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Comparative effectiveness of efavirenz-based antiretroviral regimens in resource-limited settings

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Abstract

Efavirenz (EFV) is a non-nucleoside widely used as first-line therapy for HIV-1 infection. Most of the research available on EFV comes from trials performed in industrialized countries and only a few studies have evaluated EFV in resource-limited settings (RLSs). In this article, we present a systematic review of the available randomized-controlled trials performed in RLSs that have compared EFV with other antiretrovirals, such as nevirapine and protease inhibitors. The data derived from these studies show that both EFV and nevirapine are adequate first-line therapy options for HIV-1 infection in RLSs, even in patients with concomitant tuberculosis. However, EFV may show a slight benefit in terms of toxicity and adverse events. By contrast, the data comparing EFV versus protease inhibitors is contradictory and further studies may be required to elucidate these discrepancies.

Keywords

atazanavir; efavirenz; lopinavir/ritonavir; nevirapine; protease inhibitor; resource-limited setting; treatment naive

Efavirenz (EFV) is a once-a-day, non-nucleoside reverse-transcriptase inhibitor (NNRTI) approved by the US FDA in 1998 for the treatment of HIV-1 [101]. Since its approval, EFV has been widely used in the USA and around the world as a first-line NNRTI in treatment-naïve individuals who start highly active antiretroviral therapy (HAART), except in pregnant women (especially during the first trimester) or in women of childbearing potential who are sexually active and do not use effective or consistent contraception. In addition, EFV is also commonly used in combination with other antiretrovirals (ARVs) to prevent HIV-1 infection in occupational and nonoccupational postexposure prophylaxis.

EFV is a noncompetitive inhibitor of HIV-1 reverse transcriptase, without any activity against HIV-2 [102]. It is extensively metabolized by the liver via the CYP450 pathway, and primarily involves the *CYP2B6* subunit, with partial involvement of the *CYP3A4* and *CYP2A6* subunits [102]. As a result, EFV has multiple drug–drug interactions of clinical importance, which include other ARVs, anti-tuberculous medications (such as rifampin),

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methadone and oral contraceptives, among others [1–3,102]. CNS and neuropsychiatric side effects are common and include somnolence, vivid dreams, sleep disturbances, agitation, dizziness, worsening depression, anxiety and, rarely, hallucinations. CNS side effects usually develop within the first few days of treatment and generally resolve by 4 weeks of continued treatment [102]. Second to CNS side effects, a self-limited, maculopapular skin rash is the most common adverse reaction observed in patients taking EFV. Gastrointestinal symptoms such as nausea, vomiting and diarrhea have also been reported [102]. The most common laboratory abnormalities associated with the use of EFV are mild-to-moderate elevation of the liver transaminases. In addition, EFV can also cause lipid abnormalities such as hypercholesterolemia, although less frequently than protease inhibitors (PIs). EFV can also cause a false-positive test for cannabis in urine toxicology screens.

EFV dosing is usually 600 mg once a day, preferably at bedtime [102]. It is manufactured in the USA as Sustiva® (200-mg capsules and 600-mg tablets) and coformulated with 300 mg of tenofovir disoproxil fumarate (TDF) and 200 mg of emtricitabine (FTC) as a single pill, Atripla®. EFV is also among the approved ARVs included in the President's Emergency Plan for AIDS Relief for distribution in resource-limited settings (RLSs) only, and is available in 50-, 100-, 200- and 600-mg tablets and coformulated with two generic nucleoside reverse-transcriptase inhibitors (NRTIs) such as FTC/TDF, lamivudine/zidovudine (3TC/AZT), 3TC/TDF or 3TC/stavudine (d4T) [103]. EFV is currently recommended as part of the first-line regimen for ARV-naïve individuals in multiple treatment guidelines [4,104,105].

Most of the research on the efficacy of EFV for the treatment of HIV-1 infection is derived from studies performed in the USA and other resource-rich countries (RRCs). Various observational cohorts in RLSs have reported data on the efficacy and safety of EFV in combination with other ARVs in treatment-naïve individuals, but few randomized clinical trials have compared EFV-based regimens to other ARVs, such as nevirapine (NVP) or PIs. In this article we present a systematic review of clinical trials that compare EFV-based regimens to NVP-based and PI-based regimens in RLSs.

Strategy & inclusion criteria

We used a search strategy to identify available publications until 30 September 2011 of clinical trials that compared an EFV-based regimen (with any drug combination used as backbone) to any other three- or four-drug regimen(s) for the treatment of HIV-1/AIDS in RLSs. We performed a search using the following key words: 'efavirenz', 'non-nucleoside reverse-transcriptase inhibitor', 'resource-limited setting', 'clinical trial' and 'antiretroviral treatment'. Our search included MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the ClinicalTrials.gov registry. We also searched for oral presentations and abstracts, from 1997 to 2011, at the following conferences: Conference on Retroviruses and Opportunistic Infections, the World AIDS Conference and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. To be included in our analysis, the studies were required to be randomized clinical trials performed in a RLS. Given the expected variability in different RLS, we did not specify a minimum duration of follow-up. The data of interest for each study included study design, number and baseline characteristics of enrolled subjects, HAART regimen, virologic response, virologic failure, immunologic response, concomitant tuberculosis (TB), mortality, tolerability and the number of individuals who discontinued the regimen for any reason. All the studies evaluated included drug combinations listed as preferred or alternative in the published guidelines [4,104,105]. The published odds ratios (ORs), hazard ratios (HRs) and confidence intervals (CIs) were incorporated into the effect size analysis when available. If not provided, we calculated the OR, HR and CI from the published primary data using EFV-

exposure and nonexposure events and achievement of primary outcome [106]. The effect-size analysis was then conducted using Comprehensive Meta-Analysis/Biostat Version 2.0 (Englewood, NJ, USA).

