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RESEARCH ARTICLE

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Transmitted drug resistance to antiretroviral drugs in Spain during the period 2019–2021

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Abstract

To evaluate the prevalence of transmitted drug resistance (TDR) to nucleoside and nonnucleoside reverse transcriptase inhibitors (NRTI, NNRTI), protease inhibitors (PI), and integrase strand transfer inhibitors (INSTI) in Spain during the period 2019–2021, as well as to evaluate transmitted clinically relevant resistance (TCRR) to antiretroviral drugs. Reverse transcriptase (RT), protease (Pro), and Integrase (IN) sequences from 1824 PLWH (people living with HIV) were studied. To evaluate TDR we investigated the prevalence of surveillance drug resistance mutations (SDRM). To evaluate TCRR (any resistance level ≥ 3), and for HIV subtyping we used the Stanford v.9.4.1 HIVDB Algorithm and an in-depth phylogenetic analysis. The prevalence of NRTI SDRMs was 3.8% (95% CI, 2.8%–4.6%), 6.1% (95% CI, 5.0%–7.3%) for NNRTI, 0.9% (95% CI, 0.5%–1.4%) for PI, and 0.2% (95% CI, 0.0%–0.9%) for INSTI. The prevalence of TCRR to NRTI was 2.1% (95% CI, 1.5%–2.9%), 11.8% for NNRTI, (95% CI, 10.3%–13.5%), 0.2% (95% CI, 0.1%–0.6%) for PI, and 2.5% (95% CI, 1.5%–4.1%) for INSTI. Most of the patients were infected by subtype B (79.8%), while the majority of non-Bs were CRF02_AG (*n* = 109, 6%). The prevalence of INSTI and PI resistance in Spain during the period 2019–2021 is low, while NRTI resistance is moderate, and NNRTI resistance is the highest. Our results support the use of integrase inhibitors as first-line treatment in Spain. Our findings highlight the importance of ongoing surveillance

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of TDR to antiretroviral drugs in PLWH particularly with regard to first-line antiretroviral therapy.

KEYWORDS
clinical resistance, HIV, TDR, transmission

1 | INTRODUCTION

The emergence of antiretroviral drug resistance, caused by transmitted drug resistance (TDR), has been linked to an increased risk of virological failure in first-line antiretroviral therapy. This risk is particularly high with nonnucleoside reverse transcriptase inhibitor (NNRTI)-based therapies.[1,2] The use of antiretroviral therapy to which the virus is resistant can lead to problems, such as lengthening the time it takes to achieve virological suppression and increasing the risk of developing resistance to active treatments.[3]

Given the importance of identifying TDR in advance, different clinical guidelines, such as those of the US Department of Health and Human Services, the European AIDS Clinical Society, the IAS-USA, and the Spanish AIDS Study Group (GESIDA), recommend studying transmitted resistance to reverse transcriptase (RT) inhibitors and protease inhibitors (PI) as part of the initial clinical evaluation of newly diagnosed people living with HIV (PLWH).[2]

In recent years, clinical guidelines have recommended first-line treatment with second-generation integrase inhibitors, which have a high genetic barrier and therefore make it more difficult to develop resistance.[4,5] Although the first integrase inhibitor-associated TDR were described in 2011,[3,6,7] it is worth noting that the prevalence of TDR to these remains very low despite the fact that the use of these drugs has increased.[8,9]

The Spanish cohort of HIV-infected naïve individuals (CoRIS) provides a large amount of clinical, demographic, and virological information, making it an excellent scenario for monitoring TDR to different antiretroviral drugs in Spain.[10] In this study we present data for the period 2019–2021 on the prevalence of TDR to nucleoside and nonnucleoside reverse transcriptase inhibitors (NRTI, NNRTI), PI, and integrase strand transfer inhibitors (INSTI). We have also evaluated transmitted clinically relevant resistance (TCRR) to antiretroviral drugs currently in use in Spain.

