Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2016;18:127-37

Safety and Tolerability: Current Challenges to Antiretroviral Therapy for the Long-Term Management of HIV Infection

Jesús Troya and José Bascuñana

Department of Internal Medicine, Hospital Universitario Infanta Leonor, Madrid, Spain

Abstract

Following the introduction of triple combination therapy in 1996, the paradigm of HIV infection has been modified by its transformation into a chronic disease and thereby significantly reducing its morbidity and mortality. The spectrum of drugs in use since then has changed dramatically with the advent of more potent molecules, new classes of drugs aimed at novel therapeutic targets and their optimization and simplification through fixed-dose combinations that are more convenient for patients, and which, taken together, have led to sustained virologic response rates in treatment-naive patients of more than 90%. However, the different drugs that make up antiretroviral therapy continue to pose problems of tolerability and toxicity (such as tenofovir-associated renal and bone toxicity, or neuropsychiatric toxicity that has been related to efavirenz and, more recently, to some integrase inhibitors), which can be detrimental to the patient's compliance to a given antiretroviral therapy and lead to virologic failure. In this context of sustained virologic response, safety has emerged as probably the single most important factor in treatment and should be given serious consideration when choosing an antiretroviral therapy regimen. Herein, we review the role of the adverse effects that result from the different drugs that are currently available, as described in data published from clinical trials and real life cohort studies, as well as possible therapeutic strategies for the management of these toxicities. **(AIDS Rev. 2016;18:127-37)**

Corresponding author: Jesús Troya García, jestrogar@hotmail.com

Key words

ART. Safety. Toxicity.

Introduction

Antiretroviral therapy (ART) has changed substantially in recent years with the advent of new drugs. Some belong to "traditional" classes of drugs, such as nucleoside analog reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). Others act on already identified novel therapeutic targets, such as fusion inhibitors, CCR5 coreceptor antagonists, and integrase inhibitors (INSTI). Moreover, new drugs and new formulations with greater potency and safety are available to us. All this has allowed us to achieve high rates of virologic suppression, more than 90% in treatment-naive patients, together with greater tolerability and safety in association with simpler dosing regimens, leading to significant improvements in the quality of life of patients. Universal access to ART, which is supported

Correspondence to:
Jesús Troya García
Hospital Universitario Infanta Leonor
Avenida Gran Vía Este, 80
28031 Madrid, Spain
E-mail: jestrogar@hotmail.com

by different clinical practice guidelines[1,2] and clinical studies[3], early diagnosis of the infection, and increasingly efficient drugs, has allowed improved epidemiological and clinical control of the patients, requiring a lower level of care. Nevertheless, the appearance of short- and long-term problems with tolerability and toxicity remains a reality for patients with HIV-1 infection[4]. These toxicities, especially those that appear in the longer term and which mostly occur in patients who have been exposed to different drugs for prolonged periods of time, in combination with the effects of aging in HIV patients and age-related comorbidities, increasingly oblige us to optimize and individualize treatment. These toxicities add a significant burden of comorbidity and can result in the decline in adherence to ART and precipitate the onset of virologic failure due to the fact that the patient will often establish a causal relationship between taking medications and the appearance of symptoms or signs of toxicity. Likewise, it is also important to keep in mind toxicities that are not directly measurable by patients but that the practitioner must be aware of when it comes to adjusting treatment to the individual patient. In this sense, safety has emerged as probably the single most important factor that distinguishes one drug from another and to guarantee long-term effectiveness. The objective of this review is to analyze the role of toxicity and tolerability of different drugs that has been recorded over the course of clinical trials and real-life cohort studies together with possible therapeutic strategies for the management of these toxicities.

The development of antiretroviral therapy over time: From efficacy to safety and tolerability

Since 1986, 26 antiretroviral drugs (ARV) have been approved for treatment of HIV. Over the years since the first anti-HIV drug, zidovudine, appeared, the challenges posed for treatment have changed. During the first stage of the HIV pandemic in the mid 1990s, the main concern was focused on the development of drugs that would be effective in adequately controlling viremia and the preservation and enhancement of the immune system. To do so, monotherapy and combination therapy approaches with available drugs, such as NRTIs like zidovudine (AZT), didanosine (ddI), zalcitabine (ddC) and stavudine (d4T), were used. These regimens did not achieve adequate and sustainable virologic control over time, and they were inconvenient and associated with a number of adverse effects, some of which were serious. In the second half of the 1990s, new drugs that were more effective, with improved safety profiles and tolerability, were developed: NNRTIs such as nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV); NRTIs: lamivudine (3TC), abacavir (ABC), tenofovir (TDF); and new therapeutic targets emerged: PIs such as saquinavir (SQV), indinavir (IDV), ritonavir (RTV), nelfinavir (NFV), amprenavir (APV) and lopinavir (LPV). From 1996, this range of therapeutic tools allowed the strategy known as "triple therapy"[5] to be adopted, which consisted of a combination of three active anti-HIV drugs (two NRTIs and one PI or one NNRTI). Adequate virologic response was achieved for the first time and it constituted a first step towards chronicity of infection, although the emergence of resistance mutations entailed limitations for sustaining long-term virologic efficacy. Schedules were complex and involved taking a large number of pills many times a day as well as significant issues with tolerability and safety.

