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Original article

Reasons for noncompliance with the national guidelines for initial antiretroviral therapy of HIV-infected patients in Spain, 2010–2015



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ABSTRACT

Introduction: Our aims were to investigate the adherence to national guidelines of initial antiretroviral therapy (ART) in the Spanish multicenter CoRIS cohort during the years 2010–2015, to identify the reasons for the prescription of nonrecommended treatments, and to explore the role of institutional constraints to guideline compliance.

Methods: ART regimens were classified as recommended, alternative or nonrecommended according to the guidelines. Physicians were asked the reasons for prescribing nonrecommended regimens. Factors associated with the prescription of non recommended regimens were assessed using multivariable logistic regression.

Results: During the study period, 586 (10.7%) of 5479 patients who started ART were given a regimen not recommended in the guidelines. The most frequent reasons for prescribing nonrecommended regimens were: enrolment in clinical trials (43.3%), comorbidities and/or interactions (10.2%), pregnancy (8.7%), and cost (7.7%). Among 37 participating centers, 16 (43%), treating 3561 patients, reported limitations related with the cost of ART, and 20 (54%), treating 1365 patients, reported restrictions for prescribing at least one recommended antiretroviral. In multivariable analysis, a higher risk of receiving nonrecommended regimens was associated with male gender, HIV acquisition by heterosexual transmission, low viral loads, initiation of treatment during the years 2011 to 2015, and initiation of treatment in a center with restricted access to at least one antiretroviral drug.

Conclusions: Compliance to clinical guidelines was high. A high proportion of centres reported cost limitations for ART or restricted access to at least one recommended antiretroviral drug, with a significant impact on the choice of initial regimens.

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Razones para no cumplir las recomendaciones de las guías de práctica clínica en el tratamiento antirretroviral inicial de pacientes con infección por VIH en España, 2010-2015

R E S U M E N

Introducción: Nuestros objetivos fueron investigar la adecuación del tratamiento antirretroviral (TAR) inicial a las guías nacionales en la cohorte multicéntrica española CoRIS durante los años 2010-2015, identificar las razones para la prescripción de pautas no recomendadas y estudiar la influencia de limitaciones institucionales en el cumplimiento de las guías.

Métodos: Se clasificaron las pautas de TAR en recomendadas, alternativas o no recomendadas según las guías de GeSIDA/Plan Nacional sobre el sida. Se preguntaron las razones para haber prescrito pautas no recomendadas a los médicos prescriptores. Se evaluaron los factores asociados a la prescripción de pautas no recomendadas mediante regresión logística multivariable.

Resultados: Durante el periodo de estudio 586 (10,7%) de 5.479 pacientes que iniciaron TAR recibieron una pauta no recomendada. Las razones más frecuentes para prescribir pautas no recomendadas fueron: participación en ensayo clínico (43,3%), comorbilidades y/o interacciones (10,2%), embarazo (8,7%) y coste (7,7%). Entre los 37 centros participantes 16 (43%), que incluían 3.561 pacientes, referían limitaciones en el coste del TAR y 20 (54%), que incluían 1.365 pacientes, referían restricciones para la prescripción de al menos un fármaco recomendado. En el análisis multivariable el riesgo de recibir una pauta no recomendada se asoció a ser varón, adquisición del VIH por vía heterosexual, carga viral baja, inicio del tratamiento durante los años 2011 a 2015 e inicio del tratamiento en un centro con acceso restringido al menos a un antirretroviral.

Conclusiones: El cumplimiento de las guías de TAR fue elevado. Una alta proporción de centros refirieron limitaciones de coste para el TAR o acceso restringido al menos a uno de los fármacos antirretrovirales recomendados; esto último influyó en la elección de pautas no recomendadas.

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Introduction

Clinical guidelines for the treatment of HIV-infected patients are developed by many scientific societies and institutional boards and are widely available.¹⁻³ Despite this, there is little information on the compliance to HIV treatment guidelines and the factors that might influence it.

Studies in different populations have found variable adherence to ART guidelines, ranging from 53 to 83% in the United States⁴⁻⁶ to over 90% in several European countries.⁷⁻¹⁰ The reasons why physicians prescribe antiretroviral drug regimens that are not recommended by the guidelines are not well known. Some studies have tried to identify factors associated with the prescription of nonrecommended regimens.^{4,5,7,9-11} However, none of these studies, with the exception of one,⁹ specifically investigated the reasons for noncompliance to the guidelines among the prescribing physicians.