2 | PATIENTS AND METHODS

CoRIS is an open, multicenter, prospective cohort of antiretroviral-naive PLWH, >13 years of age, including both seroprevalent (patients with no evidence of seroconversion) and seroconverter (patients with a documented prior HIV-negative sample) patients. Subjects are recruited and followed up in 47 HIV units from 14 of the 17 Autonomous Communities of Spain; a total of 18 573 individuals have been included since the beginning of the cohort. Ethics approval was obtained from participating sites and a written informed consent was obtained from every patient included in the study. Detailed descriptions of the cohort have been previously published.[11–13] Sites are asked every year to provide a FASTA viral sequence, encoding the HIV protease (Pro) and RT obtained at the time of inclusion, available from routine resistance testing. Despite the fact that in Spain it is not indicated to carry out baseline resistance to INSTI, those sites where these sequences were available also provided them.

Study period for this analysis was from 2019 to 2021 and only naïve patients with availability of a FASTA sequence of medium or high quality were included. Sequencing data may be available to qualified researchers upon request.

Stanford HIV database (version 9.4.1, available at https://hivdb.stanford.edu/hivdb/by-sequences/) was used for sequence alignment, quality assessment, resistance interpretation, and rapid subtype assignment; to evaluate the prevalence of surveillance drug resistance mutations (SDRM) we used the Calibrated Population Resistance (CPR) tools (integrase and RT-Pro) available at Stanford HIV website. We defined clinically relevant resistance as a Stanford (Stanford v.9.4.1 HIVDB Algorithm) resistance level of ≥3, which includes those drugs that have a low level of resistance (level 3), intermediate resistance (level 4) and high level of resistance (level 5); categories are given by the sum of each mutation penalty score for a drug (detailed information can be obtained at https://hivdb.stanford.edu/page/release-notes/#drm.penalty.scores.and.resistance.interpretation). For a more subtype in-depth study, we performed a maximum likelihood-based phylogenetic tree of the subtypes, using the Neighbor-Joining algorithm and the Jukes and Cantor Nucleotide substitution model with the CLC Genomics Workbench tool (available at https://digitalinsights.qiagen.com/products-overview/discovery-insights-portfolio/analysis-and-visualization/qiagen-clc-genomics-workbench/).

Gender, age, country of origin, education level, transmission route, CD4 count, viral load, and HBV or HCV coinfection were recorded.

Resistance was described using prevalence, and the corresponding confidence intervals were calculated with an analytically derived variance estimator.

3 | RESULTS

Clinical, demographical, and virological characteristics of the 1824 PLWH that have been included in the study during the period 2019–2021 are shown in Table 1. Of note, most of the patients were male (80.4%), men that have sex with men (MSM) (67.5%), in the

TABLE 1 Demographic, clinical, and virological characteristics of the population included in the study.

		TDR					TCRR		
	n (%)	NNRTI	NRTI	PI	INSTI	*p*	NRTI	INSTI	*p*
Year									
2019	755 (41.7%)	41 (5.4%)	24 (3.2%)	5 (0.7%)	1 (0.1%)	ns	16 (2.1%)	9 (3.6%)	ns
2020	537 (30.4%)	41 (7.4%)	26 (4.7%)	7 (1.3%)	0		14 (2.5%)	4 (2.4%)	
2021	532 (27.7%)	29 (5.7%)	16 (3.2%)	4 (0.8%)	0		9 (1.8%)	3 (1.4%)	
Gender									
Male	1466 (80.4%)	98 (6.7%)	5 (0.3%)	11 (0.7%)	1 (0.1%)	ns	33 (2.2%)	11 (0.7%)	ns
Female	156 (8.6%)	9 (5.8%)	7 (4.5%)	2 (1.3%)	0		4 (2.6%)	2 (1.3%)	
Unknown	202 (11.1%)	ns					ns		
Age (years)									
≤25	281 (15.4%)	23 (8.2%)	10 (3.6%)	4 (1.4%)	0	ns	5 (1.8%)	2 (0.7%)	ns
26–35	641 (35.1%)	48 (7.5%)	24 (3.7%)	5 (0.8%)	1 (0.2%)		16 (2.5%)	6 (0.9%)	$p = 0.035$, NNRTIs
36–45	398 (21.8%)	18 (4.5%)	14 (3.5%)	1 (0.2%)	0		11 (2.8%)	2 (0.5%)	ns
46-55	189 (10.4%)	10 (5.3%)	10 (5.3%)	3 (1.6%)	0		4 (2.1%)	3 (1.6%)	
>55	114 (6.3%)	8 (7%)	4 (3.5%)	0	0		1 (0.9%)	0	
Unknown	201 (11.0%)	ns					ns		
Origin									
Spain	744 (40.8%)	45 (6%)	33 (4.4%)	4 (0.5%)	0	ns	17 (2.3%)	6 (0.8%)	$p = 0.012$, NNRTI; $p = 0.001$, PI
Europe (not-Spain)	157 (8.6%)	8 (5.1%)	7 (4.5%)	2 (1.3%)	0		3 (1.9%)	3 (1.9%)	ns
Africa	61 (3.3%)	6 (9.8%)	3 (4.9%)	0	0		1 (1.6%)	0	
Latin/Central America	633 (34.7%)	48 (7.6%)	19 (3%)	7 (1.1%)	1 (0.2%)		16 (2.5%)	4 (0.6%)	
Others	26 (1.4%)	0	0	0	0		0	0	
Unknown	203 (11.1%)	ns					ns		
Education level									
Nonstudies	18 (1.0%)	1 (5.5%)	1 (5.5%)	0	0	ns	0	0	ns
Primary	111 (6.1%)	13 (11.7%)	2 (1.8%)	0	0		1 (0.9%)	0	
Secondary	662 (36.3%)	46 (6.9%)	26 (3.9%)	5 (0.7%)	1 (0.1%)	$p = 0.042$, NNRTI	16 (2.4%)	5 (0.7%)	$p = 0.001$, INSTI

