Clinical Infectious Diseases

MAJOR ARTICLE

Transmitted drug resistance to integrase based first-line HIV antiretroviral regimens in the Mediterranean Europe

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Objective: To study the prevalence of transmitted drug resistance (TDR) to INSTIs and NRTIs, and of clinically relevant resistance (CRR), in newly-diagnosed people with HIV (PWH) naïve to antiretroviral therapy (ART) in Europe.

Methods: MeditRes HIV is a consortium that includes ART naïve PWH newly diagnosed in France, Greece, Italy, Portugal, and Spain during the years 2018-2021. Reverse transcriptase (RT) and Integrase (INSTI) sequences were provided by participating centers. To evaluate the prevalence of surveillance drug resistance mutations (SDRM) we used the CPR tools from Stanford HIV-website. To evaluate clinically relevant resistance (CRR), defined as any resistance level >= 3, we used the Stanford v.9.1HIVDB Algorithm.

Results: We included 2705 PWH, 72% men, median age of 37 (IQR, 30-48); 43.7% infected by non-B subtypes. The prevalence of INSTI-SDRMs was 0.30% (T66I, T66A, E92Q, E138T, E138K, Y143R, S147G and R263K, all n=1), and of NRTI-SDRMs was 5.77% (M184V n=23, 0.85%; M184I n=5, 0.18%; K65R/N n= 3, 0.11%; K70E n=2, 0.07%; L74V/I n=5, 0.18%; any TAMs n=118, 4.36%). INSTI-CRR was 2.33% (0.15% dolutegravir/bictegravir; 2.29% raltegravir/elvitegravir), and 1.74% to first-line NRTIs (0.89% tenofovir/tenofovir alafenamide fumarate; 1.74% abacavir; 1.07% lamivudine/emtricitabine).

Conclusions*:* We present the most recent data on TDR to integrase based first-line regimens in Europe. Given the low prevalence of CRR to second generation integrase inhibitors and to first-line NRTIs, in the years 2018-2021 it is unlikely that newly diagnosed PWH in MeditRes countries would present with baseline resistance to a first-line regimen based on second generation integrase inhibitors.

Keywords: HIV; resistance; transmission.

INTRODUCTION

Testing for transmitted drug resistance (TDR) in the reverse transcriptase (RT) and protease (Pro) in newly diagnosed people with HIV (PWH) is recommended by clinical guidelines, as a part of the initial clinical assessment [1-4]. TDR testing was shown to be beneficial in the early 2000s [5]. Use of a drug to which the virus is resistant could be detrimental in the long-term as it

prolongs the time to achieve virological suppression and increases the risk of developing resistance to active treatments [6-10].

However, changes in HIV treatment have led to first-line treatments including agents with a high barrier to resistance, such as second-generation integrase strand transfer inhibitors (INSTIs). These regimens have become preferred regimens for first-line antiretroviral therapy across the world, including INSTI-based dual therapy with dolutegravir and lamivudine. In addition, there is a growing interest on rapid initiation of first-line therapy, so real time data on the prevalence of TDR to the drugs included in these regimens is of great interest.

TDR to INSTIs was first described in 2011 [11-12]. Although there has been an increased use of this drug class, a very low prevalence of TDR to INSTIs has been documented so far [13-16]. At present, INSTI baseline resistance is not recommended by clinical guidelines, so surveillance programs offering these data in real time are needed; however, no recent calendar representative report on TDR to INSTIs in Europe has been presented. As MeditRes HIV offers a valuable source of clinical, demographic, and virological information to perform epidemiological monitoring of resistance, here we aim to study the prevalence of TDR to the INSTIs and the NRTI backbone in newly diagnosed PWH that are naïve to antiretroviral therapy (ART), throughout the period 2018-2021.

Patients and Methods

MeditRes HIV is a consortium that includes ART-naïve PWH that have been newly diagnosed in France, Greece, Italy, Portugal, and Spain during the years 2018 to 2021.

