Poster 529

High prevalence of NNRTI and INI-resistant polymorphic virus in primary HIV infection

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Objective

According to the French ANRS program for HIV-1 resistance surveillance, we estimated the prevalence of transmitted drug resistance associated mutations (TDRAMs) in primary infected patients (PHI) diagnosed in France in 2014-2016.

Methods

Genotypic resistance studies were performed at the time of PHI on protease, reverse transcriptase and integrase genes. TDRAMs were sought in plasma samples from 355 patients in 2014, 381 in 2015 and 385 in 2016 (n=1121), from 46 clinical centers. Protease and reverse-transcriptase TDRAMs were identified from the 2009 Stanford Resistance Surveillance list; etravirine, rilpivirine and integrase mutations from the IAS and ANRS lists. Doravirine-associated mutations identified *in vitro* and defining DOR resistance in this study were: V106A, V106M, V108I, H221Y, F227L, F227C, F227V, M230I, L234I, P236L. The HIV envelope gene was sequenced and HIV tropism was determined using Geno2Pheno algorithm (FPR 10%). HIV-1 subtype and analysis of transmission cluster were determined after phylogenetic analysis of the RT sequence.

Univariate and multivariable logistic regressions were used to identify the factors associated with RAMs. Univariate analysis was used to determine whether continuous variables were better modeled as continuous variables or as categorical variables (tertiles), based on Akaike's information criterion (AIC). Variables with univariate p-values<0.10 were retained for the multivariable analysis.

Table 1. Population Characteristics at baseline

Men (n. %)	1009	90 %
Age, median, IQR (years)	36	[28, 45]
Risk Group (n. %)		
Homosexual	789	74%
Heterosexual	199	19%
Others or unknown	77	7%
CD4/mm3, median, IQR	479	[329, 636]
HIV-1 RNA (log_{10} copies/ml), median, IQR	5.5	[4.7, 6.4]
Subtype		
B	638	57%
Non B	483	43%

Results

RAMs to at least 1 ARV (NRTI, NNRTI, PI) were identified in 10.8% strains, 95% CI [9.0-12.8] using the Stanford 2009 list and in 18.6%, 95% CI [16.4-21.0] using both the Stanford list and the ANRS 2017 algorithm definition.

The prevalence of PI-, NRTI- first-generation NNRTI-associated RAMs was 2.9%, 95% CI [2.0-4.1], 5.0%, 95% CI [3.8-6.4] and 4.0%, 95% CI [2.9-5.3], respectively. RAMs to second-generation NNRTI (RPV and ETR) were observed in 9.4%. Overall, resistance to at least one NNRTI was 12.7%, 95% CI [10.8-14.8] .

Prevalence of sequences with at least 1 Doravirine RAMs was 0.95%, 95% CI [0.5-1.7]. INI RAMs were observed in 46/855 (5.3%, 95% CI [4.0-7.1]): L74M n=8, E92Q/G n=1, T97A n=12, E138K n=3, E157Q n=17, S230R n=2, R263K n=1. Double mutants E92Q+T97A and L74M+T97A were observed in 1 patient, respectively.

Table 2. RAMs according to the Stanford list and the ANRS algorithm 2017

At least 1 RAM using WHO list	**10.8%**
At least 1 NRTI RAM using Stanford list	5.0%
At least 1 NNRTI RAM using Stanford list	4.0%
At least 1 PI RAM using Stanford list	2.9%
At least 1 RAM using Stanford + ANRS (2017)	**18.6%**
At least 1 NNRTI RAM using Stanford list + ANRS (2017)	12.7%
At least 1 II RAM (ANRS 2017)	5.3%
At least 1 Doravirine RAM	0.9%

Figure1. Frequency of transmitted drug resistant mutations to NRTI, NNRTI, PI and INI according to the year of inclusion

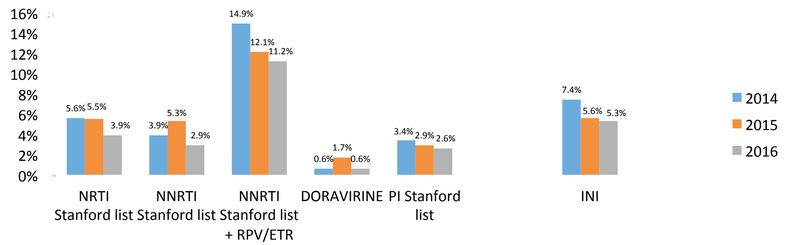
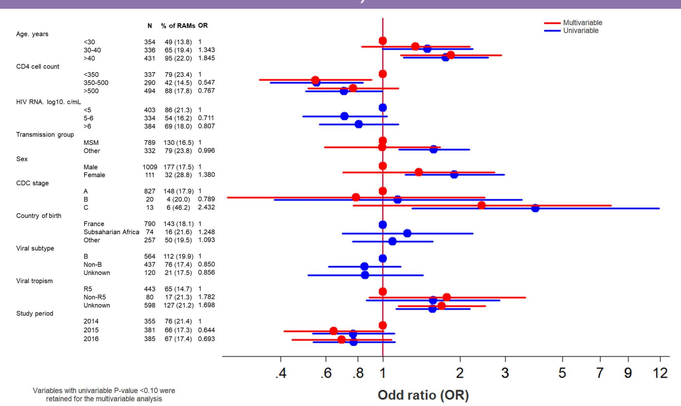


Table 3. Univariate and multivariable analysis, risk factor for RAMs (Satnford+ ANRS)



At enrolment, 80 out of 523 (15.3%) harbored a X4/DM-tropic virus.

Although subtype B still predominates in France (57%), the frequency of non-B viruses increased significantly in patients with PHI between 2014-2016 (43%) and 1996-1998 (10%).

After phylogenetic analysis, viruses from 40% of PHI cosegregated into 151 transmission chains.

In a multivariable analysis, age (>30 years) and non-R5 tropic virus were the only factors significantly associated with TDRAMs while baseline characteristics such as gender, transmission route, CD4 count, viral load, subtype and year of inclusion were not. Patients with non-R5 tropic virus and those aged of 40 years or more had a 1.8-fold increase risk of harboring virus with resistant mutations in *RT* and *PR* genes.

Conclusions

In France in the 2014/2016 period, the overall prevalence of TDRAMs was 10.8%, similarly to the previous surveys (going back to 1996 for PI, NRTI and NNRTI 1st generation). However, we describe a high level of NNRTI resistance (12.7%) including ETR and RPV (only 0.9% of resistance to doravirine) and a high prevalence of INI RAMs.

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