(Continues)

TABLE 1 (Continued)

		TDR					TCRR		
	n (%)	NNRTI	NRTI	PI	INSTI	*p*	NRTI	INSTI	*p*
University	500 (27.4%)	23 (4.6%)	5 (1%)	6 (1.2%)	0	ns	12 (2.4%)	4 (0.8%)	ns
Unknown	533 (29.2%)	ns					ns		
Transmission route									
PWID	10 (0.5%)	0	1 (10%)	0	0	ns	0	0	ns
MSM	1231 (67.5%)	82 (6.7%)	46 (3.7%)	10 (0.8%)	1 (0.1%)	$p = 0.001$NRTI	31 (2.5%)	9 (0.7%)	$p = 0.02$ all ARV
MSW	324 (17.8%)	21 (6.5%)	12 (3.7%)	3 (0.9%)	0	ns	4 (1.2%)	4 (1.2%)	ns
Other	9 (0.5%)	1 (11.1%)	2 (22.2%)	0	0		1 (11.1%)	0	
CD4 counts (cells/mm^3)									
<200	345 (18.9%)	19 (5.5%)	18 (5.2%)	0	1 (0.3%)	ns	7 (2%)	6 (1.7%)	ns
200–350	400 (21.9%)	26 (6.5%)	6 (1.5%)	2 (0.5%)	0		3 (0.7%)	2 (0.5%)	
351–1000	842 (46.2%)	59 (7%)	37 (4.4%)	11 (1.3%)	0		26 (3.1%)	5 (0.6%)	$p = 0.034$, NRTIs; $p = 0.023$, NNRTIs; $p = 0.027$, PI
>1000	31 (1.7%)	2 (6.4%)	1 (3.2%)	0	0		1 (3.2%)	0	ns
Unknown	206 (11.3%)	ns					ns		
Viral load (copies/mL)									
<100 000	829 (14.2%)	58 (7%)	32 (3.9%)	7 (0.8%)	0	ns	18 (2.2%)	4 (0.5%)	$p = 0.004$, BIC/DTG
100 000–500 000	466 (25.5%)	31 (6.6%)	18 (3.9%)	2 (0.4%)	0		13 (2.8%)	4 (0.9%)	$p = 0.009$, PI
>500 000	270 (14.8%)	16 (5.9%)	11 (4.1%)	3 (1.1%)	1 (0.4%)		6 (2.2%)	4 (1.5%)	$p = 0.006$, DRV; $p = 0.02$ RAL
Unknown	259 (14.2%)	ns					ns		
Viral subtype									
B	1455 (79.8%)	92 (6.3%)	60 (4.1%)	13 (0.9%)	1 (0.1%)	ns	35 (2.4%)	11 (0.7%)	$p = 0.001$ NRTI/NNRTI
CRF02_AG	109 (6.0%)	5 (4.6%)	0	1 (0.9%)	0		0	4 (3.7%)	ns
C	46 (2.5%)	3 (6.5%)	1 (2.2%)	1 (2.2%)	0		1 (2.2%)	0	
A	50 (2.8%)	0	5 (10%)	1 (2%)	0		0	0	
F	66 (3,6%)	2 (3%)	4 (6.1%)	0	0		1 (1.5%)	0	
Others	97 (5.3%)	4 (4.1%)	2 (2.1%)	0	0		2 (2.1%)	1 (1%)	

