

Impact of Antiretroviral Drugs in Pregnant Women and Their Children in Africa: HIV Resistance and Treatment Outcomes

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The global community has committed itself to eliminating new pediatric HIV infections by 2015 and improving maternal, newborn, and child health and survival in the context of HIV. Such objectives require regimens to prevent mother-to-child transmission (pMTCT) which, while being highly efficacious, protect the efficacy of future first-line antiretroviral therapy (ART). Major obstacles to eliminating vertical transmissions globally include low rates of adherence to ART and non-completion of the 'pMTCT cascade' due to programmatic and structural challenges faced by healthcare systems in low-income countries. Providing all pregnant women with lifelong ART regardless of CD4 count/disease stage (Option B+) could be the most effective option to prevent both HIV transmission and resistance, assuming adherence is successfully maintained. This strategy is more likely to achieve sustained undetectable HIV viremia, does not involve ART interruptions, is simpler to implement, and is cost-effective. Where Option B+ is not available, options A (short course zidovudine with single-dose nevirapine and an ARV "tail") and B (combination ART during pregnancy and breastfeeding, with ART cessation after weaning in women not qualifying for ART for their own health) are also efficacious, highly cost-effective and associated with infrequent resistance selection if taken properly.

Keywords. mother-to-child transmission; HIV; prophylaxis; antiretroviral therapy; resistance.

INTRODUCTION: NO CHILD INFECTED WITH HIV BY 2015

The only way of achieving a world without human immunodeficiency virus (HIV)/AIDS is by preventing new HIV infections. While an effective preventive HIV vaccine remains elusive, blocking HIV replication in individuals living with HIV through antiretroviral treatment (ART) has proved to be extremely effective at

preventing HIV transmission. Both treatment-as-prevention and prevention of mother-to-child-transmission (pMTCT) regimens block >96% of HIV transmissions in ideal conditions of antiretroviral (ARV) drug supply, access, and adherence [1]. However, such conditions do not often exist. Preexisting ARV drug resistance could, in theory, reduce the efficacy of pMTCT, but that is rarely observed. Conversely, exposure of pregnant women with HIV to suboptimal ARV drug levels often leads to selection of resistant HIV [2], which can be transmitted to the child [3] and impair the efficacy of future ART in both mothers [4, 5] and infants [6].

The global community has committed to accelerate progress for pMTCT through an initiative whose primary goals are to eliminate new pediatric HIV infections by 2015 and improve maternal, newborn, and child health and survival in the context of HIV [7].

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The overall targets of the “Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive” of the Joint United Nations Programme on HIV/AIDS (UNAIDS) are to reduce the number of new HIV infections among children by 90% and reduce the number of HIV-associated deaths among women during pregnancy, delivery, and puerperium by 50%. Such goals are to be met by 2015 through an ambitious, four-pronged strategy: (1) reducing HIV incidence in women 15–49 years old by 50%, (2) reducing the unmet need for family planning among women to zero, (3) reducing MTCT of HIV to 5% by ensuring that 90% of mothers and children receive ART or ARV prophylaxis, and (4) providing 90% of pregnant women in need of ART for their own health with lifelong therapy.

It is key to realize that ARV drug resistance considerations cannot be disconnected from public health approaches. In 2010, the estimated pMTCT coverage with the most effective regimens, as recommended by the World Health Organization (WHO), was 48% in all low- and middle-income countries, and only 35% of pregnant women received an HIV test in the previous 12 months [8]. Although such figures improve every year, they highlight the need for providing effective, yet simple, affordable, implementable, and sustainable means to prevent MTCT.

The WHO HIV Resistance Network (ResNet) and the European Union’s 7th Framework Program–funded Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN) group met in Geneva on 10–11 October 2012 to discuss how ARV drug resistance considerations could inform public health approaches against HIV/AIDS in low-income countries. This review focuses on the resistance implications of short courses of ART to prevent MTCT in Africa. The objective of the review is to provide a state-of-the-art summary of the subject, including evidence and evolving concepts, as well as to summarize the group discussions around the topic.