The Spanish national guidelines for HIV treatment are published jointly by the Spanish AIDS Study Group (GeSIDA) and the National Plan for AIDS (PNS); they are updated annually and are widely known in Spain.¹² Only two studies have assessed the adherence to antiretroviral treatment (ART) guidelines in our country in earlier years^{10,11}; both found a high percentage (over 90%) of compliance to the guidelines for initial ART. However, since both studies were published treatment guidelines have changed substantially, and during the later years cost-containment policies have been implemented in the Spanish healthcare system.¹³⁻¹⁵ Whether these changes could have influenced the adherence to the guidelines is not known.

The aims of this study were to investigate the adherence to national guidelines of initial ART in the Spanish CoRIS cohort during the years 2010-2015, to identify the reasons why physicians prescribe treatments that are not recommended by the guidelines, and to explore possible institutional constraints to guideline compliance.

Materials and methods

Patients and data collection

Patients were selected from the Cohort of the Spanish AIDS Research Network (CoRIS), which has been described in detail elsewhere.^{16,17} CoRIS is a prospective multicentre cohort of HIV-positive treatment-naïve patients aged >13 years, recruited from 42 centres from 13 Autonomous Regions in the Spanish public healthcare system. We included patients who started their first ART from January 2010 to November 2015. Five of the centres did not have any patients starting treatment during the study period and therefore were not included in the analysis.

During the study period the guidelines were updated yearly, and changes introduced were taken into account from the date of publication of each update.¹⁸⁻²³ Treatments were classified as preferred, alternative or not recommended, according to the guidelines' recommendations for initial ART. The recommendations for treatment initiation in each period are shown in Table 1. Any treatment that was not classified as preferred or alternative by the guidelines was considered not recommended. We analyzed only the first treatment administered and any further treatment changes were ignored.

The reasons for prescribing nonrecommended treatments were obtained from all the participating centres. Each principal investigator was sent a list of all the patients from his/her centre who started treatment with a nonrecommended regimen during the study period, and was asked to provide the reason why a preferred or alternative regimen was not prescribed. Each principal investigator contacted the prescribing physician from his/her centre and the clinical records were reviewed for each patient. After reviewing the responses of all centres, reasons for prescribing nonrecommended regimens were classified as: enrolment in clinical trial, pregnancy, comorbidities/interactions, cost, primary resistance, high viral load, other, and unknown.

Table 1

Preferred and alternative drug combinations for treatment initiation in HIV-infected patients according to national guidelines, updated during the study period.

2010				
Preferred	TDF, ABC	FTC, 3TC	EFV, NVP, ATV/r QD, DRV/r qd, FPV/r bid, LPV/r qd or bid, SQV/r bid, RAL	One drug from the 2 nd column, one drug from the 3 rd column and one drug/combination from the 4 th column
Alternative	AZT, ddi	FTC, 3TC	ATV, FPV BID, FPV/r qd	One drug from the 2 nd column, one drug from the 3 rd column and one drug/combination from the 4 th column
Alternative	AZT + 3TC + ABC, AZT + 3TC + ABC + TDF			
2011				
Preferred	TDF/FTC + EFV, ABC/3TC + EFV, ^a TDF/FTC + NVP, TDF/FTC + ATV/r, TDF/FTC + DRV/r, TDF/FTC + LPV/r, ABC/3TC + LPV/r, ABC/3TC + ATV/r, ^a TDF/FTC + RAL			
Alternative	ABC/3TC + FPV/r, TDF/FTC + SQV/r, Ddi + 3TC + EFV, AZT/3TC + EFV, AZT/3TC + ABC, ^a AZT/3TC + ABC + TDF, ^a AZT/3TC + MVC			
2012 ^b				
Preferred	TDF/FTC + EFV, ABC/3TC + EFV, ^a TDF/FTC + NVP, TDF/FTC + ATV/r, TDF/FTC + DRV/r, TDF/FTC + LPV/r, ABC/3TC + ATV/r, ^a ABC/3TC + LPV/r, TDF/FTC + RAL			
2013 ^b				
Preferred	TDF/FTC + EFV, TDF/FTC + ATV/r, TDF/FTC + DRV/r, TDF/FTC + RAL, ABC/3TC + EFV, ^a TDF/FTC + RPV, ^a TDF/FTC + NVP, TDF/FTC + LPV/r, ABC/3TC + LPV/r, ABC/3TC + ATV/r, ^a ABC/3TC + RAL			
2014				
Preferred	TDF/FTC + EFV, TDF/FTC + RPV, ^a TDF/FTC + ATV/r, ABC/3TC + ATV/r, ^a TDF/FTC + DRV/r, ABC/3TC + DTG, TDF/FTC + DTG, TDF/FTC + EVG/c, TDF/FTC + RAL, ABC/3TC + RAL			
Alternative	ABC/3TC + EFV, ^a TDF/FTC + NVP, ABC/3TC + DRV/r, TDF/FTC + LPV/r, ABC/3TC + LPV/r			
2015				
Preferred	ABC/3TC + DTG, TDF/FTC + DTG, TDF/FTC + RAL, TDF/FTC + RPV, ^a TDF/FTC + EVG/c			
Alternative	TDF/FTC + EFV, ABC/3TC + RAL, TDF/FTC + DRV/r (o DRV/c), TDF/FTC + ATV/r (o ATV/c), ABC/3TC + ATV/r (o ATV/c) ^a			