TABLE 1 (Continued)

		TDR					TCRR		
	n (%)	NNRTI	NRTI	PI	INSTI	*p*	NRTI	INSTI	*p*
HBV coinfection									
No	1220 (66.9%)	81 (6.6%)	44 (3.6%)	9 (0.7%)	1 (0.1%)	ns	28 (2.3%)	10 (0.8%)	$p = 0.003$, INSTI
Yes	34 (1.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	0		0	0	$p = 0.04$, EFV
Unknown	570 (31.3%)	ns					ns		
HCV coinfection									
Yes	38 (2.1%)	0	2 (5.3%)	1 (2.6%)	0	ns	1 (2.6%)	0	ns
No	1474 (80.8%)	99 (6.7%)	56 (3.8%)	10 (0.7%)	1 (0.1%)		35 (2.4%)	11 (0.7%)	$p = 0.017$ all ARV
Unknown	312 (17.1%)	ns					ns		

Note: Association with transmitted drug resistance (TDR) and/or transmitted clinically relevant resistance (TCRR).

Abbreviations: ARV, antiretroviral; BIC/DTG, bictegravir/dolutegravir; DRV, darunavir; EFV, efavirenz; HBV, hepatitis B virus; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; MSW; men who have sex with women; NNRTI, nonnucleosid reverse transcripase inhibitor; NRTI, nucleosid reverse transcripase inhibitors; PI, protease inhibitor; PWID, person who inject drug; RAL, raltegravir.

TABLE 2 INSTI, NRTI, and PIs surveillance drug resistance mutations (SDRM), as defined by the Stanford CPR tool.

SDRM INSTI	*n* (%)	95% CI
E92Q	1 (0.1%)	0.0%–0.9%
Total[a]	1 (0.1%)	0.0%–0.9%
SDRM NRTI	***n* (%)**	**95% CI**
M184I/V	13 (0.7%)	0.4%–1.2%
K70E/R	1 (0.1%)	0.0%–0.3%
L74V/I	2 (0.1%)	0.0%–0.4%
T69D	2 (0.1%)	0.0%–0.4%
M41L	22 (1.2%)	0.7%–1.8%
D67E/N/G	6 (0.3%)	0.1%–0.7%
L210W	11 (0.6%)	0.3%–1.1%
T215D/S/E/C/V/F/I/Y	26 (1.4%)	0.9%–2.1%
K219E/Q/N/R	12 (0.7%)	0.3%–1.1%
Total[a]	67 (3.8%)	2.8%–4.6%
SDRM NNRTI	***n* (%)**	**95% CI**
L100I	1 (0.1%)	0.0%–0.3%
K101E/P	14 (0.8%)	0.4%–1.3%
K103N/S	90 (4.9%)	3.9%–6.1%
V179F	2 (0.1%)	0.0%–0.4%
Y181C/I/V	2 (0.1%)	0.0%–0.4%
Y188C/H/L	6 (0.3%)	0.1%–0.7%
G190A/E/S	13 (0.7%)	0.4%–1.2%
P225H	5 (0.3%)	0.1%–0.6%
Total[a]	111 (6.1%)	5.0%–7.3%
SDRM PIs	***n* (%)**	**95% CI**
M46I/L	11 (0.6%)	0.3%–1.1%
I47A/V	2 (0.1%)	0.0%–0.4%
D30N	1 (0.1%)	0.0%–0.3%
V82A/C/F/L/M/S/T	1 (0.1%)	0.0%–0.3%
L90M	1 (0.1%)	0.0%–0.3%
Total[a]	16 (0.9%)	0.5%–1.4%

Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Totals are expressed as the number of patients with TDR to the ARV class.

