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Title

Impact of transmitted HIV-1 drug resistance on the efficacy of first-line antiretroviral therapy with two nucleos(t)ide reverse transcriptase inhibitors plus an integrase inhibitor or a protease inhibitor.

Running head: transmitted drug resistance and efficacy of first-line antiretroviral therapy

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Key words: transmitted drug resistance, HIV-1, first-line antiretroviral therapy, integrase inhibitors, protease inhibitors

Abstract

Objectives

The aim of this study was to examine the impact of transmitted drug resistance (TDR) on response to first-line regimens with integrase strand transfer inhibitors (INSTI) or boosted protease inhibitors (bPI).

Methods

From an Italian observational database (ARCA) we selected HIV-1 infected drug-naïve patients starting 2 nucleoside reverse transcriptase inhibitors (NRTI) and either an INSTI or a bPI, with available pre-ART resistance genotype. The endpoint was virological failure (VF: plasma HIV-1 RNA >200 copies/ml after week 24,). WHO surveillance drug resistance mutations and the Stanford algorithm were used to classify patients into three resistance categories: no TDR (A), TDR but fully-active ART prescribed (B), TDR and at least low-level resistance to one or more prescribed drug (C).

Results

We included 1,365 patients with a median follow-up of 96-weeks (IQR 54-110): 1,205 (88.3%) starting bPI and 160 (11.7%) INSTI. Prevalence of TDR was 6.1%, 12.5%, 0.5% and 0% for NRTI, NNRTI, bPI, and INSTI, respectively.

Cumulative Kaplan-Meier estimates for VF at 48-weeks were 11% (10.1-11.9) for the bPI- and 7.7% (5.4-10) for the INSTI-group.

In the INSTI-group, cumulative estimates for VF at 48-weeks were 6% (4-8) in resistance category A, 5% (1-10) in B and 50% (30-70) in C ($p<0.001$). Resistance category C (versus A, adjusted hazard ratio, aHR 12.6, 3.2-49.8, $p<0.001$) and nadir CD4 (+100 cells/μL, aHR 0.6, 0.4-0.9, $p=0.03$) predicted VF. In the bPI-group, VF rates were not influenced by baseline resistance.

Conclusions

Our data support the need of NRTI-resistance genotyping in patients starting an INSTI-based first-line ART.

Introduction

Transmission of drug resistant HIV-1 is a well-known phenomenon detected in around 8% of newly diagnosed individuals in Europe, with significant differences depending on viral subtype, geographic area, risk group and migration timeline.[1-3] Transmitted drug resistance (TDR) is increasing in Southern and Eastern Africa, particularly to the antiretroviral class of non-nucleoside reverse transcriptase inhibitors (NNRTI), a cornerstone of recommended first-line antiretroviral therapy (ART) in these countries.[4] TDR may significantly influence the outcome of ART,[5-7] therefore drug resistance testing is recommended for the choice of the first-line regimen in resource-rich countries.[8-11]

The risk of virological failure was increased in patients harboring pre-treatment drug resistance to at least one of the prescribed drugs in NNRTI-based regimens, as compared with individuals without pre-treatment drug resistance, but not in patients with pre-treatment drug resistance and fully active ART.[12]

International panels currently recommend first-line ART regimens including integrase strand transfer inhibitors (INSTI) or boosted protease inhibitors (bPI), because of their efficacy and tolerability.[9-11] However, in the absence of resistance testing, some authors suggest to use bPI due to their higher genetic barrier compared with INSTI.[8] Indeed, the influence of TDR on the efficacy of INSTI-based first-line regimens has not yet been established, due to the exclusion of individuals carrying TDR from clinical trials and the sparse data from observational cohorts.[5,6,13-16]

The aim of this study was to examine the impact of TDR on response to first-line regimens in naïve patients starting INSTI-based 3-drug antiretroviral therapy. As a reference, we also analyzed the impact of TDR on the efficacy of boosted PI-based regimens.

Methods

Protease, reverse transcriptase and integrase genotype sequences from treatment-naïve HIV-1 infected adults starting a first-line therapy including 2 nucleoside or nucleotide

reverse transcriptase inhibitors (NRTI) plus 1 INSTI or 2 NRTI plus 1 bPI from January 2008 to June 2016 were selected from the Antiviral Response Cohort Analysis (ARCA), an Italian multicenter virological and clinical database [http://www.dbarca.net], including cases with at least 1 plasma HIV-1 RNA value after 24 weeks of follow up. The database was approved by the local Ethics Committees and written informed consent was obtained from all patients before participation. The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki (7th revision).

