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WHO Option B+: Early Experience of Antiretroviral Therapy Sequencing after Cessation of Breastfeeding and Risk of Dermatologic Toxicity

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To the Editors:

The WHO recently updated guidelines for the use of antiretroviral therapy among pregnant women, including “Option B+” – the initiation of combination antiretroviral therapy (cART) during pregnancy and continued for life ¹ regardless of CD4+ cell count. Numerous countries have begun implementing Option B+ and scaling-up lifelong cART initiated during pregnancy. Option B+ includes either lopinavir/ritonavir (LPV/r), abacavir, or efavirenz (EFV)-based cART initiated after the first trimester of pregnancy for women with CD4+ cell counts above 350 cells/mm³ versus nevirapine (NVP) or EFV-based cART for women with CD4+ cell counts 350 cells/mm³ or lower. Option B+ is cost-effective for Uganda ² and benefits include near elimination of perinatal and breastfeeding HIV transmission, promotion of women’s health, and markedly diminished risk of sexual HIV transmission.

As Option B+ is implemented, clinicians will face challenging management issues, particularly in resource constrained settings when women starting Option B+ regimens have indications for a change in antiretroviral therapy due to reasons such as desire for additional pregnancies, contraceptive choice, in-country availability or cost. Moreover, women will be starting, and potentially changing, combination antiretroviral therapy at higher CD4+ cell counts raising questions regarding the safety of switching to NVP-based regimens. We

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provide early data on HIV-infected pregnant women treated with combination antiretroviral therapy at all CD4+ cell counts who were switched to a NVP-based regimen at the cessation of breastfeeding.

We performed a secondary analysis of PROMOTE-Pregnant Women and Infant Study (NCT00993031), an open-label randomized controlled trial of HIV-infected pregnant women comparing efficacy of LPV/r versus EFV in preventing placental malaria in Tororo, Uganda. Women at all CD4+ cell counts are enrolled at 12-28 weeks gestation and receive LPV/r or EFV-based cART from enrollment until 1 year postpartum. At 1 year postpartum, women are given the opportunity to continue non-study cART, and care is transitioned to a community-based HIV clinic. Women's non-study regimens are chosen based on their reproductive intentions, contraceptive choice and available in-country regimens.

Between March 7, 2011 and April 3, 2012, women receiving LPV/r were switched to NVP at the end of trial participation if they were transitioning to a local clinic without LPV availability. Women on EFV who desired future childbearing or were not using long-acting or permanent contraception were switched to NVP. The day after study medication discontinuation, women on LPV/r received 2 weeks of once-daily NVP followed by twice daily NVP, while women on EFV switched to twice daily NVP³⁻⁵. All women on NVP returned to the study clinic for a 2 week follow-up visit. Community-based clinics in close proximity to the study provided follow-up for women after trial participation. Adverse events were assessed at all unscheduled and scheduled visits and graded using Division of AIDS standardized Toxicity Table for Grading Severity of Adult and Pediatric Adverse Events, Version 1.0. We calculated the incidence of dermatologic adverse events among women transitioned to NVP.

Between March 7, 2011 and April 3, 2012, when the NVP transition plan was in place, 121 participants reached 1 year postpartum. Of these 121 women, 79 were switched to a NVP-based regimen, including 42 women on LPV/r and 37 women on EFV. Forty-two women remained on the same regimen, including 20 women on LPV and 22 women on EFV. Among the 79 women in the NVP switch cohort, the median nadir CD4 + cell count was 272 cells/mm³ (interquartile range [IQR] 195-362) and nadir CD4 + cell count was > 250 cells/mm³ and > 350 cells/mm³ among 59.5% and 27.9%, respectively. The median pre-treatment CD4 cell count was 318 cells/mm³ (IQR 246-441, range 55-1342).

