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1. Introduction

Continuous administration of the drugs included under the term Highly Active Antiretroviral Therapy (HAART) has turned AIDS into a chronic disease, at least in developed countries (Panos et al., 2008). The initial development of these drugs was particularly rapid and focused on clinical efficacy before all other considerations. However, as the disease has come under control, there has been growing emphasis on the long-term adverse effects associated with this therapy.

The first drug for the treatment of HIV infection, zidovudine (AZT), was approved in 1987. The number of other antiretroviral drugs already approved for use or under development continues to grow, and the primary aim of researchers in the field is to improve their efficacy, safety and tolerability. Currently, there are 25 licensed antiretroviral drugs that belong to 6 different families: eight nucleoside (nucleotide) reverse transcriptase inhibitors (N(t)RTI) which inhibit competitively the viral reverse transcriptase, four non-nucleoside reverse transcriptase inhibitors (NNRTI), which produce a direct inhibition of the reverse transcriptase and a reduction in its catalytic activity, ten protease inhibitors (PI), which inactivate the HIV protease and prevent the generation of new viruses capable of infecting other cells, one fusion inhibitor, which prevents the fusion of the virus envelope with the host-cell membrane, one CCR5 inhibitor, which blocks the interaction of the virus with one of its receptors on the host cell, and, finally, one integrase inhibitor, whose function is to block viral DNA integration in the nuclear genome.

HAART aims to slow the rate of viral replication to the point of reducing the viral load and producing a significant immune system reconstitution that increases circulating levels of CD4+ T cells. HAART usually combines the three major families of drugs: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. According to current guidelines, HAART regimens for initial treatment consist of two N(t)RTI plus either a NNRTI or a boosted PI (Hammer et al., 2008). NNRTI-based regimens have been in use for over a decade now, with the NNRTI of choice being Nevirapine (NVP) (for first line therapy in countries with limited resources) and Efavirenz (EFV) (for the treatment of naïve patients). Although considered to be safe and well-
tolerated drugs, their low genetic barrier against the development of resistance and new and growing evidence of potential long-term toxicity associated with their use has generated a need for new improved drugs in this class. One new arrival is etravirine, which has already been approved by the Food and Drug Administration (FDA), and there are currently four other compounds in different stages of clinical development (rilpivirine, RDEA806, IDX899 and lersivirine).

Fig. 1. Currently employed antiretroviral drugs and clinical guidelines in the treatment of HIV infection. The approved compounds are listed for each family.

2. NNRTI

This family is composed of highly specific inhibitors of HIV-1 characterized by a long-plasmatic half-life that allows once-daily dosing. Although all NNRTI have heterogenic chemical structures, they reduce HIV-1 replication through the same mechanism, which consists of non-competitive inhibition of the viral reverse transcriptase through binding to a hydrophobic pocket located close to the enzyme’s catalytic site and inducing conformational changes that affect the catalytic activities of the enzyme (Sluis-Cremer, 2004). It is important to note that NNRTI are biotransformed in the liver via the cytochrome P450 pathway, which means there is potential for interactions with other drugs whose metabolism uses the same pathway.

The first member of this family to be approved by the FDA was NVP, in 1996, followed by Delavirdine (DLV) in 1997 and EFV in 1998. Nowadays, the NNRTIs of choice are NVP and EFV, which are still essential components of first-line HAART. On the other hand, DLV is no longer used due to its limited efficacy. First generation NNRTI exhibit a somewhat
ineffective genetic barrier to the development of resistance, and have been shown to induce several moderate-to-severe side effects whose frequency and severity vary significantly with each compound, including hepatotoxicity, cutaneous reactions, central nervous system toxicity, metabolic alterations and gastrointestinal adverse events (van den Berg-Wolf, 2008; Jena, 2009). These disadvantages have fuelled the search of new NNRTI with an improved resistance profile and higher efficacy and tolerability, such as Etravirine (ETR), which was approved by the FDA in 2008 (Martínez, 2010). The chemical structures of the NNRTI currently available and in clinical development are shown in Figure 2.

