TECHNICAL BRIEF

SURVEILLANCE OF ANTIRETROVIRAL TOXICITY

GLOBAL HIV, HEPATITIS AND STIs PROGRAMME

WHAT'S NEW IN PERSON-CENTRED HIV PATIENT AND ANTIRETROVIRAL DRUG TOXICITY MONITORING

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In April 2020, new directions in global guidance for HIV strategic information and treatment monitoring were updated. This technical update outlines the key developments with respect to recommended indicators and approaches and tools for monitoring antiretroviral drug toxicity with the purpose of strengthening country implementation and ensuring the safe use of antiretroviral drugs.

In 2018 and 2019, WHO antiretroviral drug guidelines recommended dolutegravir (DTG) as part of the preferred first-line treatment for adults, adolescents and children *(1,2)*. With the release of these recommendations and the availability of a generic fixed-dose combination of DTG with tenofovir and lamivudine (TLD), more countries are transitioning to using DTG for preferred first-line antiretroviral therapy. This rapid scale-up creates an important opportunity to optimize and standardize HIV treatment, with health ministries leading the response, but it also poses certain risks, such as the potential for new drug-related toxicities and suboptimal treatment outcomes. Recent data suggest a potential risk of weight gain associated with newer antiretroviral drugs (notably DTG and tenofovir alafenamide) and highlight the need for active toxicity monitoring in countries as they scale up or introduce these drugs *(3)*. The signal of neural tube defect associated with DTG in May 2018 reinforced the importance of robust data and surveillance systems to evaluate the safety of new antiretroviral drugs in pregnancy in low- and middle-income countries *(4)*. Within this context, WHO recommends that countries consider a combination of approaches to monitor antiretroviral drug toxicity and promote patient safety, including surveillance of safety in pregnancy and active and routine toxicity monitoring in all populations, including adults, adolescents and children *(5–7)*.

1. Antiretroviral drug toxicity monitoring is now a priority national indicator for routine monitoring of the health sector response to HIV

In 2015, the WHO consolidated HIV strategic information guidelines recommended a new indicator on antiretroviral drug toxicity to assist countries in assessing the impact on treatment outcomes and in guiding policy on antiretroviral drug regimens and strategies for preventing and managing toxicities *(5)*. In 2017, WHO recommended this indicator as part of a set of 17 additional indicators that may be collected in countries with electronic reporting systems and accompanying person-centred patient monitoring tools that capture toxicity were published *(6)*.

In the new 2020 HIV consolidated strategic information guidelines, the antiretroviral drug toxicity indicator (ARV.9) has been given priority as one of 40 key national HIV indicators recommended to provide programme managers the information needed to improve services in real time while still being feasible to collect *(8,9)*. In addition, the 2020 guidelines also recommend collecting information on the programmatic reasons for switching antiretroviral therapy regimens or treatment interruption, defined as the percentage of people receiving antiretroviral therapy who switch or stop their antiretroviral drug regimen. Table 1 provides the full definition of the priority antiretroviral drug toxicity indicator that countries are encouraged to include in their national HIV indicator set.

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TABLE 1. NEW NATIONAL ANTIRETROVIRAL DRUG TOXICITY INDICATOR RECOMMENDED FOR ROUTINE MONITORING WITHIN HIV PROGRAMMES

Indicator name and code	Percentage of people receiving antiretroviral therapy with treatment-limiting toxicity[a] (ARV.9)
Overview	This indicator measures the prevalence of serious[a] antiretroviral drug toxicity among people receiving antiretroviral therapy. Routine monitoring will provide data on the clinical significance of serious toxicity and how they affect patient outcomes and attrition.
Rationale	• As antiretroviral therapy use is scaled up, people living with HIV are likely to have prolonged exposure to antiretroviral drugs and the possibility of experiencing toxicity related to antiretroviral drugs. • Toxicity associated with antiretroviral drugs is one of the most common reasons reported for lack of adherence to antiretroviral therapy, treatment discontinuation or drug substitution. • Information on the prevalence of toxicity can inform national guidelines and efforts to prevent and limit antiretroviral drug toxicity.
Numerator	Number of people receiving antiretroviral therapy who have stopped treatment or switched regimen because of toxicity in the reporting period
Denominator	Number of people receiving antiretroviral therapy in the reporting period
Method of measurement	*For the numerator and denominator:* Programme records (antiretroviral therapy register, cohort reporting forms and patient records)
Disaggregation	• Gender (female, male, transgender) • Age (<10, 10–19, >19 years) • Pregnant or breastfeeding women • Antiretroviral drug regimen • Type of toxicity (gastrointestinal, skin, central nervous system, weight gain, hepatic dysfunction, haematological, fatigue, bone dysfunction, metabolic, headache, kidney dysfunction, cardiovascular)

[a] Serious toxicity defined as: life-threatening illness, death, hospitalization or disability or any adverse drug reaction that leads to treatment interruption or requires changing the drug or regime *(8)*.

