRTI and NRTI.

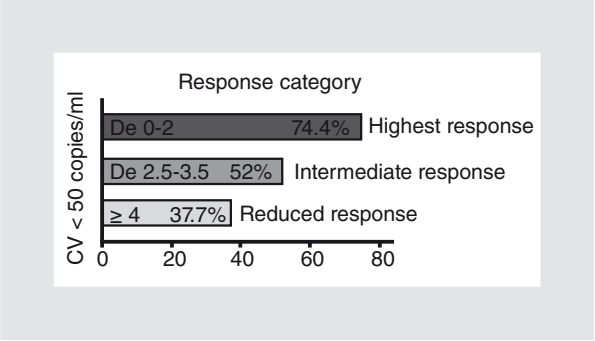

Figure 3. *Relation between the weighted score and the virologic response (CD4 < 50 copies/ml)* (figure built with data from Vingerhoets, et al. HIVDRW 2008 [poster 24]).

Recently, Ceccherini-Silberstein, et al. underlined the importance of certain RT mutations usually considered as polymorphisms in viral evolution under NNRTI selection pressure[20]. For example, the L74V and H221Y mutations are associated with the selection of Y181C during nevirapine exposure, while the I135M/T mutation is associated with the selection of K103N during efavirenz exposure. Moreover, the presence of the I135T mutation in NNRTI-naive patients could facilitate the selection of mutation K103N by stabilizing the RT pocket closure induced by mutation K103N. Wirden, et al. have also reported that the L74I mutation is associated with efavirenz-containing antiretroviral regimens[21]. All these data underline the importance of interactions among RT mutations and should probably be taken into account in the interpretation of first-generation NNRTI resistance mutations and in the design and development of second-generation NNRTI.

Although most mutations conferring resistance to RT inhibitors are located in the region encoding the enzyme's polymerase activity, mutations located in the region of the connection domain of HIV RT, and especially N348I, are also important[22,23]. The N348I mutation is more frequent in pretreated patients and appears early during treatment, especially with the zidovudine/nevirapine combination. N348I is significantly associated with mutations conferring resistance to thymidine analogs, as well as with mutation M184V and mutations K103N and Y181C. When introduced into a wild-type virus, the N348I mutation increases zidovudine resistance two- to fourfold, nevirapine resistance 7.4-fold and efavirenz resistance 2.5-fold. The main mechanism underlying this synergy is the reduction in adenosine triphosphate-mediated 3`-azido-3`-deoxythymidine excision through a reduction in ribonuclease H cleavage when an NNRTI is bound to the RT[24].

Hypersensitivity to non-nucleoside reverse transcriptase inhibitors

Some mutations conferring resistance to NRTI have been found to confer phenotypic hypersensitivity (defined by a resistance index ≤ 0.4) to the first-generation NNRTI efavirenz and nevirapine. Recent data on etravirine tend to confirm the existence of this phenomenon, the reduction in the etravirine resistance index growing with the number of NRTI mutations, even in the presence of one or two NNRTI mutations[25,26]. The clinical implications of these findings remain to be determined.

Transmission of non-nucleoside reverse transcriptase inhibitor-resistant viruses

Recent studies of the transmission of NNRTI-resistant viruses to previously uninfected patients show that the incidence has been stable in recent years. In France, the ANRS Primo cohort shows that the incidence has been stable at about 4% since 2000, and that no viruses initially resistant to etravirine have been detected[27]. The European Spread study showed a prevalence of 2.6% for the year 2002-2003. In most cases only one mutation was detected, conferring high-level cross-resistance between nevirapine and efavirenz and a very low level of resistance to etravirine[28]. In the Swiss cohort, an overall prevalence of 1.9% over a 10-year period was found, with an increase to 6% in 2005[29]. The frequency of transmission of viruses initially resistant to etravirine is very low (0.1%). Studies conducted in the USA showed a prevalence of about 7% in the most recent period (2003-2006)[30,31]. All these data support continued genotyping of patients with primary infection and, more generally, pretreatment genotyping. Indeed, NNRTI resistance significantly undermines the response to efavirenz-containing treatments and increases the risk of virologic failure (Fig. 4)[32,33]. Transmission of viruses with several NNRTI mutations seems to be rare, however.