range of 26–35 years of age (35.1%), and originating from Spain (40.8%). Late diagnosis (CD4 cell count <350) and viral load (VL) > 100 000 copies/mL were frequent (46.2% and 40.3%, respectively), and most of the patients were infected by subtype B [79.8% (95% CI, 75.7%–83.9%)]. As for the distribution of non-B subtypes, the majority were CRF02_AG [*n* = 109, 6% (95% CI, 4.9%–7.2%)],

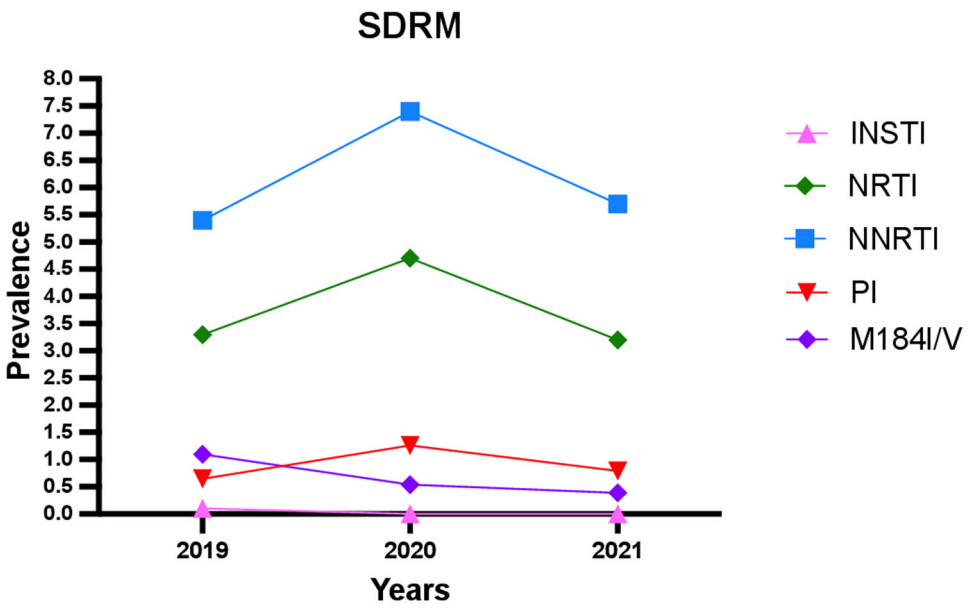

FIGURE 1 Prevalence of INSTI, NRTI, NNRTI, and PI SDRMs and M184i/V during the 2019–2021 period. INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SDRM, surveillance drug resistance mutation.

followed by F (3.7%, [95% CI 2.8%–4.6%)], A [2.8%, 95% CI 2%–3.6%)], C [2.5%, 95% CI 1.8%–3.4%)], and others [5.3%, 95% CI 4.3%–6.5%)]. As for the subtypes obtained by phylogeny, it should be noted that 10 A1 subtypes [0.55%, 95% CI 0.26%–1%)] and 18 A6 subtypes [0.98%, 95% CI 0.6%–1.5%)] were obtained; one of the A6 subtypes was classified as B and the remaining 17 A6 subtypes were classified as subtype A by Stanford rapid subtyping tool. Only a few patients were coinfected by hepatitis B virus (1.9%) or hepatitis C virus (2.1%). Recruitment through the different calendar time periods of sequences with RT/Pro and Integrase (IN) respectively was: 2019, $n = 762$ and $n = 250$; 2020, $n = 554$, and $n = 167$; 2021, $n = 505$ and $n = 212$.

