HIV/AIDS Programme

TECHNICAL UPDATE ON TREATMENT OPTIMIZATION

USE OF EFAVIRENZ DURING PREGNANCY: A PUBLIC HEALTH PERSPECTIVE

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TECHNICAL UPDATE ON TREATMENT OPTIMIZATION

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SUMMARY

Efavirenz (EFV) has been recommended as the preferred option for a non-nucleoside reverse transcriptase inhibitor in optimized first-line antiretroviral regimens. However, concerns persist about its safety in early pregnancy, resulting in more complex treatment algorithms for HIV-infected women who might become pregnant and for women in early pregnancy, and ongoing confusion regarding when to use EFV and when to use nevirapine (NVP). The clinical consequences arising from this include switching to alternative and more complex antiretroviral regimens in pregnancy, more frequent regimen changes from EFV to NVP, increased complexity in the management of tuberculosis (TB) coinfection due to interactions between anti-TB drugs and NVP, and a potential increase in the number of pregnancies terminated due to a belief that EFV use in early pregnancy may be teratogenic. Programmatic consequences include difficulties in simplifying antiretroviral therapy regimens for adults (including for pregnant women and those of reproductive age) and harmonizing them with those for prevention of mother-to-child HIV transmission (PMTCT) programmes. This has resulted in higher costs and increased complexity of treatment guidelines, clinical management and drug procurement.

This technical update reviews the evidence on the safety, tolerability and efficacy of EFV, as well as the clinical and programmatic consequences of multiple algorithms due to uncertainty regarding the risk of teratogenicity from the use of EFV in pregnancy. Review of the available data and programmatic experience provides reassurance that exposure to EFV in early pregnancy has not resulted in increased birth defects or other significant toxicities. In addition, new evidence suggests that EFV is clinically superior to NVP, as it provides better long-term viral suppression, has fewer adverse events and less risk of resistance. Finally, the cost of EFV has decreased considerably, and it is now increasingly available as part of once-daily fixed-dose combinations. Based on the available data, programme experience and a public health perspective, this interim guidance provides further support for the use of EFV as part of the World Health Organization (WHO) strategy to optimize and simplify first-line treatment, including among pregnant women and those of reproductive age. Further review of the safety of EFV and its use in pregnant women and those of reproductive age will be included as part of a comprehensive revision of the WHO ART guidelines, planned for 2013.

INTRODUCTION

Over the past decade, guidelines for the treatment of HIV in resource-limited settings have recommended one of two non-nucleoside reverse transcriptase inhibitors (NNRTIs) – efavirenz (EFV) or nevirapine (NVP) – as part of a first-line antiretroviral therapy (ART) regimen.[1–3] Recently, as part of the effort to simplify and optimize first-line ART, the World Health Organization (WHO) has recommended EFV as the preferred first-line NNRTI under the Treatment 2.0 initiative.[4] In addition, in a recent programmatic update on antiretrovirals (ARVs) for pregnant women, WHO has suggested the benefit of using an EFV-based regimen harmonized with that for first-line adult ART as part of a fixed-dose combination for the prophylaxis and treatment approaches of Options B and B+ for prevention of mother-to-child HIV transmission (PMTCT).[5] However, both the WHO 2010 adult ART guidelines and the ARV guidelines for pregnant women recommend that women who plan to become pregnant, who may become pregnant, or who are in the first trimester of pregnancy, should avoid using EFV, owing to uncertainty concerning the risk of teratogenicity (neural tube defects) with the use of EFV in the first trimester of pregnancy.[2,3]

At present, the majority of people on ART in resource-limited settings are taking NVP-based regimens, although practice is changing in many countries.[6] In addition to concerns about its use in pregnant women and those with childbearing potential, widespread use of EFV-based regimens has been limited until recently by its higher cost and limited availability in once-daily fixed-dose combinations. However, an increase in the available evidence and wider programmatic experience warrant a review of the use of EFV, particularly in relation to pregnancy. This technical update summarizes the currently available evidence and experience that provide the basis for favouring EFV use as the preferred NNRTI option in first-line therapy, including for pregnant women, and examines the broader consequences of the current uncertainty concerning the risk of teratogenicity with EFV use in pregnancy.

RATIONALE FOR THIS UPDATE

Since the release of the WHO 2010 guidelines for ART in adults and adolescents, and pregnant women,[2,3] a number of important changes have taken place. These changes, which are summarized in this technical update, include the following:

- An accumulation of evidence indicating that EFV has superior efficacy and tolerability compared with NVP
- Substantial reductions in the price of EFV, and increased availability as part of once-daily fixed-dose combinations
- Updated data suggesting a low risk of birth defects associated with EFV use during the first trimester of pregnancy
- Programmatic experience highlighting the complications associated with switching HIV-positive pregnant women and those who may become pregnant from EFV to NVP.

