Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial

Christian Laurent, Charles Kouanfack, Sinata Koulla-Shiro, Nathalie Nkoué, Anke Bourgeois, Alexandra Calmy, Bernadette Lactuock, Viviane Nzeusseu, Rose Mougnutou, Gilles Peytavin, Florian Liégeois, Eric Nerrienet, Michèle Tardy, Martine Peeters, Isabelle Andrieux-Meyer, Léopold Zekeng, Michel Kazatchkine, Eitel Mpoudi-Ngolé, Eric Delaporte, for the ANRS 1274 study group

Lancet 2004; 364: 29–34

See Comment page 3

Institut de Recherche pour le Développement and Department of International Health, University of Montpellier (UMR 145), Montpellier, France (C Laurent PhD, A Bourgeois MD, F Liégeois, M Peeters PhD, Prof E Delaporte MD); **Central Hospital, Yaoundé, Cameroon** (C Kouanfack MD, Prof S Koulla-Shiro MD, V Nzeusseu MD, M Tardy MD); **Projet PRESICA/PARVY, Military Hospital, Yaoundé, Cameroon** (N Nkoué MD, B Lactuock MD, R Mougnutou MD, F Liégeois, E Mpoudi-Ngolé MD); **Médecins Sans Frontières, Geneva, Switzerland** (A Calmy MD, B Lactuock, I Andrieux-Meyer MD); **Laboratoire de Toxicologie et de Dosage de Médicaments, Centre Hospitalier Universitaire Bichat Claude Bernard, Paris, France** (G Peytavin PhD); **Centre Pasteur, Yaoundé, Cameroon** (E Nerrienet MD); **Laboratoire de Santé et d'Hygiène Mobile, Yaoundé, Cameroon** (L Zekeng PhD); **National AIDS Program, Yaoundé, Cameroon** (L Zekeng); **and French National Agency for Research on AIDS (ANRS), Paris, France** (Prof M Kazatchkine MD)

Correspondence to:
Prof Eric Delaporte, Institut de Recherche pour le Développement-UMR 145, 911 avenue Agropolis, BP 64501, 34394 Montpellier cedex 5, France
Eric.Delaporte@mpl.ird.fr

Summary

Background **Generic fixed-dose combinations have been prequalified by WHO to treat HIV-infected patients in resource-limited countries. Despite their widespread use they are, however, not yet recommended by some of the major donor agencies owing to scarcity of clinical data on effectiveness, safety, and quality. We aimed to assess these issues for one of the most frequently prescribed treatments in Africa, a generic fixed-dose combination of nevirapine, stavudine, and lamivudine.**

Methods **60 patients were followed in an open-label, 24-week multicentre trial in Cameroon. All patients received one tablet of the fixed-dose combination drug twice daily. The primary outcome measure was the proportion of patients with viral load less than 400 copies per mL at the end of the study period, in an intention-to-treat analysis.**

Findings **At baseline, 92% of patients (n=55) had AIDS; median CD4 count was 118 cells per μL (IQR 78–167) and median plasma HIV-1 RNA was 104 736 copies per mL (40 804–243 787). The proportion of patients with undetectable viral load (<400 copies per mL) after 24 weeks of treatment was 80% (95% CI 68–89). Median (IQR) change in viral load was –3·1 $\log_{10}$ copies per mL (–2·5 to –3·6) and in CD4 count 83 cells per μL (40–178). The probability of remaining alive or free of new AIDS-defining events was 0·85 (95% CI 0·73–0·92). Frequency of disease progression was 32·0 (95% CI 16·6–61·5), severe adverse effects 17·8 (7·4–42·7), and genotypic resistance mutations 7·1 (1·8–28·4) per 100 person-years. Mean reported adherence rate was 99%. Median drug concentrations in tablets were 96% of expected values for nevirapine, 89% for stavudine, and 99% for lamivudine.**

Interpretation **Our findings lend support to use and funding of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine as first-line antiretroviral treatment in developing countries.**

Introduction

Access to antiretroviral drugs for HIV-infected patients in developing countries is a global public health priority. With the support of multilateral and bilateral programmes, non-governmental organisations, and national authorities, WHO has the ambitious objective to treat 3 million people with highly active antiretroviral therapy (HAART) by 2005.[1] WHO currently recommends first-line therapy with two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-NRTI (NNRTI), a combination with good efficacy, tolerability and simplicity, low cost, and good adherence to treatment.[2]