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; ATV/r, atazanavir/ritonavir; ATV/c, atazanavir/cobicistat; ddi, didanosine; DRV/r, darunavir/ritonavir; DRV/c, darunavir/cobicistat; DTG, dolutegravir; EFV, efavirenz; EVG/c, elvitegravir/cobicistat; FOS, fosamprenavir; FPV/r, fosamprenavir/ritonavir; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; SQV/r, saquinavir/ritonavir; TDF, tenofovir.

^a Not recommended if viral load >100.000 copies/ml.

^b No recommendations for alternative treatments were issued for the years 2012 and 2013.

Additionally, the principal investigators from all participating centres were asked to respond to an electronic survey with the following open questions referred to the study period (years 2010–2015): 1. Has there been any limitation due to the cost of ART in your center or Autonomous Region?; and 2. Has there been any drug that you were not able to prescribe in your center after it was approved as a preferred treatment by the Spanish guidelines during the study period? What drug and during what period? The centres were then classified with two binary variables (yes or no): (1) limitation to the cost of ART in the centre, and (2) restricted access to at least one antiretroviral drug. This variable was considered “yes” if the centre had no access to at least one of the preferred antiretrovirals, or it had access only under restricted circumstances that required a clinical report for requesting the drug, for more than one year.

Statistical analysis

Descriptive analysis of patients' characteristics was carried out using frequency tables for categorical variables and median and interquartile range for continuous variables.

Patients who received nonrecommended treatments because they were pregnant or enrolled in a clinical trial were classified as receiving a recommended or alternative regimen.

We calculated the prevalence and its 95% confidence intervals of nonrecommended treatments, overall and according to selected covariates, either patient-related (i.e. gender, age at ART initiation, route of transmission, CD4 count and viral load at ART initiation, chronic hepatitis B and C, education, country of origin, AIDS diagnosis and year of initiation of ART) or center-related (i.e. number of beds, limitation to the cost of ART and restricted access to at least one antiretroviral drug). Multivariable logistic regression models were used to identify independent risk factors for prescribing nonrecommended treatments.

Wald tests were used to calculate p-values. All analyses were performed using a 95% confidence level. Statistical analyses were performed in Stata software (version 14.0; Stata Corporation, College Station, Texas, USA).

Ethics

All patients signed informed consent forms. The participation in the cohort was approved by the Ethics Committees of all the participating centres. The study was approved by the Ethics Committee of Instituto de Salud Carlos III (Madrid).

Results

During the study period, 5479 patients initiated ART. The clinical and demographic characteristics of the study population are shown in Table 2. Of these patients, 586 (10.7%) received a nonrecommended treatment.

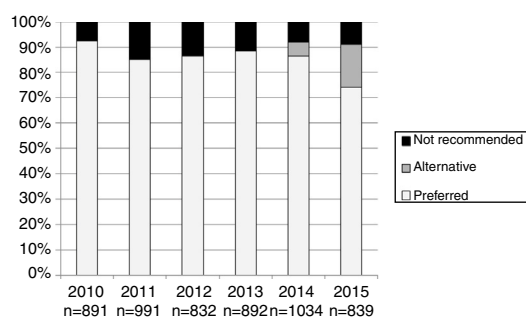
The number and proportion of patients starting ART with a preferred, alternative, and nonrecommended treatment by year of treatment initiation are shown in Fig. 1. The category “alternative treatments” was only used in the guidelines during the years 2010, 2011, 2014 and 2015. Compared to the year 2014, in 2015 there was a significant increase of alternative treatments (from 5.3% of all ART prescribed in 2014 to 17.0% in 2015) and a parallel decrease in preferred treatments (from 86.5% in 2014 to 74% in 2015: $p < 0.001$), with a similar proportion of nonrecommended treatments (8.2% and 8.9% in 2014 and 2015, respectively). The proportion of patients receiving nonrecommended treatments showed large differences among the 13 Autonomous Regions, ranging from 1% to 20.1% of all the initial regimens ($p < 0.001$).

