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ORIGINAL ARTICLE

Indications for the use of next-generation antiretroviral drugs in current clinical practice

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Multiple drug resistance;
Antiretroviral treatment;
HIV infection

Abstract
Objective: To describe the indications for use, in medical practice, of next-generation antiretroviral drugs (NGA): darunavir, raltegravir, maraviroc and etravirine.
Method: An observational, transversal and descriptive study conducted in adult patients who have started to receive a NGA between May 2008 and April 2009. The variables associated with the use of NGA were defined as follows: a) Variables related to efficacy: resistance confirmed by geno/phenotype tests or potencial resistance as a result of extensive exposure to antiretroviral agents, and/or severe immunological deterioration (CD4 less than 200 cells/mcl). b) Variables related to safety: prior toxicity to classic antiretroviral drugs and/or comorbidity which compromises their use. c) Combined efficacy and safety variable (main variable): prioritizing the variables which were detected, the patients were classified into three groups: multiresistant geno/phenotype (multi-G/P), multiresistant as a result of treatment history and other situations. Data was obtained from electronic medical records, laboratory tests, and records of interviews and drugs dispensed by the Pharmacy Service.
Results: Seventy three patients, 40%of whom had an undetectable viral load and 38.4%who showed severe immunological deterioration, were included in the study. Multi-G/P occurred in 45%and multiresistance as a result of treatment history was found in 33%of patients. Patients classified as belonging to the "other situations" category were characterized by having a greater viral load and a poorer immunological status. In 90%of the patients without multi-G/P two or more variables associated with the use of NGA were detected.
Discussion: The medical reality of using NGA shows that they play a role in clinical situations which are very different, specific and difficult to manage.

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PALABRAS CLAVE
Darunavir;
Maraviroc;
Etravirina;
Raltegravir;
Resistencia multiple a medicamentos;
Tratamiento antirretroviral;
Infección por VIH

Indicación de uso de los antirretrovirales de última generación en la práctica clínica actual

Resumen
Objetivo: Describir el perfil de utilización en la práctica asistencial de los antirretrovirales de última generación (AUG): darunavir, raltegravir, maraviroc y etravirina.
Método: Estudio observacional, transversal y descriptivo realizado en pacientes adultos que hubiesen iniciado tratamiento con algún AUG entre mayo de 2008 y abril de 2009. Se definieron las variables asociadas al uso de AUG: a) relacionadas con la eficacia: resistencias según pruebas geno/fenotípicas, o potenciales por amplia experiencia previa a antirretrovirales; y/o deterioro inmunológico grave (CD4 inferior a 200 células/mcl). b) Relacionadas con la seguridad: toxicidad previa a antirretrovirales clásicos, y/o comorbilidad que condiciona su uso. c) Variable combinada de eficacia y seguridad (variable principal): priorizando las variables detectadas se clasificaron a los pacientes como multirresistencia geno/fenotípica (multi-G/F), mutirresistencia según histórico de tratamiento, y otras situaciones. Los datos se obtuvieron de la historia clínica informatizada, las pruebas de laboratorio, y el registro de la entrevista y las dispensaciones del Servicio de Farmacia.
Resultados: Se incluyeron 73 pacientes de los que el 40% tenía carga viral indetectable y el 38,4% deterioro inmunológico grave. La multi-G/F ocurrió en el 45%, y la multirresistencia según histórico en el 33% de los pacientes. Los pacientes clasificados como «otras situaciones» se caracterizaron por tener mayor carga viral y peor situación inmunológica. De los pacientes que no presentaron multi-G/F en el 90% se detectaron dos o más variables asociadas al uso de AUG.
Discusión: La realidad asistencial del uso de los AUG muestra su papel en situaciones clínicas muy variadas, particulares y difíciles de manejar.

Introduction

Four new antiretroviral (ARV) drugs, effective at treating HIV-infected adults, have been marketed over the past two years. These drugs have greatly contributed to the therapeutic arsenal, given that they widen the antiretroviral therapy boundaries with new action mechanisms, meaning that effective rescue treatment can be designed for multiresistant patients. The new ARV drugs are darunavir, raltegravir, maraviroc and etravirine, which have been called next-generation antiretroviral drugs (NGA) in this study.