Plasma genotypic resistance was determined by Sanger's population sequencing using commercially available or homebrew systems. TDR was defined as the detection of at least one mutation among those included in the WHO-recommended surveillance drug resistance mutation (SDRM) list for NRTI, NNRTI, bPI[17] and those included in the Stanford HIVdb SDRM Worksheet for INSTI [https://hivdb.stanford.edu/pages/SDRM.worksheet.INI.html]. The Stanford HIVdb algorithm (version 8.4, https://hivdb.stanford.edu) was used to classify patients into three resistance categories:[4] absence of TDR mutations (resistance category A), presence of TDR mutations but use of a fully-active ART regimen (B), or presence of TDR mutations and at least low-level resistance to at least one prescribed drug (C). HIV-1 subtyping was available as automatically performed by BLAST upon sequence upload and further analyzed by phylogenetic analysis in case of <95% homology to the pure subtype reference panel.

The primary outcome was virological failure, defined as a plasma HIV-1 RNA >200 copies/mL after week 24, ignoring treatment changes. Survival analysis, using Kaplan-Meier curves, was employed to estimate the probability of virological failure. Predictors of virological failure were investigated using Cox regression models. All analyses were performed using SPSS (version 22, IBM, Armonk, NY).

Results

A total of 1,365 patients were included, 1,205 (88.3%) treated with 2 NRTI plus 1 bPI and 160 (11.7%) treated with 2 NRTI plus 1 INSTI. Baseline patients' characteristics are shown in table 1. The main differences between the two treatment groups were a higher baseline plasma HIV-1 RNA and lower baseline and nadir CD4 cells counts in

the bPI group. Patients in the INSTI group were cared more frequently in Southern Italy and started therapy more recently. The most frequently prescribed INSTI was raltegravir (RAL) (39%), followed by dolutegravir (DTG) (35%) and elvitegravir/cobicistat (EVG/c) (26%). The most frequently used bPI was lopinavir/ritonavir (LPV/r) (41%), followed by atazanavir/ritonavir (ATV/r) (30%) and darunavir/ritonavir (DRV/r) (28%).

The overall prevalence of any TDR mutation was 18.4%, without differences between groups. NRTI, NNRTI, PI and INSTI resistance mutations were detected in 83 (6.1%), 171 (12.5%), 35 (2.6%) and 0 (0.0%) patients, respectively. While there was a similar prevalence of NRTI TDR in the two treatment groups, NNRTI TDR was more frequent in the bPI group (13.1% versus 8.1% in the INSTI group, p=0.043), whereas PI TDR was less frequent in the PI group (2.1% versus 6.3%, p=0.05).

During a median follow-up time of 96 weeks (IQR 54-110) virological failure occurred in 195 individuals in the PI-group and in 11 in the INSTI-group, with an estimated cumulative probability at 48 weeks of 11% (CI 95% 10.1-11.9) and 7.7% (CI 95% 5.4-10), respectively (p=0.01 by log-rank test).

In the INSTI group, resistance category C showed a significantly higher estimated probability of 48-week virological failure (50%, 95% CI 30-70) versus A (6%, 95% CI 4-8) and B (5%, 1-10) (p<0.001). By contrast, in the bPI group the estimated probability of virological failure at 48 weeks was similar in three categories: category A 11% (95% CI 10-12), B 12% (95% CI 10-14) and C 9% (95% CI 5-13) (p=0.390) (Fig.1). In the INSTI group, but not in the PI group, resistance category C (versus A, adjusted hazard ration, aHR 12.6, 3.2-49.8, p<0.001) and nadir CD4 (+100 cells/μL higher, aHR 0.6, 0.4-0.9, p=0.03) independently predicted virological failure. In the PI group, in a multivariable model adjusting for gender, nationality, TDF/FTC use, viral subtype, type of bPI and TDR to NRTI, independent predictors of virological failure were AZT/3TC use (aHR 2.3, CI 95% 1.4-3.9, p=0.002), calendar year (per 1 year more recent, aHR 0.9, CI 95% 0.8-0.9, p=0.04) and LPV/r use (versus DRV/r, aHR 1.4, CI 95% 1.0-2.0, p=0.03).

