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Effectiveness of antiretroviral therapy in treatment-naïve patients. Results at 24 and 48 weeks

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Abstract

Introduction: Since 2015, integrase strand transfer inhibitors (INSTI)-based regimens have been considered as the preferred option for antiretroviral therapy (ART)-naive patients. The main objective of this study was to identify the ART-regimens selected for treatment-naïve patients during 2015 in two tertiary hospitals, determine the rate of virological failure at 24 and 48 weeks, and compare the results with those of previous years (2012-2014).

Material and methods: Four-year retrospective study. Adult ART-naïve patients who had started treatment between 2012 and 2015 were selected. Clinical data, laboratory tests performed, and ART selected were recorded.

Results: A total of 536 patients were included, 137 from 2015 and 399 from 2012-2014. The most common ART regimens prescribed in 2015, compared to 2012-2014, were INSTI-based regimens (68.6% vs. 4.8%), followed by non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (20.4% vs. 52.8%) and PI-based regimens (10.9% vs. 42.5%). Most patients received a single-tablet regimen (78.8% vs. 51.9%). In 2015, 72.3% of patients had a viral load (VL) < 50 copies/ml at week 24 and 83.9% at week 48, compared to 55.1% and 74.7%, respectively, in 2012-2014. During the 48-week follow-up, the ART regimen was changed in 22.6% of patients in 2015 and 29.3% in 2012-2014. The main reason was simplification (45.2% vs. 22.2%) followed by side effects (25.8% vs. 38.5%).

Conclusions: In 2015, INSTI-based regimens were prescribed in nearly 70% of ART-naïve patients. This change in trend in the starting ART regimen results in a greater number of patients achieving a VL < 50 copies/ml at weeks 24 and 48 and in a reduction in ART changes due to adverse effects.

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Key words: adult, anti-HIV agents, HIV infections, treatment outcome, viral load.

Introduction

Most scientific associations currently recommend starting antiretroviral therapy (ART) in all human immunodeficiency virus (HIV)-infected patients [1-3] because evidence suggests that delaying ART initiation is associated with greater mortality and serious acquired immunodeficiency syndrome (AIDS)- or non-AIDS-related complications [4, 5].

With the combinations of ARTs available these past few years, the target viral load (VL) of < 50 copies/ml was

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achieved in more than 75% of cases at 48 weeks [1, 6, 7] The number of preferred combinations for ART-naïve patients has been progressively reduced since 2015, especially in the Spanish GESIDA guidelines, which were the first ones to give integrase strand transfer inhibitors (INSTI) precedence over other drug families [1].

The success of strategies in achieving sustained virological suppression depends on the appropriate selection of the starting regimen, the performance of a prior drug resistance mutation (DRM) test, and good adherence. Other factors that are considered as predictors of success are low pre-therapy baseline viraemia and baseline CD4 count above 200 cells/µl [1, 2, 6-8].

Although one of the treatment goals described in all the guidelines is the achievement of prolonged suppression, there are discrepancies regarding the concept of virological failure (VF). While most guidelines [1, 3, 9] concur in their definition of VF as two consecutive measurements of VL > 50 copies/ml at 24 weeks following ART initiation, the DHHS [2] defines it as the inability to achieve or maintain viral replication below 200 copies/ml. VF is also considered if, following the achievement of virological suppression at week 24, VL becomes detectable again in two consecutive measurements.

Furthermore, increased importance has been given over the last few years to the CD4/CD8 ratio in patients with HIV infection. In these patients, an inversion of this ratio to levels below 1 is considered as a surrogate marker of immunosenescence, available in standard clinical practice, and has shown to be an independent predictor of mortality in the elderly [10].

The primary objective of this study was to determine the type of ART selected as starting therapy for naïve patients throughout 2015 in a real-life situation in two tertiary hospitals, the rate of VF at 24 and 48 weeks, and whether results differed from 2012-2014.

The secondary objectives were to analyse changes in ART and reasons for change, variations in the CD4/CD8 ratio, and the relationship between the different predictors of success described and the results obtained.

