REVIEW

SAFETY, STRENGTH AND SIMPLICITY OF EFAVIRENZ IN PREGNANCY

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The WHO recommends starting lifelong ART for all pregnant women with a CD4 count at or below 350 cells/mm^3, which recognises the important component of 'when to start' and the role that timing of initiation plays in reducing mortality and disease progression. The data on 'what to start' are conflicting, and options for resource-limited settings are limited. The choice of an ART regimen for pregnant women is complicated by the need to take into account the health and safety of both the mother and baby. Particularly contentious is whether to use a nevirapine- (NVP) or efavirenz- (EFV) based regimen. This review presents the latest evidence on the safety and efficacy of EFV and NVP in pregnancy and offers recommendations for improving maternal and child health outcomes and avoid mother-to-child transmission as South Africa moves toward turning back the tide on its HIV epidemic.

Estimates for South Africa for 2010 were that approximately 5.6 million people were HIV-infected,[1] accounting for the largest number of cases in a single country.[2] According to the latest South African National Antenatal Survey (2010), 30.2% of pregnant women in South Africa were HIV-positive,[3] maternal mortality was 6 times higher among HIV-positive women, and more than half of all maternal deaths were attributable to HIV.[4] About 40 000 children in South Africa are infected with HIV each year, with HIV/AIDS a major contributor to infant mortality in South Africa.[5] But amidst the bad news has been some good: more than 1.56 million people in South Africa are now receiving ART, and the introduction of more robust and better-tolerated antiretrovirals (ARVs) such as tenofovir disoproxil fumarate (TDF) for first-line therapy is narrowing the gap between recommended treatment protocols in rich and poor countries. In addition, exciting new knowledge and evidence about the concept of 'treatment as prevention' (TasP) has emerged, showing not only the therapeutic but also the potential preventive benefits of ART. Prevention of mother-to-child transmission (PMTCT) as TasP is not new – but it currently lags behind other programme goals and ART scale-up efforts.[6] Earlier initiation of treatment for pregnant women provides extra benefits in PMTCT. While efavirenz (EFV) has been recommended in the WHO guidelines for initiation of eligible women after the first trimester; its use in pregnant women has been restricted in the South African Clinical PMTCT guidelines, where all pregnant women are initiated on a nevirapine (NVP)-based regimen.[7] In consequence, as South Africa seeks ways in which new knowledge can be integrated into existing programmes that could have measurable effects on mortality and morbidity,[8] this review presents the latest evidence of safety and efficacy of EFV in pregnancy.

IS THERE REALLY AN OPTION FOR WOMEN?

To date, limited and complicated PMTCT and treatment options exist for women infected with HIV. The latest WHO PMTCT guidelines offer lifelong ART for those with CD4<350 cells/mm^3 and allow resource-limited settings two options for those with CD4 >350 cells/mm^3: A or B.[9] Option B offers all women triple therapy for the duration of pregnancy until the cessation of breast feeding for those with CD4>350 cells/mm^3. The view that option B is superior to option A is emerging, for several reasons:[10]

- its simplicity for women and programmes, as option A is especially complicated and requires many regimen changes[6]
- option B allows more women to have sustained exposure to HAART. For those who may fall pregnant during breastfeeding, HAART allows women to survive longer,[11] which is important for survival of their children.
- option B may have an added preventative benefit for pregnant women's partners in discordant relationships[12]
- the unknown risk of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance in the mother or infant, despite prophylaxis[13]
- safety, effectiveness and feasibility of daily infant NVP beyond 6 months of age; and maternal and infant acceptability of daily infant prophylaxis for a long period as well as acceptability in programme settings is largely unknown
- option B may be better for women, with a growing consensus demonstrating that there are individual benefits for the mother as well as for public health.[10]

Option B, although simpler, has some drawback for women who fall pregnant again or become eligible for lifelong ART, as they would need to restart HAART. This essentially translates into treatment interruption. Some countries, such as Malawi, have elaborated on option B. Malawi is now implementing what is termed 'Option B+', which is lifelong ART for all pregnant women, irrespective of CD4 cell count, from 14 weeks' gestation. To achieve this, Malawi has included EFV as part of a fixed-dose once-daily formulation for treatment of pregnant women. This decision was justified on the basis that the limited potential risk of birth defects owing to efavirenz is far outweighed by the increased public health benefit, coverage, and reduced overall mortality of initiating mothers on HAART.[14]

IS EFAVIRENZ SAFE TO USE IN PREGNANCY?