Generic fixed-dose combinations of such regimens are widely regarded as crucial for scaling-up AIDS treatment in developing countries. These treatments improve adherence owing to the fewer daily doses relative to individual formulations. Supply, storage, and distribution are also easier because the range of products is smaller. Generic drugs are generally much cheaper than brand-name formulations. Several generic fixed-dose combinations have been prequalified by WHO[3] after assessment of manufacturers' product data (including data for purity of all ingredients, stability of the finished products, and results of in-vivo bioequivalence tests), actual pharmacological composition, and manufacturing practices. However, these formulations are not yet recommended by some of the major donor agencies, such as the US government's multi-billion dollar PEPFAR (President's emergency plan for AIDS relief funding) programme for developing countries.[4] In addition to political considerations, particularly on the legitimacy and consequences of using generic instead of brand-name drugs, this situation is partly explained by the absence of clinical studies showing the efficacy and tolerability of generic fixed-dose combinations. Quality control of different drug batches is also a difficulty in most developing countries.

The generic fixed-dose combination of nevirapine, stavudine, and lamivudine (Cipla, Mumbai Central, Mumbai, India) is one of the most frequently prescribed treatments in African countries. In Cameroon, a central African country with more than 15 million inhabitants, the prevalence of HIV infection is increasing rapidly, with up to 11·8% of town-

dwelling pregnant women infected.[5] HIV-1 predominates, and HIV-1 groups M, N, and O and many subtypes and circulating recombinant forms co-circulate.[6] A national antiretroviral access programme is ongoing, with more than 7500 people currently receiving HAART, most usually based on the generic combination of nevirapine, stavudine, and lamivudine owing to its low price (US$20 monthly).

A pilot project on access to antiretroviral drugs in Yaoundé, the capital of Cameroon, was initiated by the country's National AIDS Program, the Military and Central Hospitals, Médecins Sans Frontières in Switzerland, and the Institut de Recherche pour le Développement in France. This project gave us the opportunity to do a clinical trial aimed at assessing the short-term effectiveness and tolerability of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine and to control the quality of the different drug batches actually received by the patients.

Methods

Our study was an open-label, one arm, multicentre trial.[7] Two hospitals in Yaoundé, Cameroon, participated in the study: the Military Hospital (Projet PRESICA/PARVY); and the Central Hospital (Department of Infectious Diseases and Ambulatory Care Unit). All patients gave their written informed consent. The national ethics committee of Cameroon approved the study protocol.

Patients

Study enrolment was between November, 2002, and April, 2003. Patients were eligible if they had confirmed HIV-1 group M infection, were older than 18 years, and had not taken antiretrovirals before (apart from for prevention of mother-child transmission). They had to have either: clinical AIDS (except for pulmonary tuberculosis) according to the 1993 revised Centers for Disease Control classification[8] (CDC group C); mild symptoms (CDC group B) or pulmonary tuberculosis and a CD4 count less than 350 cells per μL; or no symptoms (CDC group A) and a CD4 count less than 200 cells per μL; and a Karnofsky score of at least 50%. The following biological criteria also applied: serum transaminases, bilirubin, and amylase amounts less than three times the upper limit of normal; serum creatinine less than 200 μmol/L; haemoglobin more than 80 g/L; neutrophils more than $0{\cdot}75\times10^9$/L; and platelets more than 50×10^9/L.

Patients were ineligible if they had HIV-2 or HIV-1 group O or N infection, active or uncontrolled opportunistic infections, peripheral neuropathy, active malignant disease (except for mucocutaneous Kaposi's sarcoma), active psychiatric disorders, were pregnant, breastfeeding, or had hepatocellular insufficiency, or if they were receiving anticancer chemotherapy, corticosteroids, immunomodulators, or other trial drugs.