Fig. 2. Chemical structures of approved NNRTI (nelfinavir, delavirdine, efavirenz and etravirine) and NNRTI in clinical development (rilpivirine, RDEA806, IDX899 and lersivirine).

2.1 Nevirapine
This NNRTI is recommended for first line therapy in resource-limited countries, but, due to its low teratogenesis and paediatric toxicity, it is also widely employed in pregnant women and young children in the developed world. This dipyridodiazepinone is usually administered in twice-daily doses of 200mg, achieving peak plasma concentrations (2 ± 0.4µg/ml) at 4h. However, several clinical trials have also shown it to be safe and effective in a once-daily regimen of 400mg (Garcia, 2000; van Leth, 2004). Despite no major differences being reported between these two regimens, once-daily dosing has been shown to produce complications, including lower minimum concentration (C_min) and higher maximum concentration (C_max) levels and a high risk of rash, which can be minimized by generating
tolerance through the administration of a twice-daily dose for a few weeks prior to treatment (Cooper, 2007). This compound is biotransformed via cytochrome P450 isoenzymes, mainly from the CYP3A family, into several hydroxylated metabolites, and its plasma half-life ranges from 45h (with a single dose) to 25 - 30h (with repetitive dosing) (Cooper, 2007). The most frequently described adverse effects of NVP are rash and hepatotoxicity.

2.2 Delavirdine
Regulatory agencies have advised against the use of DLV in initial therapy, and so current regimens rarely contain this bis(hetero-aryl)piperazine, as it is less effective than other NNRTI, is accompanied by complex drug interactions and requires a more inconvenient administration. It is characterized by a rapid absorption following oral administration, with peak plasma concentrations occurring approximately 1 hour after dosing. The recommended dosage of DLV is 400mg three times per day, which results in a \( C_{\text{max}} \) of 35 ± 20\( \mu \)M and a \( C_{\text{min}} \) of 15 ± 10\( \mu \)M, and a mean half-life of 5.8h. CYP3A isoenzymes of the cytochrome P450 system are the main effectors of DLV conversion into several inactive metabolites, although \textit{in vitro} data also suggest the involvement of CYP2D6. The major manifestation of its toxicity is rash (Repositorio official FDA information, 2011).

2.3 Efavirenz
EFV, combined with two NRTI, is the recommended option for initial therapy and is the most widely used NNRTI. This benzoxazinone has a long half-life (at least 52h with single doses and 40 - 55h with multiple doses), which makes it suitable for once-daily dosing, with 600mg being the recommended dose for adults. Peak EFV plasma concentrations are reached 3 - 5h after a single oral dose and become steady at 6 - 7 days (Maggiolo, 2009). An important pharmacokinetic inter-individual variability has been reported in patients taking EFV: a daily dose of 600mg usually results in a \( C_{\text{max}} \) of 12.9 ± 3.7\( \mu \)M and a \( C_{\text{min}} \) of 5.6 ± 3.2\( \mu \)M (Starr, 1999; Staszewski, 1999), but higher levels (between 30 - 50\( \mu \)M) have been observed in as many as 20% of patients (Marzolini, 2001; Burguer, 2006). This drug is extensively biotransformed into inactive hydroxylated metabolites via the cytochrome P450 system, and CYP2B6 is likely to be the corresponding isoenzyme. Moreover, \textit{in vitro} studies suggest that the wide inter-individual variability in the expression and activity of CYP2B6, in addition to its genetic polymorphisms, could lie behind the variability in EFV pharmacokinetics (Ward, 2003). It is also important to note that EFV levels can vary if it is co-administered with other drugs that influence this isoenzyme. Despite its apparent safety, several adverse events of EFV-containing therapies have emerged, such as rash, neuropsychiatric disturbances, lipid and metabolic alterations, and hepatotoxicity (Maggiolo, 2009).