Efavirenz's FDA rating was changed from category C to category D in 2005, based on data from animal studies and retrospective case reports of neural tube defects.[15] Evidence of teratogenicity linked

TABLE 1. ARV PROPHYLAXIS OPTIONS RECOMMENDED FOR HIV-INFECTED PREGNANT WOMEN WHO DO NOT NEED TREATMENT FOR THEIR OWN HEALTH

Option A: Maternal AZT

Mother

- Antepartum AZT (from as early as 14 weeks' gestation)
- sd-NVP at onset of labour*
- AZT + 3TC during labour and delivery*
- AZT + 3TC for 7 days postpartum*

*sd-NVP and AZT+3TC can be omitted if mother receives >4 weeks of AZT antepartum

INFANT

Breastfeeding infant

Sd-NVP at birth plus daily NVP from birth until one week after all exposure to breast milk has ended

Non-breastfeeding infant

Sd-NVP at birth plus AZT or NVP from birth until 4 - 6 weeks

Option B: Maternal triple ARV prophylaxis

Mother

Triple ARV from 14 weeks until one week after all exposure to breast milk has ended

- AZT + 3TC + LPV/r
- AZT + 3TC + ABC
- AZT + 3TC + EFV
- TDF + 3TC (or FTC) + EFV

INFANT

Breastfeeding infant

AZT or NVP from birth until 4 - 6 weeks

Non-breastfeeding infant

AZT or NVP from birth until 4 - 6 weeks

Source: WHO Rapid Advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, November 2009. Revised June 2010.

TABLE 2. COMPARATIVE RATES OF BIRTH DEFECTS FOR WIDELY USED ARVS IN THE FIRST TRIMESTER

First trimester exposure ARV	Defects/live births	Prevalence (95% CI)
Indinavir	6/285	2.1% (0.8% - 4.5%)
Lopinavir	16/738	2.2% (1.2% - 3.5%)
Atazanavir sulfate	12/502	2.4% (1.2% - 4.1%)
Stavudine	19/797	2.4% (1.4% - 3.7%)
Ritonavir	33/1401	2.4% (1.6% - 3.3%)
Tenofovir	26/1092	2.4% (1.6% - 3.5%)
Nevirapine	25/987	2.5% (1.6% - 3.7%)
Emtricitabine	17/641	2.7% (1.5% - 4.2%)
Efavirenz	17/623	2.7% (1.6% - 4.3%)
Abacavir	22/744	3.0% (1.9% - 4.5%)
Lamivudine	118/3864	3.1% (2.5% - 3.7%)
Zidovudine	118/3620	3.3% (2.7% - 3.9%)
Nelfinavir	46/1193	3.9% (2.8% - 5.1%)
Didanosine	19/406	4.7% (2.8% - 7.2%)

Source: Antiretroviral Pregnancy Register (APR) Interim report 2011[18]

to the use of EFV in pregnancy has been limited since then, and current evidence suggests that the risk is lower than previously thought.[16,17]

Current WHO guidelines recommend avoiding EFV in the first trimester only, but also note that overall rates of birth defects in infants exposed to EFV, NVP and TDF are similar to those in the general population.[9] It is evident that the risk of birth defects on exposure to any of the widely used antiretroviral agents shows a similar risk (NVP 2.5%, EFV 2.7% and AZT 3.3%) (Table 2). In addition, the risks are similar for first, second and third trimester exposures (Table 3). In review of the data till 31 January 2011, among the prospective Antiretroviral Pregnancy Registry (APR) reports, the prevalence of birth defects per 100 live births among women with a first trimester exposure to any of the antiretroviral therapies included in the APR is 2.9% (95% confidence interval (CI) 2.5 - 3.4) i.e. 164 outcomes with defects of 5 555 live births.[18] The prevalence of defects is not significantly different from the prevalence of defects among women with an initial exposure during the second and/or third trimester of 2.7% (prevalence ratio 1.08, 95% CI 0.88 - 1.32)/205 birth defects in 7 483 live births.[18] The APR result for EFV exposure in the first trimester is 2.7% (95% CI 1.6 - 4.3), and 2.9% (95% CI 0.3 - 10) for second- and third-trimester exposure to EFV. The most recent updated meta-analysis as at July 2011 (which reviews the APR and other prospective cohorts) showed a pooled prevalence of 2% (95% CI 0.82 - 3.18) and relative risk of birth defects in EFV-containing ART regimens to non-EFV-based ART as 0.85 (95% CI 0.61 - 1.20).[17] This confirms no increased risk of overall birth defects among women receiving first-trimester efavirenz. Comparatively, the risks in the general population are also quite similar (Table 3): in the USA, the prevalence of birth defects in the general population is approximately 3% of live births; and in South Africa the prevalence is estimated at 5.3%.[19]