The characteristics of the participating centres are shown in Table 3. A total of 16 centres from three Autonomous Regions reported a limitation to the cost of the prescribed ART during the study period in all the centres from each of the three regions. Four

Table 2
Clinical and demographic characteristics of the study population.

Total, n	5479
Gender	
Male	4703 (86%)
Female	776 (14%)
Age at ART initiation (years; median, IQR)	36 (30–44)
Age at ART initiation (years)	
18–29	1335 (24.4%)
30–49	3457 (63.1%)
>=50	687 (12.5%)
Year of ART initiation	
2010	891 (16.3%)
2011	991 (18.1%)
2012	832 (15.2%)
2013	892 (16.3%)
2014	1034 (18.8%)
2015	839 (15.3%)
Route of transmission	
Heterosexual	1467 (26.8%)
Men who have sex with men	3495 (63.8%)
Intravenous drug user	285 (5.2%)
Other/unknown	232 (4.2%)
CD4 count at ART initiation (cells/microl) (median, IQR)	341 (210–473)
CD4 count at ART initiation (cells/microl)	
<200	1205 (22.0%)
201–499	2875 (52.52%)
>=500	1113 (20.3%)
Unknown	286 (5.2%)
Viral load at ART initiation (log 10 copies/ml) (median, IQR)	4.8 (4.3–5.2)
Viral load at ART initiation (log 10 copies/ml)	
≤5.0	3264 (59.6%)
>5.0	1912 (34.9%)
Unknown	303 (5.5%)
Chronic hepatitis C	
No	2546 (47.0%)
Yes	437 (8.0%)
Unknown	2466 (45.0%)
Chronic hepatitis B	
No	2835 (43.5%)
Yes	125 (2.3%)
Unknown	2969 (54.2%)
Education	
University/secondary education	2785 (50.8%)
Primary/no education	1686 (30.8%)
Unknown	1008 (18.4%)
Country of origin	
Spain	3988 (72.8%)
Foreign born	1468 (26.8%)
Unknown	23 (0.4%)

Values are n (%), unless otherwise stated. IQR: interquartile range.

**Fig. 1.** Proportion of patients starting treatment with a preferred, alternative or not recommended regimen each year. *No recommendations for alternative treatments were issued for the years 2012 and 2013.**Table 3**

Characteristics of the participating centres, including limitations to cost of antiretroviral therapy (ART) and restrictions of access to antiretrovirals that were recommended by the national Spanish guidelines, 2010–2015.

	Centres (n, %)	Patients (n, %)
Total n = 37	Total n = 5479	
Number of hospital beds		
≤500	7 (18.9%)	485 (8.8%)
501–1000	18 (48.6%)	1990 (36.3%)
>1000	12 (32.4%)	3004 (54.8%)
ART cost limitation	20 (54.1)	3561 (65)
Restricted access to antiretrovirals		
Any ARV	11 (29.7)	1375 (25.1)
TDF/FTC/EVG/c	8 (21.6)	1176 (21.5)
ABC/3TC/DTG and DTG	3 (8.1)	490 (8.9)
ABC/3TC/DTG ^a	1 (2.7)	70 (1.3)
TDF/FTC/TPV and RPV	2 (5.4)	183 (3.3)
TDF/FTC/TPV ^a	1 (2.7)	33 (0.6)
TDF/FTC/EFV ^a	3 (8.1)	593 (10.8)
DRV/c and ATV/c ^b	2 (5.4)	270 (4.9)

3TC, lamivudine; ABC, abacavir; ATV/c, atazanavir/cobicistat; DRV/c, darunavir/cobicistat; DTG, dolutegravir; EFV, efavirenz; EVG/c, elvitegravir/cobicistat; FTC, emtricitabine; RPV, rilpivirine; TDF, tenofovir.

^a Restricted access to the single tablet regimen but no restrictions for the use of its separate components.