2.4 Etravirine
The most recent approved NNRTI is a di-aryl-pyrimidine. It has shown sustained clinical efficacy in HIV-1 strains that are resistant to other compounds of the same family and has a higher genetic barrier to the development of resistance than older NNRTI. ETR is less susceptible to drug-resistant mutations, probably due to the fact that it binds to the reverse transcriptase in multiple conformations (Dickinson, 2010; Martinez, 2010). Although several recent trials suggest that its long half-life (30 - 40h) makes it suitable for once-daily dosing
(400mg), the current recommended dosage for ETR is 200mg twice daily, which results in a $C_{\text{max}}$ of 0.79 - 0.80 $\mu g/ml$ 4h after administration. As with other NNRTI, its metabolism depends on several isoforms of the cytochrome P450, primarily CYP3A4, CYP2C9 and CYP2C19. Thus, its use in combination with other drugs that also induce the cytochrome P450 is not recommended. Existing clinical evidence shows that ETR is well tolerated in patients, with low rates of discontinuation as a result of detrimental effects. In the Phase III trials DUET-1 and DUET-2, the primary adverse effect associated with ETR was mild-to-moderate rash, and no association was found with hepatic/lipid abnormalities or with a higher incidence of psychiatric disorders (Lazzarin, 2007; Madruga, 2007; Schiller, 2009). However, data about ETR are still limited due to its recent commercialisation, and further clinical and in vitro analyses are needed in order to determine the full side effects of this compound.

2.5 NNRTI in clinical development

New NNRTI are currently being developed as part of the quest to find efficient compounds with greater resistance and a lower frequency of adverse effects. The information available about the clinical relevance and pharmacokinetic and toxicological profiles of the four NNRTI currently under clinical development is limited, which makes it difficult to predict their potential as therapy for HIV infection. Nevertheless, several ongoing trials are investigating the efficacy, safety and tolerability of these drugs.

2.5.1 Rilpivirine (TMC278)

The pharmacokinetics of this di-aryl-pyrimidine compound allow once-daily dosing, usually with 25mg, and its good bioavailability makes it a potential candidate for co-formulation. In fact, studies are underway to develop a new once-daily fixed-dose antiretroviral regimen containing Emtricitabine, Tenofovir disoproxil fumarate and Rilpivirine hydrochloride (de Béthune, 2010). Rilpivirine has an in vitro resistance profile comparable to that of ETR (Azijn, 2010), and results from week 96 of a Phase IIB trial (TMC278-C204) in naïve patients have demonstrated a potent and sustained efficacy similar to that of EFV, while it seems to produce fewer adverse events. Indeed, rilpivirine is associated with fewer incidences of neuropsychiatric events and rash, and a smaller rise in lipid levels than EFV (Pozniak, 2010).

2.5.2 RDEA806

In vitro studies have reported that this triazole compound exerts a potent activity against both wild-type and NNRTI-resistant HIV-1 strains similar to that of ETR. Data from Phase IIA of a short-term monotherapy trial evaluating the antiviral activity, safety and pharmacokinetics of RDEA806 have demonstrated that this compound exerts a robust antiretroviral activity in HIV-1 positive, antiretroviral-naïve patients treated once daily for 7 days. All doses of RDEA806 tested were well tolerated and no patient’s treatment was discontinued due to adverse effects (Moyle, 2010).

2.5.3 IDX899

This 3-phosphoindol compound also has a potent in vitro activity against wild-type and NNRTI-resistant strains of HIV-1, and possesses a high genetic barrier to resistance. Preliminary data from a Phase IIA trial of treatment-naïve patients undergoing 7 day
monotherapy with IDX899 suggest a potent antiviral activity and tolerability with all the doses evaluated (Klibanov, 2010).

### 2.5.4 Lersivirine (UK-453061)

This compound belongs to the pyrazole family and exhibits a good resistance profile in vitro. Results from a phase IIA clinical trial in which asymptomatic HIV-1 infected adults were treated once or twice daily with lersivirine in a 7-day monotherapy regimen demonstrate its high antiviral activity and good safety and tolerability profile. Nevertheless, some minor adverse effects (headache, fatigue and nausea) have been reported (Corbau, 2010; Fätkenheuer, 2009).