However, concerns have been raised, owing to retrospective reports of myelo-meningocoeles received after the FDA category change. The risk of neural tube abnormalities exists before it closes by 28 days. The prevalence of neural tube defects (NTD) globally is 0.1 - 0.4%, while in South Africa it is estimated at 0.23 - 0.36%.[19]

TABLE 3. PREVALENCE OF BIRTH DEFECTS

General US pop[18]	General South African pop[19]	1st trimester exposure to any ARV[18]	2nd/3rd trimester exposure to any ARV[18]	1st trimester exposure to EFV[18]	2nd/3rd trimester exposure to EFV[18]	1st trimester exposure to EFV[17]
3%	5.3%	2.9%	2.7%	2.7%	2.9%	2.0%
95% CI:		(2.5 - 3.4)	(0.88 - 1.32)	(1.6 - 4.3)	(0.3 - 10.0)	(0.82 - 3.18)
Numbers:		164/5 555	205/7 483	17/643	2/70	39/1 437

Relative risk 1st trimester EFV to non-EFV ART was 0.85 (0.61 - 1.20)[17]

TABLE 4. FDA CATEGORIES OF RISK

Category	Description
A	**Controlled studies show no risk** Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
B	**No evidence of risk in humans** Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals **or** In the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.
C	**Risk cannot be ruled out** Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus, or are lacking as well. There is a chance of foetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk.
D	**Positive evidence of risk** Studies in humans, or investigational or post-marketing data, have demonstrated foetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	**Contra-indicated in pregnancy** Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient.

Source: FDA[20]

The recent 2011 meta-analysis shows the incidence of neural tube defects (until July 2011) to be low, at 0.07 (95% CI 0.002 - 0.39).[17] Given the low baseline prevalence of neural tube defects, many more first-trimester efavirenz exposures would be required to quantify the risk. Potentially, it would take a long time for a South African (or another country's) registry to accumulate sufficient data to allow firmer conclusions to be drawn. In addition, a major problem of retrospective reports is the reporting bias. Retrospective reports can be biased toward the reporting of more unusual and severe cases, and are less likely to be representative of the general population experience. Therefore, the calculation of prevalence from these reports is often inappropriate and needs to be interpreted with caution.

To summarise: current data on efavirenz use in pregnancy shows little and poorly supported evidence of risk to the fetus, with a non-significant relative risk of only 0.85 (95% CI 0.61 - 1.20) with EFV, compared with non-EFV-based exposure in the first trimester. There is no significant increase in risk of NTDs with EFV exposure.

Importantly, as for any ARV drug, it is not possible to conclusively say that EFV is safe, and drug companies and regulatory bodies are therefore unlikely to change the EFV rating out of fear of litigation. Noteworthy is the difference between category X and category D (Table 4); and the latter allows policy decision-makers, clinicians and patients alike to weigh up the evidence and allow judgment in their best interests. The FDA is currently proposing to update its approach to labeling.[20]

CONSEQUENCES ON COMPREHENSIVE SEXUAL REPRODUCTIVE HEALTH

Another potentially harmful consequence of the EFV category D rating is reported in data on termination of pregnancy (TOP) for women exposed to efavirenz-containing and non-efavirenz-containing regimens. These reveal a RR of 2.81 (95% CI 0.94 - 8.36) for efavirenz-exposed women.[17] These TOPs are not informed by prenatal screening and could mean that women on EFV are almost 3 times more likely to have a potentially distressing and unnecessary TOP based on the potential risk of teratogenicity and not the actual presence of a birth defect. This has far-reaching harmful consequences for the woman and for clinicians who could be inadvertently ill-advising patients on the basis of poorly supported evidence of risk.