THE PROBLEM OF SINGLE-DOSE NEVIRAPINE

Single-dose nevirapine (sdNVP) has not been recommended by the WHO as a regimen for pMTCT since 2006. However, a number of low- and middle-income countries in Africa and Asia continue to use this approach to various degrees [7]. SdNVP effectively reduces MTCT by close to 50% [1], is an inexpensive and simple regimen that can be implemented in settings with poor access to antenatal care, and does not appear to lose efficacy during consecutive pregnancies [9]. However, NVP drug resistance mutations are frequently detected after sdNVP, arising early and remaining detectable for several months in viral populations [10]. These resistant variants can adversely affect the future treatment of NVP-exposed women and children, especially in the setting of recent (within 6–12 months) exposure [5, 11]. The case of sdNVP illustrates the

difficulties of finding the right balance between having simple, affordable regimens and preventing the emergence of HIV resistance.

Mathematical models and empiric studies using ultrasensitive genotyping assays suggest that single nonnucleoside reverse transcriptase inhibitor (NNRTI)–resistant mutants may preexist at low levels, even in the absence of NNRTI exposure. Nevirapine is eliminated slowly from the body, resulting in exposure to suboptimal drug levels in maternal plasma, breast milk, and infant plasma up to 2–3 weeks after intake of a single dose of NVP [12]. Suboptimal NVP levels promote rapid selection of NVP-resistant viruses. In a meta-analysis of NVP resistance after sdNVP exposure in mothers and infants [2], 37.5% (pooled estimate) (95% CI: 23.0; 50.6) of women exposed to sdNVP with or without additional ante/intrapartum ARV regimens were found to have NVP resistance using bulk HIV sequencing methods. Rates of postpartum NNRTI resistance decreased to 4.5% (pooled estimate) (95% CI: 2.1; 9.4) when NVP was given with zidovudine (AZT) and lamivudine (3TC) postpartum. The summary estimates from this same meta-analysis for NNRTI-resistance selection in children were 52.6% (37.7–67.0) for those exposed to sdNVP only, and 16.5% (8.9–28.3) for those exposed to sdNVP plus antenatal, intrapartum, postpartum, or postnatal AZT plus 3TC [2]. In studies that used ultrasensitive genotyping techniques, 40%–89% of women exposed to intrapartum sdNVP with or without ante/intrapartum AZT developed NNRTI-resistant HIV[2].

Once selected, NNRTI-resistant mutants decay slowly in both plasma and peripheral blood mononuclear cells, being detectable as major or low-frequency variants up to 1–3 years after sdNVP exposure in rare cases [10]. Importantly, NNRTI-resistant mutants become integrated in the virus reservoir [13], and can reemerge during subsequent exposure to NNRTIs. Moreover, NNRTI-resistant mutants—as well as NVP—can be transmitted through blood or breast milk [3]. When mothers and infants use the same ARVs to prevent MTCT, drug-resistant HIV can easily be transmitted from mother to child.

IMPLICATIONS OF RESISTANCE SELECTION DURING PMTCT FOR CLINICAL MANAGEMENT

Observational studies and treatment studies nested within placebo-controlled pMTCT trials have shown that exposure to sdNVP triples the risk of virologic failure to first-line NNRTI—including ART if the exposure occurs within the previous 6 [5] or 12 [11] months of starting therapy. If exposure to sdNVP occurs 18–36 months before starting ART, presence of minority lysine-to-asparagine mutation at codon 103 (K103N) mutants before treatment is strongly associated with increased risk of virological failure [14]. Interestingly, detection of minority

NNRTI-resistant variants in women not previously exposed to sdNVP was not associated with increased risk of virological failure in the Optimal Combination Therapy After Nevirapine Exposure (OCTANE)/AIDS Clinical Trials Group (ACTG) 5208 Trial 2 study, while presence of such minority NNRTI-resistant viruses was associated with virological failure in women with prior sdNVP exposure in the 5208 Trial 1 study [15]. In one observational trial [5], virologic failure by the 6-month visit occurred in significantly more infants who had received sdNVP than in infants receiving placebo. Such findings have been confirmed in randomized clinical trials in women and children.