The prevalence of NRTI SDRMs was 3.8% (95% CI, 2.8%–4.6%) (M184IV $n = 13$, 0.7%; L74V/I $n = 2$, 0.1%; T69D $n = 2$, 0.1%; T215 D/S/E/C/V/Y/F/I $n = 26$, 1.5%; any TAMS $n = 49$, 2.68%); Of note, NRTI singleton mutations were present in 52 PLWH (2.8%, 95% CI, 2.1%–3.7%). The prevalence of NNRTI-SDRMs was 6.1% (95% CI, 5.0%–7.3%) (K103N/S $n = 90$, 4.9%; K101 E/P $n = 14$, 0.8%; G190 A/E/S $n = 13$ (0.7%); Y188 C/H/L $n = 6$ (0.32%); P225H $n = 5$ (0.3%). In the PI, the prevalence among the group was 0.9% (95% CI, 0.5%–1.4%) (M46 I/L $n = 11$, 0.7%; I47 A/V $n = 2$, 0.1%). Finally, the prevalence of INSTI SDRMs was 0.2% (95% CI, 0.0%–0.9%) (E92Q $n = 1$, 0.1%). These data, along with a detailed description of TAMS, are shown in Table 2. As seen in Figure 1, the prevalence of NRTI, NNRTI, IP, and INSTI SDRMs was not significantly different across the 3-year study period; interestingly, the prevalence of M184V/I remained stable from 2019 ($n = 8$, 1.1%) to 2021 ($n = 2$, 0.4%).

As shown in Table 3, TCRR, was 2.1% (95% CI, 1.5%–2.9%) to the components of the NRTI backbones (1.4% to tenofovir/TAF resistance (1.2% intermediate resistance); 2.1% to abacavir-0.3% fully resistant-; 0.8% to lamivudine/emtricitabine). The highest prevalence, 11.8%, was for NNRTIs (95% CI 10.3%–13.5%): 6.57% to efavirenz, 7.2% to rilpivirine and 2.6% to doravirine). For INSTI, it was 2.5% (95% CI, 1.5%–4.1%) (0.2% to dolutegravir and bictegravir; 2.4% to raltegravir). Finally, for the PIs, the prevalence was the lowest, 0.2% (95% CI 0.1%–0.6%), being 0.2% to lopinavir and 0.1% to atazanavir and darunavir. Again, as shown in Figure 2, the prevalence of NRTI, NNRTI, INSTI, and PI TCRR remained stable and was not significantly different from 2019 (INSTI, $n = 9$, 3.6%; NRTI, $n = 16$, 2.1%; NNRTI, $n = 78$, 10.2% and PI, $n = 13$, 1.7%) to 2021 (INSTI, $n = 3$, 1.4%; NRTI, $n = 9$, 1.8%; NNRTI, $n = 67$, 13.3% and PI, $n = 1$, 0.2%), being 2.4% ($n = 4$) for INSTI, 2.5% ($n = 14$) for NRTI, 12.6% ($n = 70$) for NNRTI and 0.7% ($n = 4$) for PI in 2020.

Finally, we sought for any of the demographic, clinical, and virological variables available related to NRTI, NNRTI, PI or INSTI, SDRM, or TCRR to first-line drugs in these classes. As shown in Table 1, for NRTI, MSM had a higher risk for presenting with NRTI SDRM (3% $p = 0.011$), and having a CD4 count of 351–1000 was associated ($p = 0.034$) with a higher risk of showing TCRR; for NNRTI, PLWH with secondary studies had a higher risk for NNRTI SDRMs (3.7%, $p = 0.042$%), and being a man between 26 and 35 years old ($p = 0.035$), of Spanish nationality ($p = 0.012$), having a CD4 count of 351–1000 ($p = 0.023$) and being infected with HBV (hepatitis B virus) (efavirenz, $p = 0.041$) were associated with higher TCRR; for PIs, being Spaniard ($p = 0.001$), presenting with a CD4 count of 351–1000 ($p = 0.027$), or with a VL 100 000–500 000 [$p = 0.009$, (>500 000 for darunavir, $p = 0.006$)] is associated to TCRR; PLWH with high school education ($p = 0.001$), with a VL < 100 000 for bictegravir and dolutegravir ($p = 0.004$) and >500 000 for raltegravir ($p = 0.002$) and no HBV coinfection ($p = 0.003$) are more likely to have TCRR to INSTI.

TABLE 3 INSTI, NRTI, NNRTI, and PI clinically relevant resistance to first-line drugs, as defined by the Stanford algorithm v9.4.1 2019–2021.