Drug trials show the efficacy of these drugs used with or without optimised background therapy for multiresistant patients. Viral load became negative after 48 weeks of treatment in 20%-35% more patients.[1] Furthermore, the efficacy of NGA has also been examined in patients with little previous antiretroviral therapy (ART) exposure and treatment-naïve patients.[2-8]

At the same time, there is data that suggest that these drugs have additional efficacy and safety advantages. Raltegravir seems to have a rapid action mechanism, given that when compared with efavirenz, it presents a greater virological response at 2, 4, and 8 weeks of treatment.[9-11] Maraviroc seems to influence immunological recovery[12,13] and darunavir could be stronger than lopinavir (both ritonavir-boosted) in some clinical situations.[2,3] There are also authors that suggest that raltegravir and maraviroc have little metabolic impact,[6,13-15] and raltegravir has a favourable drug interaction profile, given that it is not a CYP450 substrate, inhibitor or inductor.[1]

Unlike other alternatives used for patients with few therapeutic options, NGA are not linked to hepatic toxicity (like tipranavir), or daily subcutaneous administration problems associated with enfuvirtide.

Nevertheless, NGA have been placed in most Spanish hospitals as a therapeutic alternative for patients with few therapeutic options, given the limitations associated with them, lack of clinical experience and evidence, and their high cost.[16]

The main ART recommendations[14,17] consider undetectable viral load as the pharmacological objective, even for patients that have few therapeutic options. To achieve this objective, regimens containing 2 or 3 completely active drugs must be used. That is why using NGA in antiretroviral regimen design seems to be vital when patients have multiresistant strains or when using other active drugs that are contraindicated or restricted by patient comorbidities or toxicity events.

The European Medicines Agency (EMEA) has collected all of these points in their drug regulation. Indications approved for all of these drugs involves pre-treated patients, but it does not specify whether patients must be multiresistant.[1]

Given the wide range of clinical situations that could require NGA use, the objective of this study is to describe the indications for use of these drugs (darunavir, etravirine,

raltegravir and maraviroc) in medical practice in a general university hospital.

Method

We conducted an observational, cross-sectional, descriptive study on HIV-infected outpatients undergoing antiretroviral treatment.

Study population

We included adult patients being treated with antiretroviral drugs, who started treatment with one or several NGA between May 2008 and April 2009, both inclusive.

We excluded patients who had initiated NGA treatment as part of a clinical trial and patients who had started their antiretroviral treatment in another hospital.

Measurement variables

The following variables were recorded:

- Demographic variables: age and sex.
- Clinical variables: viral load (VL) and average CD4 count before NGA treatment.
- Antiretroviral treatment variables: complete antiretroviral regimen, annual cost, adherence rate for the year before NGA treatment. Non-adherence was considered when the adherence rate was below 90% according to the dispensing records.
- NGA use-related variables: variables that are likely to prompt NGA use:
  1. Antiretroviral regimen's *efficacy*-related variables:
     1.1 Resistance documented in geno- or phenotype testing: strains with mutations are found in all resistance tests which confirm medium- or high-level resistance to any ART. Patients were classified depending on the type of mutation detected:
        1.1.1 *Multiresistant:* mutations that confirm medium- or high-level resistance to the three classic antiretroviral agent families (nucleoside analogue reverse transcriptase inhibitors [NARTI], non-nucleoside reverse transcriptase inhibitors [NNRTI] and protease inhibitors [PI]), or all drugs from two of the three classic families (even when there is no resistance mutation to the third family, owing to the risk of functional monotherapy using only classic antiretroviral drugs).
        1.1.2 *Some resistance mutations:* mutations that confirm medium- to high-level resistance to some of the drugs from one or two of the three classic families.
        1.1.3 *Undocumented resistance mutations:* low-level drug resistance mutations detected or mutations that do not confirm resistance, or patients that do not have resistance testing data.
     1.2 Potential resistance due to extensive exposure to antiretroviral agents: the patient has received previous antiretroviral treatment with at least one drug from each of the traditional antiretroviral families for at least six months.
     1.3 Severe immunological deterioration: the CD4 count before NGA treatment is less than 200 cells/mcl.
  2. Treatment *safety*-related variables:
     2.1 *Toxicity that contraindicates any ART:* i.e. a clinically diagnosed, severe adverse reaction (limiting the patients ability to enjoy a normal life or leading to hospital admission), associated with any NARTI, NNRTI or PI that contraindicates its use (e.g.: abacavir hypersensitivity reaction, tenofovir-related severe kidney failure, lactic acidosis pancreatitis, NNRTI-induced skin rash, nevirapine-induced toxic hepatitis, life-limiting neurological disorders, atazanavir-induced severe hyperbilirubinaemia or cholestasis).
     2.2 *Comorbidity that directly influences ART use:* i.e. a chronic disorder that may be due to or boosted by any ART, and which could shorten patient survival (e.g.: cardiovascular disease, diabetes mellitus, hyperlipidaemia, severe liver disease (stage>3 or cirrhosis), osteopaenia, or chronic renal failure).
     2.3 *Comorbidity that indirectly influences ART use:* the following situations are considered:
        - Comorbidity which requires a pharmacological treatment that could interfere with antiretroviral agents
        - Comorbidity involving significant clinical deterioration (e.g.: epilepsy, COPD, pulmonary hypertension, lymphoma or tuberculosis).
     2.4 *Toxicity caused by any ART, which affects quality of life:* lipodystrophy or diarrhoea associated with PI-based ART.
  3. Combined efficacy and safety variable: the main NGA use-related variable. We defined 5 different categories in accordance with the algorithm shown in Figure 1, which prioritises the previously described variables likely to prompt NGA use.

For patients who modified their NGA treatment during the study period, we recorded the demographic, clinical, NGA use-related variables and adherence rate for the first drug regimen that they started. We analysed the cost and antiretroviral regimen for the last NGA treatment prescribed.

Data sources

We reviewed the following data sources:

- Software application for clinical history: unified access since 2005 to analysis data, clinical reports from outpatient units and hospital discharges, and imaging tests since 2003.
- Pharmaceutical Care Records with data collected in a clinical interview.
- Computerised dispensing records, available since 1998.
- Resistance test reports, directly provided by the Microbiology Department. We have used Truegene® for genotype testing (Visible Genetics, Canada) since 2002 and Vircotype® HIV 1 for virtual phenotype testing (Virco, Belgium) since 2003.

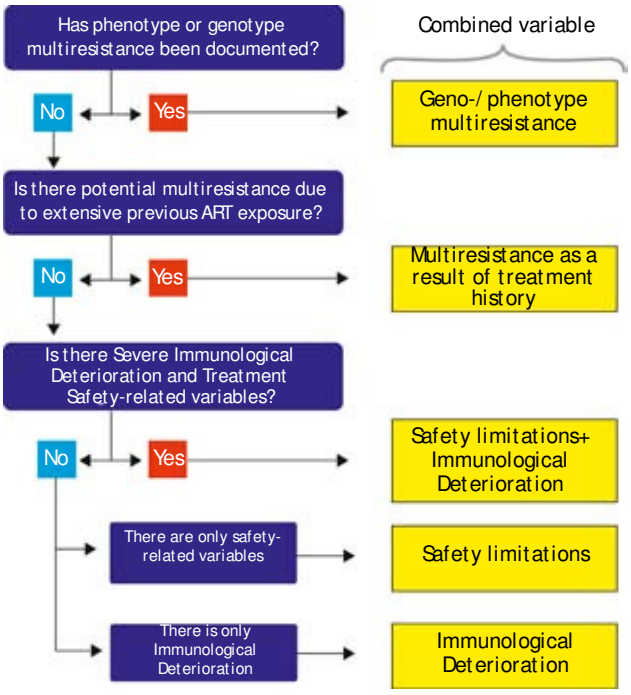

Figure 1 Algorithm which prioritises variables likely to prompt next-generation antiretroviral use to establish the efficacy and safety combined variable*.
***Combined variables: safety limitations+immunological deterioration, safety limitations, and immunological deterioration, are grouped together in another category "Other situations".**
ART indicates antiretroviral therapy.

