Long-Term Benefits of Highly Active Antiretroviral Therapy in Senegalese HIV-1–Infected Adults

Christian Laurent, PhD, Ndeye Fatou Ngom Gueye, MD, MPH,† Cheikh Tidiane Ndour, MD,‡ Pape Mandoumbé Gueye, MD,§ Martin Diouf, MD,† Ndella Diakhaté, MD,‡ Ndeye Coumba Touré Kane, PhD,‖ Isabelle Lanièce, MD, MPH,* Adama Ndir, MD,‡ Laurence Vergne, PhD,* Ibrahima Ndoye, MD,¶ Souleymane Mboup, PhD,‖ Pape Salif Sow, MD‡ and Eric Delaporte, MD, PhD* for the ANRS 1215/1290 Study Group*

Objectives: To assess the long-term survival, as well as the immunologic and virologic effectiveness, adherence, and drug resistance, in HIV-infected patients receiving highly active antiretroviral therapy (HAART) in one of the oldest and best-documented African cohorts.

Methods: A prospective observational cohort study included the first 176 HIV-1–infected adults followed in the Senegalese government-sponsored antiretroviral therapy initiative launched in August 1998. Patients were followed for a median of 30 months (interquartile range, 21–36 months). HAART comprised 2 nucleoside reverse transcriptase inhibitors and either 1 protease inhibitor or 1 nonnucleoside reverse transcriptase inhibitor.

Results: At baseline, 92% of patients were antiretroviral naive and 82% had AIDS; the median CD4 count was 144 cells/mm^3, and median viral load was 202,368 copies/mL. The survival probability was high (0.81 at 3 years; 95% CI, 0.74–0.86) and was independently related to a baseline hemoglobin level <10 g/dL and a Karnofsky score <90%. Antiviral efficacy was consistently observed during the 3 years of treatment (−2.5 to −3.0 $\log_{10}$ copies/mL; 60–80% of patients with viral load <500 copies/mL) and the CD4 count increase reached a median of 225 cells/mm^3. Most patients reported good adherence (80–90%). The emergence of drug resistance was relatively rare (12.5%).

Conclusion: This study shows that clinical and biologic results similar to those seen in Western countries can be achieved and sustained during the long term in Africa.

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From the *Institut de Recherche pour le Développement and Department of International Health, University of Montpellier (UMR 145), France; †Ambulatory Care Unit/Croix-Rouge, Fann University Teaching Hospital, Dakar, Senegal; ‡Department of Infectious Diseases, Fann University Teaching Hospital, Dakar, Senegal; §Military Hospital, Dakar, Senegal; ‖Le Dantec University Teaching Hospital, Dakar, Senegal; and ¶Multisectorial AIDS Control Program, Dakar, Senegal.

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Reprints: Christian Laurent, Institut de Recherche pour le Développement–UMR 145, 911 avenue Agropolis, BP 64501, 34394 Montpellier cedex 5, France (e-mail: Christian.Laurent@mpl.ird.fr).

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Preliminary results from the scarce African highly active antiretroviral therapy (HAART) experiences are encouraging and appear to be comparable to those seen in Western countries.[1–4] However, they relate only to short-term follow-up (mostly 12 months), whereas experience in Western countries shows that HAART management becomes more difficult with time (increasing toxicity, decreasing adherence, emergence of drug resistance, and treatment switches). Frater et al[5] reported better virologic responses in European than African patients after 21 months of treatment, despite similar initial responses. Here we report longer-term outcomes of HAART in terms of survival, immunologic and virologic effectiveness, adherence, and emergence of viral resistance, in one of the oldest and best-documented African cohorts.