These considerations, together with the impetus provided by the Treatment 2.0 initiative to optimize and simplify treatment delivery as far as possible,[4] lead to a clear preference for EFV as part of first-line treatment, including among pregnant women and those who may become pregnant.

COMPARATIVE DATA ON THE EFFICACY AND TOXICITY PROFILES OF REGIMENS CONTAINING EFV AND NVP

In the 2010 WHO ART guidelines for adults and adolescents, NVP and EFV were considered to have comparable clinical efficacy when administered in combination regimens, and were recommended in combination with either zidovudine (AZT) or tenofovir (TDF) plus either lamivudine (3TC) or emtricitabine (FTC).[2] This recommendation was based on a meta-analysis of seven trials of EFV and NVP, which concluded that there was no difference in clinical efficacy at 48 weeks. However, this analysis also noted a higher risk of NNRTI resistance mutations among patients taking NVP.[7] These findings were driven mainly by the results of the 2NN study, the largest single trial to date comparing NVP- and EFV-based regimens.[8]

However, long-term analysis of these trials and recent cohort data suggest clinical superiority of EFV over NVP in terms of suppression of viral load and length of time to treatment failure.[9,10] Data from programmatic cohorts (including one study involving more than 27 000 patients) indicate superior virological suppression among patients taking EFV compared with those taking NVP.[11,12] Another review that analysed trial data comparing NVP with EFV in TDF-containing backbone regimens also concluded that EFV had superior virological efficacy.[13] In a modelling study, the potentially superior virological efficacy of EFV was translated into a 1.6-year life expectancy gain for women of childbearing age on EFV compared with those on NVP.[14]

Another recent modelling study projected the clinical benefits and risks of prescribing EFV and NVP to women of childbearing age in sub-Saharan Africa. Based on demographic and clinical data from Côte d'Ivoire, the model assumed comparable efficacy, a conservatively higher rate of acute toxicity for NVP based on published data, and a marginally higher rate of birth defects for EFV. The study concluded that ten years after ART initiation, the small risk of additional birth defects associated with EFV was significantly outweighed by the survival benefit resulting from fewer toxicity-driven regimen switches.[15]

EFV and NVP have different toxicity profiles and both require clinical monitoring.[2,16] The main toxicity of EFV is central nervous system (CNS) side-effects, while that of NVP is rash, Stevens–Johnson syndrome and hepatic toxicity.[2,17,18] The EFV-associated CNS side-effects typically resolve after two to four weeks. However, in some cases they can persist for months or not resolve at all. Thus, EFV should be avoided in patients with a history of psychiatric illness. Toxicity to NVP continues to be a significant concern, particularly among women with higher CD4 counts. This has led to a more complex "lead-in" dosing strategy for the initiation of NVP, and to different recommendations on the use of NVP in pregnant women, depending on the CD4 count.[2,3] A recent study from the USA reported that overall, 21.7% of women on NVP developed a new rash (grades 1–4) after therapy initiation.[18] In this study, women on NVP with a baseline CD4 count >250 cells/mm^3 had a significantly higher rate of rash that was grade 2 or higher, a finding consistent with data from early clinical trials[8,19,20] and observational cohorts.[21,22]

