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HIV-1 subtype B-infected MSM may have driven the spread of transmitted resistant strains in France in 2007–12: impact on susceptibility to first-line strategies

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Background: Our study describes the prevalence of transmitted drug resistance (TDR) among 1318 French patients diagnosed at the time of primary HIV-1 infection (PHI) in 2007–12.

Methods: HIV-1 resistance-associated mutations (RAMs) were characterized using both the 2009 WHO list of mutations and the French ANRS algorithm. A genotypic susceptibility score was estimated for each first-line recommended ART combination.

Results: Patients were mainly MSM (72.6%). Non-B variants were identified in 33.7% of patients. The proportion of TDR was estimated as 11.7% (95% CI 10.0–13.5). The prevalences of PI-, NRTI-, first-generation NNRTI and etravirine/rilpivirine-associated RAMs were 2.5%, 5.2%, 3.9% and 3.2%, respectively. Single, dual and triple class resistance was found in 9.6%, 1.0% and 1.1% of cases, respectively. Additionally, 5/331 strains isolated in 2010–12 had integrase inhibitor (II)-related RAMs (isolated E157Q mutation in all cases). TDR was more common among MSM than in other groups (12.9% versus 8.6%, $P=0.034$), and in case of B versus non-B subtype infections (13.6% versus 7.9%, $P=0.002$). The proportions of fully active combinations were ≥99.2%, ≥97.3% and ≥95.3% in cases of PI-, II- and NNRTI-based regimens, respectively. In 2010–12, the proportion of fully active efavirenz-based ART was lower in cases of subtype B versus non-B infection ($P=0.021$).

Conclusions: Compared with our previous studies, the proportion of NRTI- and first-generation NNRTI-related TDR has continued to decline in French seroconverters. However, subtype B-infected MSM could drive the spread of resistant HIV strains. Finally, we suggest preferring PI- or II- to NNRTI-based combinations to treat PHI patients.

Keywords: HIV-1, resistance-associated mutations, primary HIV infection

Introduction

European studies have reported that the prevalence of HIV-1 transmitted drug resistance (TDR) ranged from 8.3% to 14%, with stable or decreasing rates of NRTI-, NNRTI- and PI-related TDR in recent years.[1–8] In most of these studies, reverse transcriptase (RT) and protease (PR) mutations were identified from the 2009 WHO consensus list for genotypic resistance surveillance of TDR.[9] This list did not include mutations conferring resistance to second-generation NNRTIs or to integrase inhibitors (IIs), which have recently taken a major place in recommended first-line combined antiretroviral therapies (cART). Indeed, few data have been published about the prevalence of rilpivirine-[10–12] and II-associated TDR.[1,13] The present work aimed to evaluate trends of TDR prevalence in patients diagnosed with primary HIV-1 infection (PHI) in France in 2007–12.

Patients and Methods

Study population

The study population comprised 1318 patients infected for less than 6 months (see enrolment criteria in Supplementary Methods, available as Supplementary data at *JAC* Online) and recruited in the PRIMO Cohort study (ANRS CO6),[14] or in the ANRS 147 Optiprim trial,[15] or through the ANRS AC11 Resistance group within the network of French virology laboratories. The study was approved by the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé and the Commission nationale de l'informatique et des libertés.

Genotypic resistance analysis

Genotypic resistance tests were performed on plasma samples collected before initiation of cART (virological methods are detailed in Supplementary Methods). HIV-1 resistance-associated mutations (RAMs) were defined using both the 2009 WHO RAMs list[9] and the French ANRS algorithm v23 (updated in September 2013; www.hivfrenchresistance.org). The ANRS algorithm includes all of the rilpivirine-, etravirine- and II-related RAMs reported in the 2013 IAS-USA resistance mutations list,[16] except for the F227C mutation (conferring resistance to rilpivirine) and the T97A mutation (conferring resistance to elvitegravir or raltegravir), which have not been studied here. The studied RAMs are listed in the Supplementary Methods. The genotypic susceptibility score (GSS) was estimated using the list of RAMs. Each drug, except ritonavir, was scored as 1 or 0 in case of 'susceptibility' or 'intermediate/high resistance', respectively, according to the ANRS interpretation algorithm. For each of the first-line recommended cART combinations in French and IAS guidelines,[17,18] the arithmetic sum of the individual scores for the specific drugs provided the total treatment-related GSS.

