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National sentinel surveillance of transmitted drug resistance in antiretroviral-naïve chronically HIV-infected patients in France over a decade: 2001–2011

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Objectives: As recommended by the French ANRS programme for the surveillance of HIV-1 resistance, we estimated the prevalence of transmitted drug resistance-associated mutations (RAMs) in antiretroviral-naïve, chronically HIV-1-infected patients.

Methods: RAMs were sought in samples from 661 newly diagnosed HIV-1-infected patients in 2010/11 at 36 HIV clinical care centres. Weighted analyses were used to derive representative estimates of the percentage of patients with RAMs.

Results: At patient inclusion, the prevalence of virus with protease (PR) or reverse transcriptase (RT) RAMs was 9.0% (95% CI 6.8%–11.2%). No integrase RAMs were observed. The prevalences of protease inhibitor, nucleoside RT inhibitor and non-nucleoside RT inhibitor RAMs were 1.8%, 6.2% and 2.4%, respectively. Resistance to one, two and three classes of antiretroviral agent was observed in 7.9%, 0.9% and 0.2% of patients, respectively. The frequency of RAMs was higher in patients infected with B compared with non-B subtype virus (11.9% versus 5.1%, $P=0.003$). Baseline characteristics (gender, age, country of transmission, CD4 cell count and viral load) were not associated with the prevalence of transmitted RAMs. However, men having sex with men (MSM) were more frequently infected with resistant virus than were other transmission groups (12.5% versus 5.8%, $P=0.003$). Compared with the 2006/07 survey, the overall prevalence of resistance remained stable. However, a significant decrease in the frequency of virus with PR RAMs was observed in 2010/11 compared with the 2006/07 survey (1.8% versus 5.0%, $P=0.003$).

Conclusions: In France in 2010/11, the global prevalence of transmitted drug-resistant variants was 9.0%, and the prevalence was stable compared with the 2006/07 survey. MSM and B subtype-infected patients are the groups with a higher prevalence of drug resistance.

Keywords: HIV-1, resistance survey, prevalence

Table 1. Patient baseline characteristics and weighted prevalence (%) of virus with at least one PI, NRTI or NNRTI drug resistance mutation in the Odyssee 2001, 2006/07 and 2010/11 surveys

	Odyssee 2001				Odyssee 2006/07				Odyssee 2010/11			
	all patients weighted (n=363)	B subtype weighted (n=240)	non-B subtype weighted (n=119)	P value	all patients weighted (n=466)	B subtype weighted (n=273)	non-B subtype weighted (n=193)	P value	all patients weighted (n=661)	B subtype weighted (n=374)	non-B subtype weighted (n=287)	P value
Men, n (%)	248 (68.3)	187 (78.0)	56 (47.5)	<0.001	339 (72.7)	248 (90.8)	91 (47.1)	<0.001	505 (76.4)	339 (90.8)	166 (57.6)	<0.001
Age (years), median (range)	38 (19–70)	39 (19–62)	34 (20–70)	0.004	37 (19–72)	37 (19–68)	36 (20–72)	0.943	38 (18–79)	39 (18–74)	38 (19–79)	0.813
Transmission group, n (%)				<0.001				<0.001				<0.001
homosexual men	113 (31.2)	91 (37.9)	19 (16.0)		223 (47.9)	202 (74.0)	21 (10.9)		311 (47.1)	259 (69.2)	53 (18.3)	
heterosexual men and women	186 (51.2)	99 (41.3)	86 (72.3)		202 (43.3)	55 (20.1)	147 (76.2)		263 (39.7)	69 (18.5)	193 (67.3)	
other, unknown	64 (17.6)	50 (20.8)	14 (11.7)		41 (8.8)	16 (5.9)	25 (12.9)		87 (13.2)	46 (12.3)	41 (14.4)	
CDC stage C, n (%)	60 (16.6)	32 (13.3)	28 (23.5)	0.170	55 (11.8)	30 (11.0)	25 (13.0)	0.887	63 (9.5)	33 (9.0)	30 (10.3)	0.808
Patients from sub-Saharan Africa, n (%)	74 (20.4)	9 (3.7)	65 (54.6)	<0.001	112 (24.0)	7 (2.6)	105 (54.4)	<0.001	142 (21.7)	6 (1.7)	135 (48.4)	<0.001
CD4 (cells/mm ³), median (IQR)	385 (2–1280)	406 (240– 538)	277 (145– 499)	0.008	352 (2–1758)	385 (265– 550)	326 (235– 470)	0.051	391 (246–535)	396 (267–542)	390 (180– 525)	0.029
HIV-1 plasma RNA (log copies/mL), median (IQR)	4.5 (3.9–5.2)	4.5 (4.0–5.2)	4.4 (3.6–5.5)	0.993	4.5 (4.0–5.0)	4.5 (4.0–4.9)	4.4 (3.9–5.1)	0.460	4.6 (4.0–5.1)	4.5 (4.0–5.0)	4.6 (4.1–5.2)	0.022
Duration of known seropositivity (years), median (IQR)	0.56 (0.05– 2.80)				0.24 (0.04– 1.67)				0.48 (0.04–2.73)			
<6 months, n (%)	180 (49.5)	100 (41.9)	76 (63.9)	0.003	275 (59.0)	163 (59.7)	112 (58.0)	0.070	331 (50.1)	161 (43.0)	170 (59.2)	<0.001
6 months to 2 years, n (%)	82 (22.6)	54 (22.3)	28 (23.5)		86 (18.5)	59 (21.6)	27 (14.0)		126 (19.0)	80 (21.3)	46 (16.0)	
2 years to 5 years, n (%)	42 (11.6)	31 (12.9)	11 (9.2)		105 (22.5)	51 (18.7)	54 (28.0)		121 (18.3)	78 (21.0)	43 (15.0)	
>5 years, n (%)	59 (16.3)	55 (22.9)	4 (3.4)						83 (12.6)	55 (14.7)	28 (9.8)	
At least one RAM, % (95% CI)	4.2 (2.1–6.2)	4.1 (1.6–6.6)			10.8 (8.0–13.7)	11.4 (7.6– 15.1)			9.0 (6.8–11.2)	11.9 (8.7–15.2)		
PI, % (95% CI)	1.0 (0.0–2.0)	1.0 (0.0–2.2)			5.0 (3.0–6.9)	4.2 (1.8–6.6)			1.8 (0.8–2.8)	2.0 (0.6–3.4)		
NRTI, % (95% CI)	3.7 (1.8–5.6)	3.6 (1.2–6.0)			5.8 (3.7–7.9)	6.1 (3.3–9.0)			6.2 (4.4–8.1)	8.4 (5.6–11.2)		