### 3. NNRTI-associated adverse effects

NVP and EFV, the most widely employed NNRTI, share a similar efficacy and genetic barrier against the development of drug resistance, but differ in their toxicological profiles. Clinical trials have generally shown NNRTI, and especially EFV, to be safe and well-tolerated drugs. However, treatment discontinuation has been reported in patients receiving EFV- and NVP-based regimens, and is mainly attributed to the appearance of several moderate-to-severe side effects, some of which are drug-specific and unrelated to NNRTI as a pharmacological group. The most common adverse effects are cutaneous reactions, hepatotoxicity, neuro-psychiatric toxicity and metabolic alterations, but other toxicities have also been described to a lesser extent (Figure 3).

Discontinuation rates of up to 16% have been reported in patients receiving EFV and two NRTI, and similar or higher levels have been found following treatment with NVP. For example, in a study comparing EFV and NVP (each in combination with Lamivudine (3TC) and Stavudine (d4T)), discontinuation was necessary in 15.8% and 24.1% of treatments with EFV and NVP respectively (van Leth, 2004). It is important to note that the incidence of discontinuation of EFV-based therapy also depends on the NRTI co-administered, being more frequent when EFV is used with 3TC and Zidovudine (AZT) or with 3TC and Abacavir (Bartlett, 2007). In the FIRST study, severe (grade 4) adverse events were approximately half as common with EFV as with NVP (van der Berg-Wolf, 2008), especially in the case of rash and hepatotoxicity. Nevertheless, NVP can be considered an alternative therapy when there is a high risk of central nervous system (CNS) toxicity because of its lack of association with neuropsychiatric events (Hawkins, 2005; van Leth, 2004).

#### 3.1 Cutaneous reactions

All NNRTI have been associated with skin reactions, but they differ in the frequency and severity of the adverse events, with being rash one of the most common manifestations. The majority of the cutaneous reactions associated NVP (including Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity) appear within the first six weeks of treatment and can lead to therapy discontinuation if serious. Data from a metaanalysis revealed that 24% of NVP-treated patients suffered rash compared with 15% of controls, while 1.7% of patients showed severe grade 3 and 4 reactions vs 0.2% of controls [40]. One of the proposed mechanisms in NVP-mediated rash involves the 12-hydroxy metabolite of this drug, which can be converted to a reactive quinone methide in the skin, thus inducing an immune response and rash (Popovic, 2010).
Future Perspectives in NNRTI-Based Therapy: Bases for Understanding Their Toxicity

Fig. 3. NNRTI-related adverse events

<table>
<thead>
<tr>
<th>Cutaneous reactions</th>
<th>Hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1:</strong> Erythema with/without pruritus</td>
<td><strong>Grade 1:</strong> Elevation of serum aminotransferases 1.25 to 2.5 times the upper normal limit</td>
</tr>
<tr>
<td><strong>Grade 2:</strong> Diffuse erythematous macular or maculopapular eruption or dry desquamation with or without pruritus or typical target lesions, without blistering, vehicles or ulceration in the lesions; Urticaria</td>
<td><strong>Grade 2:</strong> Elevation of serum aminotransferases 2 to 5 times the upper normal limit</td>
</tr>
<tr>
<td><strong>Grade 3:</strong> Diffuse erythematous macular or maculopapular eruption or moist desquamation with or without pruritus together with blistering and vesication. Angioedema, exudative dermatitis, or diffuse rash and serum sickness or diffuse cutaneous eruption plus one of the following cutaneous bullae with widespread sheet-like detachment of skin</td>
<td><strong>Grade 3:</strong> Elevation of serum aminotransferases &gt;5 times the upper normal limit</td>
</tr>
<tr>
<td><strong>Grade 4:</strong> Toxic epidermal necrolysis</td>
<td><strong>Grade 4:</strong> Elevation of serum aminotransferases &gt;10 times the upper normal limit</td>
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<table>
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<tr>
<th>CNS toxicity</th>
<th>Metabolic alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate:</strong> Dizziness, headache, confusion, depersonalization, drowsiness, euphoria, hallucinations, impaired concentration, amnesia, sleep abnormalities such as insomnia or vivid dreams, nervousness, anxiety and/or depression.</td>
<td><strong>Lipodystrophy:</strong> reduction of hypogenesis and differentiation in adipocytes, decrease of adipokine release</td>
</tr>
<tr>
<td><strong>Severe:</strong> Severe depression, delusions, suicidal ideation and paranoic reactions</td>
<td><strong>Changes in metabolic profiles:</strong> hyperglycemia, hypertriglyceridemia, hypercholesterolemia</td>
</tr>
</tbody>
</table>