For this study, participating sites were asked to provide a FASTA viral sequence, encoding the HIV integrase and RT obtained at the time of inclusion. All naïve PWH consequently diagnosed during the study period from the participating centres, with an available sample were included. The integrase region from HIV was sequenced by different protocols used at testing sites, including Sanger sequencing or next generation sequencing (NGS) based assays; as for NGS sequences, a 20% consensus was generated and used for this study; Stanford HIV database (version 9.1, available at https://hivdb.stanford.edu/hivdb/by-sequences/) was used for sequence alignment, quality assessment, resistance interpretation and 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. To evaluate clinically relevant transmitted resistance, we used the Stanford v.9.1 HIVDB Algorithm. Information on participating centres, their geographic localization, and the sequencing method used (Sanger or NGS) is provided in Supplementary Table 1.

We followed Stanford HIV DB recommendations to re-categorize Stanford resistance interpretation into a three-level category (Resistant-R-, Susceptible-S-, Intermediate-I, https://hivdb.stanford.edu/page/release-notes/#hivalg). The following codons in the RT that are related with NRTI activity were considered as mutations of interest: 41, 65, 67, 69, 70, 74, 75,

77, 115, 116, 151, 184, 210, 215 and 219. All codons of interest for NRTIs are also considered as SDRMs by the Stanford CPR tool [17]. The following codons in the integrase were considered as mutations of interest: **66**, 74, **92**, 97, **118**, **121**, **138**, **140**, 142, **143**, 145, 146, **147**, **148**, 149, 151, 153, **155**, 157, 163, **230** and **263**. Codons that are investigated as SDRMs in the integrase by Stanford CPR tools are highlighted in bold and have been published elsewhere [18].

Gender, age, country of origin, 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. Comparisons across groups of categorical variables and linear trends over the study period were analysed using chi-square or Fisher's exact tests; a "p" value of <0.05 was considered as significant. Statistics were performed on R Studio and Graph Pad Prism V8 software.

Before entering national cohorts, ethics approval is obtained from each of the participating sites and a written informed consent obtained from PWH included in the study. In addition, for the MeditRes INSTI TDR Surveillance Programme, specific ethics approval was obtained from Hospital Universitario San Cecilio´s Ethics Committee (Internal Reference nº 2305-N-19).

RESULTS

Clinical, demographical, and virological characteristics of the 2705 PWH that have been included in the study are shown in table 1. Of note, most of them were male (72.2%), men that have sex with men (43.0%), in the range of 30-50 years of age (45.3%) and originating from Europe (47.2%). Late diagnosis (CD4 cell count <350) and viral load >100.000 copies/ml were frequent (44.9% and 44.2%, respectively), and 56.3% of PWH were infected by subtype B. Only a few PWH were coinfected by hepatitis B virus (5.7%) or hepatitis C virus (2.4%). Recruitment through the different calendar time periods was: 2018, n=952; 2019, n=933; 2020, n=594 and 2021, n=226.

Three hundred and fifty-eight integrase sequences (13%) only reached codon 170, as in some Spanish centres specially during 2018 and 2019 a next generation sequencing protocol that did not cover positions of interest 230 and 263 was used.

The prevalence of INSTI Surveillance Drug Resistance Mutations (SDRMs) was 0.30% (IC95%, 0.13-0.59%) (T66I, n=1; T66A, n=1; E92Q n=1; E138T, n=1; E138K n=1; Y143R, n=1; S147G, n=1; and R263K n=1). The prevalence of NRTI-SDRMs was 5.77% (IC95%, 4.92-6.72%) (M184V n=23, 0.85%; M184I n=5, 0.18%; K65R/N n= 3, 0.11%; K70E n=2, 0.07%; L74V/I n=5, 0.18%; any TAMS n=118, 4.36%). These data, along with a detailed description of TAMS, are shown in supplementary table 2. Of note, NRTI singleton mutations were present in 85 PWH (3.14%, IC95%, 2.52-3.87%). As seen in Figure 1, the prevalence of either INSTI nor NRTI SDRMs was not significantly different across the 4-year study period; interestingly, the

prevalence of M184V/I remained stable from 2018 (n=9, 0.95%) to 2021 (n=2, 0.88%), being 1.29% (n=12) in 2019 and 0.84% (n=5) in 2020.