From 2003 onwards and particularly from 2006, new drugs appeared, which on the one hand were more potent and had a higher genetic barrier, and on the other hand were safer. New drugs were added to the previous classes: PIs such as atazanavir (ATZ), tipranavir (TPV), and darunavir (DRV), new NRTIs such as emtricitabine (FTC), new NNRTIs such as etravirine (ETV) and then rilpivirine (RPV). Moreover, new classes of drugs appeared that had new therapeutic targets: fusion inhibitors such as enfuvirtide, CCR5 coreceptor antagonists such as maraviroc (MVC) and INSTIs such as raltegravir (RGV), elvitegravir (EVG), or dolutegravir (DGV), which achieve better control of the disease. The rates of virologic response in treatment-naive patients are now higher than 90%. Furthermore, they provide significant improvements in both safety and tolerability. In addition to the development of new drugs with better safety profiles, the existence of genetic factors that have an influence on drug toxicity (toxicokinetics) began to be known. An individualized approach to the choice of therapy among different preferred options is key to trying to minimize ART-associated toxicity in the long term[6].

One development that contributed considerably to improving adherence, and as a consequence led to improvement in the duration of virologic response, was the reduction in twice-daily dosing to once a day, together with the emergence of fixed-dose combinations of ARVs. These combinations afford greater convenience to the patients and have the effect of adding value because they "normalize" the disease and quality of life of the patients.

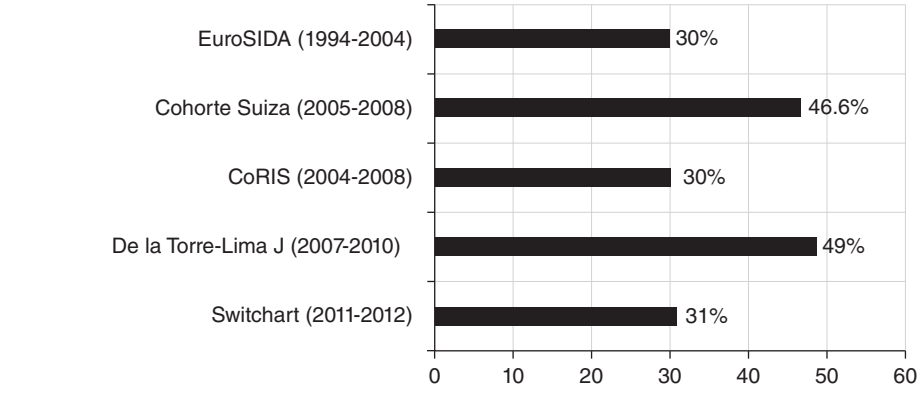

Figure 1. *Changes in antiretroviral therapy as a result of toxicity in cohort studies.*

This gradual improvement in ART efficacy, through a combination of higher rates of virologic response and greater safety, tolerability, and convenience of administration, has led to significant increases in life expectancy and quality of life of HIV patients.

The current challenge for ART is to sustain virologic response over the course of time while providing maximum safety to the patients, and to minimize the negative impact treatment has on their quality of life. In this three-variable equation, the safety and convenience of ART contributes to adherence and acceptance of the treatment, which is crucial to achieving sustained virologic response.

Antiretroviral therapy-related toxicity in clinical trials and real-life cohort studies

The toxicity of ART, particularly long-term toxicity, tends to be underestimated in clinical trials, probably due to the limited duration of follow-up (the studies usually run for 48-96 weeks). This is likely the fundamental reason that explains the differences in the incidence, prevalence, and effects of toxicities between clinical trials and observational real-life cohort studies. Observational studies are better at reflecting ART-related toxicity and show that at present, the most common cause for changes in treatment is precisely toxicity (Fig. 1).

The EuroSIDA[7] cohort study analyzed the reasons for discontinuing first-line ART from 1999 to 2004. From 1999 to 2001, virologic failure was the main reason for 15-16% of treatment regimen changes. However, from 2001, discontinuation of treatment due to toxicity reached 25-35% (as opposed to 5% because of virologic failure). A Swiss[8] cohort study of 1,318 HIV patients that was conducted from January 2005 to June 2008 showed that toxicity issues were responsible for 46.6% of treatment regimen changes, especially during the first four weeks of treatment, whereas virologic failure was described in only 5.9% of patients. The analysis of the Spanish CoRIS[9] cohort study between 2004 and 2008 showed that toxicity was the main cause behind treatment regimen changes in more than 30% of cases, while virologic failure was the cause in less than 6%. La Torre-Lima, et al.[10] reported similar data in a multicenter study of 600 patients who initiated ART between January 2007 and June 2010. The main reason for discontinuation in 49% of patients was toxicity (gastrointestinal disorders, cutaneous reactions, neuropsychiatric symptoms, liver, kidney, and metabolism disorders). Finally, although the Switchart[11] retrospective

observational study of 246 patients conducted between 2011 and 2012 shows that in 31% of cases ART was modified due to toxicity, the most frequent cause for change was simplification of treatment (36%).

What these observational cohort studies show is how, on the one hand, over the last few years the main cause for change of treatment has shifted from virologic failure to ART-related toxicity and simplification strategies, and on the other hand, how useful they are for estimating the incidence, prevalence, and effects of toxicity in "real life" with respect to clinical trials. Long-term follow up of patients (cohorts, registers) and long-term phase IV safety surveillance may allow us to better understand long-term toxicity, which is especially important with regard to the newer drugs.