In a prospective, randomized clinical trial, [4] coformulated tenofovir (TDF)/emtricitabine (FTC) plus ritonavir-boosted lopinavir (LPV/r) was superior to TDF/FTC plus NVP for initial ART in women previously exposed to sdNVP, but not among women without prior reported sdNVP exposure [16]. The difference between groups in the primary endpoint (time to virological failure or death) was greater among women with detectable NVP resistance, using bulk sequencing. In multivariate analyses, baseline NVP resistance was associated with an increased risk of virologic failure or death (hazard ratio [HR], 8.7; 95% confidence interval [CI], 3.5–21.6), whereas a higher baseline CD4⁺ lymphocyte cell count was associated with a decreased risk (HR per increase of 100 cells/ μ L, 0.2; 95% CI, .1–.4). Again, increasing time since exposure to sdNVP was associated with decreasing difference in treatment outcomes, although rates of virological failure were not comparable across the ART arms until 2 years after sdNVP exposure.

An analogous prospective randomized trial conducted in children 6–36 months of age living with HIV in 6 African countries showed that initial ART with AZT/3TC + LPV/r was associated with lower rates of virologic failure or discontinuation of treatment by study week 24 than AZT/3TC + NVP, both in children exposed [6] and not exposed [17] to sdNVP. These differences were consistent for children older and younger than 12 months of age. Baseline resistance to NVP was detected in 18 of 148 children exposed to sdNVP (12%) by bulk HIV sequencing and was predictive of treatment failure. Overall virological failure rates and the magnitude of the differences between treatment groups were higher among children aged <12 months, although these differences did not achieve statistical significance. In the study where children not exposed to sdNVP, only 5 of 257 children (2.0%) with samples that could be evaluated had mutations conferring NVP resistance (tyrosine-to-cysteine mutation in codon 181 (Y181C) in 4 and K103N in 1) at baseline; only 1 of these 5 children was randomly assigned to the NVP group. Therefore, although LPV/r and NVP-including regimens are equivalent in non-sdNVP-exposed adults [16], LPV/r-regimens are superior in sdNVP-exposed and -unexposed children [17].

NNRTI RESISTANCE IS SIGNIFICANTLY REDUCED BY PROVIDING NVP ALONGSIDE OTHER ANTIRETROVIRALS

Strategies to minimize NNRTI resistance attempt to shelter the period of exposure to suboptimal NVP levels following NVP dosing with other antiretrovirals possessing a high genetic barrier and/or fast drug-level decay after treatment interruption. When possible, such strategies also seek to further reduce vertical HIV transmission, while preserving simplicity and feasibility as much as possible.

Using ultrasensitive genotyping in an observational prospective cohort study of pregnant women in pMTCT programs in Beira, Mozambique, addition of short-course AZT, starting at \geq 32 weeks' gestation and continuing for 1 week postpartum to sdNVP during labor, reduced the rates of NVP resistance at 2–8 weeks postpartum relative to sdNVP alone (35.5% vs 72.7%, respectively; $P = .003$) [18].

In a prospective, randomized 3-arm study, short-course, coformulated AZT/3TC for 4 or 7 days initiated simultaneously with sdNVP and given to mothers and infants significantly reduced emergent NNRTI resistance mutations in both mothers and children relative to administering sdNVP alone to both mother and child [19]. Postpartum resistance rates in women were 59.2%, 11.7%, and 7.3% in the sdNVP, NVP + AZT/3TC (4 days), and NVP + AZT/3TC (7 days), using bulk sequencing. Resistance mutations were observed in 7/8 (87.5%), 4/25 (16.7%) and 0/10 (0%) infants in the sdNVP, NVP + AZT/3TC (4 days), and NVP + AZT/3TC (7 days) arms, respectively. This study confirmed the importance of adding an AZT/3TC tail after exposure to sdNVP and resulted in a modification of the WHO guidelines to prevent MTCT, forming the basis for current WHO "Option A."

In a prospective, 2-arm, randomized study in Lusaka, Zambia, pregnant women were randomized 1:1 to receive standard-of-care (sdNVP at labor plus antenatal AZT from week 32 of gestation) or standard-of-care plus single-dose coformulated TDF/FTC at labor [20]. Women given single-dose TDF/FTC were 53% less likely than controls to have NNRTI resistance mutations by bulk HIV sequencing 6 weeks after delivery. Coformulated TDF/FTC is slowly becoming available in low-income countries.