Results

Our search yielded a total of ten published or presented clinical trials that met the entry criteria for a total of 5827 patients [5–14]. We identified seven studies that compared EFV versus NVP (four that compared 3TC/d4T/EFV vs 3TC/d4T/NVP and three that compared 3TC/AZT/EFV vs 3TC/AZT/NVP) and three studies that compared EFV versus a PI (two that compared EFV vs lopinavir [LPV]/low-dose ritonavir [r] and one that compared EFV vs atazanavir [ATV]). The studies by van Leth *et al.* [6] and Campbell *et al.* [8] also included patients in RRCs (North America, Australia and Europe), but they were included in our analysis because the larger part of their recruitment occurred in a RLS. One study from Cameroon and Senegal that compared FTC/TDF/EFV versus FTC/TDF/NVP versus FTC/TDF/AZT versus TDF/LPV/r has been recently completed, but no results have been published, therefore, it was not included in this review [107]. Table 1 presents the study designs, eligibility, drug regimens and primary outcome(s) of interest. As noted, all the studies were randomized and most of them were open-label. EFV was dosed at 600 mg/day in all reviewed studies, except when coadministered with NVP in the 2NN study by van Leth *et al.* [6]. This dose adjustment was made on the basis of a theoretical decrease in EFV levels when used in conjunction with NVP, not in the presence of TB. The largest study was the Phidisa cohort from South Africa, which evaluated 1771 individuals between 2004 and 2007 [12]. The next two largest studies were the 2NN and the ACTG A5157 PEARLS, both of which were international, multicenter trials, for a combined total of 2787 patients in 22 countries [6,8]. The smallest study was performed in Mexico in 2001 and included only 58 patients [5]. Most of the studies included patients who were ≥ 18 years of age, although the study by Ratsela *et al.* in South Africa had a minimum age of 14 years for enrollment [12]. Three studies had no specific CD4 requirements for enrollment [5,6,7], but in the study by Ayala Gaytan *et al.*, patients were initiated on HAART when their CD4 dropped below 350 cells/mm³, according to the ARV use guidelines prevalent in Mexico at the time [5,15]. The minimal requirement in HIV-1 viral load (VL) varied among the studies. The duration of follow-up ranged from 48 to 156 weeks.

Virologic failure (detectable HIV-1 VL at 12 or 16 weeks), and/or disease progression (AIDS event) and/or severe side effects (grade 2–4) and/or death were the primary outcomes in five studies [6,8,10,12,13], while viral suppression at 48 weeks (either HIV-1 VL <400 copies/ml or HIV-1 VL <50 copies/ml) was the primary outcome in four studies [5,9,11,14]. The remaining study by Sow *et al.* had a combined primary outcome that included efficacy, safety, compliance, quality of life and adverse effects, but the specific parameters of these outcomes were not provided [7]. One study was interrupted by the Data Safety Monitoring Board because the comparison arm of FTC/didanosine-enteric coated/ATV was inferior to the EFV plus 3TC/AZT arm and the individuals in that arm were switched to a different regimen [8]. Three studies focused on enrolling patients with active TB, and the median time to HAART ranged from 4 to 8 weeks after TB treatment was initiated [9,13,14]. The study by van Leth *et al.* did not perform a subanalysis or provide any specific data on the outcome of the HIV-1–TB–coinfected patients in the EFV 800 mg/day arm [6]. In all the other studies, the EFV dose was 600 mg/day regardless of the presence of concomitant TB.

The participant demographic and baseline characteristics were similar across studies as noted in Table 2. An overall 63.6% of individuals were men, with a median age that ranged from 32 to 37 years. Despite the younger population participating in the study by Ratsela *et al.*, the median age in this study was 35 years, which was comparable to what was observed

in the other studies [12]. In terms of disease stage, the median CD4 cell count ranged from 56 cells/mm³ to 199 cells/mm³, and the HIV-1 VL ranged from 4.7 to 5.8 log₁₀ copies/ml. Eight studies enrolled individuals who had CD4 cell counts of <350 cells/mm³ [5,8–14], including two studies that required individuals to have CD4 cell counts of <200 cells/mm³ [11,12]. The rate of HIV-1–TB-coinfection ranged from 10.6 to 18% in the studies that did not focus on enrolling TB-infected patients, and the study by Sierra-Madero *et al.* specified TB coinfection as an exclusion criteria [8,10,11].

