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High levels of resistance to nucleoside/nucleotide reverse transcriptase inhibitors in newly diagnosed antiretroviral treatment-naïve children in sub-Saharan Africa

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Exposure of infants to antiretroviral drugs for prevention of mother-to-child transmission can induce resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Data from nine national surveys of pretreatment drug resistance in children newly diagnosed with HIV show high levels of resistance to NRTIs included in first-line antiretroviral treatment (ART) regimens (dual abacavir-lamivudine/emtricitabine resistance). Additional research is needed to determine the impact of NRTI resistance on treatment response and optimize infant ART.

Exposure of infants to antiretroviral drugs for prevention of mother-to-child transmission (PMTCT) can induce resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) [1–5].

We assessed the prevalence of NRTI resistance in ART-naïve children 18 months or less of age who were newly diagnosed with HIV through early infant diagnosis programs. Data were obtained from nine nationally representative surveys in sub-Saharan Africa, conducted between 2011 and 2016 in Eswatini (2011), Uganda (2011), Mozambique (2012), Togo (2012), Zimbabwe (2012), Cameroon (2014), South Africa (2014), Nigeria (2016), and Malawi (2016).

Drug resistance was predicted using the Stanford HIVdb algorithm Version 8.3 [6]. Sequences classified as having low-level, intermediate-level or high-level resistance were designated ‘resistant’. Prevalence estimates were calculated for each country using Stata 14 (StataCorp, College Station, Texas, USA) as per the survey analysis plan [7]. Differences between groups were assessed on unweighted data by logistic regression. Nonresearch determination approval for routine surveillance studies was obtained from the individual countries’ national research ethics committees.

Data on HIV drug resistance and antiretroviral prophylaxis were available for 2684 and 2282 (85%) infants (all surveys except South Africa), respectively (Table 1). Of the infants, 1229 (53.9%) were exposed to maternal prophylaxis.

The prevalence of NRTI resistance in the nine surveys ranged from 2.0% (95% CI: 0.1–4.0) to 25.8% (95% CI: 17.5–36.4) and was significantly higher in surveys conducted after in-country adoption of the WHO’s policy for maternal lifelong ART [23.4 (95% CI: 19.4–27.9) vs. 9.9 (95% CI: 8.6–11.1, $P < 0.0001$]. The prevalence of NRTI resistance was also higher among infants exposed to maternal prophylaxis (with or without infant prophylaxis) compared with those exposed to only infant prophylaxis or with unknown exposure history (Table 1).

NRTI resistance was mainly driven by abacavir (ABC) and emtricitabine/lamivudine (XTC) resistance. The prevalence of dual ABC/XTC resistance ranged from 2% in Eswatini (2011) to 28.1% in Nigeria (2016) (Table 1).

Overall, the prevalence of resistance to zidovudine (ZDV) and tenofovir (TDF) was less than 10% across all surveys except in Togo where ZDV resistance was 11.6%, and in Nigeria where ZDV and TDF resistance were 15% and 11.3%, in infants exposed to maternal prophylaxis, respectively.

We made several key observations in this study. First, children exposed to maternal prophylaxis had higher levels of NRTI resistance compared with infants not exposed to maternal prophylaxis. This is consistent with previous studies that showed selection of drug-resistant HIV in children exposed to sub-therapeutic concentrations of maternal drugs ingested during breast-feeding [1,5]. Similar to findings from recent studies, we observed higher levels of NRTI resistance in surveys conducted after adoption of WHO recommendations for maternal lifelong ART; this suggests that the prevalence of NRTI resistance could increase further over time as the WHO policy is more widely implemented [3,4].

Second, although WHO recommends ritonavir-boosted protease-inhibitor (PI/r)-based first-line pediatric regimens in children greater than 4 weeks of age who weigh less than 20 kg, this recommendation has not been widely implemented in many sub-Saharan African countries because of limited availability and high cost of pediatric-friendly formulations. Consequently, NNRTI-based regimens are still widely used [8]. The increasing

prevalence of NRTI resistance, combined with still substantial use of NNRTI-based ART (for which resistance exceeds 50%) in infants [9,10], suggests that most young children may be treated ineffectively and risks poor treatment outcomes. These findings emphasize the urgent need to accelerate access to child-friendly PI/r-based regimens.

Third, although PI/r regimens have been shown to remain effective in those who have resistance to two co-administered NRTIs [11], most studies have been conducted in adults receiving regimens that include TDF/XTC or ZDV/XTC. It is not clear whether these findings can be extrapolated to children receiving regimens with ABC/XTC. The efficacy of PI/r-based regimens in the setting of NRTI resistance is partially attributed to an antagonistic effect of the M184V mutation; this mutation causes hyper-susceptibility of HIV to ZDV and TDF, but not to ABC [12]. Additional studies are needed to assess the efficacy of PI/r-based regimens in children with resistance to ABC.

Although ZDV and TDF are potential alternatives to ABC, we find that resistance to these drugs may also be high in some countries. This suggests the need to accelerate research and access to newer NRTIs and nucleoside-sparing ART combinations particularly for this population.

Fourth, our findings have direct implications for pediatric regimens recommended in the 2019 WHO guidelines (i.e. raltegravir in infants <4 weeks of age and dolutegravir in children weighing >20 kg) [13]. As raltegravir has a low genetic barrier for resistance [14], its use in neonates with NRTI resistance may lead to emergence of resistance, potentially compromising future use of dolutegravir [15,16]. There is limited evidence to support the use of dolutegravir in infants with NRTI resistance. Therefore, caution is needed when considering use of dolutegravir with ABC/XTC in young children in countries with a high prevalence of ABC/XTC resistance.

Given the limited number of ART regimens available to children living with HIV, careful attention is needed to avoid inducing NRTI resistance early in life. The WHO recommendation for use of triple-drug neonatal prophylaxis (or presumptive treatment) should be considered in low-income and middle-income countries [17].

This study has several limitations. First, we may have overestimated the prevalence of ABC resistance by using the Stanford HIVdb algorithm; this algorithm classifies the M184V mutation as causing low-level ABC resistance (<https://hivdb.stanford.edu>, accessed 21 November, 2019). However, findings from the CNA3003 study [18], as well as the REGA and French ANRS drug resistance interpretation algorithms, suggest a minimal

impact of this mutation on ABC resistance (<https://hivdb.stanford.edu>, accessed 21 November, 2019). When we excluded M184V as a cause of ABC resistance, the prevalence dropped from 19.8% to 12.7% in Nigeria and from 20.6% to 12.6% in Malawi. Second, our findings were from regions where most women on ART were receiving NNRTI-based therapy. Additional studies are needed to estimate the prevalence of NRTI resistance in infants, whose mothers were taking dolutegravir-based regimens. Dolutegravir is also transferred through breast-milk at concentrations that are unlikely to suppress HIV replication fully [19], and may potentially select for both dolutegravir and NRTI resistance.

In conclusion, the increasing prevalence of ABC and XTC resistance in infants who are infected with HIV despite antiretroviral prophylaxis merits attention. Further studies are needed to understand the impact NRTI on pediatric regimens.

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Conflicts of interest

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Nonmelanoma skin cancer and melanoma in HIV-1-infected patients

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In the cART era, the incidence of AIDS-defining cancers decreased, whereas a persistence of non-AIDS-defining cancers has been observed. In particular, concerning the risk of melanoma and non-melanoma skin cancers in HIV patients, conflicting data are available. In this study, our aim was to assess the occurrence of cutaneous malignancies in 97 HIV-positive individuals visited in our Institute,