Mild-to-moderate rash has also been described in patients receiving EFV-based regimens, and is usually resolved as therapy continues, although approximately 2% of patients discontinue their treatment. These reactions usually appear as maculopapular skin eruptions within the first two weeks of treatment, but less than 1% patients develop severe rash, characterised by blistering, moist desquamation or ulceration, and only 0.1% suffer grade 4 rash, manifested as erythema multiforme or Stevens-Johnson syndrome. In controlled trials, the incidence of skin reactions was 26% in patients treated with 600mg per day of EFV compared to 18% in controls (AIDSinfo, 2010). In the 2NN trial, the frequency of moderate-to-severe rash was significantly greater with NVP than EFV when both were administered once daily, but there was no significant difference between NVP twice daily and EFV once daily (van Leth, 2004).

DLV and ETR have also been related to the onset of mild-to-moderate skin reactions. DLV-induced rash usually appears within 1 to 3 weeks of treatment and is resolved in 3 to 14 days. In the DUET studies, the only significant side effect observed in the ETR group was rash, which was usually maculopapular and of mild-to-moderate severity (1.3% grade 3), occurred a median of 14 days after initiation of therapy, and lasted approximately 15 days. Severe rash was not reported, and only 2.2% of patients discontinued treatment due to this side effect.

3.2 CNS toxicity

EFV is widely associated with CNS toxicity, which is responsible for the discontinuation of treatment in at least 4-10% of patients (Muñoz-Moreno, 2009). Between 25 and 70% of
patients receiving EFV exhibit neuropsychiatric disturbances, including dizziness, headache, euphoria, hallucinations, impaired concentration, confusion, depersonalization, drowsiness, amnesia, sleep abnormalities (e.g. insomnia or vivid dreams), nervousness, anxiety and depression. More severe cases, consisting of depression, delusions, suicidal ideation and paranoid reactions, have been reported in 0.4 - 1.6% of EFV-treated patients (Staszewski, 1999; Hawkins, 2005; Fumaz, 2002). These side effects usually appear within the first few days of treatment and are resolved after 2-4 weeks, although there are cases in which they continue to manifest themselves for several months or even longer periods (Muñoz-Moreno, 2009; Arendt, 2007). The clinical evidence available, though extensive, is insufficient to clarify the mechanisms underlying EFV-induced CNS alterations, but recent data implicate neurotoxic events induced by HIV itself and cytokine production by EFV. These adverse effects in the CNS seem to be dose-related (Marzolini, 2001). For instance, the higher incidence of such events in Afro-Americans than in European-Americans or Hispanic populations is attributed to the greater prevalence of the CYP2B6 T/T genotype in the former population, which results in a slower EFV metabolism and, consequently, higher plasma drug concentrations (Haas, 2004).

None of the remaining NNRTI has been associated with neuropsychiatric adverse effects. Moreover, switching from EFV to ETR produces an improvement in EFV-induced toxicity, with a significant reduction of CNS events such as insomnia, abnormal dreams and nervousness (Waters, 2011).

