

Impact of genotype resistance mutations on clinical and immunological outcomes in HIV infected adults receiving antiretroviral therapy in Abidjan, Côte d'Ivoire

Catherine Seyler^{a,c}, Christiane Adjé-Touré^b, Nicole Dakoury-Dogbo^c, Delphine Gabillard^a, Eugène Messou^{a,c}, Siaka Touré^{a,c}, François Rouet^d, Richard Marlink^e, Monica Nolan^b, Xavier Anglaret^{a,c},

^a INSERM U593, Bordeaux 2, France ; ^b Projet RETRO-CI Abidjan Côte d'Ivoire ; ^c Programme PACCI and Association ACONDA Abidjan, Côte d'Ivoire ; ^d CoDRes, CHU de Treichville, Abidjan, Côte d'Ivoire ; ^e Elizabeth Glaser Paediatric AIDS Foundation (EGPAF), Washington, DC, USA

Background

- Rare studies have suggested a rapid selection of drug resistance mutations after antiretroviral therapy initiation in sub-Saharan Africa.
- The impact of HIV-1 drug resistance mutations on clinical and immunological outcomes in African adults on HAART has never been reported.
- We studied the medium-term clinical and immunological evolution in HIV-infected adults receiving antiretroviral therapy in Abidjan, Côte d'Ivoire, according to the presence or absence of resistance mutations.

Methods

- Participants : all adults who previously participated in the ANRS 1203 cohort study in Abidjan and who were receiving HAART in July 2004
- Baseline characteristics: at study entry, all participants had viral load (VL) measurements (real time PCR, threshold of detectability 300 copies/ml). Patients with detectable VL had genotype resistance tests (Viroseq™ Genotyping System). Mutations were classified as major or minor (International AIDS Society October 2006 consensus).
- Follow-up: all patients were followed until March 31st 2006 ; main outcomes were death, severe morbidity (WHO stage 3 or 4-defining events) and CD4 count evolution

Results

Table 1. Characteristics of the 106 participants

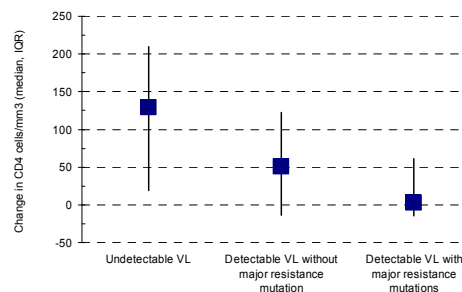
Characteristics at HAART initiation	n	(%)
Women, number (%)	63	(59%)
Age in years, median (IQR)	38	(33-44)
Nadir of CD4+ cell count/mm ³ , median (IQR)	122	(88-226)
Initial HAART regimen**, number (%)		
2 NRTIs + 1 PI	61	(58%)
2 NRTIs + 1 NNRTI	37	(35%)
Others	8	(8%)
Characteristics at inclusion in the study		
Previous time on HAART in months, median (IQR)	37.4	(27.2-48.3)
Drug regimen change since HAART initiation, number (%)		
None	40	(38%)
Patients with one change	27	(25%)
Patients with ≥ 2 changes	39	(37%)
CD4+ cell count/mm ³ , median (IQR)	266	(159-407)
Current HAART regimen**, number (%)		
2 NRTIs + 1 PI	56	(53%)
2 NRTIs + 1 NNRTI	47	(45%)
Others	2	(2%)
Virological status		
Undetectable viral load, number (%)	62	(58%)
Detectable viral load, number (%)	44	(42%)
With ≥ 1 major mutations	23	(21%)
With no major mutations	21	(20%)
Follow-up after inclusion in the study		
Follow-up time in months, median (IQR)	20.5	(19.7-21.1)
At least one serious clinical event during follow-up, number (%)	29	(27%)
Characteristics at study termination		
CD4+ cell count/mm ³ , median (IQR)	338	(214-519)
Status, number (%)		
Deceased	1	(1%)
Lost to follow-up	1	(1%)
Alive and in active follow-up	104	(98%)

Table 2. Distribution of mutations in the 23 patients with major mutations at inclusion in the study

Patient	Resistance mutations to NRTIs	Resistance mutations to NNRTIs	Resistance mutations to PI	Number of classes *
1	M184V	None	None	1
2	M184V, M41L, D67N, L210W	None	None	1
3	M184V, M41L, T215Y	None	None	1
4	M184V	None	None	1
5	M184V	None	None	1
6	M184V	None	None	1
7	D67N	None	None	1
8	M184V, M41L, K70R, D67N, K219Q	None	None	1
9	M184V	None	None	1
10	None	K103N	None	1
11	None	K103N	None	1
12	None	K103N	None	1
13	None	K103N, L100I	None	1
14	None	None	L90M	1
15	M41L	K103N	None	2
16	M184V, T215F, K70R, K219Q	K103N, M230L, P225H	None	2
17	M184V	K103N	None	2
18	M184V, T215Y	K103N, M230L	None	2
19	M41L, D67N, L210W	K103N	None	2
20	M184V	K103N, P225H	None	2
21	M184V	None	L90M	2
22	M184V, K70R, D67N	None	R4V	2
23	M184V, T215Y, D67N, M41L, D67N	None	L90M	2

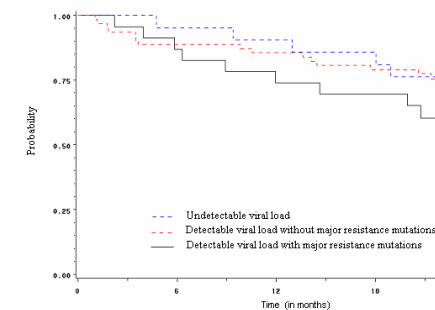
NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor ; * number of antiretroviral drug classes affected

Figure 1. Change in CD4 cell count between inclusion and study termination, according to virological status at inclusion



* undetectable VL vs. detectable VL without major mutations: p=0.50
† undetectable VL vs. detectable VL with major mutations: p=0.07
VL: viral load (plasma HIV-1 RNA level)

Figure 2. Probability of remaining alive and free of severe morbidity within time, according to virological status at inclusion *



Log rank :
p = 0.19 for undetectable VL vs. detectable VL with major resistance;
p = 0.91 for undetectable VL vs. detectable VL without major resistance
* Only one patient died (group "major resistance mutations")

Discussion

- Among these sub-Saharan African adults on HAART as a median of three years, 58% had undetectable VL, 20% had detectable VL with no major resistance mutations and 22% had ≥ 1 major drug resistance mutations. Within the following 20 months, patients with major mutations tended to have higher rate of serious morbidity but their CD4 count remained stable and only one of them died.
- Within the following years, millions of sub-Saharan African adults will receive HAART. In these patients, changing regimen for treatment failure will have to be based on clinical and immunological outcomes. The timing of acquisition of resistance mutations and the number of mutations will be impossible to determine. Failing therapeutic regimens will thus be maintained during incompressible periods of time.
- Our data suggest that most patients with major drug resistance mutations might maintain stable CD4 cell count and stay alive for more than one year.

We thank the Programme National de Prise en Charge (PNPEC, Ministry of Health, Côte d'Ivoire), the Pediatric Emergency Plan For AIDS Relief (PEPFAR), and the Agence nationale de Recherches sur le SIDA et les Hépatite Vitale (ANRS, France)