Place of non-nucleoside reverse transcriptase inhibitors in the prevention of mother-child HIV-1 transmission

Prevention of mother-child transmission (PMCT) has evolved as new clinical trial findings have been published. In rich countries, NNRTI are not recommended for PMCT. In France, it is recommended to start a three-drug regimen during the third trimester of pregnancy in order to limit the duration of fetal exposure to

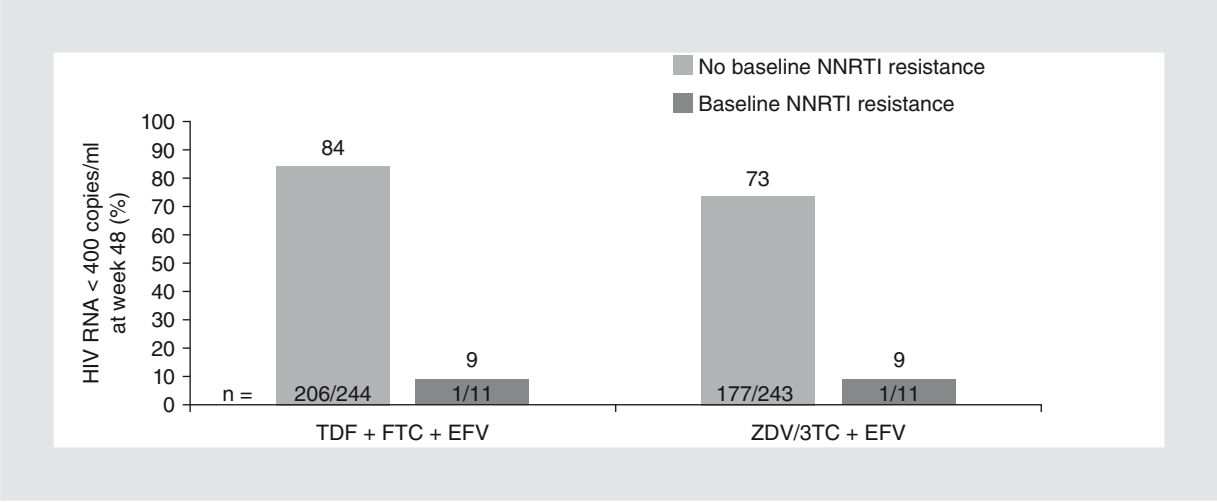

Figure 4. *Baseline NNRTI resistance mutations and virologic failure. Light grey: no non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations detected at enrollment; dark grey: NNRTI resistance mutations detected at enrollment. This slide shows data from the GS 934 study, which was a head-to-head comparison in treatment-naive patients treated with tenofovir/emtricitabine vs. zidovudine/lamivudine, each plus efavirenz. These data show the proportion of patients with HIV-1 RNA < 400 copies/ml at 48 weeks based on whether or not the patient had NNRTI resistance at baseline. Again, it is important to notice that the number of patients with baseline NNRTI resistance was quite small. A large proportion of patients with no baseline resistance had HIV-1 RNA < 400 copies/ml (tenofovir/emtricitabine: 84%; zidovudine/lamivudine: 73%). However, the proportion was dramatically lower in patients with baseline NNRTI resistance. Only 1 out of 11 in each treatment arm achieved HIV-1 RNA < 400 copies/ml at 48 weeks. Clearly, NNRTI resistance at baseline has a very large impact on the outcome of NNRTI-based therapy, and this is the major reason why baseline resistance testing is recommended. TDF: tenofovir; FTC: emtricitabine; EFV: efavirenz; ZDV: zidovudine; 3TC: lamivudine* (Gallant JE, et al. N Engl J Med. 2006;354:251-60).

antiretroviral drugs and to drive maternal plasma viral load below the detection limit at the time of delivery. These three-drug regimens classically include two NRTI and one ritonavir boosted protease inhibitor. Three-drug regimens comprising an NNRTI are not to be used if other options are available. Nevirapine carries a high risk of hepatic and/or cutaneous toxicity during pregnancy. Efavirenz is contraindicated during the first trimester of pregnancy because of the risk of malformations, and its use in the second trimester has not been studied. No relevant data are available for second-generation NNRTI such as etravirine.

In the southern hemisphere, NNRTI are more widely used for PMCT. The latest World Health Organisation guidelines, published in 2006, discuss the use of antiretroviral combinations in pregnant women in different operational settings, according to whether or not the woman herself needs antiretroviral therapy[34]. The three-drug regimens available in low-income countries often include the stavudine/lamivudine/nevirapine combination (Triomune®; Cipla Medpro). If a three-drug regimen is available, it is recommended to treat, both during pregnancy and at the time of the delivery, all women with $CD4^+$ T lymphocyte counts < 200/mm^3 or clinical stage IV-WHO, or a $CD4^+$ T-cell count < 350/mm^3 and clinical stage III. Treatment should be considered if the woman has a $CD4^+$ cell count < 350/mm^3 and clinical stage I or II. In these two situations, the three-drug regimen must be continued in the postpartum period and the child must receive zidovudine prophylactically for seven days. If the woman has no personal treatment indication, or if a three-drug regimen is not available, then zidovudine must be started, if possible, from week 28 of pregnancy. Zidovudine and single-dose nevirapine must be given at the time of delivery and the mother must receive zidovudine/lamivudine for seven days to prevent the emergence of nevirapine resistance. The child must receive single-dose nevirapine and zidovudine for 1-4 weeks, depending on the duration of maternal treatment. In countries where drugs such as zidovudine are not available, it is recommended to give single-dose nevirapine to the mother at the time of delivery and to the child during the first 72 hours of life.