Procedures

All patients received one tablet of the study treatment (nevirapine 200 mg; stavudine 30 mg for patients weighing <60 kg or 40 mg otherwise; and lamivudine 150 mg) twice daily. To minimise the adverse effects of nevirapine, we gave patients one tablet of the study treatment once daily and one tablet of both lamivudine (Cipla, Mumbai Central, Mumbai, India) and stavudine (Bristol-Myers-Squibb, New York, NY, USA) 12 h later, for the first 14 days.

Patients attended study visits at weeks 0, 2, 4, 6, and 8, and every 4 weeks thereafter until week 24. During every visit we reviewed the patient's medical history, did a physical examination, and if necessary, undertook standardised laboratory tests. We measured plasma HIV-1 viral load with the Bayer bDNA HIV-1 Quantiplex ultrasensitive assay version 3.0 (Bayer Diagnostics, Emeryville, CA, USA) at weeks 0, 12, and 24. We assessed CD4 cell counts with FACSCount apparatus (Becton Dickinson, Mountain View, CA, USA) at weeks 0 and 24. Biological assessments of tolerability included measurement of serum transaminase activities, amount of haemoglobin, and white blood cell and platelet counts at weeks 0, 4, 8, 12, and 24 (and weeks 2 and 6 for transaminase assays), and amylase concentration at weeks 0 and 24. We screened for HBsAg with an enzyme immunoassay (Monolisa Ag HBs Plus, Bio-Rad, Marnes la Coquette, France). To screen for antibodies to hepatitis C virus (antiHCV) we used a third-generation enzyme immunoassay (Ortho HCV ELISA 3.0, Ortho-clinical Diagnostics, Riratan, NJ, USA); we confirmed positive samples with a recombinant immunoblot assay (Chiron RIBA HCV 3.0 SIA, Chiron Corporation, Emeryville, CA, USA). Both tests were done at baseline.

To look for antiretroviral resistance mutations we sequenced HIV protease and reverse transcriptase genes when a suboptimum virological response was obtained or when plasma viral load increased after being undetectable (1000 copies per mL for both criteria), as previously described.[9] Patients with detectable virus underwent genotypic resistance testing at baseline and time of treatment failure.

We defined disease progression by occurrence of new clinical AIDS-defining events or death. To assess adverse effects of study treatment we used clinical and biological criteria and graded them with the toxicity scale used by the French National Agency for Research on AIDS (ANRS). Adherence to study treatment during the previous 7 days was self-reported by patients to their doctors at every study visit; we also assessed adherence by measurement of plasma nevirapine, stavudine, and lamivudine concentrations at weeks 2, 4, and 24 with validated reverse-phase high-performance liquid chromatography coupled with ultraviolet detection assays, after liquid-phase or solid-phase extraction (see below).[10–12] Limits of quantification for nevirapine,

stavudine, and lamivudine were 50 μg/L, 10 μg/L, and 10 μg/L, respectively. We judged nevirapine plasma concentration to be adequate if it reached 3400 μg/L;[13] owing to the drug's long plasma half-life, an amount less than 50 μg/L suggested probable non-adherence for several days.

We assessed the quality of the generic tablets macroscopically, weighed them, and then measured the quantities of the three drugs. At least two tablets from every batch given to patients were analysed. To measure the quantity of every drug, we crushed the tablets and accurately weighed a homogeneous sample of powder, which we dissolved (in gauged flasks) in either methanol for nevirapine and stavudine or distilled water for lamivudine. Technical processing was validated with the corresponding European approved drug: Viramune (Boehringer Ingelheim, Paris, France) for nevirapine, Zerit (Bristol-Myers-Squibb, Puteaux, France) for stavudine, and Epivir (GlaxoSmithKline, Marly-le-Roi, France) for lamivudine.

Statistical analysis

So we could detect a decrease in viral load to less than 400 copies per mL in at least 70% of patients (α=5%, one-sided test; β=15%), we calculated that 57 patients had to be included, which we rounded up to 60.

Primary endpoints for antiretroviral effectiveness were proportion of patients who had plasma HIV-1 RNA values less than 50 and 400 copies per mL; we did an intention-to-treat analysis that included all patients, even those who died, were lost to follow-up, or discontinued study treatment. We judged missing data to represent treatment failure. As-treated analyses—including only patients who took study treatment and for whom data were available—were also done for the same endpoints. We estimated 95% CIs of percentages by the binomial exact method.