INSTI	*n* (%)	95% CI
Raltegravir	15 (2.4%)	1%–4%
Dolutegravir	1 (0.2%)	0.0%–0.9%
Bictegravir	1 (0.2%)	0.0%–0.9%
Cabotegravir	2 (0.3%)	0.0%–1.1%
Total[a]	16 (2.5%)	0.5%–1.4%
NRTI	***n* (%)**	**95% CI**
Tenofovir alafenamide	25 (1.2%)	0.9%–2.0%
Abacavir	39 (1.8%)	1.5%–2.9%
Lamivudine/Emtricitabine	15 (0.80%)	0.5%–1.4%
Total[a]	39 (2.1%)	1.5%–2.9%
NNRTI	***n* (%)**	**95% CI**
Efavirenz	120 (6.6%)	5.4%–7.8%
Rilpivirine	132 (7.2%)	6.1%–8.6%
Doravirine	48 (2.6%)	1.9%–3.5%
Total[a]	215 (11.8%)	10.3%–13.5%
PI	***n* (%)**	**95% CI**
Lopinavir	4 (0.2%)	0.1%–0.6%
Atazanavir	2 (0.1%)	0.0%–0.4%
Darunavir	1 (0.1%)	0.0%–0.3%
Total[a]	4 (0.2%)	0.1%–0.6%

Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Totals are expressed as the number of patients with TCRR to the ARV class.

PLWH that are not coinfected with HCV (hepatitis C virus) ($p = 0.017$) and MSM ($p = 0.02$) are more likely to show resistance to all ARTs (antiretrovirals); finally, being infected by a B subtype was also associated with a higher risk of having TCRR to NRTI ($p = 0.001$) and NNRTI ($p = 0.001$).

4 | DISCUSSION

The emergence of antiretroviral drug resistance, caused by TDR, has been linked to an increased risk of virological failure in first-line antiretroviral therapy. Here, we provide the most recent data on NRTI, NNRTI, PI, and INSTI TDR in Spain, and in addition of TCRR. We describe a relatively low TCRR to first-line drugs, while it remains the highest for the NNRTI. Our findings show that in Spain is unlikely that newly diagnosed PLWH have baseline resistance to drugs recommended in first-line treatment; however, we consider ongoing surveillance programs to monitor trends in TDR to antiretroviral drugs in PLWH, particularly with regard to first-line antiretroviral therapy, are necessary.

To our knowledge, this is the most updated study showing transmitted resistance to ARV in Spain.[14–22] SDRM detection, in our study, was in line with recent studies published worldwide[18,23–26] with ours again being one of the studies presenting data from a most recent calendar period. NRTI SDRM remained stable and in similar values as in our previous reports[2,10,27]; very interestingly, M184V remains transmitted in a very low proportion and most of the SDRMs are transmitted as singletons. PI and INSTI SDRM, as reported in the most recent studies keep being low (PI) to very low (INSTI). As expected, and as it is also happening globally, NNRTI-SDRM are at the highest levels of TDR, and in our opinion could be infra-estimated, as an update of SDRM for this family including specific rilpivirine and doravirine mutations may be urgently needed.[28]

In this study, as in previous papers, conducted in Europe and Spain[2,29–32] in addition to TDR, we have analyzed TCRR, which may result in a more accurate estimate for the choice of clinicians on the first-line regimen. To evaluate the clinical resistance, we used the Stanford algorithm. As shown in Table 3, we found that 15 PLWH (0.8%) showed TCRR to emtricitabine/lamivudine, 25 (1.2%) to tenofovir/TAF and 39 (1.8%) to abacavir (only 0.2% and 0.3% being fully resistant respectively). The highest prevalence of clinically relevant resistance was found for the NNRTI, with rilpivirine showing the highest levels of resistance ($n = 132$, 7.2%); rilpivirine and doravirine show a different mutational pattern for resistance, compared with efavirenz and nevirapine, which, in our opinion explains that in ours, as in other studies, the higher TCRR prevalence was found for NNRTIs (11.8%). For the PI, TCRR remains low (0.2%, $n = 4$, 2, 1 for lopinavir, atazanavir, and darunavir respectively), and even lower than the SDRM prevalence, fact that may be understood considering the high genetic barrier to resistance of PI,[33] for which it is very unlikely that only one mutation may be associated to resistance. This is also the case for the second generation INSTI, as we found that only one PLWH (0.1%) showed some level of resistance to dolutegravir and bictegravir; in contrast to INSTI SDRM prevalence (0.2%, $n = 1$), clinically relevant resistance to the first-generation INSTI raltegravir ($n = 15$; 2.4%) was higher, fact that was driven by the detection of mutations scored for resistance by the Stanford algorithm but that are not in the SDRM INSTI list.[34]

Regarding the factors that could condition higher levels of TDR or TCRR, MSMs had a higher risk for presenting with NRTI SDRM, and having a CD4 count of 351–1000 or being infected by a B subtype were associated with a higher risk of showing NRTI TCRR; PLWH with high school education ($p = 0.001$), with a VL < 100 000 were more likely to show TCRR to INSTI. However, although the levels of TDR or TCRR were higher in this population, they did not reach a prevalence that could hamper any of the conclusions regarding first-line start in Spain.