^b No restrictions for the use of darunavir or atazanavir associated with ritonavir.

additional centres from four Autonomous Regions reported cost limitations for the prescription of ART in their centre (but not in their Autonomous Region). In both cases, the cost limitation was established as a recommendation for the maximum average cost of ART per patient per year. The 20 centres with cost limitations to ART were treating 65% of the study population (Table 3). Eleven centres treating 25% of the patients reported restricted access to at least one of the recommended antiretroviral drugs during all or part of the study period; the details about the specific restrictions, and the number of centres and patients involved, are shown in Table 3.

Reasons for prescribing nonrecommended treatments included enrolment in clinical trials (254 patients, 43.3%), comorbidities and/or interactions (60 patients, 10.2%), pregnancy (51 patients, 8.7%), cost (45 patients, 7.7%), high viral load (14 patients, 2.4%), primary resistance (12 patients, 2%), other (16 patients, 2.7%) and unknown (134 patients, 22.9%). “Other” reasons included unavailability of resistance test results at ART initiation in 6 patients, availability of ART regimen in an immigrant patient’s country of origin in 6 patients, and patient’s request in 4 patients. Most pregnant women (44 patients, 86.3%) were receiving regimens that were recommended/alternative in the guidelines for pregnant women but not recommended in the general guidelines; the majority of these women (41 patients) were receiving regimens that included zidovudine.

After considering patients enrolled in clinical trials and pregnant women as receiving preferred/alternative treatments, only 281 (5.1%) patients would have received a nonrecommended treatment. The factors associated with receiving a nonrecommended treatment in multivariable analysis are shown in Table 4. Male patients, those who acquired HIV by heterosexual transmission (compared to MSM), those with viral loads ≤5log copies/ml, those who started treatment during the years 2011–2015 (compared to 2010), and those who started treatment in a center with restricted access to at least one antiretroviral drug had a significantly higher risk of receiving a nonrecommended treatment (Table 4). We found no significant association of the prescription of a nonrecommended treatment with age at treatment initiation, geographic origin, level of education, CD4 cell count at treatment initiation, number of hospital beds, or cost limitation for ART after adjusting for other risk factors.

Table 4
Factors associated with receiving a nonrecommended treatment.^a

Variable	Patients receiving nonrecommended treatment [n (%), total]	Univariable		Multivariable	
		OR (95% CI)	p	OR (95% CI)	p
<i>Gender</i>					
Male	248 (5.3%)/4703	1	0.21	1	0.011
Female	33 (4.3%)/776	0.80 (0.56–1.13)		0.58 (0.38–0.88)	
<i>Mode of transmission</i>					
MSM	159 (4.6%)/3495	1	0.09	1	<0.001
Heterosexual	84 (5.7%)/1467	1.27 (0.98–1.65)		1.60 (1.18–2.18)	
Other/unknown	38 (7.4%)/517	1.66 (1.04–2.65)		1.88 (1.29–2.74)	
<i>Viral load at ART initiation</i>					
≤5 log copies/ml	184 (5.6%)/3264	1	0.09	1	0.035
>5 log copies/ml	80 (4.2%)/1912	0.73 (0.54–0.99)		0.70 (0.53–0.92)	
Unknown	17 (5.6%)/303	1.00 (0.60–1.64)		0.95 (0.57–1.60)	
<i>Year of initiation of ART</i>					
2010	19 (2.1%)/891	1	<0.001	1	<0.001
2011	46 (4.6%)/991	2.23 (1.30–3.84)		2.32 (1.34–4.00)	
2012	62 (7.4%)/832	3.69 (2.19–6.23)		3.75 (2.22–6.34)	
2013	62 (7.0%)/892	3.42 (2.03–5.78)		3.58 (2.12–6.05)	
2014	49 (4.7%)/1034	2.28 (1.33–3.91)		2.26 (1.32–3.88)	
2015	43 (5.1%)/839	2.5 (1.43–4.29)		2.46 (1.42–4.27)	
<i>Restricted access to ARV</i>					
No	195 (4.8%)/4104	1	0.029	1	0.028
Yes	86 (6.2%)/1375	1.34 (1.03–1.74)		1.35 (1.03–1.75)	

^a After considering patients who were pregnant or who were participating in clinical trials as receiving recommended or alternative treatment.