Recent studies in Johannesburg show that issues around providers and information transferred to patients about efavirenz risk in pregnancy are often misunderstood. In one study, 40.7% of 851 women declared that the healthcare provider had not discussed pregnancy options with them. A small proportion (6.4%) said a provider had told them not to have more children, and 36% were unsure whether their provider had approved of them having children.[21] Furthermore, women on both EFV and NVP had similar

pregnancy intentions – either trying to conceive or planning to do so.[21] Pettifor and Rees found in 2005 that roughly 33% of women planned their pregnancies.[22] Complexity of personal reproductive health issues for women and their relationship with healthcare providers must be acknowledged.

WHAT DO WE KNOW ABOUT THE ALTERNATIVE – NEVIRAPINE?

Current WHO guidelines affirm the role of ARVs for pregnant women, and recommend the use of ARVs in differing combinations, depending on CD4 cell count, in all pregnant HIV-infected women. Consequently, according to current South African guidelines, many more women will be initiated on NVP-based regimens. Today, NVP is the recommended alternative to EFV in women of childbearing age.

The 2NN study[23] (the largest randomised controlled trial (RCT), with more than 1 200 patients) found no difference in efficacy between NVP and EFV, and a systematic review of 7 RCTS[24] also found no difference at 48 weeks. The authors recognise, however, that 48 weeks of follow-up is shorter than other cohort studies, which shows that the difference between EFV and NVP grows larger over time.[23] When the Parkland cohort study data were censored at week 48 (using the endpoint in 2NN), there were no significant differences in time to virological failure (EFV = 38.9 weeks v. NVP = 37.2 weeks, $p = 0.20$); however, when the patient cohort data were not censored at 48 weeks, significant differences were seen between EFV and NVP at 192 weeks ($p<0.001$).[25,26] EFV was specifically found to provide a significantly longer time to treatment failure than NVP (EFV = 132 weeks v. NVP = 94.1 weeks, $p = 0.027$).[25,26] Additionally, in the 2NN study, fewer patients taking EFV than those taking NVP experienced treatment failure (37.8% v. 47.3%).[23]

These results underscore the need to observe patients for longer periods of time to determine the extended durability of antiretroviral regimens. Since clinical trials are often difficult and expensive to maintain, observational cohort analyses may be an alternative for examining long-term durability. Many observational cohorts show that EFV is superior, with an increased risk of virological failure on NVP-based ART regimens.[27-30] In June 2011, at the IAS conference, a meta-analysis comparing TDF-containing regimens raised concerns that TDF/3TC/NVP might have decreased virological efficacy compared with the EFV-containing TDF regimens.[31] Therefore, we should be concerned about initiating women or switching them to a NVP-based regimen that might not necessarily be superior because of our poorly supported evidence of teratogenicity.

To date, there is conflicting evidence of severe adverse events (rash and hepatotoxicity) in pregnant women who have higher CD4 cell counts, initiating HAART with a NVP-containing regimen. In 2004, Boehringer-Ingelheim, manufacturers of NVP (Viramune) performed a retrospective analysis of hepatoxicity events and found no consistent CD4 cell-count cut-off that could be identified in women, that was associated with an increased risk of liver enzyme elevations. The analysis also demonstrated no significant differences in the rate of serious hepatic events among ARV regimens, including between the non-nucleoside reverse transcriptase inhibitors NVP and EFV.[32] Further scrutiny of this analysis revealed that patients with symptomatic events were not included in the subset analysis. It also revealed the risk of rash-associated hepatic adverse events was 3 times higher in women than in men. A rash-associated hepatic event was also associated with a higher CD4 cell count, with women with pre-treatment CD4 count >250 cells/mm^3 having a higher risk of hepatotoxicity than women with CD4 <250 cells/mm^3.[33] Following these results, the company changed the *Summary of Product Characteristics* to include a caution that women with higher CD4 cell counts are at increased risk of hepatic toxicity.[34]

Previously, it was not recommended to initiate women on NVP if their CD4 cell count was above 250 cells/mm^3.[35-37] Data are now emerging from both high-income[38,39] and resource-limited settings,[32] suggesting that it is safe for patients who have experienced good increases in their CD4 cell counts on anotherARV regimen to switch to NVP (provided they have an undetectable viral load), even when their CD4 count is above the level recommended for initiating treatment. In 2009, Ouyang and colleagues showed that NVP is not uniquely associated with hepatoxicity in pregnancy but rather that pregnancy itself may be an independent risk factor.[40] The same study also showed that NVP is not associated with hepatoxicity at higher CD4 cell counts. Chu *et al*.[41] found in 2010 no association of CD4 cell count and hepatotoxicity; however, the median CD4 cell count in their cohort was low (112 cells/mm^3) and, with resource-limited settings still pervaded by patients presenting late and initiated at low CD4 cell counts, this study highlights one of the possible reasons for the lack of observed difference between high-income and resource-limited settings.

