HIV/AIDS Programme

TECHNICAL UPDATE ON TREATMENT OPTIMIZATION

USE OF EFAVIRENZ DURING PREGNANCY: A PUBLIC HEALTH PERSPECTIVE

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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]

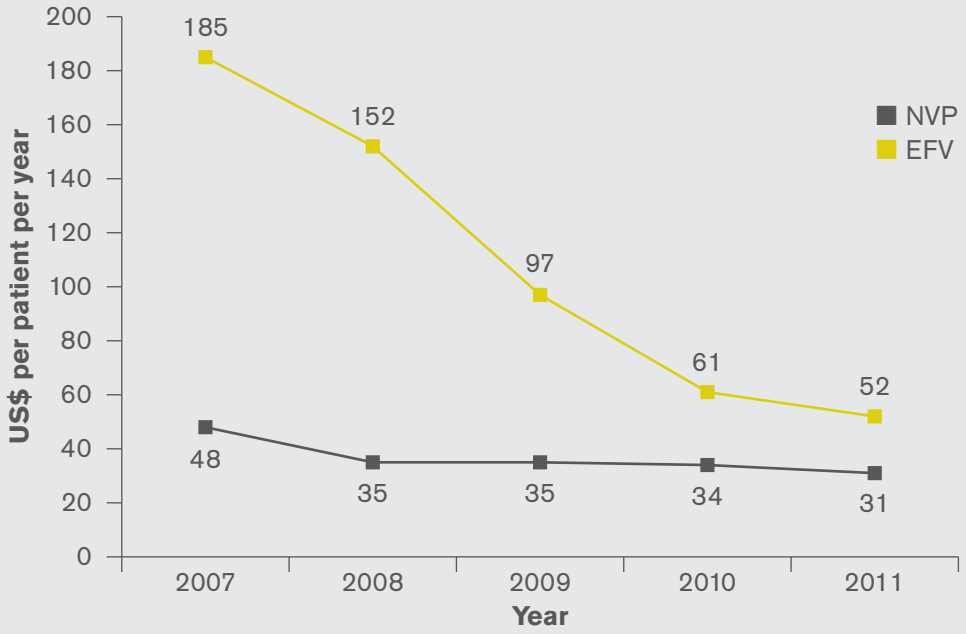
Although the association between CD4 count and NVP toxicity has not been consistently reported,[23–27] caution and close monitoring are recommended if NVP is used in women with a CD4 count >250 cells/mm^3.[2] The 2010 WHO PMTCT ARV guidelines recommend against the use of NVP for prophylaxis in women 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

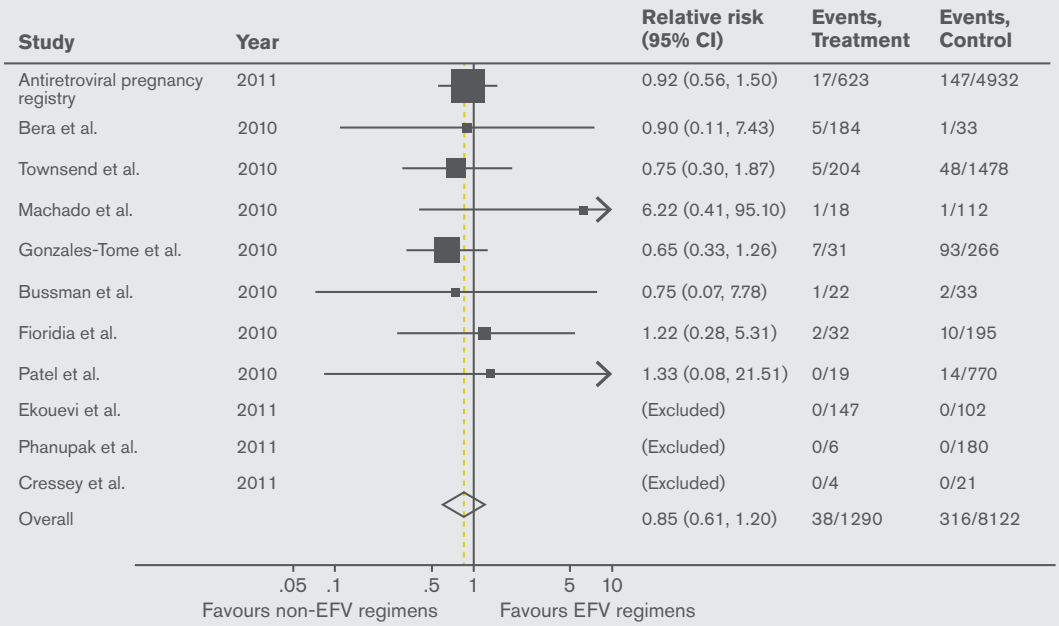
Concerns persist about the safety of using EFV during pregnancy, particularly during the first 28 days. These concerns originate from preclinical data from teratogenicity studies in animals. However, there is actually very limited evidence on the risk of EFV causing neural tube defects in humans, and 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 pregnancy is largely based on neural tube defects noted in early animal studies and retrospective human case reports.[36]