Methodology

The Pharmacy Department wrote a report for each patient when they were recruited in the study. The report systematically described the data available and it was structured in accordance with the Spanish AIDS study group and the AIDS plan's (GESIDA/PNS) recommendations for selecting antiretroviral regimens,[14] as follows:

- Description of ART using NGA.
- Resistance testing results: mutation interpretation data according to Truegene® and Vircotype® HIV 1 was crossed with those obtained by the Stanford University's drug resistance interpretation system. This system prioritises the treatment options in accordance to the resistance mutations found in the patient. This system can be accessed through the Stanford University website (http://hivdb.stanford.edu/pages/algs/sierra_mutation.html).
- ART history and adherence rate for the year before NGA treatment.
- Comorbidities and ARV-related toxicities.
- Concomitant medication and analysis of the potential interactions.

These reports were presented in our centre's Antiretroviral Management Group meetings, and the variables were later entered in a database for overall data mining. We only continued analysing the other NGA use-related variables when the combined variable was not *geno/phenotype (G/P) multiresistance*.

Statistical analysis

Data are expressed as frequencies and percentages for qualitative variables and as mean±standard deviation (SD) for quantitative variables. We used the chi-square test and the Fisher's exact test for the qualitative variables, and the Mann-Whitney U, Kruskal-Wallis and ANOVA tests for the quantitative variables. We considered results with a *P* value less than 0.05 as statistically significant. Statistical analysis of the data was performed using the SPSS 16.0 for Windows.

Results

A total of 83 patients started NGA antiretroviral treatment during the study period, and 73 of them met the inclusion criteria. Recruitment of patients who started NGA treatment throughout the study period is shown in Figure 2.

66% were men and the mean age was 46±10 years. Viral load was undetectable for 40% of the patients, 11% had between 50 and 1000 copies/ml, 40% between 1000 and 100 000 copies/ml, and 9% more than 100 000 copies/ml. The average CD4 count was 347±276 cells/mcl and 38.4% of the patients had severe immunological deterioration.

Treatment consisted of 3.4±0.9 ARV, including 1.6±0.8 NGA. 42% of patients used more than three ARV (without considering ritonavir as a booster), and 59% of the regimens examined included one single NGA. 34.4% of the patients had not adhered to treatment the year before starting NGA. The average annual cost per patient was €21 674.

NGA use-related variables

Table 1 shows the number of patients according to NGA use-related variables. 45% had G/P multiresistance, 22% some resistance mutations, and 33% did not have any resistance mutations documented.

Forty patients did not present G/P multiresistance, for whom we analysed the other NGA use-related variables. Two or more of these variables were detected in 90% of these patients, and more than three in 62%. At least one safety-related variable was found for 30 patients (75%): 30% of them had experienced toxicity that contraindicated ART use, 52.5% of them had some sort of comorbidity which restricted ART use directly and 20% indirectly, and 17.5% of them had developed ARV-induced toxicity which affected their quality of life.

Distribution according to the main NGA use-related variable was as follows: 45% of patients presented G/P multiresistance and 33% multiresistance as a result of treatment history. Safety limitations and severe immunological deterioration occurred in 6 patients (8.2%). Safety limitations were the main variable for 5 patients