Table 3 summarizes the number of treated subjects in the EFV arms, the proportion of individuals who achieved the primary outcome, the increase in CD4 cells and the number of deaths in the EFV-based versus non-EFV-based treatment arms. A total of 3442 patients were randomized to EFV in the ten trials, including 209 participants randomized to both EFV and NVP in the 2NN study [6]. Of the 3120 patients randomized to a non-EFV arm, 1617 were randomized to NVP. A primary outcome of VR at 48 weeks (HIV-1 <400 copies/ml or HIV-1 <50 copies/ml) was met by a total of 327 out of 509 (64.2%) individuals for the EFV arms versus 285 out of 478 (59.6%) individuals for the non-EFV arms [5,9,11,14]. A primary end point of VF/progression/adverse effect/death was reached in 6.6–43.0% of participants in the EFV arms versus 9.6–46.0% of participants in the non-EFV arms [6,8,10,12,13]. Mean or median immunologic recovery data for all participants was available in seven studies [5–7,9–11,13]. The increase in CD4 cells ranged from 109 to 274 cells/mm³ in the EFV arms and from 133 to 259 cells/mm³ in the non-EFV arms. Seven trials reported mortality for a total of 173 deaths in the EFV regimens and 162 in the non-EFV arms. The mortality rates, reported in eight trials, ranged from 0 to 11.9% in the EFV arms versus 0 to 11.5% in the non-EFV arms. The study with the highest mortality reported was the Phidisa cohort, both for the EFV and non-EFV arms [5,6,8,9,11–14]. Figure 1 provides the OR and CI for viral suppression (panel A) and the HR and CI for virologic failure/death/disease progression (panel B) in the nine studies that provided such information, or from which these could be determined based on the published data [5,6,8–14]. The study by Sow *et al.* did not provide sufficient information to determine the OR for meeting the primary outcome [7].

The safety and tolerability of EFV in these randomized controlled trials (RCTs) is presented in Table 4. Grade 1–4 adverse events (AEs) were reported in a total of nine trials [5,6,8–14]. Rash/dermatologic toxicity developed in 346 out of 2888 (11.9%) patients in the EFV arms and in 362 out of 3155 (11.4%) patients in the non-EFV arms (93 out of 1582 randomized to NVP). Of those, 86 versus 67 were specifically reported as grades 2–4. A total of 200 out of 2532 (7.8%) participants in the EFV arms developed any CNS/psychiatric AEs compared with 98 out of 2729 (3.5%) in the non-EFV arms (124 vs 56 were reported grade 2–4). Liver toxicity was documented in 160 out of 1970 (8.1%) participants in the EFV arms, versus 131 out of 2174 (6.0%) in the non-EFV arms. The concomitant use of EFV and NVP in the 2NN trial resulted in the highest number of AEs in that trial [6]. Last, eight trials reported a total of 460 participants who discontinued EFV for any cause versus 463 in the non-EFV arms (303 randomized to NVP).

Discussion

The body of literature available to date from RCTs supports the use of EFV plus two NRTIs as a potent and effective first-line drug regimen in treatment-naïve patients [4,104,105]. EFV has shown to be equivalent [16,17] or superior [18] to NVP and superior to triple NRTI and PIs in multiple RCTs [19–22]. In addition, none of the other ARVs that have been compared with EFV such as ATV [23], raltegravir [24] or maraviroc [25] have proven to be superior in virologic suppression. As previously noted, it is important to keep in mind that these studies have been performed in RCTs and that their results may not be completely

transferrable to RLS, where a large proportion of individuals present for treatment with advanced disease and there is a higher incidence of HIV-1–TB-coinfection. Contrary to the guidelines developed in industrialized countries, ARV selection in RLS may not always reflect the most recent findings from large clinical trials, but may respond to needs such as ease of medication use (i.e., minimum monitoring of side effects, few drug interactions, low pill burden and few dietary restrictions) and cost [107]. Therefore, the RLS trials evaluated in this review offer unique and strong evidence-based medicine towards the initial treatment choice in these settings.

EFV versus NVP

NVP is the most widely available NNRTI in low- and middle-income countries, thus most of the studies in RLS have focused on comparing EFV versus NVP. Similarly to what has been documented in the USA and Europe, EFV and NVP showed similar efficacy in all but one of the RLS studies included in this review. Of the seven trials evaluated, only the study by Swaminathan *et al.* demonstrated inferiority of a NVP-based regimen [13]. It is important to emphasize that this study enrolled patients with HIV-1–TB-coinfection (treated with rifampin) and that a 2-week NVP lead-in phase was used after the anti-TB treatment induction. The authors hypothesized that one of the possible explanations for their findings were suboptimal NVP plasma levels during the lead-in phase caused by the concomitant use of rifampin and proposed eliminating the lead-in phase and recommended the use of full dose NVP in this circumstances. This strategy was evaluated in the CARINEMO-ANRS 12146 trial recently presented by Bonnet *et al.* [14]. In this study, HIV-1–TB-coinfected patients on rifampin, who were randomized to NVP, did not receive a lead-in NVP dose, and the primary end point of HIV-1 VL <50 copies/ml at 48 weeks was similar for both arms. Thus, noninferiority of NVP versus EFV was not established in this trial. Similar results were obtained in the study by Manosuthi *et al.*, in which virologic and immunologic response did not differ in patients with HIV-1–TB-coinfection who received EFV-based versus NVP-based HAART, despite the fact that these patients also received a lead-in phase [9]. An interesting finding in this study was that plasma levels 12 h after dosing (C_{12}) were less compromised for EFV than NVP and that they correlated with treatment failure in both arms, particularly in patients who weighed <60 kg. Therefore, despite the noninferiority of NVP, the authors recommended the use of EFV in HIV-1–TB-coinfected patients treated with rifampin.