Secondary endpoints for effectiveness included reduction in $\log_{10}$-transformed viral load and increase in CD4 cell count from baseline, on an intention-to-treat basis. Viral load less than 50 copies per mL (detection limit of assay) or more than 500 000 copies per mL (upper limit of quantification) were assigned these respective values. Median changes are reported with the IQR.

Incidence of disease progression, adverse effects of study treatment, and genotypic resistance mutations were expressed as the number of events per 100 person-years of follow-up, from enrolment to the week 24 visit. Patients lost to follow-up were censored at their last study visit and those who died at time of death. We estimated the cumulative probability of remaining alive or free of new AIDS-defining events with the Kaplan-Meier method.

We included all patients who took at least one dose of study treatment in the analyses and we used Stata 7.0 software (Stata, College Station, TX, USA).

	Number of patients (n=60)
Demography	
Women	41 (68%)
Age (years)	34·5 (29·0–40·5)
Anthropometry	
Bodyweight (kg)	63·0 (54·3–70·0)
Body-mass index (kg/m²)	23·1 (21·6–24·2)
HIV infection	
Time since diagnosis of HIV seropositivity (months)	12·2 (3·2–37·0)
CDC clinical stage	
A	10 (17%)
B	25 (42%)
C	25 (42%)
CD4 count (cells per μL)	118 (78–167)
Viral load (copies per mL)	104 736 (40 804–243 787)
Haematology	
Haemoglobin concentration (g/L)	104 (98–117)
Neutrophil count (×10⁹/L)	2·032 (1·409–2·663)
Platelet count (×10⁹/L)	160·0 (130·5–215·5)
Biochemistry	
Alanine aminotransferase (U/L)	22 (14–30)
Amylase (U/L)	68 (33–156)
Hepatitis serology	
HBsAg positivity	5 (8%)
AntiHCV positivity	11 (18%)
History of antiretroviral therapy	
Naive	58 (97%)
Nevirapine for mother-child prevention	2 (3%)

Data are median (IQR) or number of patients (%).

Table: **Baseline characteristics**

Role of the funding source

This study was supported by a grant from ANRS, which reviewed the protocol but did not request substantial changes in the study design and had no role in data collection, data analysis, data interpretation, or writing of the report. No pharmaceutical companies were involved.

Results

61 patients were enrolled, 41 (67%) at the Military Hospital and 20 (33%) at the Central Hospital. One patient never took the study treatment and was excluded from all analyses. All patients were Cameroonian; the table shows their baseline characteristics. 55 had AIDS (92%), on the basis of clinical and biological criteria. Only two women had taken nevirapine for the prevention of mother-child transmission at delivery (once each). One patient was lost to follow-up after 15 weeks; one did not attend one visit (week 2) and two missed two consecutive visits (weeks 6 and 8, and weeks 16 and 20).

One patient discontinued study treatment because of nevirapine cutaneous toxic effects and was switched to indinavir after 24 days. Treatment was stopped for reasons other than toxic effects in two individuals: nevirapine was replaced by efavirenz after 23 and 69 days owing to pulmonary tuberculosis.

In the intention-to-treat analysis, the proportions of patients whose plasma HIV RNA level fell below