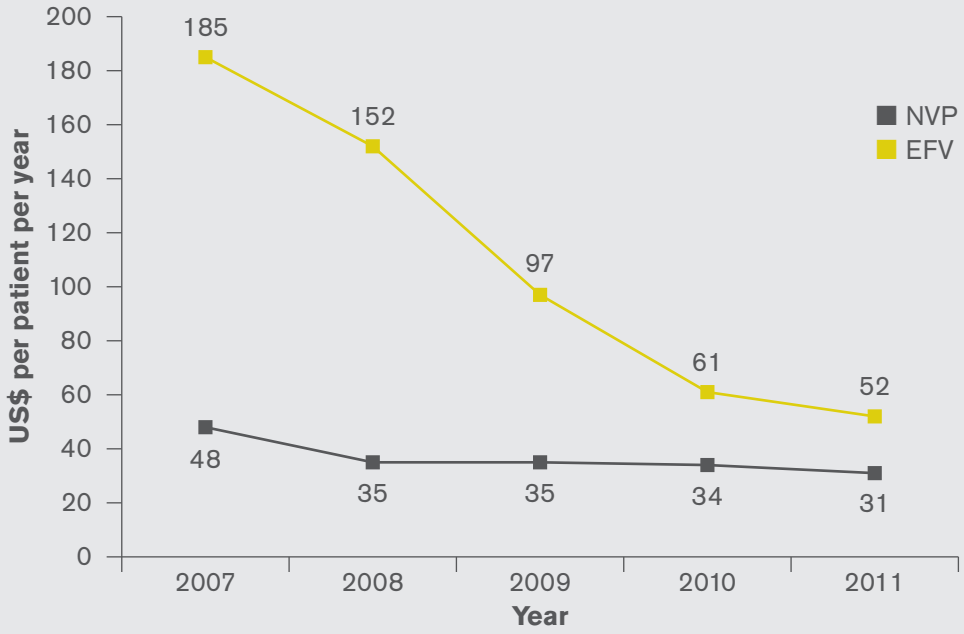
Although the association between CD4 count and NVP toxicity has not been consistently reported,[23–27] caution and close monitoring are recommended if NVP is used in women with a CD4 count >250 cells/mm^3.[2] The 2010 WHO PMTCT ARV guidelines recommend against the use of NVP for prophylaxis in women with CD4 counts >350 cells/mm^3.[3] This recommendation is likely to be an increasingly important limitation for NVP use, as more programmes move towards the PMTCT Option B approach (i.e. providing all HIV-infected pregnant women with a triple ARV regimen during the risk period for mother-to-child transmission, and continuing eligible women on lifelong ART) and PMTCT Option B+ (providing lifelong ART to all HIV-infected pregnant women).[5] Case reports of pregnant women developing Stevens–Johnson syndrome following a switch from EFV- to NVP-based therapy illustrate the dilemma faced by health providers when trying to decide between EFV and NVP in pregnancy.[28] While the overall risk of severe hepatic reactions to NVP appears to be low, this also remains an important concern. Overall rates of severe hepatic events due to NVP are less than 1% in clinical trials,[29] but are reported to be in the range of 3%–6.5% in cohort studies.[30,31]

The management of potential toxicity and adverse events is a challenge in resource-limited settings where capacity for clinical and laboratory monitoring may be limited. In addition, adverse events are a risk factor for poor adherence[32] and patient-initiated treatment interruptions,[33] and lead to more frequent regimen changes. While NVP is one of the most effective ARV drugs for use in first-line ART, it is associated with clinical and programmatic difficulties. On balance, EFV appears to be better tolerated and has much less risk of severe adverse events than NVP. In addition, recent evidence shows that virological suppression with EFV is superior to that with NVP.

COST AND AVAILABILITY OF EFV AND NVP AS FIXED-DOSE COMBINATIONS

The cost of EFV is decreasing (*see* Figure 1) and it is now available in simplified formulations as part of a generic, fixed-dose, once-daily regimen recommended by the 2010 WHO ART guidelines (triple ARV regimens with NVP are available only in twice-daily formulations). These guidelines recommend the use of either a TDF- or AZT-based first-line regimen in combination with either NVP or EFV.[2] Many countries have chosen a TDF-based first-line regimen in conjunction with EFV due to its more favourable clinical profile and programmatic advantages. In addition, the costs of TDF and EFV have fallen substantially in recent years due to increased demand, generic competition and improvements in the synthesis of the active ingredients (Figure 1). In parallel with the decreasing cost of EFV as a separate compound (which is approaching the cost of NVP), the one-year treatment cost of generic formulations of once-daily TDF/3TC/EFV has decreased to approximately US$ 180, and is now close to the US$ 131 annual cost of twice-daily AZT/3TC/NVP (WHO/HIV Department/AMDS Unit, personal communication, May 2012, and http://apps.who.int/hiv/amds/price/hdd/). However, access to affordable generic versions, particularly as fixed-dose combinations, remains a problem for some countries where current drug patent laws and licensing agreements restrict purchasing options.[34]

Figure 1. Price evolution of NVP and EFV*



Source: MSF, 2011[34]

**Note*: the pricing comparison above reflects generic prices for each of the drugs alone.

SAFETY OF EFV USE DURING PREGNANCY

Concerns persist about the safety of using EFV during pregnancy, particularly during the first 28 days. These concerns originate from preclinical data from teratogenicity studies in animals. However, there is actually very limited evidence on the risk of EFV causing neural tube defects in humans, and recent data and experience are reassuring. Overall, neural tube birth defects are relatively rare in humans, with an estimated incidence of 0.1% in the general population.[35] In 2005, EFV was classified by the US Food and Drug Administration (FDA) as a pregnancy class D drug, resulting in a recommendation against its use during the first trimester of pregnancy. The recommendation against using EFV in