In contrast to the similar efficacy between EFV versus NVP, various RCTs in RLSs identified some advantages that favor EFV over NVP in terms of safety and tolerability. Most of the studies observed trend toward increased frequency of any grade rash and liver toxicity in the NVP arms versus the EFV arms, although these differences were not statistically significant. An interesting finding was the similar frequency of liver toxicity for EFV versus NVP among the three studies that specifically enrolled HIV-1–TB-coinfected patients [9,13,14]. Even in the study where no lead-in NVP was used, grade 3–4 liver toxicity was reported in 17 (5.9%) versus 20 (7.0%) of patients in the EFV and NVP arms, respectively. As expected, CNS/psychiatric AEs were more common in the EFV arms. The study by Swaminathan *et al.* reported that 77% of the participants randomized to the EFV had any grade neurological/psychiatric AEs, however, but a large proportion of them (16 out of 59; 27.1%) had par-esthesia attributable to didanosine [13]. Therefore, we only identified 29 out of 59 (49.1%) patients that had EFV-related CNS/psychiatric AEs, such as dizziness or vivid dreams, none of which were reported to be grade 3–4. The study by van Leth *et al.* was the only one in which EFV CNS/psychiatric AEs reached statistical significance when compared with NVP; in addition, two deaths were directly attributed to NVP in this trial [6].

Based on the results of these seven RCTs, both EFV and NVP are appropriate options for first-line NNRTI regimen in treatment-naïve patients in RLS, including those patients with

concomitant TB who are being treated with rifampin. However, the slightly better toxicity profile of EFV compared with NVP should be taken into consideration when an initial ARV regimen is being chosen, especially in patients who are being treated for TB.

EFV versus PIs

Three RCTs have compared the efficacy of EFV versus a PI-based regimen in RLS [8,11,12]. Contrary to the compelling data that support the use of either EFV or NVP in RLS, the results of these three trials are contradictory. In the ACTG A5157 PEARLS trial by Campbell *et al.*, ATV without ritonavir boosting was clearly inferior to EFV – particularly in men – and the study was prematurely discontinued by the Data Safety Monitoring Board [8]. These results are contrary to a previous RCT performed by Squires *et al.* in the USA in which ATV was comparable in efficacy and safety to EFV [23], although a different NRTI backbone was used in that study. A possible explanation for these differences could be elucidated from the pharmacokinetic findings derived from the PEARLS trial, where ATV metabolism was faster in men compared with women and where ATV clearance was 60% higher among subjects from South Africa and Peru and 38% higher in the participants from Brazil, Thailand, Zimbabwe and Malawi when compared with participants from the USA, Haiti and India [26]. Due to the fact that the study by Squires *et al.* enrolled mostly Caucasian and Hispanic patients in the USA, a gender- and race-driven difference in the metabolism of ATV (probably influenced by genetic factors in the multiethnic cohort enrolled in PEARLS) could explain the different results between these two trials.

The remaining two studies that compared EFV versus a PI also found opposing results in ARV efficacy. The study performed in Mexico by Sierra-Madero *et al.* demonstrated a statistically significant advantage of EFV over LPV/r in achieving virologic suppression at 48 weeks [11]. By contrast, the Phidisa trial by Ratsela *et al.* found a similar rate of AIDS and death for EFV and LPV/r, and thus concluded that both regimens were equivalent [12]. However, this study had a lower than expected number of clinical end points achieved (320 out of ~635) due to an early interruption derived from d4T toxicity, which could have underestimated the benefit associated with the EFV-based therapy. Another possible explanation for these differences could be the relatively more advanced disease stage observed in the study by Sierra-Madero *et al.*, in which the median CD4 count at enrollment was 56 cells/mm³ compared with 106 cells/mm³, in the study by Ratsela *et al.*, despite the fact that both studies enrolled patients with CD4 <200 cells/mm³. Last, the statistically significant higher frequency of LPV/r-associated gastrointestinal AEs (nausea, vomiting and diarrhea) that was documented in one of the two studies [12] could also partially explain the benefit associated with the EFV arms on the basis of decreased adherence, which would be consistent with what has been previously reported in other studies [23]. By contrast, no other significant differences in cutaneous, CNS/psychiatric or hepatic AEs were documented between EFV and LPV/r. The incidence of lipodystrophy was also evaluated in the Phidisa trial, and no difference between the EFV versus LPV/r arms was found.

Special considerations for the use of EFV in RLSs

Given the unique circumstances that prevail in low- and middle-income countries, the data derived from the RCTs analyzed here should be used with caution. Like many of the available ARVs, EFV requires relatively close clinical and laboratory monitoring to maximize efficacy and minimize toxicity. Unfortunately, one of the main obstacles that exist in RLSs is the feasibility to closely monitor patients on ARV therapy. The most recent WHO treatment guidelines postulate a ‘minimum package’ of laboratory monitoring that includes an initial CD4 cell count prior to HAART, which should be repeated at least twice a year in treated patients [108,109]. WHO also recommends that, when possible, HIV-1 viral load should be measured prior to initiation of HAART and prior to any switch in treatment

regimens (using a value of 5000 copies/ml as a threshold for failure); however HIV-1 viral load is still considered 'desirable', but 'not essential', given the cost and complexity associated with some laboratory techniques in RLSs.