Eleven patients, mostly (9/11) harboring viral subtype B, experienced virological failure in the INSTI group: 8 were on treatment with RAL, 2 with DTG and 1 with EVG/c. At failure, plasma HIV-1 RNA ranged between 210 and 213,200 copies/mL and higher values were detected in patients with lower baseline CD4 counts. Three of the 11 failing INSTI carried TDR to NRTI: 2 M41L and 1 M184V, while none carried resistance to INSTI. Seven patients changed antiretroviral therapy after virological failure, with 6 patients switching to a bPI-based regimen. Among those that continued the previous regimen, 3 reached virological re-suppression at the subsequent visit and 1 was lost to follow up.

Discussion

The key finding of this study is the impact of pre-treatment HIV-1 drug resistance on the risk of virological failure in patients initiating ART with 2 NRTI plus INSTI. Despite the small number of cases, the magnitude of this effect was very relevant, with a more than 10-fold higher adjusted hazard of virological failure as compared to patients without TDR. To our knowledge, this is the first report showing a significant impact of TDR to NRTI on the activity of first-line regimens with 2 NRTI plus INSTI, the current standard of care of first-line ART. Indeed, previous observational studies on the influence of TDR did not include INSTI-based regimens and clinical trials with INSTI excluded patients with TDR.[1,2,5,13,18,19] Interestingly, in the same group, TDR not affecting the activity of the prescribed drugs did not show any impact on virological efficacy. This finding is reassuring, suggesting that even in the presence of TDR, INSTI-based first-line regimens are effective when fully active accompanying drugs are selected based on the resistance test result.

The overall prevalence of TDR in this cohort was 18.4%, higher than usually reported in European cohorts, and was primarily driven by NNRTI resistance.[1-3] This could be explained by the fact that, detection of TDRmay have advised to use high-genetic barrier bPI therapy, resulting in an overestimate of TDR in the case file. In addition, bPI-based regimens were preferentially prescribed to more challenging patients, such as those with higher baseline viral load and lower CD4 counts, possibly explaining at least in part the higher virological efficacy of INSTI-based as compared with PI-based regimens observed here. The relatively long period of observation (2008-2016) may

also explain some imbalance observed between the two treatment groups reflecting drug availability over time. In the PI-group, AZT/3TC and LPV/r use were associated to more frequent virological failure, suggesting a crucial role of their lower tolerability and efficacy.

The main limitations of this study are the retrospective nature, the small number of patients treated with INSTIs and the relatively limited sample size in the INSTI treatment groups, which did not allow a sufficient power to detect differences among drugs with different genetic barrier. Future analyses including a larger and balanced INSTI group are necessary to confirm our findings and clarify whether NRTI TDR has a different impact on virological efficacy using different types of INSTI.

In conclusion, our findings support the need of pre-treatment drug resistance testing to NRTI in order to optimize antiretroviral therapy in patients starting first-line INSTI-based regimens.

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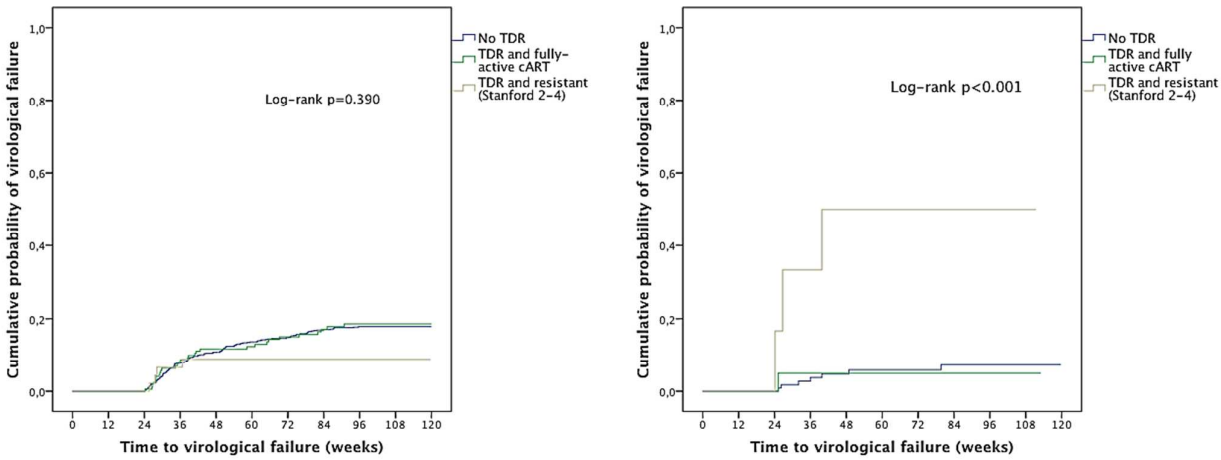
337 Fig.1 Kaplan–Meier curves showing the impact of the different pre-treatment HIV-1
338 drug resistance categopry on the virological outcome of first-line regimens based on 2
339 NRTI plus either a boosted PI (a) or an integrase inhibitor (b).
340



