First-line Antiretroviral Therapy in Africa – How Evidence-based are our Recommendations?

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Abstract

According to the World Health Organization guidelines, a non-nucleoside reverse transcriptase inhibitor (NNRTI) along with two nucleoside reverse transcriptase inhibitors (NRTI) is the treatment of choice as first-line antiretroviral therapy. The results of the 2NN and different cohort studies performed in developed countries do not provide sufficient evidence by which to select between nevirapine and efavirenz as the first-line NNRTI for antiretroviral therapy in Africa. The current first-line NNRTI-containing antiretroviral therapy regimens used in Africa are certainly not ideal. Nevirapine interacts with rifampicin and therefore is not indicated in patients with tuberculosis. On the other hand, efavirenz should not be given to pregnant women. NNRTI-containing regimens may be less effective in women who received nevirapine monotherapy at delivery. Stavudine, used in the nucleoside backbone, may lead to lipoatrophy, lactic acidosis and polyneuritis. Zidovudine may cause serious anemia. Mainly because of cost considerations, the generic fixed-drug combination of nevirapine plus two NRTI seems at the moment to be the best choice. It is clear, however, that antiretroviral programs should not rely only on this combination for initial antiretroviral treatment. Most importantly, more HIV clinical trials need to be conducted in Africa, and African cohorts of patients on antiretroviral therapy need to be established in order to develop recommendations that are evidence based. **(AIDS Reviews 2005;7:148-54)**

Key words

HIV. Antiretroviral therapy. First-line therapy. Non-nucleoside reverse transcriptase inhibitors. Countries with limited resources.

Introduction

Despite the World Health Organization's "3 by 5" initiative[1], access to antiretrovirals remains very difficult in resource-poor settings. According to the WHO guidelines, a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTI) is the treatment of choice for first-line antiretroviral therapy (ART)[2]. Concerning the choice of NNRTI, there are two possibilities: nevirapine or efavirenz. According to recently published results of the 2NN study (a large, multicenter, randomized, clinical trial comparing three first-line NNRTI regimens), the efficacy of a nevirapine-containing regimen is comparable to an efavirenz-containing regimen[3]. On the other hand, several cohort studies suggest that an efavirenz-containing regimen may have a higher antiviral efficacy[4-6]. In this paper we discuss how relevant these findings are to HIV patient care in Africa.

Data for this review were identified by searches of Medline and abstracts of the 2nd IAS Conference on HIV Pathogenesis and Treatment in Paris 2003, the XV International AIDS Conference in Bangkok (2004),

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Table 1. African cohort studies involving at least 200 HIV+ patients using NNRTI regimens as first-line antiretroviral treatment

Authors, country, reference	Number of patients, type of patients, study type	Treatment regimen, months (m) of follow-up	Immunologic/virologic outcome	Mortality (%)
Jeannin, et al. Malawi[8]	1266, 96.8% ART-naive Cohort	Fixed dose generic d4T/3TC/NVP: 79.1% Length of treatment: at least 6 m	VL: 84.1% < 400 copies/ml	12.9
Coetzee, et al. South Africa[9]	287, 100% ART-naive Cohort	ZDV+3TC+EFV: 60%; ZDV+3TC+NVP: 38%; Length of treatment: median 13.9 m.	Mean CD4 count: +184/µl at 12 m, VL: 84.2% < 400 copies/ml at 12 m	13.7
Hudspeth, et al. South Africa[10]	352, 96.6% ART-naive Cohort	d4T+3TC+EFV: 92% Length of treatment: 3m		1.4
Stringer, et al. Zambia[11]	1043, Cohort	ZDV or d4T+3TC+NVP Length of treatment: 6 m.	Mean CD4 count: +143/µl at 6 m	10.5
Ndwapi, et al. Botswana[12]	306, 100% ART-naive Cohort	ZDV+3TC+NVP: 47.5% ZDV+3TC+EFV: 52% Length of treatment: median 9 m	Mean CD4 count: +204/µl at 9 m VL: 84.5% < 400 copies/ml at 6 m	10.8
Sanne, et al. South Africa[35]	468, 100% ART-naive Randomized clinical trial 3TC *vs.* FTC containing HAART regimen	ZDV+3TC/FTC+NVP: 82% ZDV+3TC/FTC+EFV: 18%	Study was stopped because 2 patients died because of NVP liver toxicity	

VL = Viral Load; ART = antiretroviral treatment; ZDV = zidovudine; 3TC = lamivudine; d4T = stavudine; FTC = emtricitabine; NVP = nevirapine; EFV = efavirenz.

and the 12th Conference on Retroviruses and Opportunistic Infections in Boston (2005). Search terms were: antiretroviral therapy, nevirapine and efavirenz, Africa, countries with limited resources. English and French language papers were reviewed.

What is the evidence?