It is obvious that the WHO guidelines clearly differ from the intensive monitoring practiced in RRCs and/or carried out in the setting of a clinical trial. For example, in most RCTs, CD4 counts are measured every 3–4 months and clinical decision-making can be influenced by those results. In comparison, although CD4 cell counting has gradually become more affordable and plausible via low-cost flow cytometry techniques, and despite the fact that several cost-effective point-of-care CD4 cell testing options are also commercially available, many RLSs still lack this and may rely on surrogate markers of CD4, such as total lymphocyte counts [27]. Similarly, the lack of HIV-1 viral load surveillance in RLSs (in comparison with the frequent HIV-1 viral load measurements in a RCT) may lead to a delayed recognition of drug resistance. An example of this was illustrated by a South African study that detected an NNRTI mutation in 62% of patients who developed viremia (>1000 copies/ml) after initial suppression while on first-line HAART; of note, 59% of those patients did not resuppress while on the same regimen [28]. These examples clearly illustrate that, despite the available evidence that supports the use of EFV in RLS, the results of RCTs may not always apply to daily clinical practice.

Another important factor to consider in RLS is adherence to HAART. Currently, in RRCs EFV is most commonly prescribed in coformulation with TDF/FTC as a single tablet regimen (STR), which may have a positive impact on adherence. By contrast, none of the RCTs evaluated in this analysis used EFV in a STR. Although this was not the main focus of any of these trials, previous studies have demonstrated an adherence benefit in individuals treated with EFV as part of a STR [29,30]. The additional cost of STR makes this option currently prohibitive in RLSs, but further research on the benefit of STR in RLSs should be performed.

The use of EFV in women of childbearing potential is also an issue with special importance in RLSs. EFV treatment during the first trimester of pregnancy is contraindicated in the basis of animal data and previous case reports in humans which describe neural tube defects associated to the use of this ARV [102]. Many women who conceive while on EFV-based HAART continue this treatment during the first trimester, before their pregnancy is diagnosed [110]. Therefore, it is currently recommended that women of childbearing age use effective methods of contraception while on EFV. However, more recent data do not support these findings. Various retrospective studies in RLSs and RRCs that have evaluated the impact of EFV on pregnancy outcomes have not found any clear evidence that the rate of birth defects with EFV exposure was greater when compared with NVP or LPV/r [31–34]. This has also been observed in the Antiretroviral Pregnancy Registry, which found that prevalence of birth defects in women exposed to EFV as part of their ARV therapy in the first trimester was approximately 2.5%, a rate that is consistent with the background prevalence [110]. According to WHO, the benefits of EFV in the second and third trimesters of pregnancy are likely to outweigh risks of teratogenicity in RLSs. As more data derive from the empirical use of EFV in women of child-bearing age, continued surveillance of the risks of first trimester EFV exposure in RLSs is of critical importance [111].

Another unique aspect in RLSs concerns use of EFV in the presence of concomitant endemic infections such as TB, malaria and hepatitis C, and the drug–drug interactions derived from treating those conditions. As previously noted, NNRTIs have well-documented interactions with the rifamycins (in particular with rifampin). Current expert recommendations and data derived from clinical trials advise against the concomitant use of NVP and rifampin [9,13,14,110]. Comparatively, an increase in the dose of EFV from 600

to 800 mg/day is suggested when used in conjunction with rifampin [112], but none of the available RCTs analyzed in this manuscript applied this strategy to their patients. Therefore, further research on the optimal dose of EFV for HIV-1–TB-coinfection should be performed. In contrast to the data on anti-TB medications, the interactions between EFV and antimalarials have not been extensively studied. Artemisinin and its derivatives are rapidly metabolized via the CYP3A4 pathway, which suggests a potential increase in the levels of these drugs when used in conjunction with EFV. One study in healthy volunteers reported delayed onset of hepatitis in two subjects treated with artesunate (an arte-misinin derivative) while receiving EFV [35]. Since optimal antimalarial treatment regimens for HIV-infected patients on HAART are not clear, continued research is needed to establish the safety and efficacy of antimalarial regimens in HAART-treated patients. Last, only limited data on healthy volunteers are available on the interactions of EFV with the new antihepatitis C PIs [36,37] and the impact of these interactions should be a priority for future research, both in RRCs and RLSs.

Conclusion

EFV is a potent and efficacious NNRTI widely used in many clinical scenarios as a first-line treatment in treatment-naïve patients. The available studies performed in RLS that have compared EFV to NVP have consistently demonstrated similar efficacy among these two NNRTIs, with a tendency towards a better toxicity profile for EFV, notably in patients with concomitant TB. Conversely, EFV has proven superior to PI-based regimens in most trials performed in RLSs, although more studies may be necessary to confirm these findings. Since low- and middle-income countries carry the largest burden of HIV-infected individuals, further research to elucidate the most efficacious and safest HAART regimens in RLSs should be a priority.

Future perspective

EFV and NVP have shown to be equivalent as first-line therapy in RLSs. By contrast, the data comparing EFV to PIs in these settings are less compelling. Since developed countries carry the largest burden of HIV infection, more prospective clinical trials should be performed in RLSs, particularly those comparing new ARV regimens.

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Executive summary

Background

- Efavirenz (EFV) is a non-nucleoside reverse-transcriptase inhibitor widely used as first-line in HIV-1 infection.
- EFV is recommended for treatment-naïve HIV-infected individuals in various US and international treatment guidelines.

EFV is equivalent to nevirapine for the treatment of HIV-1 infection

- Various randomized clinical trials in industrialized countries have shown EFV to be equivalent or superior to nevirapine (NVP) as a first-line therapy.
- EFV and NVP are equivalent for treatment-naïve patients in resource-limited settings (RLSs), including patients with concomitant tuberculosis.
- EFV may offer a more benign adverse-effect profile than NVP. These an antiretroviral regimen.