On the other hand, other factors to take into consideration are the underrepresentation in clinical trials of populations who show greater complexity, such as patients who have a low CD4 count, coexistence of opportunistic infections, or significant comorbidities. The difficulties in their management, the fragility of the patients, and the inherent risks of morbidity and mortality, which become apparent in observational studies and remain underestimated in clinical trials, cause making the right choice of ART and its safety to become an even greater priority, if that is possible, for the practitioner.

Present toxicity of antiretroviral therapy: Short- and long-term toxicity

In addition to the early toxicity that results when ART is started, we have to add long-term adverse effects, which are closely related to it due to the need for indefinite administration of treatment given the impossibility of eradicating HIV[12]. Depending on the time to onset of toxicity after starting the drug, the adverse effects can be classified as follows: (Table 1)[13].

Early or short-term toxicity

This is the easiest type to diagnose and treat as it usually occurs within a few days or weeks after exposure to the drug. The immediate adverse effects are well defined, in some cases they can be anticipated, and they are usually easy to manage. This type of toxicity is mainly digestive, cutaneous, or neuropsychiatric and its incidence and associated factors are well known. For the most part it is usually transient and does not require the drug to be withdrawn, although on occasion there can be serious adverse effects that may be life-threatening, making it necessary to withdraw the drug.

Cutaneous and hypersensitivity reactions

Generally speaking, cutaneous reactions begin to appear soon after starting the ARV. Most of the time they are benign and only in a small proportion of cases do they become serious and threaten the patient's life[14]. The most common cutaneous reactions are exanthematous (morbilliform or maculopapular eruptions) that affect 8-12% of patients receiving ART. The NNRTIs and ABC are the drugs most frequently involved. Of the NNRTIs, NVP[15] and EFV are the main culprits and there is also increased risk for cross-reaction, but this is not the case for ETV and RPV. This type of reaction has also been described for PIs such as DRV, although there the incidence is < 1%.

Severe reactions include drug-induced hypersensitivity syndrome (DIHS), Stevens-Johnson syndrome, and toxic epidermal necrolysis. DIHS has been described for many ARV drugs, though the highest risk is associated with ABC (5%), which can cause extremely severe reactions that oblige an immediate withdrawal of the drug[16]. On the other hand, Stevens-Johnson syndrome and toxic epidermal necrolysis are entities that seldom occur in patients receiving ART, with NVP being the drug that is most frequently involved (0.5-1.0%).

Very rarely do integrase inhibitors cause adverse cutaneous reactions (< 1%).

Gastrointestinal toxicity

Gastrointestinal adverse effects are common and are the main reason for changing ART. The ones most frequently reported are nausea, vomiting, and diarrhea, and PIs are the drug class responsible for most of them[17]. Low-dose ritonavir (r)-boosted PIs DRV and atazanavir (ATV) cause many fewer gastrointestinal disorders (15-20%) than older PIs. Substituting cobicistat for ritonavir as enhancer has helped to further improve the tolerability profile of DRV and ATV.

The tolerability profiles of integrase inhibitors EVG and DTG have been shown to be worse than that of RVG, as was observed in the Striving study of DTG or the Study 103 of EVG. In these studies, rates of nausea and diarrhea of up to 13-18% and 21-23%, respectively, were observed[18].

Both NRTIs and NNRTIs, and the latter in particular, induce relatively few gastrointestinal disorders.

Table 1. Antiretroviral therapy-related adverse effects

Antiretroviral	Severe adverse event	Common adverse event (> 5%)
Nucleoside analog reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil	Tubular injury, decrease in eGFR	
fumarate (TDF)	Osteopenia	
	Exacerbation of hepatitis B if the drug is withdrawn	–
Abacavir (ABC)	Hypersensitivity reactions	
	Myocardial infarction	–
Emtricitabine (FTC)	Exacerbation of hepatitis B if the drug is withdrawn	–
Lamivudine (3TC)	Exacerbation of hepatitis B if the drug is withdrawn	–
Non-nucleoside analog reverse transcriptase inhibitors (NNRTI)		
Rilpivirine (RPV)	–	Rash
		Dizziness
		Abnormal dreams
Etravirine (ETV)	Rash	Nausea
Efavirenz (EFV)	Rash, Stevens-Johnson syndrome	Dizziness
	Hepatotoxicity	Insomnia
	Teratogenicity	Vivid dreams (> 50%)
		Headache
		Gynecomastia
		Elevated transaminases
Nevirapine (NVP)	Rash, DIHS, Stevens-Johnson syndrome	Elevated transaminases
	Hepatotoxicity	
Protease inhibitors (PI)		
Darunavir (DRV/r)	Stevens-Johnson syndrome	Rash
	Erythema multiforme	Nausea. Diarrhea
	Hepatotoxicity	
Atazanavir (ATZ)	First-degree AV block	Hyperbilirubinemia
	Nephrolithiasis	
Lopinavir (LPV)	Myocardial infarction	Hypertriglyceridemia
		Asthenia
		Nausea, diarrhea
Integrase inhibitors (INSTI)		
Raltegravir (RGV)	–	Headache
		Increased creatine phosphokinase
Elvitegravir (EVG)	–	Headache
		Nausea, diarrhea
Dolutegravir (DGV)	–	Headache
		Sleep disturbance
		Insomnia
		Depression
		Diarrhea

DIHS: drug-induced hypersensitivity syndrome; eGFR: estimated glomerular filtration rate.