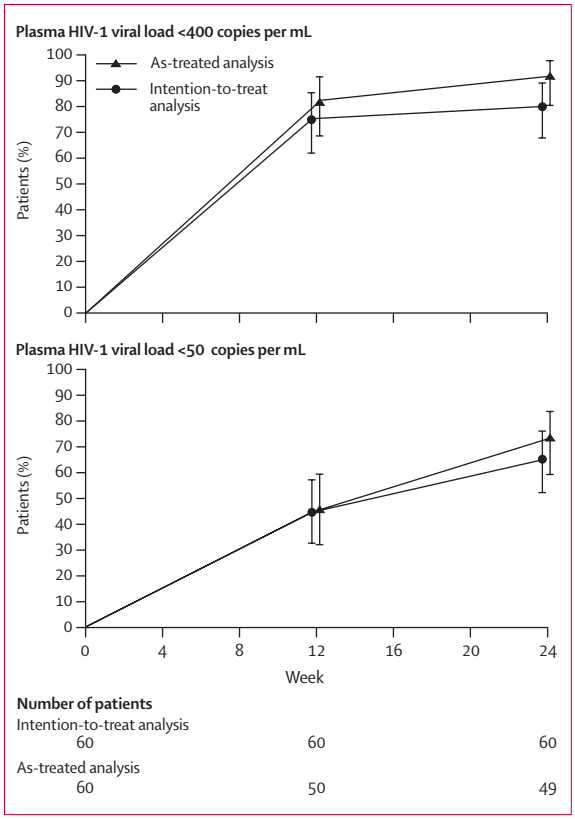

Figure 1: **Plasma HIV-1 viral load**
Vertical bars represent 95% CIs.

400 copies per mL were 75% (95% CI 62–85) at week 12 and 80% (68–89) at week 24, and those whose level fell below 50 copies per mL were 45% (32–58) at week 12 and 65% (52–77) at week 24 (figure 1). In the as-treated analysis, 82% (69–91) fell below 400 copies per mL at week 12, 92% (80–98) did at week 24; the proportions of patients whose HIV RNA level fell below 50 copies per mL were 46% (95% CI 32–61) at week 12 and 73% (59–85) at week 24. Median (IQR) decline in viral load from baseline was 3·0 $\log_{10}$ copies per mL (2·5–3·5) at week 12 (n=55) and 3·1 $\log_{10}$ copies per mL (2·5–3·6) at week 24 (n=54). After 24 weeks of treatment, the median (IQR) increase in the CD4 count was 83 cells per μL (40–178, n=53). Half the patients (n=27) reached an absolute CD4 count of 230 cells per μL (155–341).

The overall frequency of disease progression was 32·0 per 100 person-years (95% CI 16·6–61·5). Four patients (7%) had new clinical AIDS-defining events (incidence 14·2 per 100 person-years, 95% CI 5·3–37·9), namely tuberculosis (n=2), Kaposi's sarcoma (n=1), and cryptococcosis (n=1). Five other patients (8%) died, giving a rate of death of 17·8 per 100 person-years (95% CI 7·4–42·7). As shown in figure 2, all but one event occurred during the first 9 weeks of treatment. The cumulative probability of remaining alive or free of new AIDS-defining events after 24 weeks was 0·85 (95% CI 0·73–0·92). Eight of the nine patients who progressed or died had AIDS at baseline; the other patient, who developed Kaposi's sarcoma, was in CDC group B2. Four of the five patients who died had baseline CD4 counts less than 50 cells per μL (1, 10, 12, and 43 cells per μL) and the fifth had 73 cells per μL. In addition to advanced HIV disease, those who died had severe anaemia (haemoglobin 47 g/L) and cachexia (n=1), pulmonary infection (n=1), headache and dizziness (n=1), or poor general health (n=2).

Five severe (grade 3) adverse effects were attributed to study treatment (incidence 17·8 per 100 person-years, 95% CI 7·4–42·7). One patient developed generalised urticaria 13 days after starting treatment and had raised alanine aminotransferase (274 U/L [normal range 0–35 U/L]); both disorders resolved when nevirapine was replaced with indinavir. Two other individuals had increased alanine aminotransferase (311 U/L and 158 U/L) after 2 and 6 weeks of treatment, respectively; concentrations returned to normal spontaneously in one and fell to 88 U/L in the second. Finally, one patient had a transient amylase rise at 24 weeks (521 U/L [normal range 0–100 U/L]) with no clinical signs of pancreatitis. The study treatment was not discontinued in these three patients. No cases of grade 3 peripheral neuropathy were recorded, only three cases of grade 1 and one of grade 2. No grade 4 adverse events occurred (95% CI 0–13·1 per 100 person-years).