EFV versus protease inhibitors

- Most of the studies comparing EFV to protease inhibitors in industrialized countries have favored EFV.
- However, the data comparing EFV versus protease inhibitors in RLSs are less compelling.

Conclusion

- EFV and NVP are adequate initial options for the treatment of HIV infection in RLSs.
- Further studies comparing EFV to PIs in RLSs are required.

Figure 1. Efavirenz-based versus non-efavirenz-based regimens in treatment-naïve patients in resource-limited settings

(A) Risk ratio (log scale) for meeting primary end point of viral suppression (odds ratio) and (B) for meeting virologic failure/death/disease progression (hazard ratio) in nine randomized controlled trials of EFV-based versus non-EFV-based regimens in resource-limited settings.

[†]EFV versus nevirapine.

[‡]EFV versus boosted protease inhibitor.

[§]EFV versus unboosted protease inhibitor.

EFV: Efavirenz.

Table 1

Study design, eligibility, regimen and outcome measures of randomized controlled trials.

Study (year)	RLS countries	Design	Eligibility criteria	Participants (n)	Treatment regimens	Primary outcome of interest	Notes	Ref.
Ayala Gaytan <i>et al.</i> (2004)	Mexico	Randomized, open label, 48-week follow-up	18 years old HAART naive Any CD4 Any HIV-1 VL	58	a. 3TC/AZT/EFV b. 3TC/AZT/NVP	HIV-1 VL <400 copies/ml at 24 and 48 weeks	HAART initiated if HIV-1 VL >55,000 copies/ml or CD4 <350 cells/mm ³	[5]
van Leth <i>et al.</i> (2004) 2NN study	NA, EUR, Argentina, Brazil, South Africa, Australia, Thailand	Randomized, open label, multicenter, 48-week follow-up	16 years old HAART naive Any CD4 HIV-1 VL >5000 copies/ml	1216	a. 3TC/d4T/NVP q.d. b. 3TC/d4T/NVP b.i.d. c. 3TC/d4T/EFV d. 3TC/d4T/EFV/NVP q.d.	Composite of VF, progression, death or treatment change	VF defined as <1 log decline in HIV-1 VL at 12 weeks, two consecutive HIV-1 VL >50 after 24 weeks or HIV-1 VL >50 at week 48	[6]
Sow <i>et al.</i> (2006)	Senegal	Randomized, controlled, 18-month follow-up	Not specified	70	a. 3TC/AZT/EFV b. 3TC/AZT/NVP	Efficacy, safety, compliance, quality of life and adverse events	Reported mean decrease in VL and increase in CD4	[7]
Campbell <i>et al.</i> (2008) ACTG 5157 PEARLS; NCT00084136	NA, Brazil, Peru, India, Malawi, South Africa, Zimbabwe, Thailand, Haiti	Randomized, open label, multicenter, 96-week follow-up	18 years old HAART naive CD4 <300 cells/mm ³ Any HIV-1 VL	1571	a. 3TC/AZT/EFV b. FTC/ddl-EC/ATV c. FTC/TDF/EFV	HIV-1 VL >1000 copies/ml (<2) at week 16, disease progression or death (any cause)	DSMB in 2008 recommended disclosure of arm a vs b comparison	[8]
Manosuthi <i>et al.</i> (2009) N2R study; NCT00483054	Thailand	Randomized, open label, 48-week follow-up	18–60 years old HAART naive Active TB infection CD4 <350 cells/mm ³ Any HIV-1 VL	142	a. 3TC/d4T/EFV b. 3TC/d4T/NVP	HIV-1 VL <50 copies/ml at 48 weeks	All patients had HIV-1 TB and median time to HAART was 5.6 weeks EFV and NVP plasma concentration at 12 h correlated with VF Patients treated with INH/RIF/ETH/PZA	[9]
Wester <i>et al.</i> (2010) TSHEPO study	Botswana	Randomized, open label, 3x2x2 factorial, 156-week median follow-up	18 years old HAART naive CD4 <350 cells/mm ³ HIV-1 VL >55,000 copies/ml	650	a. 3TC/AZT/NVP b. 3TC/AZT/EFV c. AZT/ddl/NVP d. AZT/ddl/EFV e. 3TC/d4T/NVP f. 3TC/d4T/EFV	HIV-1 VL >5000 copies/ml at 16 weeks with drug resistance and treatment-related toxicity	Randomized and stratified by CD4 DSMB recommended discontinuation of AZT/ddl arms due to inferiority in 2006 Adherence intervention for patients with elevated VL	[10]