At the time of development of the WHO 2010 ARV PMTCT guidelines, the limited data available were sufficient only to rule out a more than tenfold increased risk of neural tube defects.[3] Accumulating surveillance data from the US-based Antiretroviral Pregnancy Registry (which includes international reports) are now sufficient to detect at least a twofold increase in birth defects overall; an increased risk at this level has not been detected with the use of EFV, providing further reassurance.[37] In fact, the overall rate of birth defects reported in association with EFV is similar to that reported for multiple other widely used ARVs, including abacavir, lopinavir/ritonavir, NVP, stavudine and TDF, and is consistent with rates reported in congenital defect registries from the general population.[37,38]

In practice, avoidance of EFV use during the first trimester of pregnancy is less of an issue for women initiating ARVs in PMTCT programmes, and more of an issue for women of reproductive age who are already on ART. In resource-limited settings, it is unusual for a pregnant woman to present to an antenatal clinic in the first trimester, especially in the first four weeks. As an example, in Kenya, only 10% of women attended antenatal care within the first trimester of pregnancy,[39] so the likelihood of a newly diagnosed HIV-infected pregnant woman being initiated on ART during the first trimester is relatively low. However, inadvertent exposure to EFV is more common as the number of pregnancies among HIV-positive women already on ART is increasing in both developed[40] and less developed countries,[41] and a large proportion of pregnancies among women on ART may be unplanned.[42]

A recent, updated meta-analysis of birth defects in infants with first-trimester EFV exposure found no overall increased risk of birth defects associated with EFV exposure during the first trimester of pregnancy (Figure 2). In 21 studies, there were 39 birth defects (of any type) among 1437 live births in women receiving first-trimester EFV (2.0%, 95% CI 0.82–3.18), which was similar to but less than that for women not exposed to EFV-based regimens in the USA Antiretroviral Pregnancy Registry (2.9%) and in the general population (6%).[43] The relative risk of birth defects overall when comparing women on EFV-based (1290 live births) and non-EFV-based regimens (8122 live births) was 0.85 (95% CI 0.61–1.20).[43]

Figure 2. Relative risk of birth defects with EFV vs non-EFV regimens



Source: Ford et al. 2011[43]

Among the study populations included in the meta-analysis, there was only one case of neural tube defect (myelomeningocele), yielding an incidence of 0.07% (95% CI 0.002–0.39). Thus, the estimated pooled prevalence of neural tube defects among HIV-positive women exposed to EFV during the first trimester of pregnancy (0.07%) was lower than that reported in the general population (0.1%). However, the low background incidence and the small number of events reported in available studies necessitate a much larger sample size to definitively rule out a doubling of risk for this rare event.[43]

Monitoring of birth defects is difficult and inconsistent. More than 80% of the available data come from four studies in which birth outcomes were prospectively reported.[43] In many resource-poor settings, the baseline risk of birth defects is not known. Determining the additional risk due to the use of EFV or other ARVs cannot be established without prospectively following up a large number of pregnancies, both with and without the exposure of interest. To achieve this, WHO is launching a Global Pregnancy Registry to support and encourage countries to register the outcomes of drug use in pregnant women; more information will be available in the near future. In addition, the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria have produced a Pharmacovigilance Technical Guidance Note to encourage standard procedures for monitoring ARV toxicity.[a,44] As part of the effort to detect any increased signal of birth-related toxicities, WHO also promotes targeted spontaneous reporting for monitoring the toxicity of ARVs.[b]

PROGRAMMATIC CONSEQUENCES OF UNCERTAINTY REGARDING EFV USE

A number of programmatic consequences result from the uncertainty regarding the real risk of teratogenicity associated with EFV use during pregnancy.

INCREASED FREQUENCY OF REGIMEN CHANGES

Among the general population, cohort studies comparing the rates of switching regimens suggest that patients on EFV are less likely to switch regimens due to adverse events than patients on NVP.[11] However, several studies have reported that among women of childbearing age, the likelihood of switching regimens is greater for women on EFV than on other ARVs due to concerns about its safety in pregnancy. In the UK, guidelines recommend that women who become pregnant while taking EFV continue this regimen unless it is failing. However, women who became pregnant while taking EFV were more than three times more likely to switch regimens compared to those taking other ARVs.[45] Over half of these switches occurred after the first 28 days of pregnancy, which is beyond the period of risk for neural tube defects. Similarly, in Italy, women who became pregnant while taking EFV were more likely to switch regimens than women who became pregnant while taking other ARV drugs.[42]

a UNAIDS, WHO. August 2011, available from: http://www.unaids.org/en/media/unaids/contentassets/documents/programmes/programmeeffectivenessandcountrysupportdepartment/gfresourcekit/20110818_Technical_Guidance_Pharmacovigilance.pdf

b Available from: http://apps.who.int/medicinedocs/documents/s19107en/s19107en.pdf and http://www.who.int/medicines/areas/quality_safety/safety_efficacy/recommendations.pdf