Clinically relevant resistance (CRR) data are presented in table 2; CRR, defined as any resistance level for Stanford interpretation >= 3, was 2.33% (IC95%, 1.80-2.97%) for INSTIs (0.15% to dolutegravir and bictegravir; 2.29% to raltegravir and elvitegravir), and 1.74% (IC95%, 1.28-2.31%) to the components of the NRTI backbones (0.89% to tenofovir/TAF intermediate resistance; none fully resistant-; 1.74% to abacavir - 0,33% fully resistant-; 1.07% to lamivudine/emtricitabine). Again, as shown in Figure 2, the prevalence of either INSTI or NRTI clinically relevant resistance remained stable and was not significantly different from 2018 (INSTIs, n=19, 2.00%; NRTIs, n=14, 1.47%) to 2021 (INSTIs, n=4, 1.77%; NRTIs, n=4, 1.77%), being 2.79% (n=26) for INSTIs and 1.82% (n=17) for NRTIs in 2019 and 2.36% (n=14) for INSTIs and 2.02% (n=12) for NRTIs in 2020.

The higher rate in the prevalence of clinically relevant resistance to INSTIs (2.33%, n=63) than SDRMs (0.30%, n=8), was driven by the detection of mutations scored for resistance by the Stanford algorithm but that are not in the CPR SDRM INSTI list. Additional mutations in the integrase responsible for clinically relevant resistance were: H51Y (n=2), T97A (n=2, in combination with S147G or S153F), S153F (n=2), E157Q (n=3, in combination with T97A, Q95K, or E138K), and G163K/N/R/T (n=48). Additional mutations of interest in the integrase, that did not confer clinically relevant resistance were L74I (n=294), L74M (n=35), Q95K (n=1), T97A alone (n=44), G149A (n=3), E157Q alone (n=57).

Finally, a univariate analysis was performed to seek if any of the demographic, clinical and virological variables available was related to INSTI or NRTI SDRM or clinically relevant resistance to first-line drugs in these classes. Age was significantly related to NRTI SDRMs and NRTI CRR: PWH below 30 had a higher risk for NRTI SDRMs (5.95% vs 3.35% PWH aged 30-50, p=0.0103; and vs 2.69% PWH aged >50, p=0.0051) and NRTI CRR (3.15% vs 1.63% PWH aged 30-50, p=0.0327; and vs 1.11% PWH aged >50, p=0.0127). In addition, females showed significantly more INSTI SDRMs (0.85%) than males (0.20%), p=0.0263. Finally, being infected by a non-B subtype was also associated with a higher risk of carrying M184V and K219R mutations (1.27% and 1.02% vs 0.53% and 0.20%, p=0.02 and p=0.004, respectively) and with having CRR to second generation integrase inhibitors (0.34% vs 0%, p=0.02), and to lamivudine/emtricitabine (1.5% vs 0.72%, p=0.05); a detailed description of the prevalence of mutations and CRR in B and non-B infected PWH is shown in Supplementary Tables 3 and 4. For the rest of variables, no differences were observed.

DISCUSSION

Integrase inhibitors, especially second-generation drugs in the class, are currently considered as preferred first-line options for ART-naïve PWH in many countries world-wide and take part of

preferred regimes for rapid ART start. Currently, there is a gap on up-to-date information on transmitted drug resistance to INSTIs in Europe, and most of the studies providing data on TDR to the accompanying NRTI backbones may be outdated. Here, we provide the most recent data on INSTI and NRTI TDR in Europe. We describe a marginal transmission of clinically relevant resistance to first-line drugs, and a low prevalence of transmitted drug resistance in the years 2018-2021. Our results show that it is unlikely that newly diagnosed PWH in MeditRes countries would present with baseline resistance to a first-line regimen based on second generation INSTIs, and, therefore, may support rapid initiation without having the information of the resistance test if a second-generation integrase first-line regimen is started.