The mean self-reported adherence rate was 99%. Only nine patients reported incidents relating to adherence: five did not take the study treatment at all during the last 7 days either because they did not attend (n=3) or postponed (n=1) the relevant study visit or because of a psychiatric disorder (n=1); three patients forgot one dose; and one missed four doses owing to dizziness. Plasma drug concentrations were available at weeks 2 (n=56), 4 (n=56), and 24 (n=50). Only two patients presented (at both weeks 2 and 4) with nevirapine, stavudine, and lamivudine plasma concentrations less than the limits of quantification. An

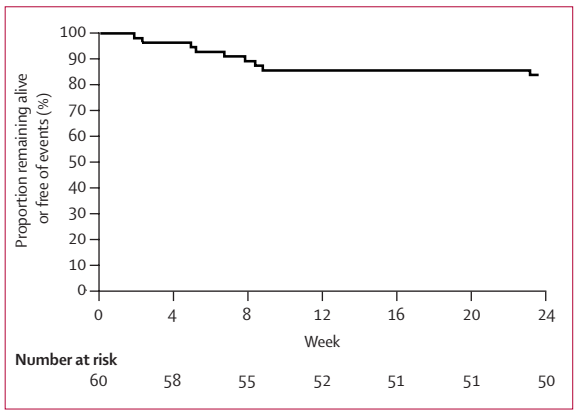

Figure 2: **Probability of remaining alive or free of new AIDS-defining events**

adequate nevirapine plasma concentration (≥3400 μg/L) was reached by 79% (95% CI 66–88) of patients at week 2, 93% (83–98) at week 4, and 84% (71–93) at week 24. Overall median plasma concentration of nevirapine was 5008 μg/L (range <50–19 122) and those measured 12 h after last drug intake were 16 μg/L (<10–107) for stavudine and 172 μg/L (12–890) for lamivudine.

Eight patients had viral load values greater than 1000 copies per mL once (n=6) or twice (n=2) during treatment. Major genotypic resistance mutations were recorded in two of these patients (frequency 7·1 per 100 person-years, 95% CI 1·8–28·4). One had Met184Val and Lys103Asn mutations at week 12 conferring resistance to lamivudine and NNRTIs (viral load 1092 copies per mL). This patient had taken one dose of nevirapine 2 months before enrolment for prevention of mother-child transmission. Her viral load fell to 106 copies per mL at week 24 with the study treatment. The second patient had the Tyr181Cys mutation conferring resistance to NNRTIs and at week 12 had viral load more than 500 000 copies per mL. This patient was subsequently lost to follow-up.

Seven batches of study treatment were dispensed. Compared with expected doses, median (range) concentrations of the three components were nevirapine 96% (89–100), stavudine 89% (84–96), and lamivudine 99% (91–103).

Discussion

Generic fixed-dose combinations of two NRTIs and one NNRTI are now among the most widely prescribed first-line antiretroviral regimens in developing countries, yet we are aware of no clinical trials assessing their effectiveness, safety, and quality in field conditions. Brief reports have been presented but these have omitted important data such as virological efficacy, adherence, and viral resistance.[14,15] In our open clinical trial, we have documented the quality of a commonly prescribed generic fixed-dose combination and shown that its effectiveness and tolerability are similar to that reported with other HAART regimens in patients with comparable baseline HIV disease status.

One key issue about the use of generic fixed-dose combinations is their quality. Very few data on the purity of generic antiretroviral drugs have been published,[16] yet incorrect dosing could have a major negative effect on tolerability, efficacy, and viral resistance. We tested all seven batches dispensed to our patients and noted that the unit dose of every component (lamivudine, stavudine, nevirapine) was as claimed.

Despite wide intersubject variability of the plasma concentrations of the three drugs in the fixed-dose combination, the ranges were as expected and consistent with those previously described for the approved drugs. Only two patients presented at both weeks 2 and 4 with nevirapine, stavudine, and lamivudine plasma concentrations lower than the respective limits of quantification, suggesting some adherence difficulties. These results accord with the excellent self-reported adherence (99%), and this finding was corroborated by the good virological response. Many factors can affect adherence to treatment, such as social support, cost, and tolerability, but treatment simplicity is one of the most important.[17] Fixed-dose combinations therefore have a clear advantage in terms of number of pills and cost. In Cameroon, the cost of the fixed-dose combination we assessed here is US$20 per month, whereas the same combination with brand-name drugs in the ACCESS programme (http://www.unaids.org) costs around $35, and six pills have to be taken instead of two with fixed-dose combinations. Our results for adherence are similar to those obtained with once-a-day didanosine-lamivudine-efavirenz therapy in Senegal.[18]