Indeed, a Cambodian cohort study in a resource limited setting found (*i*) that higher CD4 cell counts at the time of NVP substitution from EFV increased the risk of subsequent NVP toxicity, and (*ii*) that ART-experienced Cambodians appear to have a risk of NVP toxicity comparable with that of ART-naive patients, despite higher CD4 counts.[42] The analysis from the large randomised clinical trial, the 2NN study, demonstrated that the rate of skin rash and hepatic events was higher in patients with CD4 counts >200 cells/ml, and also that women with CD4 counts >200 cells/mm^3 had a significantly greater risk of developing a rash than men.[23,24] The most recent data from Uganda presented at the IAS conference in June 2011 have documented 3 cases of Stevens-Johnson syndrome in stable **experienced** HAART patients when switched to NVP.[43] Overall, the meta-analysis of 7 randomised controlled trials (RCTs) show that EFV had a lower incidence of adverse events (AEs) and fewer discontinuations than NVP.[24] Fewer patients taking EFV discontinued therapy because of any AE or HIV event than patients taking the other treatment regimens. Two deaths were directly associated with NVP use (one from toxic hepatitis and the other from Stevens-Johnson syndrome); no deaths were associated with EFV. Overall, EFV was associated with a more favorable tolerability profile than NVP, with less grade 3 or 4 clinical AEs, fewer discontinuations for AEs, and numerically less treatment changes with EFV than with NVP.[23]

There therefore seems to be insufficient evidence to recommend that it is safe to switch NVP for EFV, in particular in settings such as South Africa with higher co-infection rates of TB i.e. women who are switched to and fro.[44] It is possible that the WHO concluded that using NVP outweighs the risk of not initiating ART precisely because of the lack of an alternative for resource-limited settings. This is why EFV in pregnancy needs to be carefully rethought in light of the most recent evidence. The more toxic and life-threatening alternative to EFV that puts a woman at increased risk needs to be urgently revisited.

IS EFAVIRENZ AFFORDABLE AND COST-EFFECTIVE?

The prohibitively high cost of EFV had prevented its widespread use in the early part of the decade, and the price evolution is demonstrative (Fig. 1). The Medicins Sans Frontieres (MSF) report *Untangling the Web* reveals that the cost of EFV has been driven down from the originator price of $347 in December 2002 to a WHO-prequalified generic price of $52 in July 2011 (per patient per year).[45] Despite cost, perhaps more important is a recent study looking to quantify the benefit (life expectancy gains) and risk, that shows that the use of non-efavirenz-based initial ART in HIV-infected women of childbearing age may reduce life expectancy gains from ART.[46] The mean life expectancy for women who would start ART at a CD4<250 on NVP-based HAART was 25.49, compared with 27.08 for EFV-based ART, with a resultant 1.6-year life expectancy gain on EFV compared with NVP.[46] In addition, survival of women who received an EFV-based ART regimen was 0.89 years greater than all non-EFV-based regimens.[46] Policymakers do indeed need to take into account cost and cost-effectiveness, but the benefit to women and their families favours EFV-based ART when reduced survival and potential life-threatening severe adverse events on NVP are quite stark. Today, the fixed-dose combination of tenofovir, lamivudine and efavirenz in a once-a-day pill is likely to have positive spill-over effects for those women who need to take treatment every day for the rest of their lives, without jeopardising their own health and further resistance through poor adherence.