To our knowledge, this is the largest and updated study showing transmitted resistance to INSTIs in Europe [19-28]. In this study, as in previous papers, conducted in Spain and Europe, [29-32] in addition to transmitted drug resistance, we have analysed clinically relevant resistance, which could impact the choice of clinicians on the first-line regimen, rather than SDRMs. As singleton mutations do not compromise the activity of tenofovir/TAF, abacavir, or dolutegravir and bictegravir, a knowledge of the level of resistance rather than the mutations themselves is of upmost importance. To check for clinically relevant resistance, we used the Stanford algorithm to tailor resistance levels to the first line drugs currently recommend regimens in Europe. For the INSTIs, we found that only four of 2705 PWH (0.15%) showed mutations with some level of resistance to dolutegravir and bictegravir; in contrast, clinically relevant resistance to the first-generation INSTIs, raltegravir and elvitegravir (n=62; 2.29%), was higher, but still at low levels. We also found that 29 PWH (1.07%) showed clinically relevant resistance to emtricitabine/lamivudine, 24 (0.89%) to tenofovir/TAF (none being fully resistant) and 47 (1.74%) to abacavir (only 0.33% being fully resistant). Interestingly none of the PWH that had clinically relevant resistance to second generation INSTIs, also showed resistance to NRTIs. Also of interest is that these data were consistent upon the 4-year period studied, as no differences were found between years when linear trends were investigated.

A proper knowledge of the level of clinically relevant resistance is key for rapid start strategies, that are now been proposed as an option for ART [33-37]. Altogether, our results show that in the Mediterranean Europe at the current time it is extremely improbable that PWH may present with a fully resistant virus to more than one of the drugs used as first-line regimens. Therefore, resistance testing should not hamper rapid start strategies. Second generation INSTI based first-line ART can be initiated without needing to wait for resistance testing results. However, a baseline genotype, in order to adhere to clinical guidelines recommendations and to provide data to monitor TDR, must always be ordered and evaluated when the results are received.

As in previous studies [29-32] we have found that looking only at SDRMs shows a very different picture from clinically relevant resistance. In the case of the INSTIs, the SDRM list misses some mutations that are important for clinically relevant resistance to first generation INSTIs. In fact, in our study up to 2.03% of PWH with CRR had no SDRMs; these PWH harboured mutations such as H51Y, S153F, and G163K/N/R/T, or combinations including T97A, or E157Q. In

addition, some other mutations that we considered as mutations of interest in the integrase, based on the ANRS algorithm, a highly recognized international interpretation system (http://www.hivfrenchresistance.org), were also more prevalent.

On the contrary, for the NRTIs, the prevalence of SDRMs was higher than the prevalence of clinically relevant resistance; as in other studies [32, 38]. Here, the explanation relies on the fact that most of PWH with SDRMs presented with singletons. In fact, only 1.22 % of our study population showed more than one NRTI transmitted mutation. Of note, only 0.33% of PWH showed viruses with full resistance to ABC, and none were fully resistant to TDF/TAF.

Notably, younger PWH showed a higher prevalence of NRTI SDRMs and CRR, and females of INSTI SDRMs. If confirmed by other studies, a higher circulation of NRTI resistance in younger PWH in Europe and of INSTI SDRMs in females may indicate that, if necessary, these groups should be prioritized for resistance testing, and may also justify that special consideration should be given to NRTI resistance testing before prescription of regimens with a low genetic barrier to resistance. The higher prevalence of resistance among younger PWH may reflect more recent diagnosis that is associated with lower risk for reversal to wild-type mutations. Interestingly, we observed a significant increased prevalence of M184V, and of CRR to dolutegravir, bictegravir and lamivudine/emtricitabine for PWH infected by non-B subtypes. Although the prevalence is still very low in non-Bs, our results, if confirmed overtime and in other studies, support the need for continuous surveillance, especially in populations that may be infected by non-Bs.