Material and methods

A four-year retrospective study at two tertiary hospitals was conducted. Adult naïve HIV-infected patients who had initiated ART between January 2012 and December 2015 were selected. Patients having started treatment because of pregnancy were excluded.

The follow-up period was 48 weeks. The data collected were demographics, and clinical and laboratory data (VL, CD4 counts, CD4/CD8 ratio) both at baseline and at weeks 24 and 48 of treatment, with a window of up to four weeks, and ART chosen. Follow-up and adherence data were also collected.

Changes in ART during the first year and reason for change were recorded.

Virological success or treatment failure was determined at 24 and 48 weeks using two types of analyses in which VF was defined as VL > 50 copies/ml 24 and 48 weeks following ART initiation, as VL that did not become undetectable at any time, or when, following virological suppression, it became detectable again in two consecutive measurements (definition of the GESIDA, EACS, and IAS guidelines) or as the inability to achieve or sustain viral replication below 200 copies/ml (DHHS guidelines).

Good follow-up was considered when patients came to more than 80% of the medical appointments scheduled for that year, and adherence was considered adequate when it was greater than 90%. Adherence records are registered in the eVIAh database based on the pharmacies' dispensation logs.

Data were analysed on an intent-to-treat and per protocol basis. Continuous variables are presented as mean (standard deviation) or median (interquartile range) depending on their distribution, and categorical variables are presented as percentages.

A univariate statistical analysis was performed comparing differences between groups using χ^2, Student's *t*, ANOVA, and Mann-Whitney *U* tests based on their distribution and the number of groups being compared. The multivariate analysis was conducted using a logistic regression to calculate the odds ratios (OR) of the statistically significant variables in the univariate analysis and variables associated to risk of virological failure in the literature. They were considered significant when $p < 0.05$.

All the data were obtained from the eVIAh database, which is a database used by both sites for the follow-up of HIV patients at the Outpatient Clinics, and they were collated with electronic medical records when necessary. Patients had signed a prior informed consent for the "Multicentre Cohort of HIV-infected adults (PISCIS)" or "CoRIS" authorising their data to be entered in this database.

Data were anonymised, and the IBM SPSS Statistics v.22 software was used for the statistical analysis.

This study was authorised by the Research Ethics Committee (REC) of the Balearic Islands, Spain (code EST-TAR-2016-01).

Results

A total of 536 patients having initiated ART were enrolled, 399 in the 2012-2014 period and 137 in 2015. Sociodemographic, clinical, laboratory, and treatment data are provided in Table 1. The most important differences between both periods were related to age at therapy initiation, CD4 counts, and type of ART selected. The most common combinations in 2012-2014 were the ones that included a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), with efavirenz (30.1%), dolutegravir (27.1%), and rilpivirine (21.6%) as the most commonly used drugs. In 2015, INSTIs represented the main family of drugs used, with dolutegravir (46%), elvitegravir/cobici-