341
342 a. PI-group b. INSTI-group

343

Table 1. Baseline characteristics of the patient population.

Characteristics	**Overall** N= 1,365	**bPI group** N= 1,205	**INSTI group** N= 160	**P-value***
Male, n (%)	1006/1355 (73.7)	880/1196 (73.0)	126/159 (78.8)	0.30
Age (year), median (IQR)	40 (33-48)	40 (33-48)	40 (30- 48)	0.60
Italian born, n (%)	982/1365 (71.9)	882/1205 (73.2)	100/160 (62.5)	0.05
Risk factor, n (%):				<0.001
Heterosexual contacts	444 (32.5)	405 (33.6)	39 (24.4)	
MSM	272 (19.9)	245 (20.3)	27 (16.8)	
Injection drug users	109 (8.0)	101 (8.4)	8 (5.0)	
Other/Unknown	540 (39.6)	454 (37.7)	86 (53.8)	
Geographical area, n (%):				<0.001
Northern Italy	584 (42.8)	540 (44.8)	44 (27.5)	
Central Italy	522 (38.2)	465 (38.6)	57 (35.6)	
Southern Italy and Islands	259 (19.0)	200 (16.6)	59 (36.9)	
Calendar year of treatment start, median (IQR)	2011 (2009-2013)	2011 (2009-2012)	2015 (2014-2016)	<0.001
Time from HIV diagnosis (years), median (IQR)	0.3 (0.1-2.5)	0.3 (0.1-2.5)	0.5 (0.2-2.9)	0.60
Baseline plasma HIV-1 RNA (log_{10} copies/mL), median (IQR)	4.9 (4.3-5.4)	4.9 (4.4-5.4)	4.7 (4-5.2)	< 0.001
Baseline CD4 cell count (cells/mm^3), median (IQR)	258.5 (103-383)	240 (96-364)	380 (198-557)	<0.001
CD4 nadir cell count (cells/mm^3), median (IQR)	230 (95-346)	222 (89-334)	323 (167-496)	<0.001
Subtype, n (%):				
B	944 (69.2)	839 (69.6)	105 (65.6)	0.30
non B	421 (30.8)	366 (30.4)	55 (34.4)	
Backbone, n (%):				
TDF/FTC	1011 (74.1)	895 (74.3)	116 (72.5)	0.63
ABC/3TC	240 (17.6)	198 (16.4)	42 (26.2)	0.002
AZT/3TC	102 (7.5)	102 (8.5)	0 (0)	<0.001
other	12 (0.9)	10 (0.8)	2 (1.3)	0.59
Anchor drug				
DRV/r		339 (28.1)		

	LPV/r		499 (41.4)		
	ATV/r		367 (30.5)		
	RAL			63 (39.4)	
	EVG			41 (25.6)	
	DTG			56 (35.0)	
Patients with transmitted drug resistance, n (%):					
	Any class	251 (18.4)	222 (18.4)	29 (18.1)	0.514
	NRTI	83 (6.1)	74 (6.1)	9 (5.6)	0.484
	NNRTI	171 (12.5)	158 (13.1)	13 (8.1)	0.043
	PI	35 (2.6)	25 (2.1)	10 (6.3)	0.05
	INSTI	0 (0.0)	0 (0.0)	0 (0.0)	

ABC/3TC, abacavir/lamivudine; ATV/r, atazanavir/ritonavir; AZT/3TC, zidovudine/lamivudine; DRV/r, cps/mL, copies/mL; darunavir/ritonavir; DTG, dolutegravir; EVG, elvitegravir; INSTI, Integrase strand transfer inhibitors; LPV/r, lopinavir/ritonavir; MSM, man who have sex with man; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; bPI, boosted protease inhibitor; RAL, raltegravir; TDF/FTC, tenofovir/emtricitabine.