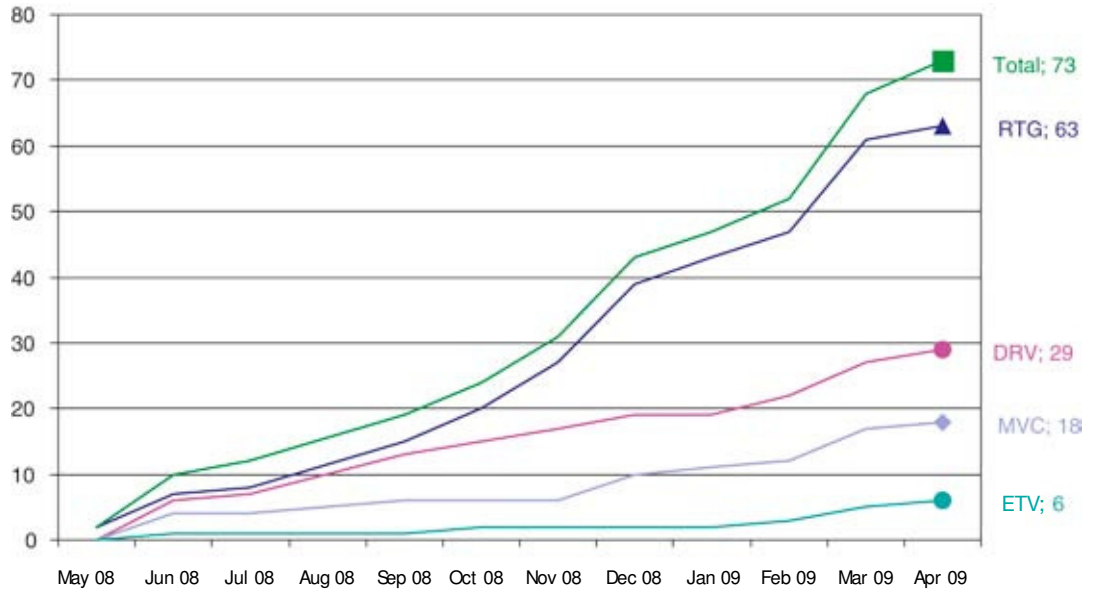

Figure 2 Trend related to the number of patients that started next-generation antiretroviral treatment. DRV indicates darunavir; ETV, etravirine; MVC, maraviroc; RTG, raltegravir.

(6.9%), and 4 of them had at least one more NGA use-related variable. The main variable for another 5 patients (6.9%) was severe immunological deterioration, which for 3 of these patients was accompanied by virological failure and some resistance mutations.

Table 2 shows the patients' characteristics according to the main NGA use-related variable. Patients with G/P multiresistance had a better immunological situation, used more NGA, and had a higher mean annual cost than the other groups (statistically significant differences).

Patients without G/P multiresistance or multiresistance as a result of treatment history had a higher viral load (statistically significant differences for both groups) and had a worse immunological situation (statistically significant

Table 1 No. patients according to NGA use-related variables

Efficacy variables			Safety variables			Combined variables				
Documented resistance	**Previous ART exposure**	**ID**	**0**	**1**	**≥2**	**Multi G/P**	**Multi H**	**Other**		
								ID+SL	**SL**	**ID**
Multiresistance	NA	NA	NA	NA	NA	33	0	0	0	0
Some resistance mutations	Previous ART exposure	Yes	1	0	2	0	3	0	0	0
		No	1	1	3	0	5	0	0	0
	No previous A	Yes	3	1	1	0	0	2	0	3
	RT exposure	No	0	1	0	0	0	0	1	0
	No data	Yes	0	0	2	0	0	2	0	0
		No	0	0	0	0	0	0	0	0
Undocumented resistance mutations	Previous ART exposure	Yes	2	3	3	0	8	0	0	0
		No	1	2	5	0	8	0	0	0
	No previous ART exposure	Yes	1	2	0	0	0	2		1
		No	0	0	3	0	0	0	3	0
	No data	Yes	1	0	0	0	0	0	0	1
		No	0	1	0	0	0	0	1	0
TOTAL			10	11	19	33	24	6	5	5

ART indicates antiretroviral therapy; ID, immunological deterioration (CD4<200 cells/mcl); Multi G/P, geno/phenotype multiresistance; Multi H, multiresistance as a result of treatment history; NA, analysis no applicable; NGA, next-generation antiretrovirals; SL, safety limitation.