The virological and immunological efficacy of the regimen used by us was at least as good as that obtained with HAART in industrialised countries; for example, in a trial of a triple-drug regimen—including a protease inhibitor (indinavir)—in patients with CD4 counts less than 200 cells per μL, a virological success rate (viral load <500 copies per mL) of 60% and an increase in CD4 count of 91 cells per μL were reported at 24 weeks.[19] The effectiveness of the combination of nevirapine, stavudine, and lamivudine has also been shown.[20] Compared with African therapeutic cohorts in which most patients also have advanced HIV disease at enrolment[21–25] our results are highly satisfactory. They also compare well with those of a cohort of African patients treated in London, UK.[26] Comparison with other studies, such as use of generic drugs in India,[15] is more difficult since the study design differs and the number of variables analysed is limited.

Nevirapine and stavudine can have troublesome adverse effects. Tolerability was good in our trial, both overall and specifically with respect to nevirapine, and was even slightly better than that usually seen in developed-world cohorts.[27] Treatment was stopped in only one individual for a cutaneous reaction to nevirapine. Hepatic tolerability was good, especially considering that 18% of patients were infected by hepatitis C virus and 8% by hepatitis B virus, with only transient or moderate rises of hepatic transaminases found.

Our results for the emergence of resistance are only preliminary owing to the fairly short follow-up (24 weeks). Virological failure (>1000 copies per mL) happened in eight patients. Only one instance of genotypic resistance to NNRTIs was recorded at week 12, in a non-compliant patient who was subsequently lost to follow-up. The other example is intriguing—a woman with a viral load of 1092 copies per mL and the Met184Val and Lys103Asn mutations at week 12 who had received nevirapine to prevent mother-

child transmission. In a report in Thailand, the virological success of HAART with nevirapine in such women was only 46% at week 24 because of a high rate of resistance mutations after one dose of nevirapine.[28] Despite these two mutations, viral load at week 24 was less than 400 copies per mL (it was still below this level at treatment week 48).

The open-label one-arm design used in this study is not as powerful as a controlled trial to show the efficacy and safety of fixed-dose combinations but it can be used to assess efficacy of treatment regimens because it preserves size, power, and simplicity.[7,18]

In conclusion, we have documented the quality, safety, and effectiveness of a generic fixed-dose antiretroviral combination in an African setting. Although controlled trials including more patients and longer follow-up will be important, our results lend support to the use and funding of generic fixed-dose combinations as first-line antiretroviral treatment in developing countries.

Contributors

The study was designed and coordinated by C Laurent, C Kouanfack, A Bourgeois, F Liégeois, M Peeters, L Zekeng, S Koulla-Shiro, A Calmy, E Mpoudi-Ngolé, and E Delaporte (principal investigator). C Laurent contributed to data collection, did statistical analyses, and, with E Delaporte, wrote the first draft of the report. N Nkoué, A Bourgeois, B Lactuock, V Nzeusseu, R Mougnutou, and F Liégeois contributed to data collection. G Peytavin, E Nerrienet, M Peeters, and L Zekeng did laboratory analyses. All authors contributed to the writing of the final report.

Conflict of interest statement

None declared.

Acknowledgments

We thank all patients and staff of the Military and Central Hospitals who participated in the study. The study was supported by a grant from the French National Agency for Research on AIDS (ANRS).

References

1 WHO, UNAIDS. Treating 3 million by 2005: making it happen—the WHO strategy. Geneva: World Health Organization, 2003. Available at: http://www.who.int/3by5/publications/documents/en/3by5StrategyMakingItHappen.pdf (accessed June 7, 2004).

2 WHO. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach—2003 revision. Geneva: World Health Organization, 2003. Available at: http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf (accessed June 7, 2004).

3 WHO. Prequalification project: procurement, quality and sourcing project—access to HIV/AIDS drugs and diagnostics of acceptable quality. http://mednet3.who.int/prequal/ (accessed June 7, 2004).

4 USAID. HIV/AIDS, President's Emergency Plan for HIV/AIDS relief, fact sheets. http://www.usaid.gov/our_work/global_health/aids/pepfarfact.html (accessed June 15, 2004).

5 UNAIDS. Report on the global HIV/AIDS epidemic, July 2002. Geneva: Joint United Nations Programme on HIV/AIDS, 2002: 226P.