The most frequently prescribed nonrecommended treatments were ABC+3TC+DRV/r (55 patients, 19.6% of all those receiving nonrecommended regimens), ABC+3TC+RPV (53 patients, 18.9%), and ABC+3TC+NVP (37 patients, 13.2%). The most frequent reasons for prescribing these regimens were cost (in 18.1%, 26.4%, and 51.3% of patients, respectively) and unknown (in 52.7%, 52.6%, and 35.1% of patients, respectively).

Discussion

In this multicenter Spanish cohort, we have investigated the compliance to the national guidelines for the initial ART during the years 2010 and 2015, and we have explored factors associated with the prescription of nonrecommended treatments. As found in two previous studies in Spain in earlier periods,^{10,11} the compliance to the guidelines continues to be high in our cohort, and even higher (over 95%) if we consider patients enrolled in a clinical trial and pregnant women as receiving recommended or alternative treatments. This is a much higher proportion than the one found by a recent study in the United States, which described 16–21% of patients receiving nonrecommended treatments.²⁴

Interestingly, there was a significant decrease in the prescription of preferred regimens in 2015, and a parallel increase in the alternative regimens, compared to the previous year. This was probably due to the more restrictive recommendations in 2015, when only integrase inhibitors and rilpivirine were considered preferred treatments and other regimens that had been recommended as preferred in 2014 (such as those including efavirenz or protease inhibitors) were classified as alternative. Clinicians were probably willing to continue prescribing regimens that were considered preferred until the year 2014 and with which they had extensive experience; also, regimens including efavirenz were considerably cheaper than those including integrase inhibitors or rilpivirine.²⁵

The reasons provided by the prescribing physicians showed that almost half of the patients receiving nonrecommended treatments had been enrolled in clinical trials. After considering patients enrolled in clinical trials and pregnant women as receiving preferred or alternative treatments, the main reasons for prescribing

nonrecommended treatments were comorbidities or interactions, as well as cost. We cannot exclude that a proportion of the nonrecommended treatments for which the reason for prescription was unknown could be really due to cost issues, as clinicians could be less willing to report that they made prescription decisions based on costs. More than half of the patients with nonrecommended treatments were receiving one of three regimens: ABC/3TC+DRV/r, ABC/3TC+RPV, and ABC/3TC+NVP. These regimens are cheaper than most of the preferred regimens²⁵ and were not included in the guidelines due to insufficient evidence to support their efficacy as initial ART.³ According to the prescribing physicians, these regimens were frequently prescribed to lower the cost of ART.

It is worth noting that physicians reported prescribing nonrecommended regimens in a small subset of patients because of a “high viral load”. These patients received intensified regimens with four or five drugs between the years 2013–2015 in different centres and most were likely to have primary HIV infection. This has also been found in another French study,²⁶ and it suggests that some clinicians still feel that high viral loads in primary infection need the prescription of additional drugs associated to the recommended regimens, despite the guideline recommendations and the evidence showing that these regimens are not more effective than three-drug treatments for primary infection.²⁷

In multivariable analysis, prescription of nonrecommended treatments was significantly associated with male sex, heterosexual mode of transmission (compared to MSM), low viral loads and more recent years (compared to 2010). Prescription of recommended regimens has been found to be more frequent in patients with high viral loads in other studies,^{5,10} as clinicians are probably more likely to prescribe treatments which have demonstrated high efficacy to this group of patients. MSM were more likely to receive recommended treatments than heterosexual patients; this could be partly explained because MSM frequently have more access to information about HIV and could have more knowledge about new treatments than other patients.²⁸

Due to restrictions in healthcare resources, the cost of ART has been limited in Spain by different means such as establishing a limit for the average annual cost for ART or restricting the prescription

of certain antiretroviral drugs. To our knowledge, these constraints have not been studied previously. The limitations for the cost of ART, and restrictions for the prescription of certain antiretrovirals, affect a high proportion of patients (65% and 25%, respectively) and are unequally distributed across different centres and Autonomous Regions. This raises concern about inequalities in the access to ART, which may be dependent on the patient's place of residence and reference centre in a public healthcare system that is supposed to give equal access to treatment irrespective of the patient's place of residence.²⁹

Our results suggest that the limitations for the prescription of antiretrovirals could influence the compliance to clinical guidelines, as the prescription of nonrecommended regimens was significantly higher in hospitals with restricted access to at least one antiretroviral drug. These hospitals were a heterogeneous group with restricted access to different recommended antiretrovirals, and most frequently newer integrase inhibitors which were preferred regimens during the later years of the study. However, prescription of nonrecommended regimens did not differ significantly between hospitals with and without cost limitations to ART.