Table 2 Patient characteristics according to the main NGA use variable

	Geno-/phenotype multiresistance (45%)	Multiresistance as a result of treatment history (33%)	Other (22%)
% VL>1000	55	29	69[a,b]
%CD4<200	18	46[a]	69[a]
%>NGA	70	13[a]	25[a]
%>3ARV	46	42	38
%Non-adherent patients	22	36	70[a]
Annual cost (€)	25 408	17 770[a]	19 829[a]

ARV indicates antiretroviral drugs; NGA, next-generation antiretrovirals; VL, viral load.
[a]Statistically significant differences with geno/phenotype multiresistance.
[b]Statistically significant differences with multiresistance as a result of treatment history.
[c]Adherence rate lower than 90%according to dispensing records.

differences with the G/P multiresistance group). Furthermore, these patients had been less adherent to previous antiretroviral treatment (statistically significant differences with the G/P multiresistance group).

Regimens

The antiretroviral combinations used for these patients were very varied. 88%used raltegravir, 40%darunavir, 24%maraviroc and 8%etravirine (Figure 2). Etravirine was the only NGA that was always used in combination, whereas the other three were used both alone and in combination with other NGA. 48%of patients used raltegravir as a sole NGA, 16%raltegravir with maraviroc, and 11%raltegravir with darunavir and maraviroc. The remaining combinations were used to a lesser extent (Figure 3). Five out of the 73 recruited patients changed their NGA during the study.

For 12%of patients, NGA were not associated with other ARV, 52% only with NARTI, and 14% with NARTI plus one PI other than darunavir (Figure 4). 75%of the regimens included a NARTI, the most used being tenofovir (84%) and abacavir (18%), mainly in combinations. 22%of the patients used a PI other than darunavir, the most used being boosted lopinavir (37%) and atazanavir (31%).

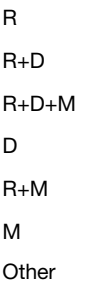

Figure 3 Distribution of patients according to use of next-generation antiretrovirals. D, darunavir; M, maraviroc; R, raltegravir.

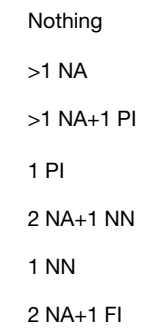

Figure 4 Distribution of patients according to antiretroviral combinations associated with next-generation antiretrovirals (%of patients).
FI indicates fusion inhibitors; NA, nucleoside/nucleotide analogue reverse transcriptase inhibitors; NN, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Discussion

This study aimed to better understand the healthcare reality and understand the use profile of the newest antiretrovirals on the market. It has highlighted that there many different clinical situations that may require next-generation antiretrovirals: darunavir, maraviroc, etravirine and raltegravir. Therapeutic possibilities were limited for most patients (45%) because they presented geno-/phenotype multiresistance, but there were also situations in which the classic treatments' efficacy or safety was much compromised for other reasons.

On one hand, 33%of patients were suspected to be multiresistant given their extensive exposure to antiretroviral agents. This situation has been considered as a main NGA use-related variable, because the current analytical techniques for detecting resistance mutations have limitations, such as low sensitivity when viral load is

less than 1000 copies/ml or low specificity when the mutations' virus population is less than 20% of the total population. That is why it is of utmost importance to analyse previous antiretroviral treatments.[14]

On the other hand, we observed that more than 20% of patients (group classified as "other situations") used enough classic active antiretroviral drugs to be considered an adequate therapeutic regimen, but they were very complex patients, who had a very critical clinical situation, with a high viral load, severe immunological deterioration and/or associated comorbidities. Furthermore, on many occasions they had a high risk of toxicity to classic antiretrovirals. Therefore, the need to use NGA in their therapeutic regimens was mainly due to a combination of several efficacy and safety-related factors.

Arribas[13] has recently reviewed the advantages and disadvantages of darunavir, etravirine, maraviroc and raltegravir, and based on this study, he has proposed the potential role of these drugs in current therapy. Our results emphasise that Arribas's theory with regards NGA is evident in clinical practice, and that in addition to its role in rescue situations, the safety-related advantages that they offer make these new drugs necessary sometimes.