Continued

Table 1. Continued

	Odyssee 2001				Odyssee 2006/07				Odyssee 2010/11			
	all patients weighted (n=363)	B subtype weighted (n=240)	non-B subtype weighted (n=119)	P value	all patients weighted (n=466)	B subtype weighted (n=273)	non-B subtype weighted (n=193)	P value	all patients weighted (n=661)	B subtype weighted (n=374)	non-B subtype weighted (n=287)	P value
	Subtype B HIV-1-infected patients				Subtype B HIV-1-infected patients				Subtype B HIV-1-infected patients			
	2001 versus 2006	2006 versus 2010	2001 versus 2006	2006 versus 2010								
NNRTI, % (95% CI)	0.4 (0.0-1.0)	0.3 (0.0-0.9)			2.8 (1.3-4.4)	2.4 (0.6-4.2)			2.4 (1.2-3.5)	3.6 (1.7-5.5)		
At least one RAM	P<0.001	P=0.301	P=0.003	P=0.824								
PI	P=0.001	P=0.003	P=0.023	P=0.095								
NRTI	P=0.166	P=0.764	P=0.188	P=0.287								
NNRTI	P=0.007	P=0.614	P=0.039	P=0.401								

The bottom section of the table shows a comparison of the prevalence of antiretroviral resistance mutations and PI, NRTI, and NNRTI resistance mutations in 2001 versus 2006 and 2006 versus 2010 in the total population and in patients with subtype B virus. RAM, resistance-associated mutation.

Introduction

Transmitted resistance has the potential to prevent first-line antiretroviral therapy being effective at the population level. Persons with transmitted drug resistance beginning antiretroviral therapy who had a lower genetic barrier to resistance had a higher risk of virological failure and a higher risk of developing resistance even to those drugs in their regimen that had originally been fully active.¹ The surveillance of transmitted resistance supports recommendations for resistance testing in clinical practice. Our objective was to survey the frequency of resistance mutations and the spread of non-B HIV-1 subtypes in a representative sample of antiretroviral-naive patients with chronic infection in 2010/11 (the Odyssee study) in France, as recommended by the Agence nationale de recherches sur le sida et les hépatites virales (ANRS).

