

OBJECTIVE: To estimate the frequency of HIV-1 displaying genotypic drug resistance in HAART-treated children in Abidjan, Côte d'Ivoire.

PATIENTS

Between October 2000 and September 2003, 269 HIV-1 infected children were included in the ANRS 1278 Cohort. Among them, 115 (median age: 6.35 years [0.7-15], 16% < 3 years) were treated with HAART for at least 6 months. Treatment consisted of 2 NRTIs associated with nelfinavir (70.5%) or efavirenz (29.5%).

METHODS

Plasma HIV-1 RNA levels and CD4+ T-cell counts were determined at baseline then every 6 months.

Genotypic resistance tests were performed on plasma samples in case of virological failure (defined as a HIV-1 RNA level $\geq 3 \log_{10}$ copies/ml after at least 6 months of HAART).

Protease- and RT resistance-associated mutations were identified according to the IAS list. Resistant virus were defined according to the 2003 French ANRS resistance algorithm (www.hivfrenchresistance.org).

To classify the HIV-1 strains according to subtype, phylogenetic analysis was performed on RT sequences.

PATIENTS' CHARACTERISTICS AT HAART INITIATION

Among the 115 children, 45% were girls and 25 children were at stage A, 68 at stage B and 19 at stage C according to the CDC definition. Median viral load and median CD4 % at baseline were 5.45 \log_{10} copies/ml [3.24-7.34] and 8.9 % [0.1-22.7] respectively.

Antiretroviral therapy consisted of two NRTIs with either one PI or one NNRTI. At baseline, in addition to nelfinavir, 37 patients (32.2%) were prescribed ZDV and 3TC; 18 (15.6%) d4T and ddI; 17 (14.8%) 3TC and d4T; 6 (5.2%) 3TC and ddI and 3 (2.6%) ZDV and ddI. In addition to efavirenz, 13 patients (11.3%) received ZDV and 3TC; 13 (11.3%) d4T and ddI; 6 (5.2%) 3TC and d4T and 2

(1.7%) ZDV and ddI.

VIROLOGICAL RESPONSE TO TREATMENT

HIV-1 RNA were measured for all 115 treated children after a median of 10.2 months [6-20.9] on HAART. 66% (76/115) of children were considered in virological success (viral load below 3 \log_{10} copies/ml); 57 of these children (49%) exhibited a viral load < 2.4 \log_{10} copies/ml and 19 presented a viral load ranged between 2.4 and 2.99 \log_{10} copies/ml. 34% (39/115) were in virological failure (viral load $\geq 3 \log_{10}$ copies/ml).

	Total	Virological success	Virological failure
N = 115		N = 76	N = 39
Age		6.5 years [1.6-15]	5.8 years [0.7-13.2]
% < 3 years		18% (14/76)	13% (5/39)
% CD4		8.2% [0.1-22.7]	10.6% [0.2-20.9]
HIV-1 RNA \log_{10} copies/ml		5.32 [3.24-6.73]	5.56 [3.72-7.34]
Efavirenz n=34 (29.5%)		24 (31.6%)	10 (25.6%)
Nelfinavir n=81 (70.5%)		52 (68.4%)	29 (74.4%)

Table 1 : Characteristics of children in virological success compared to children in virological failure (HIV-1 RNA $\geq 3 \log_{10}$ copies/ml after at least 6 months of HAART) at HAART initiation.

RESULTS OF HIV-1 GENOTYPIC RESISTANCE (1)

We performed a genotypic resistance test for 38 of the 39 samples from children in virological failure. Wild-type viruses were detected in 11 cases (11/38, 29%) and viruses resistant to at least one ARV drug were detected in 27 cases (27/38, 71%, 95%CI [56.6-85.4]). 13 had a virus resistant to 1 drug, 9 harbored mutated strains resistant to 2 molecules of their treatment and 5 harbored virus resistant to the 3 molecules of their HAART. Thus, resistant viruses were found in 24% (27/114) of all ARV-treated children.