First, it is important to note that only a limited number of African patients were enrolled in the 2NN study (in South Africa) and that, to date, all cohort studies comparing nevirapine- versus efavirenz-containing regimens were performed in developed countries. If we look at the baseline characteristics of the patients in the 2NN study as well as in published cohort studies from developed countries it is clear that patients enrolled in these studies were quite different from those generally treated in Africa. Patients enrolled in the 2NN study had a mean CD4+ lymphocyte count of 190/µl. Patients from the large cohort studies treated with nevirapine or efavirenz had even higher CD4+ lymphocyte counts at baseline (mean CD4+ lymphocyte count > 200/µl). As a rule, in Africa ART is only started when the CD4+ lymphocyte count drops below 200/µl, and most patients begin therapy with a CD4+ lymphocyte count that is far lower. In both the 2NN study and the cohort studies the majority of patients were male. This contrasts with the situation in Africa, where most patients with AIDS who require ART are female[7]. A summary of African cohorts involving at least 200 patients on a first-line NNRTI-containing regimen is shown in table 1. All these studies, and a few smaller ones[13-16], despite the enrollment of patients with advanced stages of disease, showed relatively good antiretroviral efficacy for both nevirapine- and efavirenz-containing regimens in patients not interrupting their treatment. Similar findings were reported from cohort studies from Asia, but in these cohorts often viral load testing to measure outcome was not performed[17-21].

Today in developed countries, there are differing opinions about what should be the ideal first-line treatment regimen, and recommendations keep changing

as new scientific information becomes available[22]. Everybody agrees that such an ART regimen should be patient-specific. For example, a person with concomitant liver disease should not be treated with nevirapine[23]. On the other hand, in a patient with a history of psychiatric problems, efavirenz should not be the drug of choice[24,25]. Adapting an ART regimen to the characteristics of the individual patient may be possible in resource-rich countries where there is access to many antiretroviral drugs, but this goal is much more difficult to realize in countries with limited resources. In these countries, the resources and infrastructure currently do not exist to "individualize" treatment for millions of very ill patients. If any of the national goals of severely affected, resource-limited countries are to be met, patient-specific regimens cannot be offered in the majority of therapy initiation.

It is not clear how to use the results of the 2NN and cohort studies for treatment decisions in countries with limited resources as it is possible that these regimens will perform quite differently in such settings.

Reasons to believe that nevirapine-containing regimens may perform better in Africa

Nevirapine in Africa is generally given as part of the generic fixed-dose combination of stavudine and lamivudine with nevirapine[26]. This is a very simple treatment: one tablet in the morning and one in the evening. This may improve adherence and therefore treatment outcome.

Reasons to believe that nevirapine-containing regimens may perform worse in Africa

A disadvantage of this fixed-dose combination is that often such treatment is not started or stopped in an ideal way. Because nevirapine induces cytochrome p450, the initial dose should be 200 mg daily, and this dose should be increased only after two weeks to 200 mg bid[27,28]. In contrast, stavudine and lamivudine should be given at a full dose from the beginning. The least expensive way to do so is to give one generic tablet of the fixed dose combination in the morning and one tablet each of lamivudine and stavudine in the evening during the first two weeks. The recently licensed generic antiretroviral combination from Aspen-Pharma (a blister packaged combination where lead-in dosing is possible) is another alternative. Only then should one switch to one tablet of the fixed-drug combination twice daily. A common problem in countries with limited resources is that treatment programs only offer the fixed-dose combination. Therefore, physicians often initiate therapy with one tablet of the fixed-dose combination twice daily. This strategy may lead to increased toxicity. Indeed, studies performed in the USA and Europe showed that initiating nevirapine 400 mg daily during 14 days was 2–4 times more likely to produce rash and toxicity then a 200 mg dose regimen[27]. Yet, by giving only one tablet of the fixed dose combination daily in the first two weeks in order to avoid toxicity, resistance might be induced by exposing patients to an insufficient dose of stavudine and lamivudine.

Conversely, problems may arise when stopping the fixed-dose combination. Because of the long half-life of nevirapine, ideally stavudine and lamivudine should be continued for about seven days after the fixed-dose combination is stopped[29]. Stopping the fixed-dose combination without continuing stavudine and lamivudine may also lead to resistance. But, if the separate drugs stavudine and lamivudine are not available this is not possible. The use of generic fixed-dose combinations has been criticized because questions have been raised about the quality of these drugs. However, in an open-label trial in Cameroon, the fixed-drug combination lamivudine, stavudine and nevirapine produced a good virologic response[13], excellent adherence, and an acceptable toxicity profile. Mean reported adherence was 99%. The mean drug concentrations in the tablets were 96% of expected values for nevirapine, 89% for stavudine, and 99% for lamivudine[13]. Other studies also showed bioequivalence between the generic fixed-dose combination with the concurrent administration of lamivudine, nevirapine and stavudine as separate drugs[30,31].