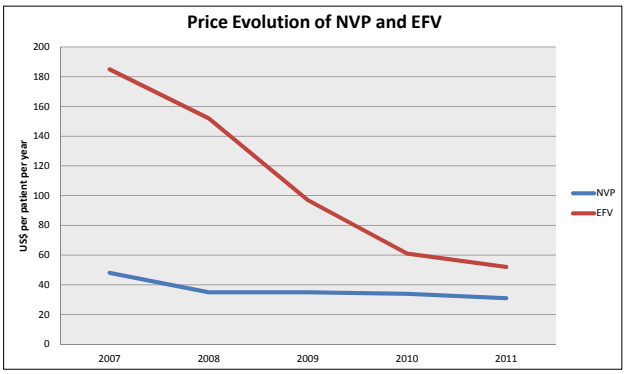

Fig. 1. Price evolution of NVP and EFV.
Source: www.utw.msfaccess.org

CONCLUSIONS AND RECOMMENDATIONS

The above describes the most recent evidence available; could we expect more robust evidence? Randomised controlled trials (RCTs) (gold standard) are not feasible, and it would take a very long time to truly assess and compare outcomes. Modeling exercises can help to inform some potential future outlook for those questions not answered by available evidence today or when RCTs are not feasible. Ouattara *et al.*'s (2012) latest projections found that starting ART with EFV, which has a lower rate of switching owing to its toxicity profile, provides a benefit over NVP in survival at 10 years i.e. more women alive; and comparatively the rate of birth defects with EFV would need to be 2.3 times the rate of NVP to balance out the number of deaths of women on NVP.[47] This seems unlikely if to date the APR birth defect rate for NVP is 2.7%, for EFV 2.9%, and the recent meta-analysis by Ford *et al*. (2011) is 2.0%.

Therefore, the risk-benefit question for women is: Does the risk of birth defects (knowing that we have low and poorly supported risk to the fetus and enough data to say we don't have a tenfold increase in risk of NTDs) after the organogenesis period on EFV outweigh the risks of life-threatening toxicity, regimen changes and a potential risk of failure when switching women from EFV to NVP? Particularly as South Africa has moved to earlier initiation of HAART at CD4<350 cells/mm^3, many more women will be picked up early at antenatal clinic with the risk of severe adverse events being potentially higher in women with higher CD4 counts if switched to NVP.

It is important to bear in mind that most studies are confounded by HIV disease stage, smoking, co-morbidities and other medication. Generally, an HIV-infected population is possibly at increased risk of adverse outcomes of pregnancy unrelated to teratology, and in South Africa there is an extra burden of fetal alcohol syndrome. 'Fetal alcohol spectrum disorder is the most common birth defect in South Africa, by far more common than Down syndrome and neural-tube defects combined,' according to Professor Denis Viljoen of the Foundation for Alcohol Related Research (FARR).[48]

Based on the evidence, there are several policy recommendations that the South African government should consider at this critical juncture while heading towards the 'getting to zero' goal.

- Firstly, it should allow for already on HAART who fall pregnant to continue on EFV-based HAART instead of switching to NVP. Most pregnancies are not detected until at least one month after conception; switching to NVP after this point may not protect against birth defects, and needs to be balanced against the risk of serious adverse events caused by switching to NVP.
- Secondly, it could allow only women who are on ART and who want to conceive to switch from EFV to NVP **before** falling pregnant.
- All women of child-bearing age should be encouraged to plan their pregnancies and be tested before conception.
- The South African government should consider moving to embrace Option B as preferred PMTCT, and to initiate all women in need of HAART them on the superior combination of TDF/3TC/EFV from 14 weeks' gestation. This has an added benefit of simplification for nurse-initiated ART as it is consistent with adult preferred first-line treatment; and has the potential to simplify the supply chain, thereby preventing potential stock-outs.
- Consider pilot projects that could ascertain the benefits and risks for individuals and at the population level, as well as programmatic implications for putting all pregnant women on HAART (Option B+).
- Regulatory bodies and the government should fast-track the registration of the fixed-dose once-daily formulation of TDF/3TC/EFV for all patients.
- Lastly, increased pharmaco-vigilance and a South Africa-wide prospective Antiretroviral Pregnancy Registry are needed. With the number of women exposed to EFV in the first trimester, however, it would take a very long time for a South African registry to accumulate enough data to allow firmer conclusions to be drawn; therefore, this should not be done at the expense of women in need of treatment now.

This paper has argued that, although we could never claim any ARV to be completely safe, weak associations in some studies are far outweighed by the benefits of HAART in pregnancy. The consideration to use EFV in the first trimester of pregnancy in resource-limited settings such as South Africa needs to move beyond concerns of poorly supported evidence to recognising new evidence of survival gains, efficacy, toxicity, direct medical and programmatic costs (including costs of simplification and scaling

up coverage) – as well as indirect costs e.g. unnecessary and distressing termination of pregnancies. This allows policymakers an opportunity to harness the evidence accumulated to date and focus on pursuing an effective strategy based on evidence and balancing risks and benefit of best prevention and treatment options for women and their families.