Finally, it is also interesting that no differences were found in the 3 years studied when linear trends in TDR and TCRR were investigated.

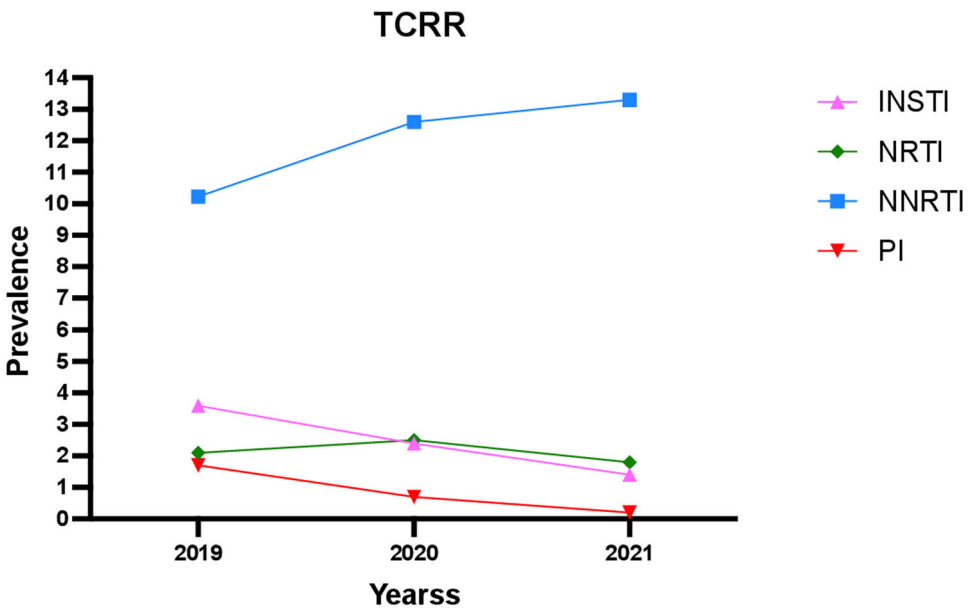

FIGURE 2 Prevalence of INSTI, NRTI, NNRTI, and PI TCRR during the 2019–2021 period. INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TCRR, transmitted clinically relevant resistance.

Within our study, we would like to highlight several limitations. First, CoRIS is an open cohort of PLWH in Spain in which different centers of the autonomous communities of Spain participate but during the COVID pandemic it was very difficult for all centers to continue with the usual care routine, and therefore the number of sequences in 2020 and 2021 was lower. Second, the design of our study was heterogeneous, as we have collected data from routine resistance tests in newly diagnosed PLWH from different autonomous communities, with diverse sampling methods and representativeness in the country; however, as shown in previous studies from our group, CORIS is fully representative of the Spanish HIV epidemic.[32] Finally, a small subset of the integrase fasta sequences provided by certain participating centers were acquired using next generation sequencing assays that did not cover positions 230 and 263.

In summary, our study from 2019 to 2021 in Spain suggests minimal risk of drug-resistant viruses to recommended first-line treatments. Resistance to NRTI, PI, and INSTI is low, but higher for NNRTI. Fully resistant viruses to first-line drugs in PLWH are highly unlikely at present. Therefore, rapid treatment initiation strategies, like second-generation INSTI-based regimens, can be used without waiting for resistance testing. However, it is crucial to request and assess a baseline genotype as it aligns with clinical guidelines. Ongoing monitoring of baseline resistance as part of routine testing is essential for national surveillance programs to track TDR trends, including integrase inhibitors, and understand the HIV landscape in the country.

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Data available to investigators upon reasonable request.

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