Our study has some limitations. First, although MeditRes HIV aimed to collect data from PWH from France, Greece, Italy, Portugal, and Spain, COVID pandemic made it very difficult for Greece and Portugal to contribute, so our data may not be representative for other European countries than those who collected the majority of PWH (France, Italy, and Spain). Secondly, our study design was highly heterogeneous, as we have collected data from routine resistance testing in newly diagnosed PWH from participating countries, with diverse inter-country sampling methods and representativeness. Third, the COVID pandemic, as expected, made the numbers of PWH recruited decrease for the years 2020 and, especially for 2021. Finally, a minor subset of the integrase fasta sequences provided mainly by the participating centres form Spain were obtained using next generation assays that did not cover positions 230 and 263; however, for the rest of our sequences (more than 85%) we did not detect any mutation in position 230 and only one PWH with R263K.

In summary, we report that in the Mediterranean Europe by the end of 2021, the chances of being infected by a virus with any grade of resistance to an INSTI based first line regimen is very low. These findings suggest that at this moment, the evaluation of resistance data may not be an issue for rapid initiation of an INSTI first-line based regimen and can be deferred until resistance data become available. However, baseline resistance should continue to be evaluated, as a part of routine testing and national surveillance programs. These programs are needed to continuously monitor the trend in TDR to these and other antiretroviral drugs, as well as for providing the HIV

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molecular information that is needed for a correct knowledge of national HIV molecular epidemiology.

NOTES

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Ethical statement: Before entering national cohorts, ethics approval is obtained from each of the participating sites and a written informed consent obtained from every PWH included in the study. In addition, for the MeditRes INSTI TDR Surveillance Programme, specific ethics approval was obtained from Hospital Universitario San Cecilio´s Ethics Committee (Internal Reference nº 2305-N-19).

Data availability: Data available to investigators upon reasonable request.

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Table 1. Demographic, clinical, and virological characteristics of people with HIV included in the study

		n, (%)
Year	2018	952 (35.2%)
	2019	933 (34.5%)
	2020	594 (22.0%)
	2021	226 (8.3%)
Gender	Male	1952 (72.2%)
	Female	473 (17.5%)
	Transgender/Other	13 (0.5%)
	Unknown	267 (9.9%)
Age, years	<30	571 (21.1%)
	30-50	1225 (45.3%)
	>50	633 (23.4%)
	Unknown	276 (10.2%)
Origin	Europe	1278 (47.2%)
	Africa	473 (17.5%)
	Asia/Oceania	76 (2.8%)
	America (South/Central)	250 (9.2%)
	Other/unknown	628 (23.2%)
Transmission Route	PWID	35 (1.3%)
	MSM	1163 (43.0%)
	MSW	741 (27.4%)
	Other/unknown	766 (28.3%)
CD4 counts (cells/mm^3)	<200	668 (24.7%)
	200-350	546 (20.2%)
	350-1000	993 (36.7%)
	>1000	35 (1.3%)
	Unknown	463 (17.1%)
Viral Load (copies/mL)	<100.000	1096 (40.5%)
	100.000-500.000	684 (25.3%)
	>500.000	511 (18.9%)
	Unknown	414 (15.3%)
Viral subtype	B	1523 (56.3%)
	CRF02_AG	441 (16.3%)
	A	160 (5.9%)
	C	141 (5.2%)
	F	124 (4.6%)
	Others	316 (11.7%)
HBV coinfection	Yes	154 (5.7%)
	No	1926 (71.2%)
	Unknown	625 (23.1%)
HCV coinfection	Yes	65 (2.4%)
	No	2034 (75.2%)
	Unknown	606 (22.4%)

