Poster n°582

Impact of Transmitted Drug Resistance on Susceptibility to First Line HAART in France (2010-2012)

Marie-Laure Chaix[1], Lambert Assoumou[2], Pierre Frange[1], Antoine Cheret[1], Laurence Morand-Joubert[3], Jean-Christophe Plantier[4], Marc Wirden[5], Florence Nicot[6], Diane Descamps[7] and Laurence Meyer[8] on behalf the ANRS AC-11 Resistance Group, the ANRS PRIMO Cohort Study and the OPTIPRIM-ANRS 147 Study Group.

Marie-laure.chaix@sls.aphp.fr

1-Laboratoire de Virologie, AP-HP CHU Necker-Enfants Malades, Université Paris Descartes EA 3620, PRES Sorbonne Paris Cité, Paris, 2- INSERM, UMR-S 943, UPMC Université Paris 6, Paris, 3-Laboratoire de Virologie, CHU Saint-Antoine, Paris 4- Laboratoire de Virologie, CHU Rouen, Rouen 5- Laboratoire de Virologie, CHU La Pitié Salpétrière, Paris 6- Laboratoire de Virologie, CHU Toulouse, Toulouse 7- Laboratoire de Virologie, AP-HP GHU Bichat-Claude Bernard and EA 4409 Université Paris-Diderot, Paris 7, PRES Sorbonne Paris Cité, Paris 8- INSERM, CESP U1018, Université Paris 11, Faculté de Médecine Paris-Sud, Service d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France.

OBJECTIVES

- Epidemiological surveillance of strains circulating in patients at the time of primary infection (PHI) in France has been conducted since 1996
- To survey the prevalence of transmitted drug resistance mutations (RAMs) in primary HIV-1-infected patients in 2010-2012 (PRIMO Survey) as recommended by the French ANRS program for HIV-1 resistance surveillance

PATIENTS

- Each year, our network included 5% of the estimated HIV-1 primary infection cases in France (about 6000 infections per year) and half of the diagnosed primary infection cases. Coverage is likely to be higher in the group of men who have sex with men (MSM) patients.
- Resistance mutations were sought in samples from 799 primary HIV-1-infected patients (< 6 months) in 2010-2012 in 36 HIV clinical centres (407 from the AC11 ANRS Group, 302 from the PRIMO Cohort and 90 from the OPTIPRIM trial).

METHODS

- Genotypic resistance studies were performed on protease, reverse transcriptase and integrase from viral plasma RNA by using the consensus technique of the ANRS Resistance study group, the TruGene HIV-1 genotyping kit (Siemens Healthcare, Eragny, France), or the ViroSeq sequencing based HIV-1 genotyping kit (Abbott, Rungis, France).
- Protease, and reverse transcriptase (RT) mutations were identified from the 2009 Stanford Resistance Surveillance list (Protease inhibitors (PI): L23I, L24I, D30N, V32I, M46I/L, I47A/V, G48V/M, I50V/L, F53L/Y, I54V/L/M/A/T/S, G73C/S/T/A, L76V, V82A/C/F/L/M/T/S, I84V/A/C, I85V, N88D/S, L90M; Nucleoside reverse transcriptase inhibitors (NRTI): M41L, K65R, D67N/G/E, T69D/Ins, K70E/R, L74V/I, V75A/M/T/S, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, F215Y/F/C/D/E/S/I/V, K219Q/E/N/R; non nucleoside reverse transcriptase inhibitors (NNRTI): L100I, K101E/P, K103N/S, V106A/M, V179F, Y181C/I/V, Y188L/H/C, G190A/S/E, P225H, M230L).
- As no transmitted resistance surveillance list is currently available for integrase resistance mutations, T66A/I/K, E92Q, F121Y, E138K, G140A/C/S, Y143C/G/H/R/S, P145S, S147G, Q148E/G/H/K/R, V151L, N155H/S/T, E157Q, were identified from the ANRS resistance algorithm (http://www.hivfrenchresistance.org/2012) and E92Q, Y143R/H/C, Q148H/K/R, N155H from the latest IAS-USA resistance mutations list (http://www.ias-usa.org)
- Phylogenetic analysis based on RT sequences were performed for subtype determination.