Finally, in a small randomized clinical trial in Nairobi, Kenya [21], pregnant women at 34 weeks' gestation were randomized to receive short-course AZT for 6 weeks before delivery plus sdNVP during labor and NVP to the infant after delivery with no nucleoside reverse transcriptase inhibitor (NRTI) tail, or short-course ART with AZT + 3TC + NVP twice a day for 6 weeks before and 6 months after delivery. No woman in either arm harbored resistant HIV by bulk sequencing 3 months after treatment cessation. However, allele-specific polymerase chain reaction testing detected the K103N or Y181C mutations in

12/16 (75%) and 2/11 (18%) women receiving short-course AZT plus sdNVP and combination ART, respectively, suggesting that low-frequency NNRTI resistance mutations may be selected when ART is discontinued.

ARE THERE WEAKNESSES RELATED TO HIV RESISTANCE IN CURRENT WHO GUIDELINES?

In 2010, the WHO recommended that women with CD4⁺ lymphocyte counts ≤ 350 cells/ μ L or with symptomatic disease defined by WHO clinical stage 3 or 4 should start lifelong ART. Pregnant women not fulfilling criteria for lifelong ART can be managed according to 1 of the following pMTCT approaches:

- **Option A** includes giving mothers antepartum AZT from as early as 14 weeks' gestation, sdNVP at onset of labor, AZT + 3TC during labor, and AZT + 3TC during 7 days postpartum. Prophylaxis in breastfeeding infants includes sdNVP at birth plus daily NVP until 1 week after all exposure to breast milk has ended; nonbreastfeeding infants must receive sdNVP at birth plus AZT or NVP from birth until 4–6 weeks.
- **Option B** includes giving mothers triple ARVs from 14 weeks until 1 week after all exposure to breast milk has ended. Regimens may include AZT + 3TC + LPV/r, AZT + 3TC + ABC, AZT + 3TC + efavirenz (EFV) or TDF + 3TC (or FTC) + EFV. When stopping any NNRTI-based regimen, guidelines recommend stopping the NNRTI first and continuing the 2 NRTIs for 7 more days to reduce the chance of NNRTI resistance. All infants should receive AZT or NVP from birth until 4–6 weeks, regardless of whether they are breastfeeding or not. In a technical update issued in 2012 [22], the WHO noted a clear preference for EFV as part of first-line ART, including among pregnant women and those who may become pregnant. These recommendations take into account cumulative 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; and programmatic experience highlighting the complications associated with switching from EFV to NVP for HIV-positive pregnant women and those who may become pregnant.

Countries using a public health approach generally offer only 1 of these options. Both strategies are comparably efficacious in preventing vertical transmission and, in studies reported to date, have been associated with low levels of resistance selection in women. Option A is more affordable, but more complex to implement, and is less likely to achieve suppression of viral replication among women receiving prophylaxis. The exposure to

