

**ABSTRACT**

**Background:** Data on resistance to antiretroviral (ARV) drugs in sub-Saharan Africa are scarce. We studied the 6-months rate of resistance to ARV drugs in HIV-1 infected adults who start HAART in Côte d'Ivoire, West Africa, where CRF02 is the predominant HIV-1 strain.

**Methods:** HAART-naïve HIV-1-infected adults with a CD4 count at 150-350/mm<sup>3</sup> were included in the pre-randomisation phase of a HAART STI trial in Abidjan (TRIVACAN ANRS 1269 trial). All patients received a continuous HAART for at least 6 months. HIV-1 plasma viral load (VL) was quantified at month-6 (real time PCR, threshold (300 copies/ml). In case of VL > 300 copies/ml, resistance genotypic test was performed.

**Results:** 824 HIV-1 infected adults (76% women, median age 34 years, median baseline CD4 count 253/mm<sup>3</sup>) started ZDV+3TC+EFV (90%) or ZDV+3TC+IDV/r (10%). At month-6, 10 patients were dead, 1 was lost to follow-up, and 15 had missing VL. Among the 799 patients with available VL, 682 (85%) had undetectable VL and 117 (15%) detectable VL (median 5500 copies/ml, IQR 1300-33900). Strains of 5 patients were not amplified (median VL 1000 copies/ml). Of the 112 remaining patients, 79 (70%) had wild-type viruses and 33 (30%) had at least one resistance mutation (patients on ZDV+3TC+EFV n=28; patients on ZDV+3TC+IDV/r n=5). The 6-months rate of resistance to at least one drug was 4.2% (33/794) overall, 3.9% (28/722) in patients receiving the NNRTI-based regimen and 6.9% (5/72) in those receiving the PI-based regimen. In patients on ZDV+3TC+EFV, the 28 drug mutations were K103N alone (n=17), K103N + M184V (n=5), M184V alone (n=5) and thymidine analogue mutations (TAMs) (n=1). In patients on ZDV+3TC+IDV/r, the 5 resistant virus had M184V mutation. In women on ZDV+3TC+EFV, the 6-months rate of resistance to NNRTI was 3.2% (17/529) overall, and: 20.4% (3/14), 0% (0/5), 0% (0/35) and 2.9% (14/475) in women with a history of pMTCT with ZDV+NVP, ZDV+3TC+NVP, ZDV alone, and no history of PMTCT, respectively.

**Conclusion:** In this large cohort of West African patients starting HAART with low genetic barrier drugs, we observed, at 6-months, a high rate of virological success (85%) and a low rate of drug resistance (4.2%). Most patients (70%) with detectable VL had no resistant virus. Most of the resistant virus observed harboured NNRTI mutations or 3TC mutation.

**OBJECTIVE**

To characterize the frequency of resistant virus and the resistance patterns six months after HAART initiation (in the pre-randomization phase) in patients with virological failure

**PATIENTS**

TRIVACAN trial was a prospective, randomised, open-label, multicentre, non-inferiority trial, to compare continuous HAART with two structured treatment interruption strategies (Danel et al. Lancet 2006). Between Dec 2002 and April 2004, all HIV-infected adults were candidates for inclusion if they had either a CD4 count between 150 per mm<sup>3</sup> and 350 per mm<sup>3</sup> or percentage of CD4 (CD4%) between 12.5% and 20%. The trial comprised two phases. In the pre-randomization phase, all patients received a continuous antiretroviral treatment. The first line regimen was ZDV + 3TC (Duovir, Cipla, Mumbai, India) plus EFV 600mg once a day (Stocrin, Merck Sharp and Dohme) or indinavir 800mg and ritonavir 100 mg twice a day (Crixivan, Merck Sharp and Dohne and Norvir, Abbott) for HIV-2 infected patients, women refusing contraception and women with a history of nevirapine PMTCT.

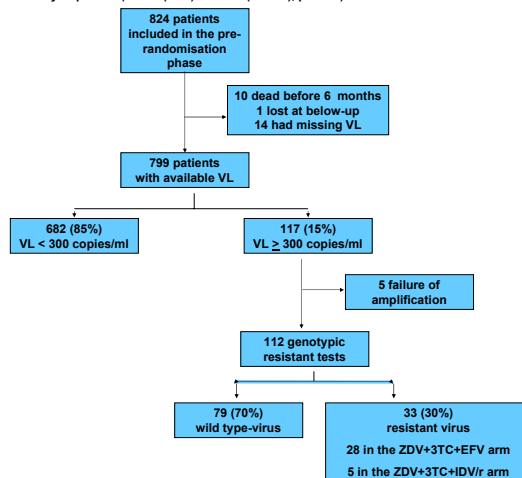
At any time between 6 months and 18 months in the pre-randomisation phase, patients were randomized into one of the 3 arms whenever they met the following criteria: CD4 count > 350 mm<sup>3</sup>, plasma HIV RNA < 300 copies/ml.

