World Health Organization

CONCEPT NOTE

HIV DRUG RESISTANCE

SURVEILLANCE OF HIV DRUG RESISTANCE IN CHILDREN NEWLY DIAGNOSED WITH HIV BY EARLY INFANT DIAGNOSIS

DECEMBER 2017

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ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral (drugs)
ATZ/r	Atazanavir/ritonavir
CI	Confidence interval
d4T	Stavudine
DBS	Dried blood spot
DRV/r	Darunavir/ritonavir
EFV	Efavirenz
EID	Early infant diagnosis
FTC	Emtricitabine
HIV	Human immunodeficiency virus
HIVdb	Stanford HIV drug resistance algorithm
HIVDR	HIV drug resistance
IN	Integrase (region of HIV-1)
INI	Integrase inhibitor
LPV/r	Lopinavir/ritonavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PCR	Polymerase chain reaction
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission (of HIV)
PR	Protease (region of HIV-1)
RT	Reverse transcriptase (region of HIV-1)
SID	Survey identification number
TDF	Tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
ZDV	Zidovudine

1. INTRODUCTION

Despite progress in scaling up interventions for the prevention of mother-to-child transmission (PMTCT) of HIV, globally an estimated 220 000 [190 000–260 000] children were newly infected with HIV in 2014. Most of these new infections occurred in sub-Saharan Africa, where more than 90% of all children infected with HIV currently live. The latest estimates indicate that, among the 2.6 million [2.4–2.8 million] children younger than 15 years living with HIV, 32% [30%–34%] were accessing treatment in 2014, up from 14% [13%–15%] in 2010.[1]

Access to antiretroviral (ARV) medicines for pregnant and breastfeeding women living with HIV has expanded. In 2013, an estimated 32% [26–36%] of mothers infected with HIV were not receiving lifelong antiretroviral therapy (ART) or prophylaxis during the breastfeeding period to reduce the risk of HIV transmission. This is a remarkable improvement from 2009, when more than 80% [79–82%] were not covered during the breastfeeding period.[2]

The continued expansion of maternal ARV drug coverage – while critical to reducing the number of new infant HIV infections – has led to increased exposure to non-nucleoside reverse transcriptase inhibitors (NNRTI). Paradoxically, this has resulted in HIV drug resistance (HIVDR) among infants and children acquiring HIV infection, despite PMTCT interventions.[3] History of NNRTI-exposure was often used as a marker to identify children who should initiate Lopinavir/ritonavir (LPV/r)-based ART. However, information about a child's ARV drug exposure is often unknown.

In 2013, the World Health Organization (WHO) recommended the use of LPV/r-based ART as the standard regimen of choice for HIV-infected children, irrespective of PMTCT exposure history.[4] Despite these guidelines, in many countries a significant proportion of children still initiate NNRTI-based regimens due to cost and feasibility issues. In these countries, an understanding of the prevalence of HIVDR among children less than 18 months of age could help accelerate the shift for this population towards LPV/r-based regimens as first-line ART.

Moreover, exposure to PMTCT ARV drugs may not be routinely recorded for children starting ART, and in many cases, previous ARV exposure is mistakenly reported as "none" or "unknown". Therefore, children who have been exposed to ARV drugs antepartum, intrapartum or postpartum may be started on an NNRTI-based regimen. Hence, it is important to evaluate the proportion of children whose PMTCT history is reported as "none" or "unknown" having mutations associated with resistance, which may affect their treatment outcome. This is particularly relevant in countries considering the introduction of protease inhibitor (PI)-sparing strategies once viral load suppression is sustained, and in countries where NNRTI-based regimens are used as second-line.

1. UNAIDS. Fact sheet 2015. Available at: http://www.unaids.org/en/resources/campaigns/HowAIDSchangedeverything/factsheet

2. UNAIDS. The GAP. UNAIDS. Geneva, Switzerland. 2014. Available at: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf

3. Kuhn L, Hunt G, Technau K-G, et al. Drug resistance among newly diagnosed HIV-infected children in the era of more efficacious antiretroviral prophylaxis. AIDS. 2014;28(11):1673–1678.

4. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO. Geneva, Switzerland. 2013. Available at: http://www.who.int/hiv/pub/guidelines/arv2013/en/

2. SURVEY PURPOSE

This concept note describes the methods used to assess the prevalence of any HIVDR and HIVDR by PMTCT exposure among children less than 18 months of age using remnant dried blood spot (DBS) specimens from early infant diagnosis (EID) over a 12-month period. Data on HIVDR and the prevalence of PMTCT exposure in this target population can provide critical information to support optimal choice of first- and second-line ART regimens. Survey limitations and potential biases are discussed in Box 1.

Box 1: Survey limitations and potential biases

The methodology presented in this concept note relies on remnant DBS specimens used for EID to assess the prevalence of HIVDR amongst treatment-naïve children less than 18 months. While this approach has important operational and practical advantages, its results must be interpreted in light of its limitations.

In particular, survey results may not necessarily represent all children less than 18 months of age infected or diagnosed with HIV-1 in the country. If EID coverage is low, many children may go undiagnosed, and survey results may not necessarily reflect the total population of children less than 18 months newly infected with HIV.

The type of sites contributing specimens to the survey may also introduce potential biases in survey results. If PMTCT sites contribute most diagnostic specimens, children with "no" or "unknown" ARV exposure may not be well represented in the survey. Alternatively, if non-PMTCT sites contribute most diagnostic specimens, children with recorded ARV exposure may not be well represented.

3. SURVEY OUTCOMES

The survey has nine main outcomes. The first six outcomes (1a, 1b, 2a, 2b, 3a and 3b) provide measures of HIVDR, while the remaining three (4a, 4b and 4c) describe the prevalence of "yes", "no" and "unknown" PMTCT exposure in the target population. These outcomes are summarized in Table 3.1.

Outcomes 1a and 1b summarize the prevalence of HIVDR regardless of PMTCT exposure. Outcomes 2a, 2b, 3a and 3b summarize the prevalence of HIVDR stratified by PMTCT exposure.

2a. Prevalence of any HIVDR among treatment-naïve children less than 18 months of age newly diagnosed with HIV with known PMTCT exposure (maternal only, neonatal only or both).

2b. Prevalence of HIVDR to NNRTI (NVP or EFV) among treatment-naïve children less than 18 months of age newly diagnosed with HIV with known PMTCT exposure (maternal only, neonatal only or both).

3a. Prevalence of any HIVDR among treatment-naïve children