Patients and methods

Study population

The study population consisted of treatment-naive, chronically HIV-1-infected patients attending clinical visits between October 2010 and March 2011 at 36 specialized AIDS centres throughout France. Up to 20 consecutive patients were enrolled at each participating virology laboratory. The results were compared with those of the previous French surveys performed in 2001 and 2006/07 using the same protocol.^{2,3} 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 analyses

Genotypic resistance studies were performed on protease, reverse transcriptase (RT) and integrase from viral plasma RNA. Protease and RT mutations were identified from the consensus statement of the list for genotypic surveillance of transmitted HIV-1 drug resistance.⁴ As no transmitted resistance surveillance list is currently available for integrase mutations, mutations were identified from the March 2013 update of the IAS-USA resistance mutations list (<http://www.ias-usa.org>). Tropism was determined on viral plasma RNA by V3-loop sequencing interpreted using the Geno2Pheno algorithm with a false positive rate of 10%.⁵

Phylogenetic analyses

The HIV-1 subtype was determined by phylogenetic analysis of RT sequences, and clusters of sequence were confirmed as previously described.³

Statistical analyses

Weighted analyses were used to derive representative estimates of the percentages of patients harbouring viruses with mutations, the weighting being based on the number of patients followed at each centre.^{6,7} The χ^2 test or Fisher's exact test was used to compare categorical variables, and univariate analysis of variance (PROC GLM in SAS with the Weight option) was used to compare continuous variables. To take into account a potential interaction between sex, transmission group and viral subtype, we created a variable combining these parameters in six categories. A logistic regression model was used to identify which population groups had the greatest risk of being infected with

resistant viruses. SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Results

Characteristics of the population

Six hundred and ninety eight chronically HIV-1-infected patients were screened. Thirty-six patients were ineligible [as they were either not treatment-naive patients ($n=29$) or were aged <18 years ($n=7$)]. The protease and RT genes were successfully sequenced in 661 of the remaining 662 patients. For integrase sequences, amplification was attempted in 561 of the 661 patients and was successful in 522 cases. The baseline characteristics of the 363, 466 and 661 patients with available genotypic results included in the Odyssey 2001, 2006/07 and 2010/11 surveys, respectively, are shown in Table 1.

Transmitted genotypic drug resistance

The overall weighted prevalence of viruses with at least one protease or RT transmitted mutation increased significantly from 2001 to 2006/07 (from 4.2% to 10.8%, $P<0.001$) and stabilized between 2006/07 and 2010/11 (from 10.8% to 9.0%, $P=0.301$) (Table 1). The weighted prevalence of protease inhibitor (PI) resistance mutations decreased to 1.8% in 2010/11 ($P=0.003$). No integrase inhibitor (INI) resistance mutations were evidenced according to the IAS-USA mutations list. Detailed transmitted drug resistance mutations for PIs, nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitor (NNRTIs) are described in Tables S1, S2 and S3, respectively (available as Supplementary data at JAC Online).

Phylogenetic analyses

From 2001 to 2010/11, the frequency of patients infected with the non-B virus subtype increased (33.1% versus 43.5%, $P=0.001$) while the proportion of CRF_02 (AG) viruses remained stable at around 20%. In 2010/11, the frequency of transmitted drug resistance mutations was higher for subtype B compared with non-B virus (11.9% versus 5.1%, $P=0.002$). Sequences from the 661 viruses revealed 46 clusters including 109 patients with a number of individuals per cluster of 2 ($n=37$), 3 ($n=6$), 4 ($n=2$)

and 9 ($n=1$). Non-B virus clusters consisted of A1 ($n=1$), D ($n=1$), G ($n=1$), CRF_01AE ($n=1$), CRF_02AG ($n=9$), CRF_33 ($n=1$), CRF_42 ($n=1$) and U ($n=1$). Twenty-nine clusters gathered individuals living in the same geographical area. The overall prevalence of viruses with an RT or protease drug resistance mutation was lower in patients belonging to a cluster than in patients not belonging to a cluster (2.1% versus 10.2%, $P=0.010$). No clusters were found in common among French patients with acute primary infection (data not shown). The corresponding figure for the most important clusters is available as Supplementary data at JAC Online (Figure S1).

Viral tropism

In 2010/11, viral tropism was determined in 429 patients. X4 and R5 viruses were evidenced in 23.2% and 76.8% of patients, respectively. The median CD4 cell count was 338 cells/mm³ (IQR 174–446) in patients with R5 versus 426 cells/mm³ (IQR 281–546) in those with X4 or dual viral tropism ($P=0.003$).

Factors associated with presence of transmitted drug resistance mutations

Patients' baseline characteristics were not associated with the prevalence of transmitted drug-resistant viruses. However, men having sex with men (MSM) were more frequently infected with resistant virus than were other transmission groups (12.5% versus 5.8%, $P=0.003$). MSM infected with B subtype was the group with the highest risk of harbouring virus with drug resistance mutations (Table 2).