Study (year)	RLS countries	Design	Eligibility criteria	Participants (n)	Treatment regimens	Primary outcome of interest	Notes	Ref.
Sierra-Madero <i>et al.</i> (2010) NCT00162643	Mexico	Randomized, open label, multicenter, 48-week follow-up	18 years old HAART naive CD4 <200 cells/mm ³ HIV-1 VL >1000 copies/ml	189	a. 3TC/AZT/EFV b. 3TC/AZT/LPV/r	HIV-1 VL <50 copies/ml at 48 weeks	Randomized and stratified by CD4	[11]
Ratsela <i>et al.</i> (2010) Phidisa study: NCT00342355	South Africa	Randomized, open label, 2x2 factorial, 24.7-month median follow-up	>14 years old HAART naive CD4 <200 cells/mm ³ and/or AIDS-related illness Any HIV-1 VL	1771	a. AZT/ddI/EFV b. AZT/ddI/LPV/r c. 3TC/d4T/EFV d. 3TC/d4T/LPV/r	AIDS or death	Study ended early to update and advise about d4T toxicity in South Africa	[12]
Swaminathan <i>et al.</i> (2011) CT00332306	India	Randomized, open label, noninferiority, 24-month follow-up	18 years old HAART naive Concomitant TB CD4 <250 cells/mm ³ Any HIV-1 VL	116	a. 3TC/ddI/EFV b. 3TC/ddI/NVP	Composite of death, HIV-1 VL >400 copies/ml, lost to follow-up or any serious adverse event	HAART initiated 2 months after TB treatment was initiated Patients treated with INH/RIF/ETH/PZA Study ended by DSMB	[13]
Bonnet <i>et al.</i> (2011) CARINEMO ANRS 12146; NCT00495326	Mozambique	Randomized, open label, multicenter, noninferiority, 48-week follow-up	18 years old HAART naive Concomitant TB CD4 <250 cells/mm ³ Any HIV-1 VL	570	a. 3TC/d4T/EFV b. 3TC/d4T/NVP	HIV VL <50 copies/ml at 48 weeks	HAART initiated 4 weeks after TB treatment was initiated Patients treated with INH/RIF/ETH/PZA	[14]

3TC: Lamivudine; ATV: Atazanavir; AZT: Zidovudine; b.i.d.: Twice a day; d4T: Stavudine; ddI: Didanosine; DSMB: Data Safety Monitoring Board; EC: Enteric coated; EFV: Efavirenz; ETH: Ethambutol; EUR: Europe; FTC: Emtricitabine; HAART: Highly active antiretroviral therapy; INH: Isoniazid; LPV/r: Lopinavir/ritonavir; NA: North America; NVP: Nevirapine; PZA: Pyrazinamide; q.d.: Once a day; RIF: Rifampin; RLS: Resource-limited setting; TB: Tuberculosis; TDF: Tenofovir/disoproxil/fumarate; VF: Virologic failure; VL: Viral load.

Table 2
Demographic and baseline characteristics of participants in randomized controlled trials.

Study (year)	Participants (n)	Demographics		Disease characteristics				Ref.
		Male (%)	Median age (years)	Median CD4 (cells/mm ³)	CD4 <200 cells/mm ³ ; n (%)	Median log ₁₀ HIV-1 (copies/ml)	Concomitant TB; n (%)	
Ayala Gaytan <i>et al.</i> (2004)	58	81	34	137	43 (74)	5.01	N/A	[5]
van Leth <i>et al.</i> (2004)	1216	63	34	187.5	438 (36)	4.7	N/A	[6]
Sow <i>et al.</i> (2006)	70	51	N/A	N/A	N/A	N/A	N/A	[7]
Campbell <i>et al.</i> (2008) NCT00084136	1571	53	34	172	957 (60.9)	5.0	18	[8]
Manosuthi <i>et al.</i> (2009) NCT00483054	142	67	37	65.3	N/A	5.8	100	[9]
Wester <i>et al.</i> (2010)	650	30	33.3	199	330 (50.8)	5.2	10.6	[10]
Sierra-Madero <i>et al.</i> (2010) NCT00162643	189	85	35	56	189 (100)	N/A	Excluded	[11]
Ratsela <i>et al.</i> (2010) NCT00342355	1771	68	35	106	1771 (100)	5.1	N/A	[12]
Swaminathan <i>et al.</i> (2011) NCT00332306	116	80	36	84	N/A	5.5	100	[13]
Bonnet <i>et al.</i> (2011) NCT00495326	570	58	32	89	N/A	5.5	100	[14]

N/A: Not available; TB: Tuberculosis.

Table 3
Primary outcome(s), immunologic recovery and death among subjects randomized to an efavirenz-based regimen.

Study (year)	Participants (n)	Number on EFV regimen	Met primary outcome(s)						Immunologic recovery (CD4 increase; cells/mm ³) [†]				Deaths; n (%)	Ref.				
			VR at 48 weeks; n (%)						VF/progression/death; n (%)									
			HIV-1 <400 copies/ml			HIV-1 <50 copies/ml			EFV regimen		Non-EFV regimen				EFV regimen		Non-EFV regimen	
			EFV regimen	Non-EFV regimen	Non-EFV regimen	EFV regimen	Non-EFV regimen	Non-EFV regimen	EFV regimen	Non-EFV regimen	EFV regimen	Non-EFV regimen			EFV regimen	Non-EFV regimen		
Ayala Gaytan <i>et al.</i> (2004)	58	30	13/19 (68.4) [‡]	13/24 (54.1)	–	–	–	–	–	–	–	144	133	0	0	[5]		
van Leth <i>et al.</i> (2004)	1216	609	411/609 (67.4) [§]	–	538/816 (65.9) [¶]	–	–	262/609 (43) [§]	376/816 (46) [¶]	155 [§]	160 [¶]	9 (1.4) [§]	16 (1.9) [¶]	–	–	[6]		
Sow <i>et al.</i> (2006)	70	35	–	–	–	–	–	–	–	109	175	–	–	–	–	[7]		
Campbell <i>et al.</i> (2008) NCT00084136	1571	1045	897 (85.8) [#]	424 (80.6) ^{††}	–	–	–	193 (18.4) [#]	108 (20.5) ^{††}	216 [#]	256 ^{††}	38 (2.8) [#]	10 (1.9) ^{††}	–	–	[8]		
Manosuthi <i>et al.</i> (2009) NCT00483054	142	71	–	–	52 (73.2)	51 (71.8)	–	–	–	274	252	2 (2.8)	6 (8.4)	–	–	[9]		
Wester <i>et al.</i> (2010)	650	325	–	–	–	–	–	–6.6	–9.6	257	259	–6.9	–5.3	–	–	[10]		
Sierra-Madero <i>et al.</i> (2010) NCT00162643	189	95	–	–	67 (70.5)	50 (53.2)	7 (7.3)	17 (18.0)	234	239	2 (2.1)	5 (5.3)	–	–	–	[11]		
Ratsela <i>et al.</i> (2010) NCT00342355	1771	888	–	–	–	–	–	163 (18.3)	157 (17.7)	–	–	106 (11.9)	102 (11.5)	–	–	[12]		
Swaminathan <i>et al.</i> (2011) NCT00332306	116	59	50 (84.7)	37 (64.9)	–	–	–	5 (8.4)	10 (17.5)	215	201	0	5 (8.7)	–	–	[13]		
Bonnet <i>et al.</i> (2011) NCT00495326	570	285	–	–	195 (68.4)	171 (60)	–	–	–	–	–	16 (5.6)	18 (6.3)	–	–	[14]		