COMPLICATIONS IN THE MANAGEMENT OF TUBERCULOSIS COINFECTION

Tuberculosis (TB) is the most common opportunistic infection for people living with HIV, particularly in sub-Saharan Africa, where the majority of new TB cases are among HIV-infected patients.[46] There are important drug interactions when NVP is given to patients who are also receiving TB treatment. Unlike EFV, NVP concentrations are reduced in the presence of rifampicin, leading to reduced efficacy, as has been reported by many, but not all studies.[47,48,49] Thus, EFV is the preferred NNRTI for the management of HIV/TB coinfected patients.[2] Up to 40% of people starting ART in sub-Saharan Africa have TB[50] and many of these are women of childbearing age,[51] with the practical consequence that a considerable number of HIV/TB coinfected women of childbearing age initiate an EFV-based regimen.

POTENTIAL INCREASE IN THE NUMBER OF PREGNANCIES TERMINATED

Despite a clear statement in the 2010 WHO PMTCT ARV guidelines that termination of pregnancy for first-trimester exposure to EFV is not recommended,[3] in some settings there has been an increase in the number of pregnancies terminated among women exposed to EFV during pregnancy. A pooled analysis of three studies reporting the frequency of induced abortion among HIV-infected women exposed to EFV- and non-EFV-based regimens showed a nearly three times higher risk of induced abortions among women exposed to EFV.[43] These studies suggest that termination of pregnancy was probably based on concerns among providers and patients of potential birth defects rather than on any confirmation of birth defects. However, this should be interpreted with caution as the analysis did not compare the reported data with that of pregnancy termination in the general population and did not report on the reasons for termination of pregnancy.

INCREASED COMPLEXITY OF TREATMENT GUIDELINES

Uncertainty about the safety of EFV in pregnancy has resulted in increased complexity of current ART and PMTCT guidelines and practice. These include the following:

1. Which first-line ART regimen should be used for women of childbearing age who are unable or choose not to access contraception?
2. Which first-line ART regimen should be used for women who are already pregnant, either during or after the first trimester?
3. What guidance is appropriate for women already on an EFV-based first-line regimen who become pregnant and present either during or after the first trimester of pregnancy?

Access to contraception in resource-limited settings is limited and, even when available, cultural barriers may prevent uptake. In sub-Saharan Africa, the majority of patients (approximately 60%) initiating ART are women, predominantly of childbearing age.[52,53] The proportion of unintended pregnancies among HIV-positive women in sub-Saharan Africa ranges from 50% to 90%.[54]

These special considerations have prevented, until now, one simplified and harmonized approach to first-line ART and PMTCT prophylaxis. The currently nuanced guidelines for pregnant women and for those who may become pregnant have resulted in unrealistic expectations from programme managers and local health-care workers. Particularly in resource-limited settings, where the availability of doctors

may be limited and management of ART is increasingly the responsibility of other health-care workers, it is questionable whether such complex guidance can be followed.

INCREASED COMPLEXITY OF SUPPLY CHAIN MANAGEMENT

According to the 2010 WHO ART and PMTCT guidelines,[2,3] countries intending to use an EFV-based first-line regimen need to maintain NVP as the preferred option for women of childbearing age who are planning to become pregnant, or who may become pregnant (i.e. are not on reliable contraception). As summarized in this update, the latest evidence, as well as important programmatic considerations, suggests that this is not necessary. Eliminating this requirement will simplify programmatic drug procurement, and enable more unified supply chain management between ART and PMTCT programmes for first-line ARVs. NVP would need to be stocked only in small amounts for those (whether pregnant or not) who need to switch from EFV.

BURDEN ON HEALTH-CARE WORKERS AND PATIENTS

In settings where task-shifting related to the management of HIV and first-line ART has occurred, guidelines may recommend referral to a higher-level health facility to manage severe side-effects or for switching a patient's regimen. This may increase the burden on health systems in terms of personnel and costs. Management of drug side-effects and difficulties associated with regimen switches may increase the number of clinic visits for patients; more travel may be required for more frequent monitoring, perhaps to a more distant facility. A regimen change may result in a higher pill burden or more frequent dosing, both of which are inconvenient and could potentially lead to adherence problems.[55] These factors have been shown to lead to resistance, requiring a switch to a second-line ART regimen, which adds to the burden on the health system, in terms of both human and financial resources. Considering all these aspects, NVP-containing regimens are significantly more complex to manage than EFV-containing regimens; NVP use is associated with skin and hepatic toxicity that can be life-threatening. In addition, NVP needs a lead-in dosing approach during the first weeks of treatment and has to be taken twice daily.