Table 1. Demographic, clinical, and treatment data

Factor	2012-2014	%	2015	%	*p*
Nº of patients	399	–	137	–	
Mean age	42.1 ± 9.9	Min: 22, Max: 80	39.1 ± 9.5	Min: 21, Max: 71	0.001
Gender					
Male	345	86.5	114	83.2	0.349
Nationality					
Spanish	160	40.1	69	50.4	0.005
Foreigner	90	22.6	17	12.4	
Not recorded	149	37.3	51	37.2	
HCV co-infection					
Yes	68	17	11	8	0.034
Transmission mechanism					
Homosexual	194	48.6	67	48.9	0.088
Heterosexual	138	34.6	55	40.1	
IDU	49	12.3	6	4.4	
CD4 range					
< 200	124	31.1	31	22.6	< 0.001
200-350	112	28.1	37	27	
350-500	128	32.1	36	26.3	
> 500	35	8.8	33	24.1	
Mean VL log	4.7 ± 0.8		4.7 ± 0.8		0.716
High baseline VL					
VL > 100,000	146	36.6	50	36.5	0.983
Prior resistance study					
Performed	281	70.4	112	81.8	0.010
Selected ART					
2NRTI + 1NNRTI	210	52.8	28	20.4	< 0.001
2NRTI + 1PI	169	42.5	15	10.9	
2NRTI + 1INSTI	19	4.8	94	68.6	
Single daily dose					
Yes	207	51.9	108	78.8	< 0.001
Discontinuation of starting ART	117	29.3	31	22.6	0.130
Start of second ART	92	23.1	25	18.2	0.240
2nd ART selected					
2NRTI + 1NNRTI	39	42.4	2	8	< 0.001
2NRTI + 1PI	32	34.8	5	20	
2NRTI + 1INSTI	20	21.7	18	72	
1PI + 1INSTI	1	1.1	0	0	
Single daily dose 2nd ART					
No	50	54.3	6	24	0.007
Yes	42	45.7	19	76	
Follow-up visits					
> 80%	336	84.2	119	86.9	0.484
< 80%	59	14.8	17	12.4	
ART adherence					
> 90%	169	42.4	74	54	0.756
< 90%	16	4	6	4.4	

ART – antiretroviral therapy, IDU – injection drug user, INSTI – integrase strand transfer inhibitor, NNRTI – non-nucleoside reverse transcriptase inhibitor, NRTI – nucleoside reverse transcriptase inhibitor, PI – protease inhibitor, VL – viral load

Table 2. Viral load results at 24 and 48 weeks

Results	2012-2014 (*n*)	Absolute (%)	Relative (%)	2015 (*n*)	Absolute (%)	Relative (%)	*p*
Results at 24 weeks							
Patients with VL data	379	95.0	100.0	126	92.0	100.0	
VL < 200 copies/ml	307	76.9	81.0	121	88.3	96.0	< 0.001
VL < 50 copies/ml	220	55.1	58.0	99	72.3	78.6	< 0.001
Results at 48 weeks							
Patients with VL data	349	87.5	100.0	124	90.5	100.0	
VL < 200 copies/ml	337	84.5	96.6	122	89.1	98.4	0.374
VL < 50 copies/ml	298	74.7	85.4	115	83.9	92.7	0.040

VL – viral load

Table 3. CD4 values (cells/mm^3) and CD4/CD8 ratio

CD4 distribution	2012-2014			2015			*p*
	n	Median	IQR	*n*	Median	IQR	
Prior to ART initiation	399	310.0	153-405	137	353.0	226.5-500	0.048
Week 48	353	478.0	309-631	124	560.5	382-818.3	0.063
Inter-subject variation in CD4 count							
Week 48	353	178.0	82-292	124	213.0	100.75-326.25	0.023
CD4/CD8 ratio							
Prior to ART initiation	204	0.32	0.2-0.48	86	0.40	0.227-0.57	0.190
Week 48	121	0.48	0.29-0.74	77	0.66	0.38-0.92	0.116
Inter-subject variation in CD4/CD8 ratio							
Week 48	102	0.19	0.07-0.30	71	0.29	0.14-0.48	0.154

ART – antiretroviral therapy, IQR – interquartile range

stat (21.9%), and rilpivirine (18.2%) as the drugs most commonly used in the starting ART.

With regard to ART effectiveness, laboratory data from 505 (94.2%) patients at 24 weeks and from 473 (88.2%) patients at 48 weeks were analysed to determine success or VF. The results in Table 2 are provided as absolute and relative values. The difference between the first and the second study period in the number of patients with a VL < 50 copies/ml at 24 weeks (58.0% vs. 78.6%) and 48 weeks (85.4% vs. 91.7%) is worthy of attention.

Data on CD4 counts, CD4/CD8 ratio, and inter-subject variations between therapy initiation and week 48 are provided in Table 3. The CD4/CD8 ratio was only recorded in one of the hospitals and not for every patient. The increase in inter-subject CD4 variation (178.0 vs. 213.0; $p = 0.023$) and in the CD4/CD8 ratio (0.19 vs. 0.29; $p = 0.023$) between both study periods is of note even though it did not reach statistical significance.