[‡] CD4 increase reported in median or mean.

[‡]No specification on loss to follow-up is made.

[§]A total of 816 patients received nevirapine (NVP) every day or NVP twice a day (including 209 who received NVP every day with EFV).

[¶]Includes all the patients receiving EFV (n = 609).

[#]The median follow-up for the zidovudine/lamivudine (3TC)/EFV versus tenofovir disoproxil fumarate/emtricitabine (FTC)/EFV comparison was 184 weeks.

^{†‡}Data Safety Monitoring Board analysis showed conclusive evidence that didanosine-enteric coated/FTC/ATV was inferior to zidovudine/3TC/EFV for the primary efficacy end point and recommended terminating this arm; median follow-up for the didanosine-enteric coated/FTC/ATV vs zidovudine/3TC/EFV comparison was 72 weeks.

EFV: Efavirenz; VF: Virologic failure; VR: Virologic response.

Table 4

Safety and tolerability of efavirenz in randomized controlled trials.

Study (year)	Participants (n)	AEs reported; n (%)	Rash/cutaneous		CNS/psychiatric		Liver toxicity		Discontinued any cause; n (%)		Ref.
			EFV regimen	Non-EFV regimen	EFV regimen	Non-EFV regimen	EFV regimen	Non-EFV regimen	EFV regimen	Non-EFV regimen	
Ayala Gaytan <i>et al.</i> (2004)	58	1–4	0	3 (10.7)	2 (6.6)	0	N/A	N/A	2 (3.4)	2 (3.4)	[5]
van Leth <i>et al.</i> (2004)	1216	3–4	27/609 (4.4) [†]	33/816 (4) [‡]	38/609 (6.2) [†]	33/816 (4) [‡]	7/609 (1.1) [†]	28/816 (3.4) [‡]	116/609 (19.0) [†]	181/816 (22.1) [‡]	[6]
Stroob <i>et al.</i> (2006)	70	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A (21)	N/A (22)	[7]
Campbell <i>et al.</i> (2008) NCT00084136	1571	3–4	29 (2.7)	8 (1.5)	67 (6.4)	13 (2.4)	91 (8.7)	30 (5.7) [¶]	272 (26.0)	149 (28.3)	[8]
Manosuthi <i>et al.</i> (2009) NCT00483054	142	2–4	3 (4.2)	2 (2.8)	N/A	N/A	0	2 (2.8)	9 (12.6)	16 (22.5)	[9]
Wester <i>et al.</i> (2010) NCT00000000	650	1–4	0	19 (5.8)	7 (2.2)	1 (0.3)	3 (0.9)	11 (3.4)	49 (15.1)	87 (27.7)	[10]
Sierra-Madero <i>et al.</i> (2010) NCT00162643	189	2–4	3 (4.4)	2 (2.9)	24 (35)	13 (19.1)	5 (7.3)	6 (8.8)	5 (5.2)	11 (11.7)	[11]
Rasela <i>et al.</i> (2010) NCT00342355	1771	1–4	254 (28.6)	259 (29.3)	33 (3.7)	34 (3.8)	N/A	N/A	<5	<5	[12]
Swaminathan <i>et al.</i> (2011) NCT00332306	116	1–4	6 (10.1)	14 (24.5)	29 (49.1) [§]	4 (7.0) [§]	2 (3.3)	0	1 (1.6)	2 (3.5)	[13]
Bonnet <i>et al.</i> (2011) NCT00495326	570	2–4	24 (8.3)	22 (7.7)	N/A	N/A	52 (18.1)	54 (18.9)	6 (2.1)	15 (5.3)	[14]

[†] A total of 816 patients received nevirapine (NVP) every day or NVP twice a day (including 209 who received NVP every day with EFV).

[‡] Includes all the patients receiving EFV (n = 609).

[§]Excludes paresthesia (attributable to didanosine).

[¶]Excludes bilirubin abnormalities.

AE: Adverse events; EFV: Efavirenz; N/A: Not available.