Idn	Age years	HIV1RNA log copies/ml	Treatment Duration (mo)	Treatments	Resistance/presentations	Presentations	Vid subtype
1	7	545	11.9	ZDV/3TC/NFV	184V	20_36154L	CRR2
2	35	699	72	ZDV/3TC/NFV	184V	20_36163IP	CRR2
3	9	599	83	ddl,d4T/NFV	Nmutation	20V_8_63P88S	CRR2
4	9	626	11.6	ddl,d4T/NFV	105V/184V/215Y	20_36188SQM	CRR2
5	12	542	95	ZDV/3TC/EFV	103N 184I 210M	20_36163P	CRR2
6	07	nd	16.5	ZDV/3TC/NFV	179I/18V	20R 8_ 4K_ 8H	CRR2
7	10	508	12.2	ddl,d4T/EFV	12N	10V_2_36141K63P	CRR2
8	3	556	10.9	ZDV/3TC/NFV	184V	10_36141K63P	UNd
9	13	nd	95	ddl,d4T/EFV	89N 10N 19E18C	11L 20136HK	CRR2
10	25	545	63	3TC/d4T/NFV	184V	10V_2_36141K	CRR2
11	6	582	6	3TC/d4T/NFV	62V_84V	20_36141K	CRR2
12	5	61	12.3	ZDV/3TC/NFV	179I/18V	20_36141K	CRR2
13	5	572	9	ZDV/3TC/NFV	103I/18V	10V_2_36141K66IT	CRR2
14	65	519	84	ddl,d4T/EFV	74V_297N 18E	20_36163P/87	CRR2
15	07	695	13.2	3TC/d4T/NFV	184V215Y	20_36182I	CRR2
16	13	466	12.2	ddl,d4T/EFV	74V/103N 18E	10V_2_36141K63H	CRR2
17	13	nd	15	ZDV/3TC/NFV	184V	20_36163I/1K63I8M	CRR2
18	5	nd	10.2	ZDV/3TC/NFV	67D 18V 18V	20_36141K62I88S	CRR2
19	10	511	85	ddl,3TC/NFV	184V	20_36171T9M	CRR2
20	8	552	11.1	ddl,d4T/EFV	65R 10M 10N	10_20V3182I	CRR2
21	57	471	11	ZDV/3TC/NFV	70R 8V	10V_2_36163P71A788SN 90M	CRR2
22	4	591	11.2	3TC/d4T/NFV	184V	20_36188S	CRR2
23	5	503	11.8	ZDV/ddl/NFV	67N 18V 215Y	20V/103I63I88SQM	CRR2
24	10	nd	20.9	ddl,d4T/NFV	41L6N 18V 8G 181V 210V_18V21E	10V_2_36141K63SQM	CRR2
25	5	683	10.4	ZDV/ddl/NFV	67P/184V 18V 7R 215Y	10V_2_36163I54V 118M	CRR2
26	10	48	11.3	3TC/d4T/EFV	101 60 10 18V 18V_26F/12 21H 20L	20V_8_41K63P71 T82I	CRR2
27	7	483	10	ZDV/3TC/NFV	41L6N 18V 84V 215Y	20_33V41K62I2I63P7T_11_82I88S	CRR2

Table 2 : Profile of resistant viruses in 27 HAART-treated children treated for at least 6 months and in virological failure ($\geq 3 \log_{10}$ copies/ml). For each patient, age at HAART initiation, HIV-1 RNA load (\log_{10} copies/ml), treatment molecules, treatment duration, and viral subtype are indicated as well as genotyping results. ZDV = zidovudine; 3TC = Lamivudine; ddl = didanosine; d4T = stavudine; EFV = efavirenz; NFV = nelfinavir; nd = not done, UNd: undetermined

RESULTS OF HIV-1 GENOTYPIC RESISTANCE (2)

Resistant viruses were detected after 6 to 20.9 months (median: 10.2 months) on therapy, with mutations conferring resistance to: 3TC (n= 17), ZDV (n=6), d4T (n=6), ddI (n=7), EFV (n=7) and NFV (n=11). Resistance to 3TC and/or to NNRTIs was frequent among the 38 children in virological failure. The mutation 184V was present in 16 of the 26 (62%) children treated with 3TC. Mutations conferring resistance to NNRTIs were present in 7 of the 9 patients (78%) who received efavirenz. The 90M, 46L, 88S and 54V mutations were found in 11 (38%) of the 29 children who received nelfinavir.

CONCLUSION

These results are similar to what is generally observed in children in industrialized countries. Despite these encouraging results, efforts are needed to maximize the long-term efficiency of treatment and to minimize the risk of emergence of drug resistance in African treated children.