SUMMARY COMPARISON OF EFV AND NVP

A comparison of the key characteristics of EFV and NVP reviewed in this technical update is shown in Table 1. EFV has a more favourable profile than NVP for the first five of these characteristics: safety and tolerability, drug interactions, convenience, efficacy and drug resistance. Although EFV and EFV-containing fixed-dose combinations are still more expensive than NVP, the price gap has closed considerably.

Table 1. Summary of clinical characteristics of efavirenz and nevirapine

	Efavirenz	Nevirapine
Safety and tolerability	▪ CNS side-effects, usually resolve after 2–4 weeks ▪ Ongoing concern but low evidence for teratogenicity (neural tube defects) during early pregnancy	▪ Severe rash and hepatotoxicity, particularly in women with CD4 counts ≥250 cells/mm^3 ▪ Stevens–Johnson syndrome ▪ Not recommended in pregnant women with CD4 counts >350 cells/mm^3
Drug interactions	No significant interactions	NVP concentrations are reduced in the presence of rifampicin
Convenience	Available as a once-daily, fixed-dose combination (with TDF and 3TC or FTC)	▪ Twice-daily regimen (with AZT or TDF) ▪ Requires lead-in dosing (i.e. use of half-dose in the first two weeks of treatment)
Efficacy	▪ Comparable efficacy in early clinical trials ▪ More recent data suggest greater efficacy for EFV in TDF-containing regimens	
Drug resistance (robustness)	Higher risk of NNRTI resistance mutations with NVP	
Cost (generic, annual, per patient)* **Single drug** **Combination FDC**	 ▪ $52 ▪ $180 (TDF/3TC/EFV once-daily fixed-dose combination)	 ▪ $31 ▪ $131 (AZT/3TC/NVP, twice-daily fixed-dose combination)

**Single drug costs (US dollars) based on generic drug costs by Médecins Sans Frontières;[34] fixed-dose combination drug costs based on early 2012 WHO estimates (HIV Department [AMDS], unpublished)*

CONCLUSION AND FUTURE DIRECTIONS

This technical update reviews the current data relating to the use of EFV during pregnancy, as well as the key differences between EFV and NVP, and provides interim advice to countries in advance of the consolidated WHO ARV guidelines revision planned for 2013. This review indicates WHO's increased confidence with the wide use of EFV, including in pregnant women and those of childbearing age, and the important programmatic advantages of simplifying and harmonizing a first-line ART regimen with an EFV-based fixed-dose combination as much as possible in different populations and service delivery settings.

EFV is an important, effective and relatively safe and well-tolerated drug, and is currently the best available NNRTI to be included as part of combination first-line ART. Regarding the risks and benefits of using EFV in pregnancy, evidence supports the benefits of EFV against the known risks and complexities of alternatives such as NVP. The current (2012) edition of the British HIV Association Guidelines recommends that EFV-based treatment should no longer be avoided in pregnant women or those who want to conceive.[56]

More countries are adopting TDF-based regimens that can be combined with 3TC (or FTC) and EFV in one tablet as a once-daily fixed-dose combination, in accordance with WHO's Treatment 2.0 initiative,[4] which emphasizes simplification, standardization and optimization of regimens. This simplified regimen should facilitate good patient adherence[55] and provides important programmatic advantages for use across different populations and in different settings.[57] Despite the development of second-generation NNRTIs such as rilpivirine, the recently demonstrated superior virological suppression with EFV will probably mean that EFV will remain the preferred first-line NNRTI for some time to come.[58,59]

The current data review of safety and risk of teratogenicity is reassuring. However, additional research and ongoing surveillance through pregnancy registries are needed, both to prospectively collect more data on birth defects and other severe adverse events resulting from exposure to EFV and other ARVs, and to better assess programme, provider and patient perspectives on the true risks and benefits of EFV use, especially in low- and middle-income countries.

Global and national guidelines need to carefully consider the impact of recommending avoidance of EFV in pregnant women or among those of childbearing age. Particularly in resource-limited settings, the consideration to use EFV in women of reproductive age and those in the early stages of pregnancy needs to move beyond concerns based on limited evidence of teratogenicity risk to recognizing new evidence of survival gains, efficacy, overall regimen tolerability, and the substantial direct clinical and programmatic benefits associated with simplification and scale up of treatment coverage. Based on currently available evidence, programmatic considerations and a careful weighing of risks and benefits, EFV should be considered as part of the preferred first-line treatment option, including among women of reproductive age and those in the early stages of pregnancy.

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