AZT monotherapy before labor has the potential for selecting for thymidine analogue mutations, which confer cross-resistance to stavudine, and can decrease susceptibility to abacavir and tenofovir. However, these mutations tend to appear slowly [23], and high-level AZT resistance, which requires the accumulation of several thymidine analog mutations (TAMs), might not frequently develop during a single pregnancy. It is unknown if repeated exposure to Option A in consecutive pregnancies might favor further accumulation of TAMs. Exposure to AZT + 3TC during labor and 7 days postpartum has the potential to select for the methionine-to-valine or isoleucine mutations in codon 184 (M184V/I) mutations, which confer high-level resistance to lamivudine and emtricitabine. M184V/I mutants decay quickly following 3TC withdrawal. The exposure to a single dose of NVP bears the potential for selection of Y181C, K103N, or other NNRTI mutations. However, development of NNRTI resistance is constrained by the administration of a 7-day AZT + 3TC tail. Given that African populations may have a longer NVP washout time (up to 14–21 days), a 7-day tail might still be suboptimal for a number of women [24]. It must be noted that both Options A and B are reserved for women with CD4⁺ lymphocyte counts >350 cells/ μ L who might be less likely to develop ARV drug resistance than those with lower CD4⁺ counts. However, the sequential administration of different antiretrovirals (AZT during pregnancy, sdNVP at delivery, AZT + 3TC intra- and postpartum) with Option A might lead to confusion. This could affect optimal adherence and, in turn, promote the emergence of ARV drug resistance. Furthermore, Option A, which requires CD4 testing and multiple different medications, may be more sensitive to disruptions in the supply chain, resulting in delayed initiation and unplanned treatment interruptions. In a study in an urban district in Tanzania [25], 40% (20/50) of women receiving a regimen resembling current Option A had detectable drug resistance by allele-specific polymerase chain reaction (ASPCR) between delivery and 16 weeks postpartum: 18% had AZT resistance mutations, 14% NVP resistance; 2% had 3TC resistance, 2% resistance to 3TC or AZT, 2% to NVP or 3TC, and another 2% to AZT, 3TC, or NVP. These findings confirm that, although emergence of NVP resistance is greatly reduced, Option A might be associated with increased AZT resistance, particularly if AZT is initiated earlier during pregnancy.

In principle, Option B might be more resilient to resistance, but suboptimal adherence and nonstaggered interruption of NNRTIs might lead to resistance selection as well. In a study in the United States [26], the M184V mutation was detected by bulk sequencing in 28.7% of women receiving 3-drug pregnancy-limited ART at 2–6 months postpartum (51.6% by ASPCR). Postpartum NNRTI resistance rates among women receiving NVP were 25% (2/8 cases) for K103N (37.5% [3/8 cases] by ASPCR) and 12.5% (1/8 cases) for tyrosine-to-cysteine mutation in codon 188 (Y188C). In a multivariate analysis, the odds

Table 1. How Can Treatment Options Be Maintained in Children and Postpartum Women Receiving PMTCT Regimens: Summary of the WHO ResNet-CHAIN Group Discussions, October 2012

pMTCT considerations in mothers:

- Women already on ART should continue their ART regimen and be managed as if they were nonpregnant.
- For women who are not on ART, Option B + bears, in principle, a lower risk of resistance than Options A or B. However, it is also affected by suboptimal ART adherence and drug stock-outs.
- Risk/benefit assessment of Options A, B, and B + :

Option A	Benefits	Risks
	<ul style="list-style-type: none"> • Overall, low risk of resistance, but such risk increases if the AZT/3TC tail is not properly followed • Cheaper strategy with similar efficacy to Option B 	<ul style="list-style-type: none"> • More complex strategy than Options B or B + • The strategy differs for women needing vs not needing lifelong ART based on CD4 counts, thus requires a fast turnaround of CD4+ tests to guide pMTCT choices; however, programs are moving to point-of-care CD4+ testing

Option B	Benefits	Risks
	<ul style="list-style-type: none"> • Maximum antiviral potency during pregnancy • Suppression of HIV replication during pregnancy more likely than with Option A • May have maternal health benefits over Option A • Overall, easier to take and monitor during pregnancy than Option A • Low risk of resistance on PI-containing regimens, but these are more expensive • TDF/3TC/EFV as a once-daily single-tablet regimen is likely to be the best option; with such regimen, the tail may not be necessary thanks to the longer half-life of TDF and FTC (unknown) 	<ul style="list-style-type: none"> • Potential, but possibly small, risk of EFV-associated teratogenicity if EFV is used in first trimester • Risk of selecting NNRTI resistance during NNRTI interruption, which might be more difficult to predict in African subjects due to PK variability: Requires a staggered stop of NNRTIs (eg, continuing TDF/3TC or AZT/3TC for 2 wk after TDF/3TC/EFV interruption, or switching to a PI-based regimen for 2 wk before interruption); this adds considerable complexity • Relative to Option B + , women might be more likely to drop out of HIV care after delivery