**METHODS**

Plasma HIV-1 RNA was measured at 6 months after HAART initiation (by real-time PCR in LTR gene, using the ANRS assay with a threshold at 300 copies/ml; Rouet F et al. JCM, 2005). In case of VL > 300 copies/ml, genotypic resistance test was performed by automated population full-sequence analysis of the RT and protease genes (ABI system) using the ANRS consensus technique. The French resistance algorithm 2006 was used for result interpretation ([www.hivfrenchresistance.org](http://www.hivfrenchresistance.org)). Compliance was defined as a VL decrease  $\geq 1$  log at M3 or M6, or by detectable levels of EFV or IDV at M1.

**RESULTS**

In the pre-randomization phase, 824 HIV-1 infected adults were included (76% women, median age 34 years, median VL 100 000 copies/ml, median baseline CD4 cell count 253/mm<sup>3</sup>, 12% < 150/mm<sup>3</sup>, 39% at WHO stage 3-4). The first line regimen was ZDV + 3TC + EFV in 90% of cases or IDV/r in 10% of cases. After 6 months of HAART, 85% (682/799) of patients had undetectable VL and 15% (117/799) had detectable VL (median 5 500 copies/ml, IQR 1300-33900). Among the 117 patients with detectable VL, 3 had a VL < 1 000 copies/ml, 5 a VL between 1 000 and 10 000 copies/ml and 7 a VL > 10 000 copies/ml. The 6-months rate of resistance to at least one drug was 4.2% (33/794) overall, 3.9% (28/722) in patients receiving the NNRTI-based regimen and 6.9% (5/72) in those receiving the PI-based regimen. The most NNRTI resistance mutation selected was the K103N. Women with history of pMTCT with nevirapine and treated with HAART containing EFV had a high risk of selection of resistant virus compared to women without history of pMTCT (20.4% (3/14) vs 2.9% (14/475),  $p = 0.02$ ).



ID	TREATMENT	RT MUTATIONS	PROTEASE MUTATIONS
CN 014	EFV	103N/K	20I, 36I, 41K
CN 019	EFV	103N	20I, 36I, 41K
CN 164	EFV	184M/I, 230I	20I, 36I, 41K
PF 026	EFV	103N, 181C	10I, 20I, 35D, 36I, 41K
PF 027	EFV	103N	20R, 36I, 41K
PF 044	EFV	103N/K	20I, 35D, 36I, 41K, 77I
PF 056	EFV	103N	20I, 36I, 41K
PF 061	EFV	103N	ND
PF 101	EFV	103N, 184V	20R, 36I, 41K
PF 126	EFV	101E, 179I	ND
PF 135	EFV	179I, 184V	10I, 35D, 36I, 41K, 63P
RB 007	EFV	103N	20I, 36I, 41K
RB 008	EFV	103N/K, 184M/V	20I, 36I, 63P
RB 070	EFV	103N, 179I	20I, 36I, 41K
RB 111	EFV	184V	10V, 20I, 36I, 41K
RB 144	EFV	103N	20I, 36I, 41K
RB 009	EFV	101E/K, 103R/K	10V/L, 13V, 20I, 36I, 41K, 69K
RB 010	EFV	188D/Y, 190G/E	ND
SM 009	EFV	103N	41K, 63A
SM 140	EFV	103N	20I, 36I, 41K
SM 64	EFV	179E, 184V, 188L	20I, 36I, 41K
SM 81	EFV	98S, 103N, 190A/G	20I, 35D, 36I, 41K, 82I
SM083	EFV	101Q/L, 103N, 184V	13V, 20I, 36I, 41K, 63P, 69K
US 054	EFV	103N/K	10V, 20I, 36I, 41K
US 072	EFV	69N, 215A	20I, 36I, 41K, 71T
US 136	EFV	101Q/K, 184V	20I, 36I, 41K, 63S
US 166	EFV	184V	20I, 36I, 41K
US 168	EFV	103N, 184V	13A, 20I, 36I, 41K, 63P, 69K
PF 025	IDV/r	184V, 219Q/K	13V, 16E/G, 20I, 36I, 41K, 69K
PF 104	IDV/r	184V	20I, 36I, 41K, 63P, 69K
RB 011	IDV/r	184V	20I, 36I, 41K, 41K
RB 066	IDV/r	179I, 184V	20I, 35N, 36I, 41K, 77V/I
RB 025	IDV/r	184V	ND

Table 1: Profiles of resistance mutations in patients with viral load  $\geq 300$  copies/ml  
 ND: not done, EFV: efavirenz, IDV/r: Indinavir/ritonavir

**CONCLUSION**

In this large cohort of West African patients starting HAART with ZDV + 3TC + EFV or IDV/r, a high rate of virological success (85%) was observed at M6. Early failures were not associated with resistant virus in 70% of cases (79/112 patients); 48 out of the 79 patients with wild type virus at M6 were finally randomized between M6 and M18 into one of the three arms as they had a VL < 300 copies/ml: the impact of this slow virological decrease will be further studied within the final analysis of the trial.

Absence of compliance and exposure to HAART with nevirapine were significantly associated with selection of resistant virus at M6 ( $p < 0.0001$  and  $p = 0.02$  respectively).

Most of the resistant virus observed harboured NNRTI mutations (K103N) or 3TC mutation. The absence of TAMs suggests that zidovudine or stavudine could be used in the second line regimen after early failure to ZDV+3TC+EFV or IDV/r.

**ACKNOWLEDGMENTS**

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