If the woman is first seen when already in labor, there are two PMCT options (provided the drugs are available): one is single-dose nevirapine plus zidovudine at the time of delivery, with the child receiving single-dose nevirapine and zidovudine for four weeks; while the other is zidovudine/lamivudine at the time of delivery and for seven days postpartum, with the child receiving zidovudine/lamivudine for seven days. If very few drugs are available, single-dose nevirapine should be given to the woman at the time of delivery and to the child

during the first 72 hours of life. If the woman was unable to receive treatment to prevent mother-child transmission, then the child should receive single-dose nevirapine plus zidovudine for four weeks.

This flexible strategy, adapted to the severity of the maternal infection and to local resources, ensures that PMCT is feasible in most settings. Unfortunately, despite repeated commitments by politicians, as well as a wide range of possible interventions and the knowledge required to use them effectively, most pregnant women requiring PMCT do not receive it. According to the last UNAIDS report for the year 2005, only about 220,000 of some two million pregnant women living with HIV received PMCT, giving an estimated coverage rate of 11% (8-16%) all drug regimens combined[35]. Moreover, a large number of pregnant women are given single-dose nevirapine, which is less effective than combination therapy and runs a risk of selecting for NNRTI resistance in both the woman and her infected child.

The use of single-dose nevirapine is indeed associated with a high level of viral resistance in the woman and her infected child: viruses with nevirapine resistance mutations are present in an estimated 19-75% of mothers[36-41] and 33-87% of their infected children[39,42] The main risk factors are a high maternal viral load and a low $CD4^+$ T lymphocyte count. The viral subtype should also be taken into account when assessing the risk of selecting resistant viruses. In the HIVNET 012 study conducted in Uganda, selection of resistant viruses was more frequent in case of subtype D than subtype A infection (35.7 vs. 19%)[43]. A more recent study done in Malawi showed an even higher frequency of resistant viruses in women infected by subtype C compared with subtype D or A (69, 36, and 19%, respectively)[44]. The plasma nevirapine concentration also affects the risk of resistant virus selection, and it is noteworthy that the nevirapine concentration reached after a single intake can vary widely from one woman to another. Nevirapine has a long half-life and remains detectable in plasma for up to 20 days after a single intake. The high frequency of resistance to this drug after a single dose is due to persistent viral replication in the persistent presence of a suboptimal inhibitor concentration. Selection pressure is maximal in these conditions.

Data on the use of nevirapine for PMCT corroborate more general data on NNRTI resistance, confirming the very low genetic barrier of this drug and the high risk of selecting resistant viruses. It is therefore recommended, if single-dose nevirapine must be used for PMCT, to combine it, if possible, with prepartum treatment and especially with a few days of postpartum treatment.

No data on etravirine in the context of PMTCT are currently available. This drug have been approved in 2009 by the FDA with category B in the context of pregnancy. Further studies are needed to evaluate the efficacy of etravirne in women previously exposed to NVP single dose.

Impact of minor variants on the response

Current genotypic tests can detect resistant variants representative of about 20-80% of the global viral population in a given patient (by direct sequencing after PCR amplification). Thus, resistant variants representing less than 20% of the viral population cannot be detected. The detection of such minor variants, especially those resistant to lamivudine and/or NNRTI, is based on a more sensitive technique such as allele-specific PCR. The prevalence of minor variants in 205 treatment-naive patients in whom wild-type viruses were detected with standard techniques was 17% (34/205) for viruses with at least one mutation and 2% for viruses resistant to at least two drug classes. The influence on virologic response of these minor variants was studied in patients receiving a first-line treatment regimen comprising efavirenz (combined with lamivudine/zidovudine+/-abacavir)[44,45]. The presence of minor variants (K103N, Y181C, M184V) correlated strongly with the risk of virologic failure.

These results are similar to those obtained in clinical trials of mother and child treatment with the stavudine/lamivudine/nevirapine combination after a single dose of nevirapine to prevent vertical transmission. Even when no nevirapine resistance was detected, the virologic response was less good in patients who had received the single dose of nevirapine than in those who did not receive it, pointing to the presence of minor resistant variants[46,47].

Resistance at the time of non-nucleoside reverse transcriptase inhibitor failure and its consequences

In rich countries

Data from the Swiss Cohort on the emergence of resistance to antiretroviral drugs in patients with a failing first-line treatment confirm the high risk of resistance selection when the regimen includes drugs with a low genetic barrier such as lamivudine and first-generation NNRTI rather than ritonavir-boosted protease inhibitor-based regimens[29].