METHODS

Study Design

This prospective observational cohort study included the first 176 HIV-1–infected adults (>15 years of age) followed in the Senegalese government-sponsored antiretroviral therapy initiative launched in August 1998.[6] Of these, 80 patients participated for the first 18 months in 2 clinical trials.[7,8] The first-line antiretroviral regimen was a triple-drug combination comprising 2 nucleoside reverse transcriptase inhibitors (NRTIs) and either 1 protease inhibitor (PI) or 1 nonnucleoside reverse transcriptase inhibitor (NNRTI). However, mildly symptomatic, antiretroviral-naive patients with viral load <10,000 copies/mL, and pretreated patients with controlled viral load and CD4 cell count by a double-drug combination, received only 2 NRTIs prior to 2001. The antiretroviral drugs were provided free of charge for the 80 patients initially included in the clinical trials. Financial participation by the other patients depended on their capacities and fell over time following drug price cuts (from around US $34 to US $4 per month).[6] The Senegalese national ethics committee on AIDS

approved this study, and all participants gave their written informed consent.

Laboratory Procedures

Plasma HIV-1 RNA levels were determined using the Amplicor HIV-1 Monitor 1.5 assay (Roche Molecular Systems, Branchburg, NJ) for the 80 patients who initially participated in the clinical trials. For the other patients, viral load was initially determined using the Bayer bDNA HIV-1 Quantiplex assay (v. 2.0; Bayer Diagnostics, Emeryville, CA) version 2.0 and subsequently with the ultrasensitive version 3.0. CD4 cell counts were determined with a FACSCount apparatus (Becton Dickinson, Mountain View, CA). Both tests were performed in Dakar. Genotypic resistance to antiretrovirals was studied by sequencing the pol gene at baseline, and when a nonoptimal virologic response was obtained after at least 6 months of treatment, or when plasma viral load rebounded during treatment after being undetectable (1000 copies/mL for both criteria, corresponding to the detection limit of the genotypic resistance test).[9]

Statistical Analysis

The survival probability was estimated by the Kaplan-Meier method. Cox proportional hazard models were used to assess the relation between survival and baseline patient characteristics. The slopes of the CD4 cell count and viral load over time were assessed using linear regression models, and the slope of adherence was assessed with a logistic regression model. Square-root transformation of the CD4 cell count was performed to normalize the distribution. Changes in viral load were assessed on a $\log_{10}$ scale. Data on adherence were recorded using a standard questionnaire for all patients at quarterly visits, based mainly on their self-reports. Adherence was automatically assigned the value zero if the patient interrupted treatment and did not attend visits. As adherence of at least 95% is required for antiretroviral efficacy, we used this cut-off for analysis. We performed random-effects analyses to evaluate the slopes of the CD4 cell count, viral load, and adherence owing to correlated successive measurements (XT commands of STATA 7.0 software; Stata Corp, College Station, TX). Analyses were performed on an intention-to-treat basis.

RESULTS

The 176 HIV-1–infected patients were enrolled between August 1998 and April 2001. There were 92 women (52.3%) and the median age was 38 years (interquartile range [IQR] 32–44 years). Most patients were antiretroviral naive (91.5%) and had AIDS (81.7%). The median CD4 count was 144 cells/mm^3 (IQR, 58–224 cells/mm^3) and median viral load was 202,368 copies/mL (IQR, 63,884–392,454 copies/mL). Five patients (2.8%) were dually infected by HIV-1 and HIV-2. At baseline, 82 patients (46.6%) received 2 NRTIs + 1 NNRTI; 76 patients (43.2%) received 2 NRTIs + 1 PI; and 18 patients (10.2%) received only 2 NRTIs. They were followed for a median of 30 months (IQR 21–36 months).

Thirty-one patients died during follow-up (17.6%). The incidence rate of death was 7.4 per 100 person-years (CI 5.2–10.5 per 100 person-years). The survival probability was 0.84 (CI 0.77–0.88) at 2 years and 0.81 (CI 0.74–0.86) at 3 years. The median time between enrollment and death was 9.1 months (IQR 4.7–16.3 months). All deaths involved patients who already had AIDS at baseline. In multivariate analysis, mortality was associated with a baseline hemoglobin level <10 g/dL (hazard ratio [HR] 2.35; CI 1.14–4.86) and Karnofsky score $<90\%$ (HR 2.57; CI 1.12–5.89).