Phylogenetic analysis

The HIV-1 subtype was determined by phylogenetic analysis of RT sequences, as previously described.[19]

Statistics

Variables were summarized as proportions for categorical variables, the median and range for continuous variables. The χ^2 test or Fisher's exact test was used to compare categorical variables and the Mann–Whitney *U*-test was used to compare continuous variables between groups. The 95% CIs were computed using a binomial distribution. A logistic regression model was used to identify which population groups had the greatest risk of being infected with resistant viruses. Analyses were performed with IBM SPSS statistics software version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Study population

Overall, 1318 patients were included in our study (Table 1). Patients were mainly MSM (72.6%); the proportion of MSM increased significantly between 2007–09 and 2010–12. The regions of birth were different between risk groups: MSM originated from France, other European countries and sub-Saharan African countries in 82.4%, 3.1% and 1.5% of cases, respectively, versus 58.5%, 4.0% and 22.4% for heterosexuals.

HIV-1 diversity

Subtype B strains were isolated in 66.3% of patients (Table 1). The most prevalent non-B variant was CRF02_AG (17.1%). The prevalence of non-B strains increased in heterosexuals between 2007–09 and 2010–12 (47.7% versus 69.1%, $P<0.001$) and concomitantly decreased in MSM (30.7% versus 24.0%, $P=0.027$).

TDR over-represented in MSM and subtype B

RAMs were identified in 114/1318 strains (8.6%, 95% CI 7.2–10.3) using the WHO 2009 list, and in 154/1318 viruses (11.7%, 95% CI 10.0–13.5) using both the WHO list and the French ANRS 2013 algorithm (Table 1). The prevalences of PI-, NRTI-, first- and second-generation NNRTI-associated RAMs were stable between 2007–09 and 2010–12. Viruses with single, dual and triple class resistance were isolated in 127 (9.6%), 13 (1.0%) and 14 (1.1%) patients, respectively. Additionally, 5/331 (1.5%) strains, isolated in 2010–12, had II-related RAMs (E157Q mutation in all cases, without any other mutation in *RT* or *PR* genes).

Factors associated with the presence of RAMs are shown in Table 2. Compared with other transmission groups, viruses isolated in MSM more frequently harboured RAMs (12.9% versus 8.6%, $P=0.034$) and PI-associated RAMs (3.0 versus 1.1%, $P=0.048$), and tended to have more frequent NRTI-associated RAMs (6.0 versus 3.3%, $P=0.07$). Compared with non-B variants, subtype B viruses more frequently harboured RAMs (13.6% versus 7.9%, $P=0.002$), PI- and NRTI-associated RAMs (3.2 versus 1.1%, $P=0.024$ and 6.8% versus 2.3%, $P<0.001$, respectively). Viruses with dual or triple class resistance were mainly isolated in MSM (22/26, 84.6%) and in case of subtype B infection (23/26, 88.5%). Logistic regression analysis showed that MSM infected with B subtype was the group with the highest risk [OR: 2.2 (1.2–2.9)] of harbouring virus with RAMs (Table 2).

A majority of patients with TDR had singleton resistance mutations

Single RAMs were isolated in 64.8% of viruses. Fifty-six strains (35.2%) harboured several RAMs, conferring single, dual and triple class resistance in 29, 13 and 14 cases, respectively (Tables S1 and S2). Overall, the prevalence of TDR related to the most commonly prescribed PIs, NRTIs and IIs was very low: 0.1% of strains were resistant to atazanavir; 0.2% were resistant

Table 1. Demographic and biological characteristics of the patients, according to the period of their PHI

	Total (n=1318)	2007–09 (n=519)	2010–12 (n=799)	P value
Sex				**0.015**
men	1166 (85.5)	443 (85.4)	723 (90.5)	
women	147 (11.2)	73 (14.1)	74 (9.3)	
missing value	5 (0.4)	3 (0.6)	2 (0.3)	
Transmission group				**0.002**
MSM	957 (72.6)	352 (67.8)	605 (75.7)	
heterosexual	277 (21.0)	128 (24.7)	149 (18.6)	
other, unknown	84 (6.4)	39 (7.5)	45 (5.6)	
Country of birth				
France	1000 (75.9)	398 (76.7)	602 (75.3)	
other European countries	42 (3.2)	17 (3.3)	25 (3.1)	
sub-Saharan African countries	79 (5.9)	38 (7.3)	41 (5.1)	
other countries	55 (4.2)	11 (2.1)	44 (5.5)	
unknown	142 (10.8)	55 (10.6)	87 (10.9)	
CD4 count (cells/mm^3), median (range)	500 (3–2872)	509 (3–1600)	490 (6–2872)	0.507
Plasma HIV-1 RNA ($\log_{10}$ copies/mL), median (range)	5.4 (2.0–8.7)	5.4 (2.0–8.7)	5.5 (2.1–8.1)	0.795
Genetic HIV-1 subtypes				0.475
B subtype	874 (66.3)	338 (65.1)	536 (67.1)	
non-B variants	444 (33.7)	181 (34.9)	263 (32.9)	
CRF02_AG	226 (17.1)	83 (16.0)	143 (17.9)	
other group-M non-B variants	217[a] (16.5)	98 (18.9)	119 (14.9)	
group N	1 (0.1)	0	1 (0.1)	
Prevalence of RAMs, % (95% CI)				
at least one RAM	11.7 (10.0–13.5)	13.3 (10.5–16.5)	10.6 (8.6–13.0)	0.160
PI RAMs[b]	2.5 (1.7–3.5)	3.3 (1.9–5.2)	2.0 (1.1–3.2)	0.154
NRTI RAMs[b]	5.2 (4.1–6.6)	5.4 (3.6–7.7)	5.1 (3.7–6.9)	0.899
NNRTI RAMs[b]	3.9 (3.0–5.1)	3.9 (2.4–5.9)	4.0 (2.8–5.6)	1.000
RPV and ETV RAMs[c]	3.2 (2.3–4.3)	3.1 (1.8–5.0)	3.3 (2.1–4.7)	1.000
II RAMs[c]	1.5 (0.5–3.5)	NA	1.5 (0.5–3.5)	1.000