REFERENCES

1. USAID HIV/AIDS Health Profile Sub Saharan Africa. http://www.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf (accessed 23 November 2011).
2. UNAIDS WorldAIDSday report_2011_en.pdf. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_en.pdf (accessed 23 November 2011).
3. National Antenatal Sentinel HIV and SyphilisPrevalence Survey in South Africa, 2009. Pretoria: Department of Health, 2010.
4. Black V, Brooke S, Chersich MF. Effect of human immunodeficiency virus treatment on maternal mortality at a tertiary centre in South Africa. Obstet Gynecol 2009;114:292-299.
5. Mid-year Population Estimates 2010. Statistics SA. http://www.statssa.gov.za/publications/P0302/P03022010.pdf (accessed 23 November 2011).
6. Stringer EM, Ekouevi DK, Coetzee D, et al. Coverage of nevirapine-based services to prevent mother-to-child HIV transmission in 4 African countries. JAMA 2010;304(3):293.
7. Clinical guidelines: PMTCT (Prevention of Mother-to-Child Transmission). Pretoria: South African National AIDS Council, 2010.
8. National Strategic Plan for HIV and AIDS, STIs and TB, 2012-2016 Draft Zero 110808 pdf final. http://www.sanac.org.za/files/uploaded/519_NSP%20Draft%20Zero%20110808%20pdf%20%20final.pdf (accessed 23 November 2011).
9. Rapid Advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, November 2009. Revised June 2010. http://whqlibdoc.who.int/publications/2009/9789241598934_eng.pdf (accessed 23 November 2011).
10. PEPFAR Scientific Advisory Board, Including the HPTN 052 Subcommittee and HPTN 052 Writing Group (Wafaa El Sadr, Myron Cohen, Kevin DeCock, et al.). PEPFAR Scientific Advisory Board Recommendations forthe Office of the US Global AIDS Coordinator:Implications of HPTN 052 for PEPFAR's Treatment Programs 2011. Available from: http://www.pepfar.gov/documents/organization/177126.pdf (accessed 23 November 2011).
11. Mills EJ, Bakanda C, Birungi J, et al. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: A cohort analysis from Uganda. Ann Intern Med 2011;155(4):209-216.
12. Mugo NR, Heffron R, Donnell D, et al. Increased risk of HIV-1 transmission in pregnancy: A prospective study among African HIV-1 serodiscordant couples. AIDS 2011;25(15):1887-1895.
13. Dorton BJ, Mulindwa J, Li MS, et al. CD4+ cell count and risk for antiretroviral drug resistance among women using peripartum nevirapine for perinatal HIV prevention. BJOG 2011;118(4):495-499.
14. Schouten EJ, Jahn A, Midiani D, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. Lancet 2011;378:282-284.
15. Important Change in SUSTIVA® (efavirenz) Package Insert – Change from Pregnancy Category C to D. http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164871.pdf (accessed 23 November 2011).
16. Ford N, Mofenson L, Kranzer K, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS 2010;24:1461-1470.
17. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS 2011;25(18):2301-2304.
18. The Antiretroviral Pregnancy Register Interim report 1 January 1989 through 31 January 2011. http://www.apregistry.com/forms/interim_report.pdf (accessed 23 November 2011).
19. March of Dimes Global Report of Birth Defects Wall Chart http://www.marchofdimes.com/downloads/BirthDefectsWallChart.pdf (accessed 23 November 2011).
20. FDA Content and Format for Labeling for Human Prescription Drug and Biological Products – Proposed Rules. Federal Register Vol. 73, No. 104. 2008. http://edocket.access.gpo.gov/2008/pdf/E8-11806.pdf (accessed 23 December 2011).
21. Schwartz SR, Mehta SH, Taha TE, Rees HV, Venter F, Black V. High Pregnancy Intentions and Missed Opportunities for Patient–Provider Communication About Fertility in a South African Cohort of HIV-Positive Women on Antiretroviral Therapy. AIDS and Behavior. 9 June 2011. http://www.springerlink.com/content/e310h87734262755/ (accessed 23 November 2011).
22. Pettifor AE, Rees HV. Young people's sexual health in South Africa: HIV prevalence and sexual behaviours from a nationally representative household survey. AIDS 2005;19:1525-1534.
23. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet 2004;363(9417):1253-1263.
24. Mbuagbaw LC, Irlam JH, Spaulding A, Rutherford GW, Siegfried N. Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004246.pub3/abstract (accessed 25 November 2011).