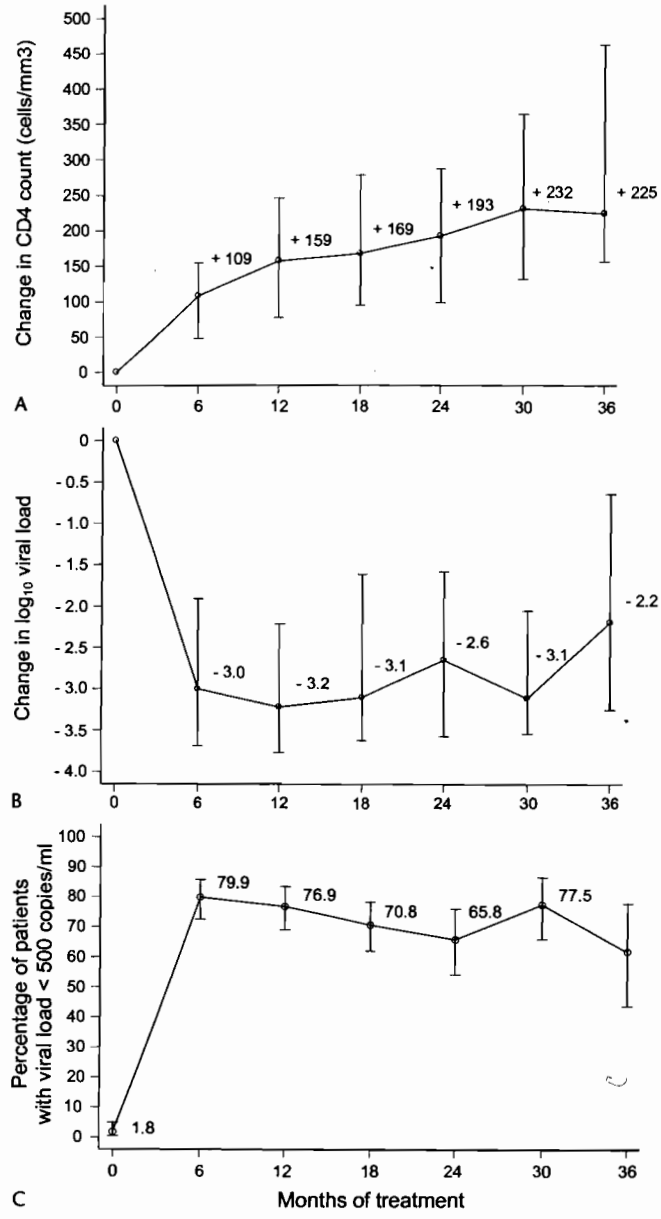
Figure 1 shows changes in the CD4 cell count ($P < 0.001$), viral load ($P < 0.001$), and percentage of patients with undetectable viral load (<500 copies/mL) throughout the study period, relative to baseline. After 2 and 3 years of treatment, respectively, the median increases in the CD4 count were 193 cells/mm^3 (IQR 99–289 cells/mm^3) and 225 cells/mm^3 (IQR 157–465 cells/mm^3), the median decreases in viral load were -2.6 $\log_{10}$ copies/mL (IQR -1.6 to -3.6 $\log_{10}$ copies/mL) and -2.2 $\log_{10}$ copies/mL (IQR -0.6 to -3.2 $\log_{10}$ copies/mL), and suppression of detectable viral load was achieved in 65.8% (CI 54.3–76.1%) and 61.8% (CI 43.6–77.8%) of patients. Forty-one percent of patients for whom values were available had CD4 cell counts >500/mm^3 at 3 years.