Values are n (%) unless otherwise indicated. Statistically significant P values are shown in bold. Abbreviations: CRF, circulating recombinant form; NA, data not available; RPV, rilpivirine; ETV, etravirine.
[a]Other group M non-B variants belonged to subtype C (n=32, 2.4%), subtype F (n=32, 2.4%), CRF01_AE (n=26, 2.0%), subtype A (n=22, 1.7%), subtype D (n=14, 1.1%), subtype G (n=10, 0.8%), CRF06_cpx (n=7, 0.5%), subtype H (n=3, 0.2%), CRF12_BF, CRF45_cpx (n=3, 0.3%, for each CRF), CRF11_cpx, CRF14_BG, CRF22_01A1, CRF42_BF (n=2, 0.2% for each CRF), CRF07_BC, CRF15_01B, CRF19_cpx, CRF27_cpx, CRF28_BF, CRF47_BF (n=1, 0.1%, for each CRF). Remaining viruses were unique recombinant forms (n=51, 3.9%).
[b]RAMs as defined in the WHO 2009 list of mutations for surveillance of TDR.[9]
[c]RAMs as defined in the French ANRS 2013 algorithm (http://hivfrenchresistance.org).

to lamivudine/emtricitabine; 0.2% were resistant to tenofovir; 0.3% were resistant to abacavir; 0.3% were resistant to lopinavir; 1.5% were resistant to raltegravir; 1.5% were resistant to elvitegravir; and none of them was resistant to darunavir or dolutegravir. These results contrast with the prevalence of NNRTI-related TDR: 4.1%, 4.3% and 4.3% of strains were resistant to efavirenz, nevirapine and rilpivirine, respectively.

Impact of TDR on NNRTI-first line strategies

The proportions of fully active (GSS=3) regimens were: 99.7% for tenofovir/emtricitabine/dolutegravir; 99.5% for abacavir/lamivudine/atazanavir/ritonavir, tenofovir/emtricitabine/atazanavir/ritonavir, abacavir/lamivudine/darunavir/ritonavir and tenofovir/emtricitabine/darunavir/ritonavir; 99.4% for abacavir/lamivudine/dolutegravir; 99.3% for abacavir/lamivudine/lopinavir/ritonavir; 99.2% for tenofovir/emtricitabine/lopinavir/ritonavir; 97.3% for tenofovir/emtricitabine/raltegravir, abacavir/lamivudine/raltegravir and tenofovir/emtricitabine/elvitegravir/cobicistat (considering that the E157Q polymorphic mutation may impact on susceptibility to raltegravir and elvitegravir); 95.8% for abacavir/lamivudine/efavirenz and tenofovir/emtricitabine/efavirenz; 95.6% for tenofovir/emtricitabine/nevirapine; and 95.3% for abacavir/lamivudine/rilpivirine and tenofovir/emtricitabine/rilpivirine.