Discussion

In 2010/11 the proportion of transmitted resistant variants reached 9% and was stable compared with the 2006/07 survey. A decrease in PI resistance mutations was observed. MSM infected with HIV-1 subtype B virus were the group with the highest risk of transmitted resistance mutations. The strength of our studies results from the number of participating centres, which were well distributed across the country, and the weighted statistical analyses providing representative estimates for France.

Table 2. Univariate logistic regression analysis of a factor associated with the risk of harbouring virus with drug resistance mutations

	Percentage of patients with		P value	Logistic regression analysis, OR (95% CI)	P value
	no mutation	at least one protease or RT mutation			
Transmission group and subtype and sex			0.027		0.039
female—non-B subtype	96.2	3.8		1	
male—not MSM—non-B subtype	94.5	5.5		1.6 (0.7–3.7)	
female—B subtype	93.4	6.6		1.9 (0.7–5.8)	
MSM—non-B subtype	92.5	7.5		2.2 (0.6–8.9)	
male—not MSM—B subtype	91.0	9.0		2.7 (1.1–6.5)	
MSM—B subtype	86.4	13.6		4.0 (1.5–10.8)	

Worldwide, the prevalence of transmitted drug resistance is highly variable, with rates ranging from 0% to 24%; the highest prevalence has been reported in regions with a long-standing use of antiretroviral therapy.⁸ In our study, this prevalence is similar to those described in Europe, the USA and Canada, with most recent estimates of transmitted resistance in Europe being around 10%.⁹⁻¹³

We reported a difference in prevalence between the drug classes and observed a significant decrease in PI resistance, whereas the prevalence of NRTI and NNRTI resistance remained stable. This finding, also described in the SPREAD study, is probably due to the widespread use of new-generation boosted PIs.¹³ Conversely, the parallel increase in NNRTI resistance mutations found in the SPREAD study was not observed in our own, probably due to the preferential use of PIs in France (<http://www.ccdde.fr>). The prevalence of the E138A polymorphic substitution, which is not on the surveillance list but which can decrease rilpivirine susceptibility, was 3.2% (95% CI 1.9%–4.6%) in 2010/11 (data not shown). This might affect the virological response to a first-line rilpivirine-based regimen. Studies have shown that even a modest number of NNRTI resistance mutations is associated with a higher rate of virological failure in patients receiving NNRTI-based regimens.^{1,14,15} Thus, our data reinforce the importance of testing for transmitted drug resistance in newly diagnosed HIV-infected patients before the initiation of therapy. No resistance mutations to INIs were detected, probably due to their recent introduction, but this might change in the future. The percentage of virus with X4 tropism was relatively high in our study and was probably accounted for by the proportion of patients entering medical care at a late stage of infection. The fact that X4 tropism was associated with the CD4 level reinforces this finding.

In 2010/11, the frequency of patients infected with non-B virus subtypes was stable compared with the figure in 2006. Patients were mostly women or had been diagnosed at a late stage of infection.¹⁶ CRF_02 (AG) viruses remained stable, and the spread of other subtypes was mainly due to a rising circulation of various CRF subtypes, accounting for higher diversity. In our study, the proportion of clusters was large compared with the size of the population, reflecting the fact that HIV transmission in naive chronically infected patients is high at this stage of infection.³ The largest cluster involved nine patients who were not related and lived in different geographical regions of the country, which is not the case in recent HIV infections, where clusters consist of multiple individuals.¹⁷⁻²⁰

For the first time since these studies had first been conducted in France, the frequency of transmitted drug resistance was higher in terms of a specific transmission group and HIV subtype. Indeed, MSM infected with HIV-1 subtype B were at higher risk of harbouring a virus with transmitted resistance-associated mutations, as was also found in the SPREAD study.¹³ When dealing with the major increase in newly diagnosed HIV infections among MSM, clinicians should consider the possibility of transmitted drug resistance when encountering a patient newly diagnosed with HIV infection, especially among this specific transmission group.

In France in 2011, the prevalence of transmitted drug resistance in antiretroviral-naive, chronically infected patients remained stable, with similar rates to those observed in other developed countries, where the prevalence of HIV-infected patients receiving antiretroviral therapy with a controlled viral load below 50 copies/mL has increased, being almost 90% in France in 2011 (<http://www.ccdde.fr>) and lowering the risk of resistance transmission. The risk of being infected with a resistant virus was higher for MSM, highlighting the need to re-emphasize safe sex messages to HIV-infected MSM under combination antiretroviral therapy. These data highlight the importance of genotypic resistance testing at diagnosis and/or before the initiation of treatment, and support the need to continue the surveillance of transmitted drug resistance for all classes of antiretroviral drugs worldwide.

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Transparency declarations

None to declare.

Supplementary data

Tables S1–S3 and Figure S1 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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