3.3 Metabolic alterations

Mounting evidence associates NNRTI with metabolic disorders involving lipid metabolism, such as alterations of body fat distribution (lipodystrophy) and dyslipidaemia (changes in plasma concentration of cholesterol, High Density Lipoprotein Cholesterol (HDL-c), Low Density Lipoprotein Cholesterol (LDL-c), triglycerides). Lipid alterations are sometimes accompanied by insulin resistance and can generate a metabolic syndrome-like condition. These effects seem to be drug-specific, but the mechanisms involved are still not fully understood. Increases in HDL-c have been reported in naïve patients treated with different NNRTI-based regimens (Negredo, 2004; van der Valk, 2001), but clinical studies have not clarified which drug(s) was/were responsible for these effects. There is conflicting evidence as to whether HDL-c is significantly altered in patients switched from a PI- to a NNRTI-based regimen (Martínez, 2000; Negredo, 2002). The lipid profile of naïve patients receiving NVP or EFV plus d4T and 3TC was evaluated in a pre-planned study within the larger 2NN trial. NVP was associated with greater increases in HDL-c (42.5% with NVP vs 33.7% with EFV) and lower increases in total cholesterol (TC) levels (26.9% with NVP vs 31.1% with EFV), which led to a decrease in the TC:HDL-c ratio in patients receiving NVP (-4.1%). No significant differences were detected in LDL-c levels. Similarly, different dysmetabolic profiles were reported in a cross-sectional evaluation of EFV- and NVP-treated patients (Manfredi, 2005), with rates of hyperglycemia, hypertriglyceridemia and hypercholesterolemia being higher in the former group. The same report showed that, when patients were switched to NNRTI-containing therapies, dysmetabolism was ameliorated by NVP, whereas it was stabilised or worsened by EFV. In the case of DLV and ETR, neither has been significantly associated with lipid abnormalities. The cellular and molecular mechanisms underlying NNRTI-induced metabolic alterations are still unclear, and many hypotheses have emerged to explain them. Some in vitro studies
have suggested that EFV-induced lipodystrophy is a result of effects on adipocyte differentiation and function, whereas such effects are not observed with NVP. In particular, clinically relevant EFV concentrations have been shown to alter the lipogenic pathway of cell differentiation by preventing lipid storage in 3T3 or human preadipocytes and to deplete triacylglycerol accumulation in 3T3-F442A mature adipocytes. These phenomena, which were attributed to the reduction in the expression of the lipogenic transcription factor SREBP-1c, may be involved in the atrophy of adipose tissue described in HAART-treated patients (Diaz-Delfin, 2008; El-Hadri, 2004). When the effects of EFV and a boosted IP, lopinavir/ritonavir (LPV/r; 4:1), were compared in human adipocytes during and after adipogenic differentiation, both compounds were found to impair adipogenesis and reduce transcript levels of adipogenic differentiation genes and master regulators of adipogenesis. In addition, they undermined the release of adipokine and enhanced the expression and release of inflammation-related cytokines. All these effects were more pronounced with EFV than with LPV/r (Gallego-Escuredo, 2010).

### 3.4 Hepatotoxicity

Hepatic adverse events are one of the main causes of mortality and morbidity in HIV-infected patients and are associated with the vast majority of antiretroviral drugs. Therefore, it is important to note that increased liver enzyme levels are a common feature of antiretroviral therapy (Palella, 2006; Weber, 2006). NNRTI, specially NVP and EFV, have been related to liver damage, but there is controversy regarding the level of toxicity of each compound and the relationship between NNRTI plasma levels and hepatotoxicity (Law, 2003). However, it is accepted that the risk of this adverse effect is increased in patients in whom liver enzymes levels were elevated prior to therapy and/or are co-infected with hepatitis B (HBV) and/or C (HCV) (Brück, 2008; Sulkowski, 2002).

Liver damage is particularly prevalent among NVP-treated patients, but most trials have not detected a positive correlation with the plasma concentration of this compound (Cooper, 2007; Kappelhoff, 2005). Liver enzyme levels normally increase within the first 18 weeks of therapy, but the risk continues thereafter, and so patients should be monitored at frequent intervals throughout their treatment. Severe life-threatening hepatotoxicity, including fatal fulminant hepatitis, has also been reported during therapy with NVP. In a recent study of NVP patients, 25.7% developed grade 1 hepatotoxicity and 2.8% displayed severe hepatotoxicity (Jena, 2009). There is also conflicting evidence about the involvement of NVP therapy in the progression of liver fibrosis in patients with a concomitant HCV infection, as some studies support this hypothesis (Macías, 2004) whereas others relate NVP to a reduction of fibrosis (Berenguer, 2008).