2. New additional toxicity indicator for pre-exposure prophylaxis (PrEP)

Mirroring the above indicator for treatment-limiting toxicity for antiretroviral therapy, the 2020 consolidated HIV strategic information guidelines recommends a new indicator on PrEP-related antiretroviral toxicity (defined in Table 2) as an additional indicator to strengthen services in specific programme areas *(9)*. The monitoring and evaluation module (module 5) of the WHO implementation tool for PrEP *(10)* outlines the recommended approaches for monitoring the toxicity of PrEP along with generic PrEP user cards and tools for monitoring adverse drug reactions.

TABLE 2. NEW PrEP TOXICITY INDICATOR RECOMMENDED FOR ROUTINE MONITORING WITHIN HIV PROGRAMMES

Indicator	PrEP-related antiretroviral drug toxicity (PR.9)
Indicator definition	The proportion of people who received oral PrEP who have discontinued or interrupted PrEP during the reporting period because of serious[a] toxicity related to antiretroviral drugs.
Rationale	The prevalence of toxicity associated with PrEP is expected to be low. However, experience with large-scale PrEP programmes and longer exposure has been limited. Active surveillance among pregnant women and toxicity monitoring for people using PrEP is therefore important to identify potential adverse outcomes that may arise as PrEP programmes scale up and reach larger numbers of people. Adverse drug reactions leading to people discontinuing or interrupting PrEP should be routinely recorded in an appropriate PrEP register for each PrEP adverse event. Action should be taken at the facility as soon as a serious adverse reaction is recorded.
Numerator	Number of people who have discontinued or interrupted PrEP because of serious[a] toxicity associated with antiretroviral drugs during the reporting period
Denominator	Number of people who received PrEP at least once during the reporting period
Method of measurement	For the numerator and denominator, PrEP user cards and registers
Disaggregation	• Age (<15, 15–19, 20–24, 25–49 and ≥50 years) • Gender (male, female or transgender) • Key population (men who have sex with men, sex workers, people who inject drugs, people in prisons and other closed settings, transgender people) • Geographical and other administrative areas of importance

[a] Serious toxicity defined as: life-threatening illness, death, hospitalization or disability or any adverse drug reaction that resulted in PrEP being discontinued.

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3. New indicators for routine monitoring of adverse pregnancy outcomes related to exposure to antiretroviral drugs

Four indicators are now recommended as part of HIV programme management and monitoring to monitor adverse pregnancy outcomes related to exposure to antiretroviral drugs *(9)*. The 2015 HIV strategic information guidelines *(5)* previously included preterm delivery (<37 weeks). In addition, three new indicators on low birth weight, stillbirth or miscarriage and major congenital anomalies at birth are recommended to enable more comprehensive monitoring of the safety of antiretroviral drugs in pregnancy (Table 3).

A higher than expected rate of adverse pregnancy outcomes based on the below indicators suggests a need for more formal assessment for example through birth defect surveillance or pregnancy registries *(7)*.

ADVERSE PREGNANCY OUTCOMES INDICATORS RECOMMENDED AS ADDITIONAL INDICATORS TO SUPPORT PROGRAMMATIC TRANSITION TO NEW ARV REGIMENS:

- Proportion of low birth weight (<2.5 kg) deliveries among HIV positive women
- Proportion of still births/miscarriages among HIV positive women
- Proportion of preterm deliveries (<37 gestation weeks) among HIV positive women
- Proportion of HIV positive women with conception and 1st trimester (<14 gestation weeks) ART exposure with a major external congenital anomaly