There were 5 cases (6.3%, 95% confidence interval [CI] 2.7-14.0) of dermatologic toxicity, all attributed to NVP. (Table 1) Among women with a CD4+ nadir of >250 cells/mm³, the incidence of any dermatologic toxicity was 10.6% (95% CI 1.6-19.6) and incidence of grade 3 dermatologic toxicity was 2.1% (95% CI 0-6.3). Three cases occurred in women switched from EFV and two cases occurred among women switched from LPV/r. The nadir CD4 + cell count was >250 cells/mm³ in all five cases and >350 cells/mm³ in three cases. All reactions were noted within 8 weeks of switching to NVP, and 3 women (3.8%; 95% CI 1.3-10.6) required discontinuation of NVP. There was 1 case (1.3%; 95% CI 0.2-6.8) of a grade 3 rash requiring hospitalization at day 48 following switching from LPV/r. All women experienced resolution of their rash. All women had normal alanine aminotransferase values prior to NVP switch, but follow-up studies at the time of the rash were not obtained.

Among women in our cohort switched to NVP with a CD4+ cell count nadir >250 cells/mm³, the incidence of any rash (10.6%) and grade 3 rash (2.1%) is similar to what has been described in NVP trials among ART-naïve and NVP switch trials among ART-experienced adults. Aaron et al. reported a 9.3% risk of grade 2 or worse rash associated with initiation of NVP among 54 non-pregnant women in the US.⁶ There was 1 case (1.9%) of Stevens-Johnson Syndrome. The nevirapine package insert reports a 2% incidence of grade 3 or 4

rash within the first 6 weeks of therapy ⁷. The manufacturer also reports a 5-7% incidence of moderate or severe rash associated with NVP in controlled trials. Among 6 randomized controlled trials evaluating switching from suppressive PI to NVP-based cART, the cumulative incidence of rash requiring NVP discontinuation was 4.2% ⁸⁻¹⁴. The mean CD4+ cell count at time of switch to NVP was 501-650 cells/mm³ for these 6 studies, but there is no information on baseline CD4+ cell count prior to cART initiation. Data suggest that while initiating NVP among ART-naïve individuals at high CD4 + cell counts is associated with increased risk of dermatologic and hepatic toxicity, switching to NVP at high CD4+ cell counts is not associated with an increased risk of such adverse events ^{15,16}. Our report extends the understanding of NVP rash by including women with a full range of pretreatment CD4 + cell counts.

In conclusion, women who transition from LPV/r or EFV during pregnancy to NVP after cessation of breastfeeding may experience serious dermatologic toxicity. The severity and frequency of rashes attributed to NVP in this setting are in the range of what has been reported previously. This remains the case when only evaluating women in our cohort with CD4+ cell count nadir > 250. Nonetheless, given the potential serious nature of dermatologic toxicity, particularly in resource-limited settings, the risks of switching to nevirapine purely for cost or to reduce the theoretical risks of teratogenicity from EFV need to be carefully weighed against the risk of toxicity requiring diligent monitoring. Settings that choose to switch women to NVP following cessation of breastfeeding should establish systems to closely monitor these women for adverse events.

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Table 1

Dermatologic toxicity attributed to nevirapine

Cas e	Arm	CD 4 na dir	High est CD4	CD4 count at deliver y	Days betwe en NVP start and rash onset	Description	Adver se Event Grade	Treatment
1	LPV /r	39 2	748	683	48	Papular rash on face, chest, abdomen, upper/lower limbs. Vesicles on back, chest and abdomen. No bullae. Oral ulcers and hyperemic conjunctiva. No ulceration of conjunctiva	3	Hospitalized for 10 days, cART/TS stopped, Administered steroids, fluids, antibiotics. Rash resolved. Restarted on LPV/r.
2	EFV	48 3	1096	999	16	Diffuse maculopapular rash on arms, legs, face; Oropharynx and tongue erythema, no ulcers	2	Hospitalized for 10 days, cART/TS stopped, Administered steroids, fluids, antibiotics. Rash resolved. Restarted on EFV.
3	EFV	33 5	596	540	20	Generalized maculopapular rash on the face, hands, legs and feet. Hyperemic conjunctiva, no ulcers	2	cART/TS stopped Administered antibiotics. Rash resolved. Restarted on EFV.
4	EFV	57 1	970	752	18	Mild maculopapular skin rash on her legs and feet. Generalized pruritis	2	cART/TS continued, Administered steroids. Rash resolved.
5	LPV /r	30 4	575	491	30	Pruritis only	1	cART/TS continued. Administered antihistamine. Rash resolved.

cART=combination antiretroviral therapy

EFV=efavirenz

LPV//r=lopinavir//ritonavir

NVP=nevirapine

TS= trimethoprim-sulfamethoxazole