The strengths of our study include a reasonably large number of patients from a multicenter, well established cohort; the recent time period that allows us to study the newer recommended regimens; the investigation of the reasons for noncompliance among the prescribing physicians (which has been previously assessed in only one study⁹); and the description of cost limitations for ART and their association with guideline compliance, which, to our knowledge, has not been previously described in Spain. The clinical and demographic characteristics of our patients are very similar to the ones of all new HIV diagnoses reported by the National HIV Surveillance System.³⁰ Our limitations include a high proportion of unknown reasons for noncompliance, and lack of information on some potential factors influencing these reasons such as physicians' experience.

Conclusions

In conclusion, our results show a high proportion of initial antiretroviral treatments that comply with national guidelines in recent years in Spain. However, some groups of patients were more likely to receive treatments that were not recommended by the guidelines, such as male patients, those who acquired HIV by heterosexual transmission, those who had low viral loads and those who were treated in hospitals with restricted access to some antiretrovirals. Although we found a high proportion of centres with limitation of the cost of ART, guideline compliance seemed to have no significant association with these cost limitations.

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Authorship

All authors were involved in the setting up of the cohort and contributed to its design. All authors were involved in data collection. ISG and IJ asked the research question presented in this paper and designed the study. IJ performed the statistical analyses. ISG wrote the first draft of the paper, which was supervised by IJ and SM. All

authors were involved in interpretation of the data and commented on interim drafts. All authors have read and approved the final draft.

Conflict of interest

All authors declare that they have no conflict of interest related to this work.

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References

1. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents; 2016.
2. [Recommendations from the GESIDA/Spanish AIDS Plan regarding antiretroviral treatment in adults with human immunodeficiency virus infection (update January 2007)]. *Enferm Infecc Microbiol Clin.* 2007;25:32–53.
3. Panel de expertos de Gesida y Plan Nacional sobre el SIDA. Documento de consenso de GeSIDA/Plan Nacional sobre el Sida respecto al tratamiento antiretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2018); 2018.
4. Holodny M, Hornberger J, Rapoport D, Robertus K, MacCurdy TE, Lopez J, et al. Relationship between antiretroviral prescribing patterns and treatment guidelines in treatment-naïve HIV-1-infected US veterans (1992–2004). *J Acquir Immune Defic Syndr.* 2007;44:20–9.
5. Cocohoba J, Wang QJ, Cox C, Gange SJ, Cohen M, Glesby M, et al. Consistency of initial antiretroviral therapy with HIV treatment guidelines in a US cohort of HIV-infected women. *J Acquir Immune Defic Syndr.* 2008;47:377–83.
6. Parikh MJ, Cheng L, Nieman LZ, Grimes RM. Medical treatment of women and adherence to HIV guidelines at an urban university-staffed public clinic. *J Womens Health (Larchmt).* 2003;12:897–902.
7. Wandeler G, Keiser O, Hirschel B, Gunthard HF, Bernasconi E, Battegay M, et al. A comparison of initial antiretroviral therapy in the Swiss HIV Cohort Study and the recommendations of the International AIDS Society-USA. *PLoS One.* 2011;6:e27903.
8. Petersen TS, Andersen SE, Gerstoft J, Thorsteinsson K, Larsen CS, Pedersen G, et al. Adherence to national guidelines for initiation of antiretroviral regimens in HIV patients: a Danish nationwide study. *Br J Clin Pharmacol.* 2011;72:116–24.
9. Brook MG, Curtis H, Johnson MA. Findings from the British HIV Association's national clinical audit of first-line antiretroviral therapy and survey of treatment practice and maternity care, 2002. *HIV Med.* 2004;5:415–20.
10. Suarez-Lozano I, Viciano P, Lacalle JR, Teira R, Lozano F, Lopez-Aldegue J, et al. The relationship between antiretroviral prescription patterns and treatment guidelines in treatment-naïve HIV-1-infected patients. *HIV Med.* 2009;10:573–9.
11. Suarez-García I, Sobrino-Vegas P, Tejada A, Viciano P, Ribas M, Iribarren J, et al. Compliance with national guidelines for HIV treatment and its association with mortality and treatment outcome: a study in a Spanish cohort. *HIV Med.* 2014;15:86–97.