In Africa, many patients are coinfected with hepatitis B and in some regions also with hepatitis C[32]. This raises the concern that nevirapine-containing regimens may perform less well because of an increased risk of hepatotoxicity[33,34]. In a recent study performed in South Africa, the occurrence of early hepatotoxicity associated with nevirapine was 17% compared with 0% with efavirenz. Female sex and low body mass index were the major risk factors for nevirapine toxicity[35]. The high percentage of liver toxicity in this population was probably related to the high baseline CD4+ lymphocyte count of the study participants (mean CD4+ count 398/µl). On the other hand, in a recent study performed in Thailand of 302 women treated with a nevirapine-containing regimen during pregnancy in MTCT-Plus pro-

grams, 9.4% developed liver and/or skin toxicities, but neither nevirapine-related mortality nor significant differences between women with a CD4+ lymphocyte count < or > 200/µl was observed[36].

If it should be true (as sometimes suggested[37] but not proven[38]) that efavirenz performs better than nevirapine in patients with a low CD4+ lymphocyte count and a higher viral load, nevirapine regimens should be expected to perform less well in developing countries, where patients start ART later in the course of their illness.

Generally, the safety profile of nevirapine in women, who form the bulk of treatment candidates in Africa, is less good with more reported side effects, particularly in pregnant women with a CD4+ lymphocyte count > 250/µl[39].

In Africa, many HIV patients develop active *Mycobacterium tuberculosis* infection, even when they are treated with highly active antiretroviral therapy (HAART)[40]. Rifampicin, because it is a cytochrome p450 inducer, decreases NNRTI drug levels, and impacts on nevirapine drug levels more than those of efavirenz[41]. Therefore, nevirapine-containing regimens are generally avoided in HIV/tuberculosis (TB) coinfected patients who are being treated with rifampicin[42]. Moreover, continuing nevirapine in patients coinfected with TB may be risky because of the potential hepatotoxicity of several commonly used anti-TB drugs. So, it could be argued that nevirapine should not be used as first-line ART in Africa, where the incidence of TB is high among HIV-infected individuals. However, recent small studies in Europe showed a good virologic response and no serious liver toxicity associated with the use of a nevirapine-containing regimen in TB patients treated with rifampicin[42].

Reasons to believe that efavirenz-containing regimens may perform worse in Africa

Efavirenz is potentially more teratogenic than other antiretrovirals[43]. Therefore, the use of efavirenz in a population in which the majority of the patients are women and most of the women are of childbearing age may be problematic. Women of childbearing age who are receiving efavirenz should use contraceptives. But often they do not. Moreover, oral contraceptives are metabolized more rapidly and have a high failure rate in women taking efavirenz[44].

In a recent study in the USA, higher drug levels of efavirenz were observed in African Americans compared with Caucasian Americans[45]. These high drug levels were associated with more side effects[46]. The proposed explanation for this phenomenon was that African Americans may metabolize efavirenz differently than Caucasian Americans[46]. If this is confirmed, it is possible that the same phenomenon will be observed in Africa. In one study, race has not been found to alter nevirapine pharmacokinetics[47], but additional studies are needed to confirm this[48].

Efavirenz is also an antiretroviral with a long half-life. Therefore, when this drug is stopped physicians should also be aware that the nucleoside backbone should still be continued for several days[49]. However, as efavirenz is generally given in association with other branded drugs, this may be less problematic than with the fixed-drug nevirapine combination.

Efavirenz is more expensive than nevirapine, and even more so if it is combined with two other branded drugs. In situations where most patients have to pay for their drugs, this high cost can complicate adherence. In Africa, the main reason both for stopping antiretrovirals and for taking them irregularly is because patients cannot continue to pay for the drugs[50]. If programs choose only to use the more costly branded drugs, fewer patients can be treated. On the other hand, if generic drugs are chosen as first-line therapy, branded drugs for second-line therapy could be bought with the money saved.

In the developed world, efavirenz has the advantage that it can be included in a once-daily regimen[51]. At the present time however, such regimens are either unavailable or too expensive to be given on a large scale in Africa[52].

Efavirenz is not to be used in young children, while nevirapine can be used.

Both nevirapine- and efavirenz-containing first-line treatment regimens may not be ideal for all patients with HIV infection in Africa

There is currently much concern about the use of NNRTI as first-line ART because of the increased use of nevirapine monotherapy to prevent mother-to-child transmission (MTCT) of HIV[53]. The risk of developing resistance after only a single dose of nevirapine has been estimated to be 32%, and after two doses of nevirapine, 35%[54,55]. A study in Thailand suggested that, in women who develop resistance because of nevirapine prophylaxis, an NNRTI-containing first-line regimen will be less effective[56].