The proportion of fully active combinations did not differ between transmission groups or between B versus non-B

Table 2. Univariate and multivariable logistic regression analysis of factors associated with the risk of harbouring virus with drug resistance mutations

	Presence of at least one RAM (%)			Univariate analysis		Multivariable analysis	
	no (n=1164)	yes (n=154)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Study period			0.160		0.143		0.077
2007–09	86.7	13.3		1		1	
2010–12	89.4	10.6		0.8 (0.6–1.1)		0.7 (0.5–1.0)	
Viral subtype			**0.002**		**0.002**		
non-B variant (n=444)	92.1	7.9		1			
B subtype (n=874)	86.4	13.6		1.8 (1.2–2.7)			
Gender			0.588		0.592		
female (n=147)	90.5	9.5		1			
male (n=1166)	88.1	11.9		1.3 (0.7–2.3)	0.394		
missing value (n=5)	80.0	20.0		2.4 (0.3–22.8)	0.453		
Transmission group			**0.034**		**0.033**		
others (n=361)	91.4	8.6		1			
MSM (n=957)	87.1	12.9		1.6 (1.0–2.4)			
Country of birth			0.283		0.248		
sub-Saharan Africa (n=79)	92.4	7.6		1			
other (n=1239)	88.1	11.9		1.7 (0.7–3.9)			
Transmission group and viral subtype			**0.007**		**0.008**		**0.005**
non-MSM: non-B variant (n=191)	92.7	7.3		1			
MSM: non-B variant (n=253)	91.7	8.3		1.1 (0.6–2.3)	0.707	1.1 (0.6–2.3)	
non-MSM: B subtype (n=170)	90.0	10.0		1.4 (0.7–2.9)	0.368	1.3 (0.6–2.8)	
MSM: B subtype (n=704)	85.5	14.5		2.1 (1.2–3.8)	**0.010**	2.2 (1.2–2.9)	**0.009**
CD4 count (cells/mm^3), median (range)	502 (3–2872)	490 (10–1485)	0.719	0.9 (0.7–13)	0.728		
Plasma HIV-1 RNA ($\log_{10}$ copies/mL) median (range)	5.5 (2.0–8.7)	5.3 (2.1–7.4)	0.579	0.9 (0.8–1.1)	0.211		

P values <0.05 are shown in bold.

subtypes. However, when restricting the analysis to the patients infected in 2010–12, a lower proportion of fully active efavirenz-based ART (with tenofovir/emtricitabine or abacavir/lamivudine) was observed in case of subtype B versus non-B infections (94.2% versus 98.5%, P=0.021).

Discussion

Compared with our previous reports in French seroconverters, the rate of TDR was stable (10.9% in 1996–2006 versus 11.7% in 2007–12).[19] However, because the present study was based on the 2013 ANRS algorithm, we described several RAMs that were not listed in the 2009 WHO RAMs list or in our previous reports. Indeed, the high frequency of several second-generation-NNRTI-related RAMs, especially the E138A polymorphic substitution, could impact the prevalence of TDRs in the present study. Restricting our analysis to the 2009 WHO RAMs list, we found a similar prevalence of TDR (8.6%) to that recently reported in European cART-naive patients in studies using the same list of RAMs.[2,4] However, when restricting the comparison to the data about recently infected patients, we herein describe a lower prevalence of TDR than in the UK or in Spain (11.7% in 2007–09 and 13.4% in 2010–12, respectively).[3,4]

The proportion of NRTI- and NNRTI-related TDR has been continuously decreasing in patients diagnosed with PHI in France over a decade.[19] Three factors could explain these results. First, the proportion of patients being virologically controlled on cART continues to increase over time in France [88% in 2011 (www.ccde.fr)]. Second, thymidine analogues are no longer recommended. As NRTI-related RAMs mainly consisted of thymidine analogue mutations, viruses with NRTI-related TDR are nowadays rarely transmitted.[1–4,6,7] Third, the low rate of first-generation NNRTI resistance is probably due to the widespread use of new-generation boosted PIs, which receive preferential use in France. TDR was much higher in HIV-1 subtype B-infected MSM compared with other patients, in line with previous European reports,[1,20] because most patients who acquired HIV through heterosexual contact were more likely to come from regions with limited access to cART (or to become infected through individuals originating from these regions).[20] Because subtype B-infected MSM may drive the spread of resistant HIV strains, we confirm the urgent need to increase not only the ART coverage of individuals diagnosed with HIV, which is already high in France (81% of diagnosed individuals, 76% of MSM), but also HIV testing opportunities.

To sum up, the proportion of NRTI- and first-generation NNRTI-related TDR continues to decline in French seroconverters. However, TDR seems to be more concentrated in the MSM epidemic. We suggest that preferential choice of PI- or II- over NNRTI-based combinations to treat individuals with PHI be implemented, as the risk of early failure and possible forward transmission of TDR will be reduced. Continuous monitoring of TDR should continue given the potential impact on the recommended first-line therapies. Importantly, monitoring of the prevalence of II-related RAMs will also be key, given the expanding role of these medications.