There were no laboratory data available at week 48 in 63 patients because no laboratory test or follow-up visit had taken place within the specified period in 39 cases, 16 patients had changed their place of residence, 15 were lost-to-follow-up, two had died, and one had withdrawn. Treatment failure occurred in 13 patients with a VL > 200 copies/ml as a result of treatment discontinuation in six cases, poor adherence in five cases, lost-to-follow-up in one case, and unknown cause in one case.

Regarding changes in therapy, 27.6% of patients changed their initial ART during the first year. The primary reason in 2015 was to simplify therapy in 14 (45.2%) patients, followed by side effects in eight (25.8%) patients, and six (19.3%) patients were lost-to-follow-up. One change was due to treatment failure, one to medical judgement, and one to pregnancy. By contrast, in 2012-2014, side effects were the primary reason for ART change in 45 (38.5%) patients, followed by simplification in 26 (22.2%) patients, and lost-to-follow-up in 23 (19.6%). There were nine discontinuations based on medical judgement, four were due to drug-drug interactions, three to patient withdrawal, three to resistance study results, two to treatment failure, one to low plasma levels, and one to death.

The types of adverse effects recorded in 2012-2014 were: CNS-related (16 patients), gastrointestinal (5), dermatological (5), renal (5), hyperbilirubinaemia/jaundice (5), bone (2), metabolic (2), malaise (2), unknown (2), and neutropaenia (1). In 2015, these were gastrointestinal (3), renal (2), dermatological (1), bone (1), and unknown (1).

Table 4. Univariate analysis of virological failure at 48 weeks of therapy

	N	VL < 200	%	VL > 200	%	*p*	VL < 50	%	VL > 50	%	*p*
High baseline VL											
VL < 100,000	293	289	98.6	4	1.4	0.017	278	94.9	15	5.1	< 0.001
VL > 100,000	176	167	94.9	9	5.1		132	75.0	44	25.0	
Baseline CD4 count											
< 200	137	132	96.4	5	3.6	0.572	108	78.8	29	21.2	< 0.001
> 200	336	327	97.3	9	2.7		305	90.8	31	9.2	
Prior RM study											
Performed	351	341	97.2	10	2.8	0.809	305	86.9	46	13.1	0.641
Not performed	122	118	96.7	4	3.3		108	88.5	14	11.5	
ART type											
2NRTI + 1NNRTI	212	207	97.6	5	2.4	0.45	196	92.5	16	7.5	< 0.001
2NRTI + 1PI	162	155	95.7	7	4.3		128	79.0	34	21.0	
2NRTI + 1INSTI	98	96	98.0	2	2.0		88	89.8	10	10.2	
Single daily dose											
Yes	281	276	98.2	5	1.8	0.067	262	93.2	19	6.8	< 0.001
No	192	183	95.3	9	4.7		151	78.6	41	21.4	
Adherence											
> 90%	229	229	100.0	0	0.0	< 0.001	209	91.3	20	8.7	< 0.001
< 90%	19	13	68.4	6	31.6		11	57.9	8	42.1	
Follow-up											
> 80%	416	406	97.6	10	2.4	0.054	366	88.0	50	12.0	0.24
< 80%	57	53	93.0	4	7.0		47	82.5	10	17.5	

ART – antiretroviral therapy, INSTI – integrase strand transfer inhibitor, NNRTI – non-nucleoside reverse transcriptase inhibitor, NRTI – nucleoside reverse transcriptase inhibitor, PI – protease inhibitor, RM – resistance mutation, VL – viral load

Of the patients who initiated a second ART, 24 had their therapy discontinued again in 2012-2014 (six for simplification, four due to lost-to-follow-up, three to side effects, three to medical judgement, three to treatment failure, two withdrawal, two change in place of residence, and one to resistance study results), and two in 2015 (one for simplification and one due to side effects).