Moreover, increasing numbers of patients in Africa are unable to continue their NNRTI-containing treatment regimens because they run out of funds. It is clear that in the future we will either need new NNRTI (ones that remain highly effective even in the presence of nevirapine/efavirenz mutations)[57] or we must use other first-line ART regimens (e.g. regimens containing a protease inhibitor). Because such new antiretroviral regimens will be much more expensive, everything should be done to avoid the development of NNRTI resistance. This will include increasing access to free antiretrovirals (ARV), switching from nevirapine monotherapy in prevention of mother-to-child transmission (PMTCT) programs to PMTCT Plus programs where mothers receive HAART[58], and using innovative methods to increase patient adherence to ART regimens.

Problems with the NRTI backbone

Because the fixed-dose combination of stavudine, lamivudine, and nevirapine is by far the least expensive regimen, patients continue such treatment even if they develop polyneuritis[59]. This may lead to severe forms of irreversible polyneuritis, even after switching to other ARV. Polyneuritis is frequently observed in AIDS patients on ART in Africa[60], probably because patients start therapy too late and because other risk factors that can induce polyneuritis are often present (e.g. opportunistic infections such as CMV, malnutrition, vitamin B deficiency, and the use of other neurotoxic drugs such as isoniazid)[61]. On the other hand, a zidovudine-containing ARV regimen is often also not optimal because many AIDS patients in Africa present with severe anemia[62]. Indeed, we have witnessed patients dying of anemia in the months after starting a zidovudine-containing HAART regimen. Whatever the reason African patients develop anemia (e.g. advanced HIV infection, helmintic infections, malnutrition, concomitant illnesses such as TB, recurrent malaria, iron deficiency, pregnancies)[62], because of the lack of laboratory facilities the diagnosis of severe anemia may be delayed. Often the anemia is not treated adequately because of limited health care services and the inability to provide safe blood transfusions. Stavudine, and to a lesser extent zidovudine, are also not ideal drugs because they may cause lipoatrophy, hyperlipidemia, and metabolic acidosis. It is clear that Africa requires greater access to tenofovir and new NRTI, with fewer side effects and less need for laboratory monitoring.

Need for HIV clinical trials in Africa

The roll out of ARVs must be carefully monitored in order to identify problems early and institute corrective measures. Multicenter cohort studies not only could be useful to compare efficacy and side effects of different HAART regimens, but also to compare different systems of rolling out ARVs. However, randomized clinical trials also need to be conducted in Africa similar to the approach taken in the West. Such trials are needed to determine optimal first-line treatment regimens as well as treatment strategies for patients with treatment failure, and we need data from randomized clinical trials performed in Africa. For reasons cited above, but also because certain ARV regimens may have a different antiviral efficacy in patients with African HIV subtypes[63], results of clinical trials performed in Europe or the USA should be interpreted with caution before considering using them for implementing treatment policies in Africa. So far it has been extremely difficult to organize such trials. Pharmaceutical companies are reluctant to provide drugs for such trials. Moreover, there is also a risk that trials sponsored by the pharmaceutical industry may not address the problems faced by African clinicians. Studies comparing combinations of branded drugs with generic combinations will find sponsorship an even a bigger challenge. USA-based agencies such as the National Institutes of Health (NIH) and the Gates Foundation may support clinical research, but as a rule they do not fund the procurement of antiretroviral drugs. On the other hand, antiretrovirals provided by the World Bank's Multicountry AIDS program (MAP) or the USA's Presidential Emergency Plan for AIDS Relief (PEPFAR) funds cannot be used for clinical trials comparing different ART regimens. Recently, the European and Developing Countries Clinical Trial Partnership (EDCTP) program was launched. But, of the more than 60 proposals for HIV clinical trials submitted in the first call for proposals, only one was accepted for funding. This situation must change. The international community, multilateral organizations, and local governments should realize that, without an evidence-based plan to scale up ART, there is a great risk that we will chose treatment regimens that are not optimal, leading ultimately to the failure of the scaling-up program.

Conclusion

The results of the 2NN and different cohort studies performed in developed countries do not provide suf-

ficient evidence by which to select between nevirapine and efavirenz as the first-line NNRTI for antiretroviral therapy in Africa. Mainly because of cost considerations, the generic fixed-drug combination of nevirapine plus two NRTIs seems at the moment the best choice. It is clear, however, that ARV programs should not rely only on this combination for initial antiretroviral treatment. In order to properly start and stop such a fixed-drug combination, single NRTIs need also to be available as separate drugs. Efavirenz should be available as an alternative to nevirapine in case of side effects, or to avoid potential drug interactions. Most importantly, more HIV clinical trials in Africa need to be conducted and African cohorts of patients on antiretroviral treatment need to be established in order to develop recommendations that are truly evidence based.

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