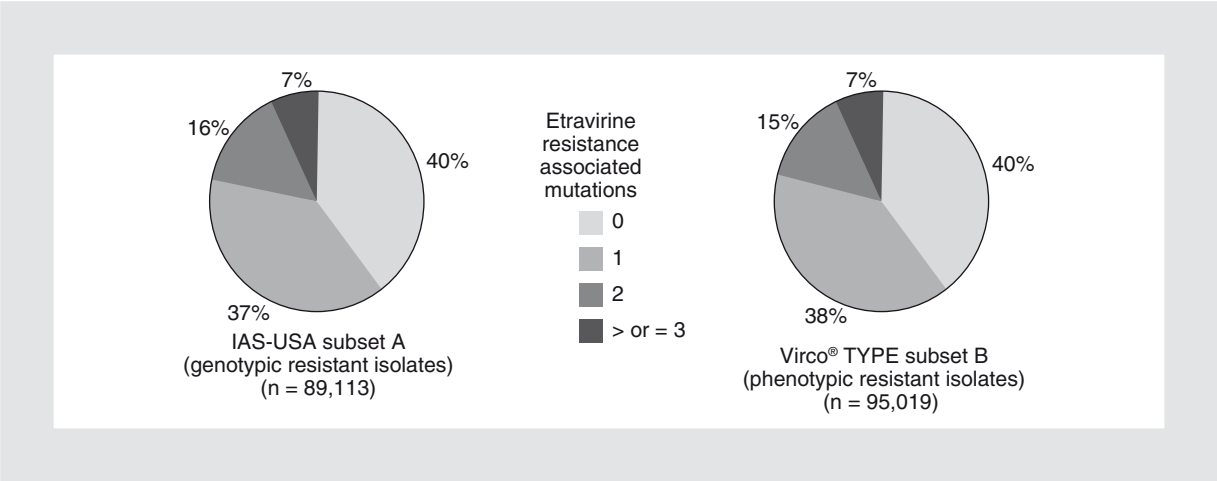

Figure 5. *Prevalence of etravirine resistance (1999-2007). Based on 225,000 clinical samples studied for resistance (VIRCO), assessment of etravirine resistance mutations on two samples of viruses with genotypic (n = 89,113) and phenotypic (n = 95,019) resistance to first-generation non-nucleoside reverse transcriptase inhibitors. Mutations conferring resistance to etravirine: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S* (ANRS algorithm AC11, July 2007).

A very recent study of the EuroSIDA cohort examined responses and resistance profiles during treatment failure in patients previously exposed to NRTI and protease inhibitors but not to NNRTI, and who received either nevirapine (n = 389) or efavirenz (n = 370)[28]. The risk of virologic failure was twice as high in patients whose treatment included nevirapine rather than efavirenz, even after adjustment for a number of cofactors. At enrollment, viruses resistant to NNRTI were detected in similar proportions of patients in the two groups (about 3%). At the time of treatment failure, resistance mutations were detected in 86% of the 131 patients who were still on NNRTI, regardless of the NNRTI received. However, the K103N mutation was most prevalent in the patients receiving efavirenz, while the Y181C and G190A mutations were most frequent in the patients receiving nevirapine.

In poor countries

A cross-sectional study conducted in Thailand and involving 1,376 patients showed a significant increase in the prevalence of NNRTI resistance between 2000-2002 (37%) and 2003-2004 (60%), which was matched by an increase in the use of the GPO-VIR generic (stavudine/lamivudine/nevirapine)[48]. Marcelin, et al. examined the prevalence of resistance in 109 patients in Mali who received Triomune® (stavudine/lamivudine/nevirapine) for at least six months and who had viral loads > 200 copies/ml[49]. Resistant viruses (usually M184V and Y181C mutants) were detected in 50% of patients in whom treatment was failing, but sensitivity to etravirine was preserved.

Recent studies of the prevalence of etravirine resistance (≥ 3 mutations) in the large database of patients previously treated with nevirapine and efavirenz but not with etravirine showed a very high proportion of sensitive strains (> 90%) in both rich countries[50-52] (Fig. 5) and poor countries (Thailand > 75%, Niger > 90%), making this a potential choice for second-line treatment[53,54].

Conclusions

The second-generation NNRTI etravirine has proven effective in patients with treatment failure who harbor viruses that are resistant to first-generation NNRTI and that carry several resistance mutations. Etravirine is the first NNRTI for which at least three mutations are necessary to undermine its efficacy. However, few data on large number of patients are available on etravirine resistance profiles. Finally, in the case of rilpivirine, a second-generation NNRTI being developed for first-line therapy, it will be important to rapidly determine the prevalence and profiles of resistance, throughout the reverse transcriptase gene, in patients with treatment failure.

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