Abbreviations: PWID, Person Who Injects Drugs; MSM, Men who have sex with men; MSW, Men who have sex with women,

Table 2. INSTI and NRTI Clinically Relevant Resistance to first line drugs, as defined by the Stanford Algorithm v9.1

INSTI	**n, (%)**	**CI 95%**
Raltegravir	62 (2.29%)	1.76% to 2.93%
Elvitegravir	62 (2.29%)	1.76% to 2.93%
Dolutegravir	4 (0.15%)	0.04% to 0.38%
Bictegravir	4 (0.15%)	0.04% to 0.38%
Total	63 (2.33%)	1.80% to 2.97%
NRTI	**n, (%)**	**CI 95%**
Tenofovir alafenamide	24 (0.89%)	0.57% to 1.32%
Abacavir	47 (1.74%)	1.28% to 2.31%
Lamivudine/Emtricitabine	29 (1.07%)	0.72% to 1.53%
Total	47 (1.74%)	1.28% - 2.31%

Abbreviations: INSTI, integrase strand transfer inhibitors; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; CI, confidence interval

FIGURE LEGENDS

Figure 1. Prevalence of INSTI and NRTI Surveillance Drug Resistance Mutations across the 4-year study period

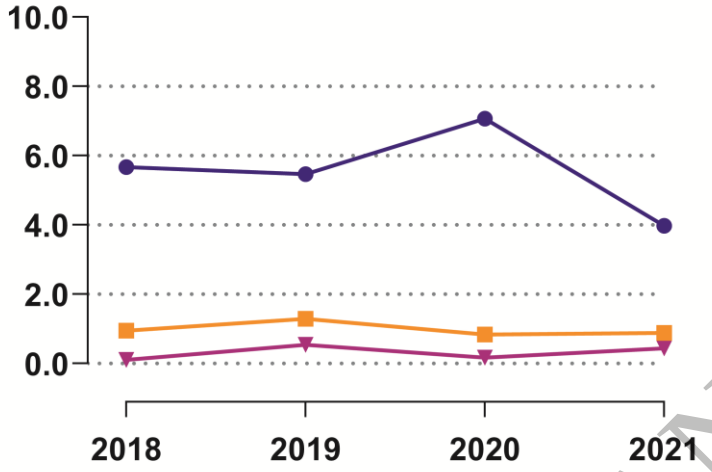
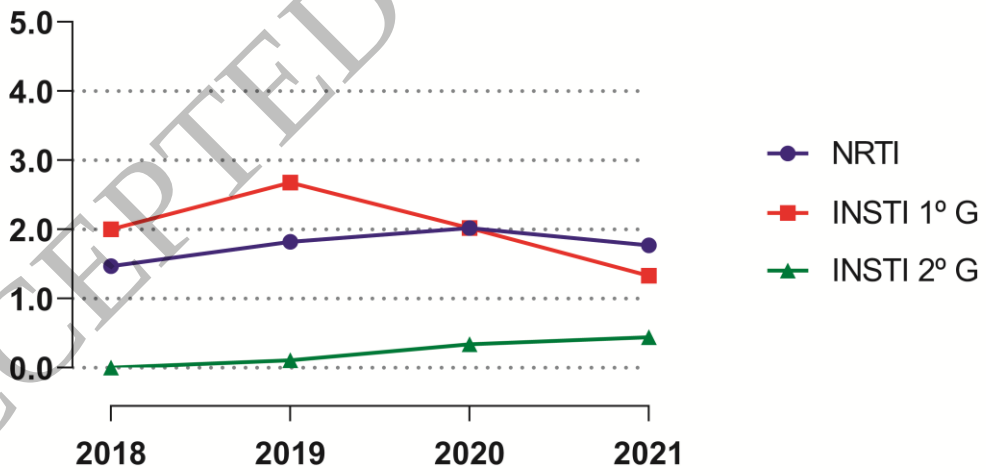


Figure 2. Prevalence of INSTI and NRTI Clinically Relevant Resistance across the 4-year study period



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