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Transparency declarations

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Supplementary data

Supplementary Methods, Tables S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Descamps D, Assoumou L, Chaix M-L *et al*. National sentinel surveillance of transmitted drug resistance in antiretroviral-naive chronically HIV-infected patients in France over a decade: 2001–2011. *J Antimicrob Chemother* 2013; **68**: 2626–31.

2 Yebra G, Delgado R, Pulido F *et al*. Different trends of transmitted HIV-1 drug resistance in Madrid, Spain, among risk groups in the last decade. *Arch Virol* 2014; **159**: 1079–87.

3 Sierra-Enguita R, Rodriguez C, Aguilera A *et al*. X4 tropic viruses are on the rise in recent HIV-1 seroconverters in Spain. *AIDS* 2014; **28**: 1603–9.

4 UK Collaborative Group on HIV Drug Resistance. Dolling D, Sabin C *et al*. Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: multicentre observational study. *BMJ* 2012; **345**: e5253.

5 Frentz D, van de Vijver D, Abecasis A *et al*. Patterns of transmitted HIV drug resistance in Europe vary by risk group. *PloS One* 2014; **9**: e94495.

6 Colafigli M, Torti C, Trecarichi EM *et al*. Evolution of transmitted HIV-1 drug resistance in HIV-1-infected patients in Italy from 2000 to 2010. *Clin Microbiol Infect* 2012; **18**: E299–304.

7 Monge S, Guillot V, Alvarez M *et al*. Analysis of transmitted drug resistance in Spain in the years 2007–2010 documents a decline in mutations to the non-nucleoside drug class. *Clin Microbiol Infect* 2012; **18**: E485–490.

8 Pineda-Peña A-C, Schrooten Y, Vinken L *et al*. Trends and predictors of transmitted drug resistance (TDR) and clusters with TDR in a local Belgian HIV-1 epidemic. *PloS One* 2014; **9**: e101738.

9 Bennett DE, Camacho RJ, Otelea D *et al*. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. *PloS One* 2009; **4**: e4724.

10 Lambert-Niclot S, Charpentier C, Storto A *et al*. Prevalence of pre-existing resistance-associated mutations to rilpivirine, emtricitabine and tenofovir in antiretroviral-naive patients infected with B and non-B subtype HIV-1 viruses. *J Antimicrob Chemother* 2013; **68**: 1237–42.

11 Parczewski M, Urbańska A, Maciejewska K *et al*. Transmitted drug resistance to rilpivirine among antiretroviral-naïve patients living with HIV from northern Poland. *J Int AIDS Soc* 2014; **17**: 18929.

12 Vingerhoets J, Rimsky L, Van Eygen V *et al*. Pre-existing mutations in the rilpivirine Phase III trials ECHO and THRIVE: prevalence and impact on virological response. *Antivir Ther* 2013; **18**: 253–6.

13 Stekler JD, McKernan J, Milne R *et al*. Lack of resistance to integrase inhibitors among antiretroviral-naive subjects with primary HIV-1 infection, 2007–2013. *Antivir Ther* 2014; doi:10.3851/IMP2780.

14 Goujard C, Bonarek M, Meyer L *et al*. CD4 cell count and HIV DNA level are independent predictors of disease progression after primary HIV type 1 infection in untreated patients. *Clin Infect Dis* 2006; **42**: 709–15.

15 Bacchus C, Cheret A, Avettand-Fenoël V *et al*. A single HIV-1 cluster and a skewed immune homeostasis drive the early spread of HIV among resting CD4+ cell subsets within one month post-infection. *PloS One* 2013; **8**: e64219.

16 Johnson VA, Calvez V, Gunthard HF *et al*. Update of the drug resistance mutations in HIV-1: March 2013. *Top Antivir Med* 2013; **21**: 6–14.

17 Groupe d'experts sous la direction du Pr Philippe Morlat et sous l'égide du CNS et de l'ANRS. Prise en charge médicale des personnes vivant avec le VIH. Actualisation 2014 du rapport 2013. Available at: http://www.sante.gouv.fr/IMG/pdf/experts-vih_actualisations2014.pdf.

18 Günthard HF, Aberg JA, Eron JJ *et al*. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. *JAMA* 2014; **312**: 410–25.

19 Chaix M-L, Descamps D, Wirden M *et al*. Stable frequency of HIV-1 transmitted drug resistance in patients at the time of primary infection over 1996–2006 in France. *AIDS* 2009; **23**: 717–24.

20 Vercauteren J, Wensing AMJ, van de Vijver DAMC *et al*. Transmission of drug-resistant HIV-1 is stabilizing in Europe. *J Infect Dis* 2009; **200**: 1503–8.