TABLE 3. NEW RECOMMENDED INDICATORS FOR ADVERSE PREGNANCY OUTCOMES

Indicator	Numerator and denominator	Disaggregation	Measurement	Programme relevance and interpretation
MT.14 **Infants with low birth weight**	**Numerator:** number of women living with HIV who received antiretroviral therapy and delivered in the reporting period and had a low-birth-weight (<2.5 kg) infant **Denominator:** number of women living with HIV who delivered at term in the reporting period	Regimen, age, timing of antiretroviral therapy initiation (before conception, during the first trimester (<14 weeks), after the first trimester but before delivery), gestational age	Integrated record of services to prevent the mother-to-child transmission of HIV	Low birth weight is widely collected and accurate. Disaggregation by gestational age will separate low birth weight due to preterm and low birth weight associated with antiretroviral therapy. Low birth weight is used as a proxy for preterm and for small for gestational age.
MT.15 **Stillbirths and miscarriages**	**Numerator:** number of stillbirths or miscarriages among women living with HIV who received antiretroviral therapy in the reporting period **Denominator:** number of pregnant women living with HIV in the reporting period	Regimen, age, timing of antiretroviral therapy initiation (before conception, during the first trimester (<14 weeks), after the first trimester but before delivery)	Integrated record of services to prevent the mother-to-child transmission of HIV	Estimates the proportion of miscarriages and stillbirths in pregnancies in which the woman is exposed to antiretroviral therapy. Since 80% of miscarriages occur before 10 weeks and are mostly not reported, the disaggregation by gestational age is not indicated.

MT.16 **Preterm births**	**Numerator:** number of women living with HIV who received antiretroviral therapy and delivered in the reporting period and had a preterm birth (<37 weeks of gestation) excluding stillbirth and miscarriage **Denominator:** number of women living with HIV who delivered in the reporting period	Regimen, age, timing of antiretroviral therapy initiation (before conception, during the 1st trimester (<14 weeks), after the first trimester but before delivery), gestational age of birth (<28 weeks, 28–32 weeks, 32–37 weeks)	Integrated record of services to prevent the mother-to-child transmission of HIV	Accurate gestational age dating may be difficult in certain contexts. However, if gestational age is estimated uniformly across all births, this should be a feasible indicator for country programmes to include.
MT.17 **Congenital anomalies**	**Numerator:** proportion of women living with HIV with exposure to antiretroviral therapy at conception and during the first trimester with a major external congenital anomaly[a] in the reporting period Denominator: number of women living with HIV who delivered in the reporting period	Antiretroviral therapy regimen, age, timing of antiretroviral therapy initiation (before conception, during the first trimester (<14 weeks), after the first trimester but before delivery), major congenital anomalies at birth	Integrated record of services to prevent the mother-to-child transmission of HIV Countries that can evaluate for heart defects are encouraged to do so (teaching hospitals) In special studies, use denominator: HIV-negative and HIV-positive women who delivered in the reporting period	The method for surface examination must be standardized for all babies delivered (including stillbirths) and should ideally include a photograph for independent expert assessment of type and clinical importance with the consent of the mother *(11)*.

[a] Major external congenital anomalies include *(1)* congenital anomalies of the nervous system: neural tube defects with anencephaly, craniorachischisis, iniencephaly, encephalocele, open spina bifida, closed spina bifida and microcephaly; *(2)* congenital anomalies of eyes and ears: anophthalmia and anotia or microtia; *(3)* cleft palate alone and cleft lip with or without palate; *(4)* congenital malformations of genital organs: hypospadias; *(5)* congenital malformations and deformations of the musculoskeletal system: talipes equinovarus or clubfoot and limb reduction deficiencies; and *(6)* congenital anomalies of the anterior abdominal wall: exomphalos or omphalocele and gastroschisis *(9)*.

4. Monitoring adverse pregnancy outcomes and antiretroviral drug toxicity within HIV case surveillance

In accordance with emerging country needs for monitoring the safety of antiretroviral drug use, countries may consider including pregnancy outcomes within HIV case surveillance. along with person-centred HIV patient monitoring as well as the HIV case surveillance toolkit to support country implementation.

5. Longitudinal monitoring recommended to address emerging concerns and risk factors related to antiretroviral drug toxicity

Recent results from clinical trials showed a potential risk of excessive weight gain *(3)* with the use of DTG with and without tenofovir alafenamide. More data are required to establish whether an association exists with the use of these drugs. WHO encourages countries to implement the longitudinal monitoring