Up to 10% of EFV-treated patients exhibit increases of liver enzymes that may require discontinuation of therapy and which have been associated both with hypersensitivity to EFV and dose-dependent accumulative effects (Angel-Moreno-Maroto, 2006; Jena, 2009; Kappelhoff, 2005; Rivero, 2007). In fact, a substudy of the 2NN trial showed a correlation between the incidence of elevated levels of liver enzymes and plasma concentrations of EFV during the first 6 weeks of treatment. The risk of hepatotoxicity in EFV-treated patients increases considerably when HIV coexists with HBV and/or HCV infection (Ena, 2003; Sulkowski, 2002), and also when patients are treated with other potential hepatotoxic medicinal products. It has been claimed that hepatitis viral co-infection results in a higher exposure to EFV. In this context, there are studies that have failed to detect any differences
in plasma EFV concentrations between uninfected and HBV/HCV-infected patients (Katsounas, 2007; Pereira, 2008), while others report increased median plasma C_{min} values leading to overdosing of NNRTI in HIV/HCV co-infected patients, especially in those at an advanced stage of liver fibrosis (Dominguez, 2010). Recent results from Phase III DUET trials have pointed to the good safety profile of ETR in patients co-infected with HIV and HBV and/or HCV, among whom the incidence and severity of hepatic adverse events were similar to those in the placebo group (Clotet, 2010). Finally, several cases of acute liver failure have been described with NVP and only a few with EFV, though this is a rarely reported hepatic event during antiretroviral therapy (Jao, 2010; Turkova, 2009).

The cellular and molecular mechanisms underlying NNRTI-induced hepatotoxicity remain elusive, and there is little and contradictory information about the in vitro toxic effects of EFV on hepatic cells.

3.5 Other toxicities

Less common side effects have also been associated with NNRTI-including therapies. Moderate gastrointestinal adverse effects have been reported with all NNRTI, but do not normally lead to the discontinuation of therapy. In general, NNRTI-related symptoms include nausea, diarrhoea, vomiting and abdominal pain, but EFV has also been associated with anorexia, dyspepsia and pancreatitis. These gastrointestinal EFV-associated adverse effects have been reported in up to 14% of patients, and increases in serum amylase concentration have been reported in 10% of patients receiving EFV compared to 6% of controls (AIDSinfo, 2010).

Several in vitro and clinical studies have raised the possibility that EFV contribute to HAART-associated cardiovascular complications in HIV-infected patients. Treatment of human coronary artery endothelial cells (HCAEC) with EFV leads to increased oxidative stress, evident in the induction of superoxide production and decrease of GSH levels, which significantly increases the in vitro monolayer permeability of these cells (Jamaluddin, 2009). In the study in question, antioxidant administration demonstrated that EFV-induced ROS also activated several cellular pathways mediated by JNK and NFκB and pointed to an involvement of this drug in inflammatory processes. Clinical evidence from a recent trial evaluating cardiovascular risk factors in patients treated for over 5 years with NVP- or EFV-based regimens associate the former drug with a better lipid and glucose profile and a lower tendency to develop subclinical atherosclerotic lesions than the latter drug (Maggi, 2011).

EFV therapy has recently been reported to induce vitamin D deficiency and elevated serum alkaline phosphatase levels, both of which are considered to be markers of bone toxicity and turnover (Welz, 2010). This compound has also been associated with significant decreases in 25-hydroxyvitamin D and an increased risk of hypovitaminosis D (Brown, 2010). Preliminary studies in rats have suggested that high doses of EFV induce nephrotoxicity, expressed by necrosis of proximal tubular epithelial cells. Although humans are exposed to higher levels of EFV, this effect has not been corroborated in patients (Gerson, 1999; Mutlib, 2000). Species selectivity with respect to this toxic effect may result from differences in the production and/or processing of reactive metabolites. Some EFV-treated patients have reported hyperhidrosis, which is manifested as excessive nocturnal sweating and could be a consequence of alterations of the body’s thermoregulation by high concentrations of this NNRTI in the cerebrospinal fluid. This adverse event can be controlled by dose reduction (Fuertes, 2009).
4. NNRTI-induced side effects: A potential role for mitochondria?