In the univariate analysis, if we consider VF as the inability to achieve a VL < 200 copies/ml at week 48, the only variables associated with VF are high baseline VL and poor adherence. If we consider VF as the failure to achieve a VL < 50 copies/ml at week 48, then, in addition to high baseline VL and poor adherence, the baseline CD4 count and the type of starting ART become relevant, and the best results are obtained with INSTIs and NNRTIs and single-tablet regimens (STRs) (Table 4).

In the multivariate analysis, high baseline VL, baseline CD4 count below 200 copies/ml, and ART type were associated with the probability of having a VL < 50 copies/ml at week 48. Adherence was excluded from the analysis because, despite having shown statistically important differences in previous analyses, it had only been recorded in 246 patients.

A total of 468 patients were included in the analysis performed with the variables mentioned. A baseline VL < 100,000 copies/ml was associated with a higher probability of treatment success (OR = 5.373; CI = 2.783-10.376; $p > 0.001$). There was a significant difference in the VL < 50 copies/ml results at week 48 according to the type of ART, with PIs being the only drugs showing differences (lower effectiveness) compared to the other drug families (OR = 0.425; CI = 0.192-0.942; $p = 0.035$).

Discussion

The demographic and clinical data obtained in our cohort of treatment-naïve HIV-infected patients are in line with the most recent report on new HIV diagnoses published by the Spanish Ministry of Health in 2016 [11].

The number of patients initiating ART each year remained stable, mean age at therapy initiation decreased nearing mean age at diagnosis (36 years), and transmission between MSM was clearly predominant while transmission between HTSX and IDUs decreased. The number of foreigners and the percentage of patients initiating ART with advanced disease (< 200 CD4/mm^3) also decreased significantly, although late diagnosis remained at about 50%, which was similar to the national mean value.

Regarding the type of ART selected as starting regimen, a significant change in drug prescription was seen in favour

of INSTIs, as recommended by the main scientific guidelines [1, 2]. Therapies were also simplified, with STRs representing almost 80% of starting ARTs.

With the change of trend in antiretroviral regimens, greater rates of patients with undetectable VL were achieved, with significant differences at week 24 in the number of patients with a VL < 50 copies/ml and VL < 200 copies/ml. At week 48, the rate of patients with a VL < 200 copies/ml was similar for both study periods, but the number of patients with a VL < 50 copies/ml remained higher in 2015 (92.7% vs. 85.4%; $p = 0.04$).

Studies published prior to 2015 (when recommendations in the guidelines changed in favour of INSTIs) found that between 5% [12] and 13% [13] of patients were changing their starting ART because of treatment failure. However, it is important to take into account that the definition of VF used in each study and the year the study was conducted or the HIV PCR technique used were not always clearly specified. In the study by Jarrin *et al*. [13], the authors only provide treatment failure/resistance data without clearly specifying what they considered as failure, and in the study by Keita *et al*. [12] treatment failure was defined not only as the inability to achieve an undetectable VL or as VL rebound but also as the onset of clinical symptoms of disease progression or the lack of increase in CD4 counts despite ART. Furthermore, other studies defined VF as "two consecutive viral loads at least 500 copies/ml or one viral load at least 500 copies/ml, followed by a modification of ART" [14], as "an HIV RNA viral load of >1000 copies/ml"[15], or as "a VL > 400 copies/ml" [16].

It is also important to note that in clinical practice it is difficult to obtain laboratory data with the same frequency at which it is generally obtained in clinical trials, so that, with the definition of therapeutic success as a VL < 50 copies/ml at 24 weeks, until 2014 this was obtained in a little over 50% of patients. As of 2015, thanks to the rapid decrease in VL achieved by INSTIs, therapeutic success increased to 72% in absolute terms at 24 weeks and was greater than 80% at 48 weeks, which is the value recommended by the current scientific guidelines [17].

Furthermore, although the global rate of treatment modifications did not decrease significantly, the number of total ART changes resulting from side effects did decrease from 11.2% of patients (38.5% of the changes) in 2012-2014 to 5.8% (25.8% of the changes) in 2015. The primary cause for changing ART in 2015 was treatment simplification, which occurred in 10.2% of patients (45.2% of total changes) and was due to the fact that for most of these patients, a starting combination of 2 NNRTI + INSTI in a single tablet had not been available when they had initiated therapy.