25. Keiser P, Nassar N, Yazdani B, Armas L, Moreno S. Comparison of efficacy of efavirenz and nevirapine: lessons learned for cohort analysis in light of the 2NN Study. HIV Clin Trials 2003;4(5):358-360.
26. Keiser P, Nassar N, Yazdani B, Armas L, Moreno S. Conference on Retroviruses and Opportunistic Infections (2004: San Francisco). The Use of Observational Databases to Compare Anti-retroviral Effectiveness. Abstract no. 559. http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102271521.html (accessed 25 November 2011).
27. Bock P, Fatti G, Grimwood A. Comparing the effectiveness of efavirenz and nevirapine for first-line antiretroviral treatment amongst an adult treatment cohort from South Africa. J Int AIDS Soc 2010;13:P10.
28. Davies M-A, Moultrie H, Eley B, et al. Virologic failure and second-line antiretroviral therapy in children in South Africa—The IeDEA Southern Africa Collaboration. J Acquir Immune Defic Syndr 2011;56:270-278.
29. Nachega JB, Hislop M, Dowdy DW, et al. Efavirenz versus nevirapine-based initial treatment of HIV infection: clinical and virological outcomes in Southern African adults. AIDS 2008;22:2117-2125.
30. Datay MI, Boulle A, Mant D, Yudkin P. Associations with virologic treatment failure in adults on antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr 2010;54(5):489-495.
31. Tang M, Kanki P, Shafer R. Virological efficacy of the four tenofovir-containing WHO-recommended regimens for initial antiretroviral therapy. IAS 2011 Abstract. http://pag.ias2011.org/abstracts.aspx?aid=2206 (accessed 25 November 2011).
32. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV-infected patients. J Acquir Immune Defic Syndr 2003;34:S21-S33.
33. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. J Acquir Immune Defic Syndr 2004;35(5):538-539.
34. Viramune [package insert]. Ridgefield, CT: Boehringer-Ingelheim Pharmaceuticals, 2008.
35. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. J Acquir Immune Defic Syndr 2004;36(3):772-776.
36. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. HIV Med 2006;7(4):255-260.
37. Jamisse L, Balkus J, Hitti J, et al. Antiretroviral-associated toxicity among HIV-1-seropositive pregnant women in Mozambique receiving nevirapine-based regimens. J Acquir Immune Defic Syndr 2007;44:371-376.
38. De Lazzari E, León A, Arnaiz JA, et al. Hepatotoxicity of nevirapine in virologically suppressed patients according to gender and CD4 cell counts. HIV Medicine 2008;9(4):221-226.
39. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. AIDS 2009;23(13):1689-1699.
40. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. AIDS 2009;23(18):2425-2430.
41. Chu KM, Boulle AM, Ford N, Goemaere E, Asselman V, Van Cutsem G. Nevirapine-associated early hepatotoxicity: Incidence, risk factors, and associated mortality in a primary care ART programme in South Africa. PLoS ONE 2010;5(2):e9183.
42. van Griensven J, Un P, Phe T, Thai S, Lynen L. Substituting nevirapine for efavirenz: risk factors for toxicity in nonnaive patients in a resource-constrained setting. AIDS 2009;23:2374-2376.
43. Kasirye Gitta P, Bakeera-Kitaka S, Kekitiinwa A. Stevens-Johnson syndrome (SJS) following switch to Nevirapine based regimen at Baylor-Uganda´s Paediatric Infectious Diseases Clinic, Mulago Hospital. http://www.iasociety.org/Abstracts/A200740712.aspx (accessed 25 November 2011).
44. Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? Lancet Infect Dis 2007;7(11):733-738.
45. Campaign for access to essential medicines. Medicins Sans Frontieres. Untangling the Web of Antiretroviral Price Reductions. http://utw.msfaccess.org/ (accessed 23 November 2011).
46. Hsu H, Rydzak C, Cotich K, et al. Quantifying the risks and benefits of efavirenz use in HIV-infected women of childbearing age in the USA. HIV Med 2011;12(2):97-108.
47. Ouattara EN, Anglaret X, Wong AY, et al. Projecting the clinical benefits and risks of using efavirenz-containing ART regimens in women of childbearing age in Sub-Saharan Africa. AIDS 2012;1. [http://dx.doi.org/10.1097/QAD.0b013e328350fbfb].
48. Fetal alcohol syndrome: dashed hopes, damaged lives. Bull World Health Organ 2011;89:398-399.