Baseline characteristics

	All patients (n=799)	B Subtype (n=536)	Non-B Subtype (n=263)	*P value*
SEX				**<0.001**
Men, n (%)	723 (90.5)	517 (96.5)	206 (78.3)	
Women, n (%)	74 (9.3)	17 (3.2)	57 (21.7)	
Missing value, n (%)	2 (0.3)	2 (0.4)	0 (0.0)	
Transmission group				**<0.001**
Homosexual men, n (%)	605 (75.7)	460 (85.8)	145 (55.1)	
Heterosexual men and women, n (%)	149 (18.6)	46 (8.6)	103 39.2)	
Other, unknown, n (%)	45 (5.6)	30 (5.6)	15 (5.7)	
Patients from sub-Saharan Africa, n (%)	41 (5.1)	10 (1.9)	31 (11.8)	**<0.001**
Median CD4 (cells/mm3) [range]	490 [6-4960]	495 [6-4960]	480 [34-2872]	0.538
Median HIV-1 plasma RNA (log copies/mL) [range]	5.5 [2.1-8.1]	5.4 [2.1-8.0]	5.6 [2.1-8.1]	**0.017**
Prevalence of RAMs				
At least one RAM, % (95%CI)	10.6 (8.6-13.0)	**12.9** (10.2-16.0)	**6.1** (3.5-9.7)	***0.003***
PI RAMs, % (95%CI)	2.0 (1.1-3.2)	**2.8** (1.6-4.6)	**0.4** (0.0-2.1)	***0.028***
NRTI RAMs, % (95%CI)	5.1 (3.7-6.9)	**6.7** (4.7-9.2)	**1.9** (0.6-4.4)	***0.003***
NNRTI RAMs, % (95%CI)	4.0 (2.8-5.6)	**5.0** (3.3-7.2)	**1.9** (0.6-4.4)	***0.035***
RPV & ETV RAMs, % (95%CI)	3.3 (2.1-4.7)	3.5 (2.1-5.5)	2.7 (3.5-9.7)	*0.672*
INT157Q, % (95%CI), n=331	1.5 (0.5-3.5)	1.3 (0.3-3.9)	1.9 (0.2-6.5)	*0.526*

CONCLUSIONS

In France in 2010-2012, the global prevalence of transmitted drug-resistant variants was 10.6% stable since1996. Although subtype B still predominates in France (67%), the frequency of non-B viruses increased significantly in patients with PHI between 2010-2012 (33%) and 1996-1998 (10%). CRF02_AG was the most predominant non B subtype (53.6%). We also described 121 strains belonging to 6 other subtypes, 12 other CRFs and 1 group N virus (found in a patient originated from Togo), reflecting the exceptional viral diversity of the French epidemic.

MSM B subtype-infected patients is the group with highest drug resistance prevalence (13.5%).

After analysis of the genotypic sensitive score (GSS) of all the 799 viruses, subtype B viruses were less sensitive to EFV containing regimen like TDF/FTC/EFV and ABC/3TC/EFV compared to non-B viruses (94.2% vs 98.5, p=0.021). No difference was found for TDF/FTC/RPV, TDF/FTC/ATV, TDF/FTC/DRV, ABC/3TC/ATV, ABC/3TC/RPV, TDF/FTC/NVP, TDF/FTC/LPV, ABC/3TC/LPV, ABC/3TC/DRV, TDF/FTC/RAL and ABC/3TC/RAL according to the subtype.

Prevalence of viruses with at least one resistance associated mutation

	no mutation (n=714)	with mutation (n=85)	p-value
Subtype			**0,003**
B (n=536)	87,1%	12,9%	
Non-B (n=263)	93,9%	6,1%	
Transmission group			0,082
Men who have sex with men (n=605)	88,3%	11,7%	
Others (n=194)	92,8%	7,2%	
Patients from			0,301
Sub-saharan Africa (n=41)	95,1%	4,9%	
Others countries (n=758)	89,1%	10,9%	
Transmission group and Subtype			**0,020**
MSM - B Subtype (n=460)	86,5%	13,5%	
No MSM - B Subtype (n=76)	90,8%	9,2%	
MSM - non-B Subtype (n=145)	93,8%	6,2%	
No MSM - non-B Subtype (n=118)	94,1%	5,9%	
CD4 count, cells/mm3, mean (sd)	539 (263)	623 (557)	0,364
Plasma HIV RNA log10, copies/mL, mean (sd)	5.5 (1.1)	5.5 (1.2)	0,363

Logistic regression analysis: risk factor for RAM

	OR (95%CI)	p-value
Transmission group and Subtype		**0.025**
No MSM - non-B Subtype	1	
MSM - non-B Subtype	1.0 (0.3 - 2.9)	0.926
No MSM - B Subtype	1.6 (0.5 - 4.8)	0.393
MSM - B Subtype	**2.5** (1.1 - 5.5)	**0.029**

ACKNOWLEDGMENTS

We thank the PRIMO Cohort COORDINATING GROUP : L Meyer, C Goujard, JF Delfraissy, ML Chaix, C Rouzioux, A Venet, A Cheret, C Lascoux-Combe, F Barin, A Saez Cirion. The full list of investigators for the French Primo Study group can be found at http://u822.kb.inserm.fr/COHAD/participantsPRIMO.htm.
The ANRS AC-11 RESISTANCE COORDINATING GROUP : V. Calvez, S. Reigadas, M.L. Chaix, D. Descamps, C. Delaugerre, J . Izopet, A.G. Marcelin, L .Morand-Joubert, JC Plantier, C. Tamalet, S. Yerly, G. Peytavin ,P Flandre, L.Assoumou, F. Brun-Vézinet and the ANRS AC-11 RESISTANCE GROUP
The OPTIPRIM ANRS 147 Trial Study Group : B.Autran, A.Chéret, C.Deveau, C.Goujard, P.Halfon, B.Hoen, A.Lafeuillade, C. Lascoux-Combe, L. Meyer, G. Nembot, D. Olive, G. Pancino, I. Ravaux, C. Rouzioux, B. Spire, C. Tamalet, JM. Tréluyer, A. Venet, A. Le Palec (TRT-5) and the ANRS.