Liver toxicity

Hepatotoxicity is a relatively common problem (5-10%) with the majority of ARV drugs and one of the most frequent reasons, from the clinical perspective, for withdrawing or changing ART. The possible mechanisms involved are multiple and its clinical presentation is highly variable, ranging from transitory, asymptomatic elevation of liver enzymes to, much less frequently, acute fulminant hepatitis[19]. Among the different ARVs, there are classes like NNRTIs that are more likely to cause hepatotoxicity. NVP is found to have a higher

risk, causing immuno-allergic reactions with liver injury or direct toxicity in patients coinfected with HCV and HBV. EFV can cause liver problems in up to 7% of patients by acting as an inducer of cytochrome CYP3A4 enzyme[20]. ETV and RPV do not present cross-reactivity and have better safety profiles. Among the NRTIs, ABC is associated with DIHS liver injury. The latest boosted PIs DRV/r and ATZ/r are much less hepatotoxic than they were formerly. ATV can cause hyperbilirubinemia through an increase in indirect bilirubin as a result of inhibition of uridine diphosphate glucuronosyltransferase enzyme (UGT1A1*28 haplotype), without having any effect on liver function.

Integrase inhibitors generally have a favorable hepatic safety profile. DTG has been associated with elevations in liver enzymes in some patients coinfected with HBV or HCV[21].

Neuropsychiatric toxicity

Neuropsychiatric toxicity has been reported for several drugs, although there has been nothing to suggest that drugs within a specific class of drugs produce similar toxicity. Most noteworthy is the toxicity caused with EFV, which occurs in about half of the patients to whom it is administered, as has been recorded in many clinical trials and cohort studies[22]. The most common symptoms are sleep disturbances, dizziness, difficulty concentrating, headache, confusion, irritability, and nervousness. They are often transient and generally disappear between four and 24 weeks after initiation of treatment, but in up to 10-15% of patients they can persist for a prolonged period. Depression has been described less frequently and suicidal ideation even more rarely.

Rilpivirine has a more favorable neuropsychiatric profile than EFV. Statistically significant differences were observed in the StAR study, which showed tolerability of RPV was better than that of EFV for all neuropsychiatric criteria, with rates of headache of 14.2%, dizziness 6.9%, insomnia 11.4%, abnormal dreams 5.8%, and anxiety 7.1%[23]. Later cohort studies have demonstrated it has a more favorable profile of tolerability with a lower rate of neuropsychiatric disturbances.

Among integrase inhibitors, EVG causes headache and insomnia in 14-15% of patients[24]. With DTG, headache, dizziness, sleep disturbances, and depression occurred in 2-5% of patients in the SINGLE study[25], a rate of toxicity that increases up to 15% in real-life cohort studies[26], as DHHS guidelines[2] already reflect, and RGV has been associated with headache in 5% of patients, while depression has been described in 2-3%[27]. Although uncommon (0.1 to < 1.0%), the three integrase inhibitors have been associated with suicidal ideation, especially in patients with a history of depression or psychiatric illnesses.

Current PIs DRV/r and ATV/r have good neuropsychiatric profiles[1,2].

Mitochondrial toxicity

This type of toxicity has been linked to thymidine analogs (d4T, AZT) and dideoxynucleotides (ddI and ddC) that are no longer in use today in the majority of developing countries, which is why the rate of incidence is now substantially lower. Lactic acidosis is the most serious form of toxicity within this group and is associated with a rate of mortality > 50%[28]. Peripheral neuropathy is very similar to that caused by the HIV infection itself (predominantly sensory axonal polyneuropathy)[29].

Chronic or long-term toxicity

This type of toxicity results from the cumulative effect of sustained exposure to a drug whose adverse effects appear months or years after exposure first begins. Since it appears after many years, it is usually not reflected in clinical trials. Less is known about the adverse effects of long-term toxicity than about early toxicity, and they are more difficult to identify and manage as they can be masked by other factors such as the patients' natural aging and preexisting or acquired comorbidities, while simultaneously aggravating these comorbidities.

Metabolic toxicity

This type of toxicity has been traditionally associated with PIs, especially older ones (IDV, NFV, RTV, LPV/r) and with thymidine analogs (d4T, AZT). The most common disorders associated with it are dyslipidemia, diabetes mellitus, and insulin resistance, more prevalent in patients with body fat redistribution[30].

Dyslipidemia has traditionally been associated with PIs, especially older ones. It is characterized by elevations in total cholesterol and triglyceride levels. Both DRV/r and ATV/r were compared to LPV/r in the ARTEMIS[31] and CASTLE[32] studies, respectively, and demonstrated better lipid profiles (total cholesterol, triglycerides and non-HDL cholesterol).

Antiretroviral therapy-related insulin resistance and disorders in glucose metabolism have been reported in many studies of older PIs IDV and LPV/r[33,34], but no causal mechanisms have been identified and they have been attributed to multifactorial problems.

Lipodystrophy is characterized by either a loss of peripheral fat (lipoatrophy) or with perivisceral fat accumulation within the abdomen or breasts (women) and in the neck, fat accumulation in the breasts (women) and neck (lipohypertrophy), and sometimes with both at the same time. Thymidine NRTIs (d4T, ddI) are the most strongly associated with this toxicity[35]. They are no longer in regular use in most developed countries, which has contributed to a decline in its incidence, way below 20%. Reports from the ACTG 5142[36] study described lipoatrophy (32%) in the EFV plus two NRTIs arm, but these data have not been reproduced in other studies with EFV. Use of PIs, particularly older ones, has also been related to abdominal fat accumulation.