12. Panel de expertos de Gesida y Plan Nacional sobre el SIDA. Documento de consenso de GeSIDA/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2017); 2017.
13. European AIDS Treatment Group. Documento de trabajo sobre el impacto de las políticas de austeridad en la respuesta al VIH/SIDA en el Estado Español; 2014.
14. Segura Benedicto A. [Cuts, austerity and health SESPAS report 2014]. *Gac Sanit.* 2014;28 Suppl. 1:7–11.
15. Soriano V, Barreiro P. [Healthcare resources restrictions and human immunodeficiency virus infection]. *Med Clin (Barc).* 2013;141:114–5.
16. Caro-Murillo AM, Castilla J, Perez-Hoyos S, Miro JM, Podzamczek D, Rubio R, et al. [Spanish cohort of naive HIV-infected patients (CoRIS): rationale, organization and initial results]. *Enferm Infecc Microbiol Clin.* 2007;25:23–31.
17. Sobrino-Vegas P, Gutierrez F, Berenguer J, Labarga P, Garcia F, Alejos-Ferreras B, et al. [The Cohort of the Spanish HIV Research Network (CoRIS) and its associated biobank; organizational issues, main findings and losses to follow-up]. *Enferm Infecc Microbiol Clin.* 2011;29:645–53.
18. [AIDS Study Group/Spanish AIDS Plan consensus document on antiretroviral therapy in adults with human immunodeficiency virus infection (updated January 2010)]. *Enferm Infecc Microbiol Clin.* 2010;28:362, e1–91.
19. [National consensus document by GESIDA/National Aids Plan on antiretroviral treatment in adults infected by the human immunodeficiency virus (January 2011 update)]. *Enferm Infecc Microbiol Clin.* 2011;29:209, e1–103.
20. [Consensus document of Gesida and Spanish Secretariat for the National Plan on AIDS (SPNS) regarding combined antiretroviral treatment in adults infected by the human immunodeficiency virus (January 2012)]. *Enferm Infecc Microbiol Clin.* 2012;30:e1–89.
21. [Consensus Statement by GeSIDA/National AIDS Plan Secretariat on antiretroviral treatment in adults infected by the human immunodeficiency virus (Updated January 2013)]. *Enferm Infecc Microbiol Clin.* 2013;31:602, e1–98.
22. [GeSIDA/National AIDS Plan: consensus document on antiretroviral therapy in adults infected by the human immunodeficiency virus (Updated January 2014)]. *Enferm Infecc Microbiol Clin.* 2014;32:446, e1–42.
23. [GESIDA/National AIDS Plan: consensus document on antiretroviral therapy in adults infected by the human immunodeficiency virus (Updated January 2015)]. *Enferm Infecc Microbiol Clin.* 2015;33:543, e1–43.
24. Tandon N, Mao J, Shprecher A, Anderson AJ, Cao F, Jiao X, et al. Compliance with clinical guidelines and adherence to antiretroviral therapy among patients living with HIV. *Current Med Res Opin.* 2018:1–9.
25. Berenguer J, Rivero A, Blasco AJ, Arribas JR, Boix V, Clotet B, et al. Costs and cost-effectiveness analysis of 2015 GESIDA/Spanish AIDS National Plan recommended guidelines for initial antiretroviral therapy in HIV-infected adults. *Enferm Infecc Microbiol Clin.* 2016;34:361–71.
26. Rouveix E, Mortier E, Beauchet A, Dupont C, Gerbe J, Daneluzzi V, et al. [Choice of initial regimen for antiretroviral-naïve HIV patients: analysis of motivation]. *Rev Med Int.* 2016;37:796–801.
27. Cheret A, Nembot G, Melard A, Lascoux C, Slama L, Mialhes P, et al. Intensive five-drug antiretroviral therapy regimen versus standard triple-drug therapy during primary HIV-1 infection (OPTIPRIM-ANRS 147): a randomised, open-label, phase 3 trial. *Lancet Infect Dis.* 2015;15:387–96.
28. Viciano P, Ocampo A, Hevia H, Palazuelos M, Ledesma F. Sociodemographic and clinical factors associated with the preference between NNRTIs and PIs for the initial treatment of HIV infection: perfiles study. *AIDS Care.* 2016;28:1321–6.
29. Hernandez-Aguado I, Santaolaya Cesteros M, Campos Esteban P. [Social inequalities in health and primary care SESPAS Report 2012]. *Gac Sanit.* 2012;26 Suppl. 1:6–13.
30. Sistema de información sobre nuevos diagnósticos de VIH. Registro nacional de casos de SIDA. Vigilancia epidemiológica del VIH y SIDA en España 2017; 2018. Actualización 30 de junio de 2018.