Until recently, the primary reasons for changing ARTs were toxicity followed by simplification, as shown in publications such as the CoRIS cohort [13], from 2008 to 2010, in which the most common reason for ART modification was shown to be toxicity (40%), followed by simplification (14%) and treatment failure/resistance (13%).

The survey by Pedrol *et al*. [18] performed in Spain in 349 HIV patients in 19 hospitals to characterise the reasons for changing ARTs also found that the most common reason for change was simplification (37%), followed by toxicity (30%) and therapeutic failure (21%). In another Spanish study [19] with 603 treatment-naïve patients initiating ART, the median time during which they remained with the same ART was 17.5 months. The ART had been discontinued in 36% of patients during the first year of follow-up, with toxicity as the primary cause for switching therapy (25%), followed by simplification (19%) and VF (15%).

Our study shows that the current drug combinations recommended as starting regimens are better tolerated than those existing previously, and this has led to a decrease in the number of treatment discontinuations caused by side effects.

With regard to patient immunological recovery, despite the fact that in 2015 the mean CD4 count with which patients initiated therapy was higher than in previous years, a greater inter-subject increase at week 48 was observed that year. This was also associated with a greater recovery of the CD4/CD8 ratio, although it was not statistically significant, probably as a result of the low number of patients with this information. CD4/CD8 ratio normalisation in patients receiving ART is important because patients with CD4/CD8 values > 1 have been shown to present a T-cell phenotype very similar to that of subjects without HIV infection. Conversely, patients with a persistently low CD4/CD8 ratio (< 0.4-0.5) show a marked immunosenescence and a greater activation of innate immunity [10].

Finally, the global univariate analysis of factors related to treatment success or failure shows that typical factors such as baseline VL, CD4 counts above 200 cells/mm^3, type of ART selected, adequate treatment adherence, and monitoring are important for the initial ART to be successful [6, 7, 17, 20]. Nevertheless, it should be noted that these factors are also influenced by the type of patient to whom a particular regimen is to be prescribed. PIs, for example, are well known to be preferably prescribed to patients with low CD4 counts, high VLs, prior DRM, or poor adherence [1], and in addition, they are not available as STRs.

By jointly analysing the influence of a high VL, the type of ART used, and baseline CD4 counts in a multivariate analysis, our study shows that only the first two factors show significant differences in the achievement of therapeutic success. Although adherence was excluded given the lack of data, it was significant in all previous analyses.

The main limitation in this study is that, because of it is a retrospective study, it lacks records of adverse reactions that did not lead to treatment modification but that could have had an impact on patient quality of life or adherence.

Another limitation is that adherence records were not complete in all patients, and a fairly high number of patients did not have records of their pre- and post-treatment CD4/CD8 ratio, given that recording of this information during patients' visits started only in the past few years and, even then, not fully in most cases.

Conclusions

In conclusion, of the patients who initiated an ART in 2015 at both hospitals under study, 72% had a VL < 50 copies/ml at 24 weeks and 84% at 48 weeks, compared to 55% and 75%, respectively, for the period 2012-2014. This improvement coincides with a change in trend in the selection of the starting ART, with INSTIs as the drug family most commonly selected for the treatment of naïve patients.

Approximately 25% of patients modified their starting ART in the first year of treatment. In 2015, the main reason for change was ART simplification, while in 2012-2014 the main reason for change was side effects.

Patient immunological recovery was greater in 2015. This could be influenced by both the type of antiretroviral regimen and an earlier initiation of ART.

In the analyses performed, a VL < 100,000 copies/ml and the type of ART continue to be predictors of treatment success. CD4 counts > 200 cells/mm^3, STR combinations, and good adherence can also play an important role in treatment outcome.

This study has enabled us to determine the rate of VF in a real-life situation in two of the main hospitals of our autonomous region and to show how treatment outcome has improved as a consequence of the inclusion of INSTIs in the current therapeutic armamentarium.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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