Furthermore, in a study conducted in 2007[18] recommendations for use for several antiretrovirals were proposed, and degree of compliance to them was analysed. Darunavir was indicated for patients that had at least one unsuccessful regimen including a PI, who had documented evidence of a virological failure (VL>1000 copies/ml) and that were able to tolerate low ritonavir doses. The results obtained from reviewing the prescriptions written for a year and a half after this drug was marketed showed that 21.2% of prescriptions had not met these requirements.

Antiretroviral toxicity is one of the most important aspects related to their use. The prevalence of toxicity varied depending on the agent family prescribed, ranging from 15% to 50% for oral treatments.[13] Martín et al[19] analysed the relationship between adverse reactions and patients' therapeutic compliance for patients in the Pharmacy Department. They found that 66% of the patients reported suffering an adverse reaction during the past 6 months. Another recently published article analysed the antiretroviral toxicity in HIV-infected pregnant women.[20] The prevalence of the adverse reactions found in the medical history, laboratory tests and patient information was 48% for this population. In our study, we evaluated safety variables in 40 patients, finding that 75% had at least one of them. Then, even though the methodologies show different results, all of the data show that our study population has a worse tolerance to ART than the average population. This also supports the hypothesis that NGA safety is an important issue that must be considered when being prescribed.

Adherence to treatment before NGA therapy was low in comparison to the latest data from our hospital. A descriptive, retrospective study was conducted between May 2007 and May 2008 on adherence during the first six months of ART in naïve adult patients, finding that 22.7% of patients were non-adherent compared with 34.4% found for NGA patients in our study. These results are logical because the two populations are very different from one another. There are two factors that NGA patients have, and the naïve population does not: they have spent much longer under treatment and have had much more negative experiences associated with it. These two factors affect adherence because the patient becomes less and less satisfied with their medication.[21]

Several studies on adherence have recently been published examining populations who have been treated with ART. Kim et al[21] found that 27.4% of patients were non-adherent using self-statement questionnaires in 2007. Another study examined 68 patients with an average of two previous virological failures, finding that 23.5% of them declared that they did not take more than 95% of their necessary doses during the month before the self-statement questionnaire.[22] In our opinion, our study found a higher percentage of non-adherent patients because the type of questionnaire that we used often over-estimates adherence, and because our definition of adherence is much more exacting, as it assessed a whole year.

On the other hand, it is interesting to note that adherence before the start of NGA treatment was much lower in the "other situations" group (70% non-adherent), than in the other two groups. The Antiretroviral Management Group from our hospital decided to arrange a special adherence follow-up programme in the Pharmacy Department, given the risk and clinical repercussion if these patients were to experience therapeutic failure because they had not adhered to their NGA treatment.

In Martín MT et al's study,[19] 38% of the patients who had adverse reactions had a compliance rate of less than 90% (measurement taken from counting surplus medication or from the dispensing records). They found statistically significant differences with the compliance rate of patients with good tolerance. These values are similar to those that we have found in our study, given that, 36% of the 30 patients who had a safety-related variable were non-adherent.

As expected, due to the high heterogeneity of the population included in this study, there has been great variability in the antiretroviral regimens used. The most used was the combination raltegravir with two nucleoside or nucleotide analogue reverse transcriptase inhibitors, probably due to raltegravir's benefits associated with tolerance and interactions. On the other hand, NGA are expensive, meaning that the average annual cost is €21 674 per patient. The mean cost of treatment in our centre is approximately €9000 per patient per year, indicating that the drugs used in these critical situations are two and a half times more expensive than the average.

We used an adequate study methodology, and the main limitation was that we did not study the medical records that were only available in paper format. This could have given us new data for the patient's clinical follow-up, which would have mainly helped us clarify the ART safety-related variables.

To summarise, this observational study has highlighted the healthcare reality of using antiretroviral agents new to the market. They are used in very particular, difficult-to-manage clinical situations, which together with a high drug cost, make therapeutic dialogue and consensus especially

interesting.

Conflict of interest

The authors affirm that they have no conflict of interest.

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