At least 95% adherence was claimed in 1323 (86.4%) of the 1532 patient-visits in which adherence was recorded. This level of adherence was reported by 79.8% (CI 71.1–86.9%) and 88.1% (CI 74.4–96.0%) of patients at years 2 and 3, respectively. However, adherence tended to decline with time ($P = 0.03$).

Twenty-two patients' viruses (12.5%; CI 8.0–18.3%) became resistant to ≥ 1 drug. Resistance emerged more frequently in the 15 antiretroviral-experienced patients (33.3%; CI 11.8–61.6%) than in the 161 antiretroviral-naive patients (10.6%; CI 6.3–16.4%). Although resistance emerged with a similar frequency to the 3 classes of drugs (NRTIs 9.7%, NNRTIs 9.1%, PIs 8.2%), it appeared more rapidly to NRTIs (median 19.8 months; IQR 18.0–36.5 months) and NNRTIs (median 18.4 months; IQR 12.4–30.2 months) than to PIs (median 29.4 months; IQR 19.8–37.1 months).

DISCUSSION

This study shows that the good results obtained during the first months of HAART among HIV-infected patients treated in Africa can be sustained in the long term. Despite the late initiation of antiretroviral therapy in the course of HIV/AIDS, our results are very similar to those seen in Western countries.[10,11] Thus, our observational cohort study does not confirm the poorer long-term virologic response observed among African patients followed in London relative to their European counterparts.[5] The authors of this latter study suggested that poorer adherence, possibly linked to cultural and language barriers among Africans treated in Western clinics, could explain this difference between the 2 populations. In our study, although undoubtedly overestimated owing to the self-reporting methodology used, adherence was high among African patients treated in their home environment, possibly as a result of supportive measures (counseling, access



No. of Assays at Each Time by Endpoint

Months	0	6	12	18	24	30	36
CD4	175	145	135	124	82	71	39
Log_{10} viral load	170	152	140	127	76	69	32
Undetected viral load	170	154	143	130	79	71	34

FIGURE 1. Immunologic and virologic responses to therapy. A, Median increase in the CD4 cell count from baseline (IQR). B, Median decrease in viral load from baseline (IQR). C, Patients with viral load <500 copies/mL (95% CI).

to discussion groups, and social and financial support) and the low cost (or gratuity) of the drugs.[6,12]

The mortality incidence rate was higher in our cohort (7.4 per 100 person-years) than among patients recruited from 1998 onwards to the EuroSIDA cohort (2.6 per 100 person-years), but it was similar to that observed among patients recruited in 1996–1997 to the same cohort (9.3 per 100 person-years).[13] It is noteworthy that baseline CD4 cell counts in our patients (median 144 cells/mm^3), as in the first patients recruited to the EuroSIDA cohort (median 223 cells/mm^3), were lower than among the patients recruited to the EuroSIDA cohort from 1998 onwards (median 380 cells/mm^3). The higher mortality rate in our study might also be explained by several other factors, such as physicians' inexperience in HAART management and the small number of available therapeutic alternatives. Indeed, from 1998 to late 2000, only 4 NRTIs (zidovudine, lamivudine, stavudine, and didanosine) and 1 PI (indinavir) were available for the Senegalese program, except for patients enrolled in clinical trials, who received a triple-drug regimen including an NNRTI (efavirenz). In early 2001, efavirenz became more widely available, along with nelfinavir and nevirapine. It is noteworthy that the conditions of our African study closely resemble those of the early years of HAART use in Western countries. Another factor possibly having a negative impact in our study was the limited access to diagnosis and treatment of other infectious diseases.

The low rate of emergence of resistant strains throughout the study period among our antiretroviral-naive patients (11%) was remarkable as compared with the rate of 28% observed after a median of 36 months in Germany and Luxembourg.[14]

In conclusion, this study shows that the clinical and biologic results obtained with HAART in Western countries can be emulated and sustained in the long term in the African setting, with good clinical, biologic, social, and logistical monitoring, and with biologic tests and triple-drug therapy provided free of charge or at a symbolic price.

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