Cardiovascular risk

Traditional risk factors are the ones that mainly determine the risk of developing cardiovascular disease in patients with HIV-1, the same as in the general population. However, in patients with uncontrolled HIV-1 infection and those who are on certain ART regimens may be at even greater risk, although these may not carry the same weight.

Some PIs have been clearly linked with increased risk for cardiovascular disease although that does not mean that this effect is exclusively due to potentially associated dyslipidemia. An analysis of the D:A:D cohort (The Data Collection on Adverse Events of Anti-HIV Drugs study) that was conducted in 2008 in over 30,000 patients found that certain PIs (IDV and LPV/r) were related to greater risk of acute myocardial infarction, in direct proportion to the duration of treatment[37]. The same analysis found that recent use (in the previous six months) of ABC or ddI was associated with greater risk for acute myocardial infarction, especially in patients at higher risk for cardiovascular events[38]. Nevertheless, the link between ABC and acute myocardial infarction is now a controversial issue, with some studies, such as the SMART study, the Swiss cohort, etc., supporting the association, whereas many other studies, such as the French cohort, ALLRT/ACTG or FDA have not found any such association nor have found any underlying causal biological mechanisms[39]. All of these studies have numerous biases that cannot be adequately controlled and which may call into question the causal association of NRTIs in the development of cardiovascular disease. Nonetheless, although there is no consensus in this regard, the 2016 DHHS Guidelines recommend ABC not be used in cases where the patient may be at risk for cardiovascular disease.

Renal toxicity

Of all ART regimens, those containing TDF are the most nephrotoxic and the real incidence, which has been recorded in many cohort studies, is somewhat greater than that found in clinical trials (1-2%), especially when there is longer-term exposure to the drug[40]. In post-marketing safety studies, which included 455,392 person-years, renal adverse events were the most common (acute renal failure in 0.5% of cases and varying degrees of an increase in creatinine levels of 2.2%)[41]. In cohort studies of patients who received TDF for one year, around 2-3% presented with moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] < 60 ml/min), especially when they presented with other risk factors[42]. Multiple concomitant factors may contribute to the development of renal toxicity, such as prior or concomitant renal impairment, diabetes mellitus, high blood pressure, use of other nephrotoxic drugs[43], old age, low body weight, and low CD4 levels.

The majority of patients with TDF-associated nephrotoxicity present with progressive deterioration of renal function (eGFR) and in some cases are found to have markers of proximal tubular dysfunction, principally glycosuria, proteinuria, proximal tubular acidosis, hypophosphatemia, and hypopotassemia[44,45]. TDF-associated nephrotoxicity usually reverses upon early termination of the drug, although the reversal may not be altogether complete and a long interval of time may be required before stability is achieved or it may even not be achievable in patients with a significant decline in eGFR that is maintained for a prolonged time, as was observed in the Collaborative cohort in which 38.6% of patients did not recover their eGFR[46].

Increased nephrotoxicity has been described when TDF is combined with PIs such as ATV and LPV, but has not been described in combination with DRV[47]. Ritonavir is a potent inhibitor of the MRP-2 tubular receptor, so it reduces the tubular excretion of TDF, giving rise to significant intracellular concentrations and increased plasma levels, up to 30%, which induces greater toxicity.

A new TDF formulation, tenofovir alafenamide (TAF), has been shown to have a better renal profile by reducing concentrations of the drug in the plasma[48]. Future

experience with TAF in real-life cohorts will give us better insight into the drug's long-term effects on the kidneys after prolonged use.

Some cohort studies, such as D:A:D, have reported that some boosted PIs, such as LPV/r and ATV/r, may be independent predictors of chronic kidney disease (eGFR < 70 ml/min)[49]. Likewise, ATV can result in renal failure due to nephrolithiasis caused by stone-induced tubular damage, which was described in 7.3% of patients in the Chelsea and Westminster cohort[50].

Bone toxicity

The intrinsic association between osteopenia and osteoporosis and HIV-1 infection has been documented. The role of ART in this disease has not been clearly established, but the use of both boosted PIs[51] as well as of TDF[52] (more often implicated in both clinical trials and observational studies) has been associated with the development of osteopenia. The presence of chronic abnormal phosphaturia within a context of tubular dysfunction would explain in part the progressive loss of bone during treatment with TDF, a condition that would result in a disturbance in the balance between phosphatemia, phosphaturia, and bone as a mechanism of progressive bone mineral density decline[53].

In symptomatic forms, osteonecrosis affects 0.1-1.3% of HIV-infected patients and in asymptomatic forms it affects 4% of patients[54]. In 85% of cases it involves the femoral head. Controlled epidemiological studies have not found a direct relation to ART, and in about a third of cases traditional risk factors, such as use of corticosteroids, alcohol abuse, or estrogen replacement therapy, may be involved.

Strategies for the clinical management of antiretroviral therapy-related toxicities

The attitude towards toxicity induced by any drug classes or compounds can be summarized in two types of action. On the one hand, preventive action prior to initiation of the drug, and on the other hand, therapeutic management after exposure to the drug.