The mechanism of mitochondria-related toxicity most commonly associated with antiretroviral therapy is the inhibition of the enzyme responsible for mitochondrial DNA replication: DNA polymerase γ (Pol γ) (Walker, 2002). This toxicity is particularly related to NRTI treatment, and not to other antiretroviral drugs considered safer for mitochondrial function. However, recent evidence demonstrates that NNRTI act on various mitochondrial parameters without affecting Pol γ, which suggests a role for this organelle in NNRTI-induced toxicities (Pilon, 2002; Karamchand, 2008). Nevertheless, the identification of a specific clinical profile related to mitochondrial toxicity is challenged by the co-administration of these compounds with NRTI. Recent research has focused on the molecular and cellular mechanisms underlying NNRTI-associated adverse events, and on the potential role of mitochondria in such processes. Studies in endothelial cells have confirmed that EFV treatment induces ROS production and decreases GSH levels, contributing to endothelial dysfunction, an early stage of atherosclerosis (Jamaluddin, 2010). Additionally, EFV has been shown to induce mitochondrial apoptosis in Jurkat T cells and human peripheral blood mononuclear cells (Pilon, 2002). In this regard, we have recently characterized specific features of both EFV- and NVP-associated toxicity that are related to the induction of hepatic damage (Apostolova, 2010; Blas-Garcia, 2010). In particular, we have reported evidence of a new mechanism of mitochondrial interference induced by EFV in human hepatic cells and which does not involve an effect on mitochondrial DNA replication. EFV decreased mitochondrial oxygen consumption by a direct inhibition of Complex I at the electron transport chain, and induced a reduction of mitochondrial membrane potential and an increase in reactive oxygen species (ROS) generation. The impairment of oxidative phosphorylation led to a reduction in cellular ATP levels and a subsequent activation of AMP-activated protein kinase (AMPK), which is the cellular master switch of energetic stress (Hardie, 2007). Indeed, the mitochondrial dysfunction observed produced alterations in lipid metabolism, increasing the lipid content in the cytoplasm in an AMPK-related fashion. These changes were accompanied by a relative increase in mitochondrial mass, without an increase in the mtDNA/nuclear DNA copy number ratio, which points to a lack of authentic mitochondrial biogenesis. EFV also compromised cellular viability and proliferation in both Hep3B and HeLa cells. Specifically, EFV led to cell cycle arrest and induced apoptotic cell death through the intrinsic (mitochondrial) pathway, which was evident in the translocation of mitochondrial apoptogenic proteins (cytochrome c and AIF), activation of caspase-3 and -9 and apoptotic changes in the nuclear morphology, such as chromatin condensation. EFV-induced toxic effects on cellular viability and proliferation were attenuated by an antioxidant treatment with the hydrophilic analog of vitamin E, Trolox, thus implicating oxidative stress in these processes (Figure 4). Interestingly, NVP had no effect on the mitochondrial parameters analysed, but did produce a toxic effect on cellular viability and proliferation. In light of these findings, it is plausible that the deleterious mitochondrial effect induced by EFV is relevant to the development not only of hepatotoxicity but also to some of the more systemic metabolic side effects associated with this drug. These results are a strong endorsement of clinical evidence that the mechanisms of hepatotoxicity induced by NVP and EFV are drug-specific and unrelated to NNRTI as a drug family.
Fig. 4. Schematic representation of the direct mitotoxic effect induced by efavirenz (EFV) in hepatic cells in vitro.

5. Conclusions

Twenty years after the identification of NNRTI as a new class of antiretroviral drugs for the treatment of HIV-1 infection, recent advances in the characterization of the causes of their toxicity and the development of new compounds have put NNRTI in the spotlight. Given that these compounds are essential elements of antiretroviral therapy, the characterization of their toxic effects and the mechanisms that underlie them may help to improve HIV therapy. The real impact of newly developed compounds on HAART remains to be seen, but they are likely to play an important role in future antiretroviral regimens. Finally, the fact that HIV is now a chronic illness means that therapy must be administered for life; therefore, the choice of drugs to be taken should be based not only on their clinical efficacy but also on their toxicological profile, bearing in mind their profound influence on other concomitant infections and age-related diseases.

6. Acknowledgement

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7. References

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The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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