Option B +	Benefits	Risks
	<ul style="list-style-type: none"> • Same benefits as Option B, plus: • Does not require ART interruption, thereby avoids selection of NNRTI resistance at the end of pregnancy • May have maternal health benefits over Options A or B • May allow simplified infant prophylaxis, particularly during breastfeeding 	<ul style="list-style-type: none"> • Potential, but possibly small, risk of EFV-associated teratogenicity if EFV is used (particularly in women becoming pregnant again while taking EFV) • Equally vulnerable to suboptimal adherence, and drug stock-outs as Options A and B • Increased net cost, although possibly highly cost-effective

Infant prophylaxis:

- The overriding aim of infant prophylaxis is to reduce vertical HIV transmission; regimens should be designed with this objective rather than for limiting antiretroviral drug resistance.
- Strategies should be designed to allow safe breastfeeding.
- It is unknown if NVP or ZDV for 6 wk is necessary in Options B or B+ or in women already on lifelong ART, as it increases complexity and may compromise scale-up of pMTCT. Conversely, providing infant prophylaxis may be particularly important in women who initiate ART late in pregnancy until the mother achieved full HIV suppression.
- Single-dose TDF or coformulated TDF/FTC could be a possible alternative to sdNVP in infants because it is less prone to develop high-level resistance after a single-dose administration; however, data are lacking and availability is still limited in many low-income countries.

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; EFV, efavirenz ; FTC, emtricitabine; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor ; PK, pharmacokinetic; pMTCT, prevent mother-to-child transmission; sdNVP, single-dose nevirapine; TDF, tenofovir.

of developing the M184V and K103N mutations increased 1.29-fold and 1.46-fold, respectively, by each additional month of AZT and AZT/3TC exposure during pMTCT. Conversely, the rates of protease inhibitor (PI) resistance remained <2%.

Similarly, in a small, randomized clinical trial, pMTCT with AZT + 3TC + NVP was associated with postpartum detection of low frequency K103N or Y181C mutants in 2 (18%) women, although no resistance mutations were detected using bulk

sequencing. In a small observational cohort study [27], postpartum NNRTI resistance was observed in 5/29 (17%) pregnant women who received NVP-containing ART during pregnancy. With current WHO guidelines, however, NVP-based regimens would not be included in Option B, so women would not have to interrupt NVP and only those with CD4⁺ <350 cells/μL after PMTCT would begin lifelong NVP-based ART. Given that PI-based PMTCT regimens are not feasible for many African countries, EFV-based regimens are the mainstay for Option B. It is thus crucial to understand what would be the effect of stopping EFV-based 3-drug ART on postpartum resistance and what is the optimal staggered stop of EFV-based regimens to minimize postpartum resistance, issues that remain largely unexplored. Measures to ensure adherence to pMTCT, to avoid drug stock-outs, and to promote correct ART interruption should also be enforced in women receiving 3-drug ART to prevent MTCT.

Of note, HIV resistance is frequently observed in the few children that, unfortunately, become infected during both Options A and B. In a secondary analysis of the Kisumu Breastfeeding Study (KiBS) [3], a single-arm open-label pMTCT trial with AZT/3TC and either NVP or nelfinavir (NFV) given to women with HIV from 34 weeks of gestation through 6 months of breastfeeding, drug resistance emerged in infants infected with HIV between 2 weeks and 6 months postpartum, most likely because of exposure to maternal ARV drugs through breast milk. Overall, 32 infants were infected with HIV by 24 months of age, and of this group, 24 (75%) infants were infected by 6 months of age. Genotypic resistance was detected by bulk sequencing in 7/15 (47%) and 9/9 (100%) infants with HIV whose mothers were on AZT/3TC/NVP and AZT/3TC + NFV, respectively. Resistance mutations to NRTIs were observed in 5/7 and 9/9 infants in the NVP and NFV arms, respectively. NNRTI resistance was detected in 6/7 infants in the NVP arm and no PI resistance was observed. Both Options A and B include components of infant prophylaxis with nevirapine, which select NNRTI mutations in the majority. Every effort should be made to diagnose HIV infection in infants as early as possible to reduce exposure to prophylaxis.