Preventive action

This takes place before prescribing a drug and is based on an individual optimization of ART in every patient by adapting the therapy to the patient's personal characteristics (aging, comorbidities or drug interactions, neuropsychiatric history, etc.) and considering all possible options. A fairly recent new tool, which is being gradually implemented in day-to-day practice, is pharmacokinetics and the capacity to determine the efficacy and/or toxicity of drugs (toxicokinetics). It aims to personalize the risk of potential toxicity before initiating ART and thereby avoid using a given drug that would be likely to cause some toxicity. At present, our knowledge of toxic factors of risk is limited. Screening for haplotype HLA-B*5701 to prevent hypersensitivity reactions to ABC[9] is a widespread practice. Other examples are the polymorphisms in the gene that codes for CYP2B6, which affects plasma concentrations of EFV and NVP; the UGT1A1 gene that is responsible for IDV and ATV associated hyperbilirubinemia; and TNFα, mitochondrial polymerase, interleukin-1, and metalloprotease-1 that are associated with the body fat redistribution related to HIV infection and to ART.

Therefore, at present, thanks to the availability of a broad range of therapeutic tools, we are in a position to individualize treatment for each situation in order to develop optimal strategies for every patient.

Therapeutic action after drug exposure

This is considered after some toxicity attributable to a drug that is used appears and which is deemed to be not acceptable. Such interventions can range from discontinuation of the ARV drug causing said toxicity and its substitution with another, to the use of other co-adjuvant drugs to lessen or undo the adverse effects caused by the ARV. Withdrawal of the drug is usually required in cases of early toxicity and is essential when adverse reactions that are serious or life threatening occur. Conversely, the addition of co-adjuvant drugs in order to control the toxicity is the usual practice for toxicity that appears as a result of long-term exposure, although on occasion it is sometimes necessary to withdraw the drug. Hence the importance of monitoring patients treated with potentially toxic drugs very closely, and of considering switching to a different regimen in a timely manner.

Although, as a general rule, an ART regimen should comprise triple therapy with NRTIs as the backbone, in many cases today the practitioner is obliged to individualize treatment to achieve safer and optimal clinical outcomes. Along these lines, in recent years different therapeutic strategies based on NRTI-free dual therapy or monotherapy have been considered, whose basic objective has been to prevent or eliminate toxicities, particularly those that appear following long-term exposure to NRTIs (Table 2). Of these strategies,

Table 2. Nucleoside analog-free therapeutic strategies for pre-treated patients

Study	Regimen	(n)	Design	Prior history	Prior ART	Efficacy (ITT)
Protease inhibitors in combination with 3TC						
ATLAS Mondi, et al. 2015	ATV/r (300/100 mg) + 3TC (300 mg)	40	Prospective 144 weeks Simplification	< 50 cop/ml 12 weeks	ATZ/r + 2 NRTIs	77.5%
SALT Pérez Molina, et al. 2015	ATV/r (300/100 mg) + 3TC (300 mg) vs. ATV/r (300/100 mg) + 2 NRTIs	143 143	Randomized 1:1 48 weeks	< 50 cop/ml 24 weeks	ATZ/r + 2 NRTIs	84% 78%
OLE Arribas, et al. 2015	LPV/r + 3TC vs. LPV/r + 2 NRTIs	123 127	Randomized 1:1 48 weeks	< 50 cop/ml 24 weeks	LPV/r + 2 NRTIs	87.8% 86.6%
DUAL Rubio R, et al. 2015	DRV/r (800/100 mg) + 3TC (300 mg) vs. DRV/r (800/100 mg) + 2 NRTIs	128 128	Randomized 1:1 48 weeks	< 50 cop/ml 24 weeks	DRV/r + 2 NRTIs	–
Protease inhibitors in combination with integrase inhibitors (raltegravir)						
SPARE Nishijima, et al. 2013	DRV/r + RGV vs. + LPV/r + FTC/TDF	28 30	Randomized 48 weeks	< 50 cop/ml > 15 weeks	LPV/r + FTC/TDF	85.7% 96.7%
BATAR Cohen, et al. 2012	ATV/r + RGV vs. ATZ + RGV vs. ATV/r + FTC/TDF	43	Randomized 1:1:1 48 weeks	< 48 cop/ml 24 weeks	ATZ/r + FTC/TDF	100% 85.4% 100%
Ruane 2010	ATZ + RGV	30	Prospective 48 weeks	< 50 cop/ml	PIs + NRTI	76.6%
Calza 2010	DRV/r + RGV	71	Prospective 48 weeks	< 50 cop/ml	PIs + NRTI	84%
KITE Ofotokun, et al. 2012	LPV/r (400 mg) + RGV LPV/r + 2 NRTIs	40 20	Randomized 2:1 48 weeks	< 50 cop/m	DRV/r + 2 NRTIs	91.7% 88.2%
Protease inhibitors in combination with non-nucleoside analogs						
NEKA Negredo, et al. 2013	LPV/r + NVP vs. LPV/r + 2 NRTIs	16 15	Randomized 48 weeks	< 80 cop/ml	LPV/r + FTC/TDF	87.5% 100%
PROBE Maggiolo, et al. 2016	DRV/r + RPV vs. DRV/r + 2 NRTIs	30 30	Randomized 1:1 48 weeks	< 1000 cop/ml (75.7% < 50 cop/ml)	PIs + NRTI	93.4% 96.7%
BITER Portilla, et al. 2010	DRV/r + ETV (bid)	99	Retrospective 24 weeks	< 50 cop/ml	PIs, NNRTI, II + NRTI	89%
Gazzola 2014	DRV/r + ETV	68	Retrospective 24 months	<50 cop/ml	PIs, NRTI + NRTI	88.8%
Integrase inhibitors (raltegravir) in combination with non-nucleoside analogs						
Reliquet. 2014	RGV + NVP	39	Retrospective	< 50 cop/ml 24 weeks	NVP regimen	82.1%
Monteiro 2014	RGV + ETV	99	Prospective 48 weeks	< 50 cop/ml	PIs + NRTI	84%
Calin 2013	RGV + ETV	35	Observational 48 weeks	< 50 cop/ml	PIs, NNRTI, NRTI	80%