6 Vergne L, Bourgeois A, Mpoudi-Ngole E, et al. Biological and genetic characteristics of HIV infections in Cameroon reveals dual group M and O infections and a correlation between SI-inducing phenotype of the predominant CRF02_AG variant and disease stage. *Virology* 2003; **310:** 254–66.

7 Fleming TR. One-sample multiple testing procedure for phase II clinical trials. *Biometrics* 1982; **38:** 143–51.

8 Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep* 1992; **41:** 1–19.

9 Vergne L, Touré Kane C, Laurent C, et al. Low rate of genotypic HIV-1 drug-resistant strains in the Senegalese government initiative of access to antiretroviral therapy. *AIDS* 2003; **17** (suppl 3)**:** S31–38.

10 Van Heeswijk RP, Hoetelmans RM, Meenhorst PL, Mulder JW, Beijnen JH. Rapid determination of nevirapine in human plasma by ion-pair reversed-phase high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B Biomed Sci Appl* 1998; **713:** 395–99.

11 Burger DM, Rosing H, van Gijn R, Meenhorst PL, van Tellingen O, Beijnen JH. Determination of stavudine, a new antiretroviral agent, in human plasma by reversed-phase high-performance liquid chromatography with ultraviolet detection. *J Chromatogr* 1992; **584:** 239–47.

12 Harker AJ, Evans GL, Hawley AE, Morris DM. High-performance liquid chromatographic assay for 29-deoxy-39-thicytidine in human serum. *J Chromatogr B Biomed Appl* 1994; **657:** 227–32.

13 Halvir D, Cheeseman S, McLaughlin M, et al. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with HIV infection. *J Infect Dis* 1995; **171:** 537–45.

14 Hosseinipour M, Namarika D, Magomero K, et al. The Malawian antiretroviral program: the first year experience with Triomune. 10th conference on retroviruses and opportunistic infections. Feb 10–14, 2003; San Francisco, CA, USA: abstr 172.

15 Kumarasamy N, Solomon S, Chaguturu SK, et al. The safety, tolerability and effectiveness of generic antiretroviral drug regimens for HIV-infected patients in south India. *AIDS* 2003; **17:** 2267–69.

16 Henry K, Brundage R, Weller D, Akinsete O, Shet A. Comparison of generic zidovudine + lamivudine (Cipla, Duovir) and the GlaxoSmithKline Brand (Combivir) tablets. *J Acquir Immune Defic Syndr* 2004; **35:** 537.

17 Chesney M. Adherence to HAART regimens. *AIDS Patient Care STD* 2003; **17:** 169–77.

18 Landman R, Schiemann R, Thiam S, et al. Once-a-day highly active antiretroviral therapy in treatment-naive HIV-1-infected adults in Senegal. *AIDS* 2003; **17:** 1017–22.

19 Hammer SM, Squires KE, Hugues MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997; **337:** 725–33.

20 van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; **363:** 1253–63.

21 Laurent C, Diakhaté N, Ngom Gueye NF, et al. The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study. *AIDS* 2002; **16:** 1363–70.

22 Weidle PJ, Malamba S, Mwebaze R, et al. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet* 2002; **360:** 34–40.

23 Djomand G, Roels T, Ellerbrock T, et al. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Côte d'Ivoire. *AIDS* 2003; **17** (suppl 3)**:** S5–15.

24 Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004; **18:** 887–95.

25 Tassie JM, Szumilin E, Calmy A, Goemaere E. Highly active antiretroviral therapy in resource-poor settings: the experience of Médecins Sans Frontières. *AIDS* 2003; **17:** 1995–97.

26 Frater AJ, Dunn DT, Beardall AJ, et al. Comparative response of African HIV-1-infected individuals to highly active antiretroviral therapy. *AIDS* 2002; **16:** 1139–46.

27 Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001; **15:** 1261–68.

28 Jourdain G, Ngo-Giang-Huong N, Tungyai P, et al. Exposure to intrapartum single-dose nevirapine and subsequent maternal 6-month response to NNRTI-based regimens. 11th conference on retroviruses and opportunistic infections. Feb 8–11, 2004; San Francisco, CA, USA: abstr 41LB.