Option B+ [28] (ie, including all pregnant women in lifelong ART therapy regardless of CD4⁺ lymphocyte counts) would eliminate resistance selection in women due to planned ART interruptions and potentially provide other public health benefits. However, the problems of adherence to lifelong ART, ART stock-outs, and inadequate retention during pregnancy and the postnatal period would not be resolved by offering lifelong ART to all pregnant women. To date, no evaluation of the rates of uptake of or resistance selection with Option B+ is available. HIV drug resistance surveillance to evaluate the risk for selection of drug resistance under the B+ approach should be planned alongside implementation at the country level.

ADHERENCE REMAINS A MAJOR CHALLENGE TO LIMIT HIV RESISTANCE DURING PMTCT

Optimal adherence to ART is a universal challenge, which is also apparent during pregnancy and the postpartum period. In a systematic review and meta-analysis of adherence to ART during and after pregnancy in low-, middle-, and high-income countries, including 51 studies involving 20 153 women [29], only 73.5% of pregnant women achieved ART adherence >80%. Of note, only 53% of women achieved ART adherence >80% during the postpartum period. Women from low- and middle-income countries were not less adherent than those in higher-income countries. The main barriers to adherence included physical, economic, and emotional stresses; depression (especially postpartum); alcohol or drug use; and ART dosing frequency or pill burden. Key factors reported in several studies were disclosure of HIV status and social support. The pooled adherence levels reported in this meta-analysis were lower than is thought to be required for viral suppression and prevention of resistance. Other studies have pointed at the fragility of overburdened healthcare systems in ensuring that pMTCT regimens are dispensed and taken correctly. Only half of women complete the entire cascade of services, including prenatal, delivery, and at least 1 infant follow-up visit; and only 13% of infants access follow-up care through 18 months. The greatest loss in the PMTCT care cascade occurs prior to infant follow-up, with one-third of women being lost to follow-up after receiving delivery care. Suboptimal adherence or structural problems complicating correct pMTCT dispensation are the Achilles heel for all pMTCT options: A, B, or B+. Loss-to-follow-up during the pMTCT cascade (ie, antenatal care, counseling, HIV diagnosis, and pMTCT prophylaxis and ART) is a major obstacle to the eradication of vertical HIV transmissions, but its effects on HIV resistance are unknown.

HOW CAN TREATMENT OPTIONS BE MAINTAINED IN CHILDREN AND POSTPARTUM WOMEN RECEIVING PMTCT REGIMENS? SUMMARY OF THE WHO RESNET and CHAIN GROUP DISCUSSIONS

To eradicate vertical HIV transmission, pMTCT regimens must provide the following: (1) be efficacious in preventing MTCT; (2) be nontoxic and well tolerated; (3) be associated with low resistance rates in mother and infants; (4) ensure the efficacy of future first-line ART in both mothers and infants; (5) be acceptable, feasible, affordable, and sustainable; and (6) must allow safe breastfeeding. Table 1 summarizes the discussions of the WHO ResNet and CHAIN groups as to how treatment options can be maintained in children and postpartum women receiving pMTCT regimens.

In summary, all currently available pMTCT options are associated with low rates of antiretroviral resistance in women, but none is completely sheltered from the harmful consequences of suboptimal adherence, pharmacy stock-outs, and human and logistic constraints to healthcare systems. Providing all pregnant women with lifelong ART may be the most effective option to prevent both HIV transmission and resistance, because it is more likely to achieve sustained undetectable HIV viremia, does not involve intended ART interruptions, and is possibly easier to implement, facilitating initiation of ART in those pregnant women who despite being eligible for ART did not have access to it. Moreover, Option B+ is associated with incremental cost-effectiveness ratios per year of life saved similar to many current HIV-related healthcare interventions [30]. However, direct comparisons between Options B and B+ with regard to HIV resistance have not been performed and, likely, other reasons (such as improved maternal and public health and programmatic simplicity) would be more relevant as countries choose the most appropriate approach for national programs. Of note, Options A and B are also efficacious, highly cost-effective [30], and associated with low resistance levels if taken properly. Any approach to prevent drug resistance selection, however, must be implemented in conjunction with comprehensive measures to strengthen healthcare systems. Vertical transmission has been virtually eradicated from high-income countries. A call for the global eradication of vertical HIV transmission over the next years has been issued. Only time will tell whether we can respond effectively.

Notes

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