3TC: lamivudine; ATV: atazanavir; DRV: darunavir; ETV: etravirine; FTC: emtricitabine; ITT: intent to treat; LPV: lopinavir; NNRTI: non-nucleoside analog reverse transcriptase inhibitor; NPV: nevirapine; NRTI: nucleoside analog reverse transcriptase inhibitor; PI: protease inhibitor; RGV: raltegravir; RPV: rilpivirine; TDF: tenofovir disoproxil fumarate.

the most extensively used at present by practitioners are dual therapies with PIs plus 3TC (DRV/r, ATV/r[55] or LPV/r[56] with 3TC), dual therapies with RGV and DRV/r[57] or RGV and ETV[58] , and more recently, DRV/r plus RPV[59].

Conclusions

Antiretroviral drugs marketed during the last decade have achieved high levels of efficacy so that HIV infection today has managed to become a chronic condition. Nevertheless, despite great improvements in the safety profile of the therapies, both short- and long-term toxicity remain the leading cause for change of treatment, as reflected in real-life cohort studies and in clinical practice. That is what makes ARV safety one of the main objectives and the greatest challenge facing the practitioner.

The aging of the population and progressive increase in comorbidities will add complexity to the chronic management of our patients. Therefore, individualizing ART to each patient and simplification strategies will gain increasing importance. As medical practitioners we should maintain an expectant attitude and move forward with changes in anticipation of new and potentially adverse effects that may appear in the long term and that may have been underestimated in pre-marketing studies. Post-marketing studies and registers can be very useful, especially for estimating the incidence, prevalence, and clinical impact of toxicity in the long term, especially for those drugs with which we have shorter experience, as well as for obtaining information on the effect of these drugs in patients whose profiles are more complex and who are not reflected in clinical trials.

Declaration of interest

The authors declare no conflicts of interest regarding this manuscript.

References

1. European Guidelines for treatment of HIV-infected adults in Europe. Guidelines version 8.0. European AIDS Clinical Society (EACS), October, 2015. Available at: http://www.eacsociety.org/files/2015_eacsguidelines_8.0-english_revised-20151104.pdf. [Accessed 04 July 2016].
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services USA, January 28, 2016. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf [Accessed 04 July 2016].
3. INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015;373:795-807.
4. Calmy A, Hirschel B, Cooper DA, et al. A new era of antiretroviral drug toxicity. Antivir Ther. 2009;14:165-79.
5. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997;337:734-9.
6. Flexner C. HIV drug development: the next 25 years. Nat Rev Drug Discov. 2007;6:959-66.
7. Mocroft A, Phillips AN, Soriano V, et al. EuroSIDA Study Group. Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: increased incidence of stopping due to toxicity or patient/physician choice in patients with hepatitis C coinfection. AIDS Res Hum Retroviruses. 2005;21:743-52.
8. Vo TT, Ledergerber B, Keiser O, et al. Swiss HIV Cohort Study. Durability and outcome of initial antiretroviral treatments received during 2000-2005 by patients in the Swiss HIV Cohort Study. J Infect Dis. 2008;197:1685-94.
9. Perez Elias MJ, Muriel A, Moreno A, Martinez Colubi M, Blanco JR, Rubio R. Spanish multicenter Cohorts (CoRIS-MD/CoRIS). Gender Differences in the pattern of use and durability of initial antiretroviral therapy (ART) in the Spanish AIDS Research Network Cohort, CoRIS-MD CoRis,1996-2008). CROI 2012. [Abstract 1043].
10. De La Torre-Lima J, Aguilar A, Santos J, et al. Durability of the first antiretroviral. Treatment regimen and reasons for change in patients with HIV infection. HIV Clin Trials. 2014;15:27-35.
11. Carrero-Gras A, Antela A, Muñoz-Rodríguez J, et al. Nuke-sparing regimens as a main simplification strategy and high level of toxicity resolution after antiretroviral switch: the SWITCHART Study. J Int AIDS Soc. 2014;17(Suppl 3):19819.
12. Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. Antivir Res. 2010;85:201-9.
13. Stolbach A, Paziana K, Heverling H, Pham P. A review of the toxicity of HIV medications II: Interactions with drugs and complementary and alternative medicine products. J Med Toxicol. 2015;11:326-41.
14. Luther J, Glesby MJ. Dermatologic adverse effects of antiretroviral therapy: recognition and management. Am J Clin Dermatol. 2007;8:221-33.
15. Antón P, Soriano V, Jiménez-Nácher I, et al. Incidence of rash and discontinuation of nevirapine using two different escalating initial doses. AIDS. 1999;13:524-5.
16. Hewitt RG. Abacavir hypersensitivity reaction. Clin Infect Dis. 2002;34:1137-42.
17. Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. AIDS Rev. 2009;11:30-8.
18. Zolopa A, Sax PE, DeJesus E et al. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr. 2013;63:96-100.
19. Soriano V, Puoti M, Garcia-Gascó P, et al. Antiretroviral drugs and liver injury. AIDS. 2008;22:1-13.
20. Efavirenz®. Data Sheet. European Medicines Agency. Available at: http://ec.europa.eu/health/documents/communityregister/2012/20120109113509/anx_113509_es.pdf [Accessed 12 July 2016].
21. Dolutegravir® Data Sheet. European Medicines Agency. Available at: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/002753/WC500160680.pdf
22. Scourfield A, Zheng J, Chinthapalli S, et al. Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals. AIDS. 2012;26:1399-401.
23. Van Lunzen J, Antinori A, Cohen CJ, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. AIDS. 2016;30:251-9.
24. Zolapa A, Sax PE, DeJesus E, et al. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 Infection: Analysis of Week 96 results. J Acquir_Immune Defic Syndr. 2013;63:96-100.
25. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369:1807-18.
26. Van der Berck G, Oryszczyn J, Blok W, et al. Unexpectedly high rate of intolerance for dolutegravir in real life setting. CROI 2016. [Abstract 948].
27. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. AIDS. 2008;22:1890-2.
28. Falcó V, Rodríguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. Clin Infect Dis. 2002;34:838-46.
29. Dalakas MC. Peripheral neuropathy and antiretroviral drugs. Peripher Nerv Syst. 2001;6:14-20.
30. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet. 1998;351:1881-3.
31. Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. HIV Med. 2013;14:49-59.
32. Molina J-M, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination

with tenofovir and emtricitabine, for management of antiretroviral- naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet. 2008;372:646-55.
33. Yarasheski KE, Tebas P, Sigmund C, et al. Insulin resistance in HIV protease inhibitor-associated diabetes. J Acquir Immune Defic Syndr. 1999;21:209-13.
34. Lee GA, Seneviratne T, Noor MA et al. The metabolic effects of lopinavir/ritonavir in HIV-negative men. AIDS. 2004;8:641-9.
35. Giralt M, Domingo P, Villarroya F. Lipodystrophy associated with highly active antiretroviral therapy for HIV infection: the adipocyte as a target of antiretroviral-induced mitochondrial toxicity. Trends Pharmacol Sci. 2005;26:88-93.
36. Haubrich RH, Riddler SA, DiRienzo G, et al. Metabolic outcomes of ACTG5142: a prospective, randomized, Phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection. 14th CROI. 25–28 February 2007, Los Angeles, CA, USA. [Abstract 38].
37. D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008;371:1417-26.
38. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. AIDS. 2008;22: F17-24.
39. Costagliola D, Lang S, Mary-Krause M, Boccara F. Abacavir and cardiovascular risk: reviewing the evidence. Curr HIV/AIDS Rep. 2010;7:127-33.
40. Monteagudo-Chu MO, Chang MH, et al. Renal toxicity of long-term therapy with tenofovir in HIV-infected patients. J Pharm Pract. 2012; 25:552-9.
41. Nelson MR, Katlama C, Montaner JS, 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.
42. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis. 2005;40:1194-8.
43. Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. Clin Infect Dis. 2006;42:283-90.
44. Kelly MD, Gibson A, Bartlett H, et al. Tenofovir-associated proteinuria. AIDS. 2013;27:479-81.
45. Casado JL. Renal and bone toxicity with the use of tenofovir: Understanding at the end. AIDS Rev. 2016;18:59-68.
46. Jose S, Hamzah L, Campbell LJ, et al. Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. J Infect Dis. 2014;210:363-73.
47. Gianotti N, Galli L, Poli A, et al. Estimated glomerular filtration rate trajectories in HIV-Infected subjects treated with different ritonavir-boosted protease inhibitors and tenofovir disoproxil fumarate or abacavir. Medicine (Baltimore). 2016;95:e3780.
48. Pozniak A, Arribas JR, Gathe J, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week results from a single-arm, multicenter, open-label phase 3 study. Acquir Immune Defic Syndr. 2016;71:530-7.
49. Ryom L, Mocroft A, Kirk o, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013;207:1359-69.
50. Rockwood N, Mandalia S, Bower M, et al. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. AIDS. 2011;25:1671-3.
51. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS. 2006;20:2165-74.
52. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis. 2010;51:963-72.
53. Casado JL, Santiuste C, Vazquez M, et al. Bone mineral density decline according to renal tubular dysfunction and phosphaturia in tenofovir-exposed HIV-infected patients. AIDS. 2016;30:1423-31.
54. Morse CG, Mican JM, Jones EC, et al. The incidence and natural history of osteonecrosis in HIV-infected adults. Clin Infect Dis. 2007;44:739-48.
55. Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. Lancet Infect Dis. 2015;15:775-84.
56. Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open- label, non-inferiority trial. Lancet Infect Dis. 2015; 15:785-92.
57. Calza L, Danese I, Magistrelli E, et al. Dual raltegravir-darunavir/ritonavir combination in virologically suppressed HIV-1-infected patients on antiretroviral therapy including a ritonavir-boosted protease inhibitor plus two nucleoside/nucleotide reverse transcriptase inhibitors. HIV Clin Trials. 2016;17:38-47.
58. Monteiro P, Perez I, Laguno M, et al. Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study. J Antimicrob Chemother. 2014;69:742-8.
59. Maggiolo F, Di Filippo E, Valenti D, et al. NRTI sparing therapy in virologically controlled HIV-1 infected subjects: results of a controlled, randomized trial (Probe). J Acquir Immune Defic Syndr. 2016;72:46-51.