World Health Organization

HIV DRUG RESISTANCE

CONCEPT NOTE

HIV DRUG RESISTANCE SURVEILLANCE IN COUNTRIES SCALING UP PRE-EXPOSURE PROPHYLAXIS

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HIV drug resistance surveillance in countries scaling up pre-exposure prophylaxis

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ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
DPV	dapivirine
DTG	dolutegravir
FTC	emtricitabine
HIVResNet	HIV Drug Resistance Network
ISO	International Organization for Standardization
INI	integrase inhibitor
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
PrEP	pre-exposure prophylaxis
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
XTC	FTC or 3TC

DEFINITIONS

HIV drug resistance is caused by a change (mutation) in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus. HIV drug resistance has three main categories.

- **Acquired HIV drug resistance** develops when HIV mutations emerge because of viral replication in individuals receiving antiretroviral drugs.
- **Transmitted HIV drug resistance** occurs when individuals are infected with HIV that has drug resistance mutations.
- **Pretreatment HIV drug resistance** refers to any drug-resistant virus detected in antiretroviral drug–naive individuals initiating antiretroviral therapy or individuals with previous antiretroviral drug exposure initiating or reinitiating first-line antiretroviral therapy.

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by HIV-negative individuals to prevent HIV acquisition. By definition, PrEP is chemoprophylaxis. Currently, PrEP tends to denote oral PrEP, which involves taking pills orally. WHO-recommended oral PrEP regimens are tenofovir disoproxil fumarate (TDF), TDF combined with emtricitabine and TDF combined with lamivudine. Other drugs and formulations of PrEP are under development, evaluation or regulatory consideration, including the use of a long-acting injectable antiretroviral drug and an intravaginal ring containing dapivirine.

WHO recommends the following oral TDF-containing PrEP dosing strategies.

- Daily PrEP is recommended for all people who are HIV negative and at risk of HIV acquisition, regardless of gender, sexual orientation or sexual behaviour. This PrEP dosing strategy consists of the use of one PrEP pill per day.
- WHO recommends event-driven PrEP only for cis-gender men who have sex with men. Event-driven PrEP is not recommended for people in other risk groups[1] or in individuals with active hepatitis B infection. This four-pill PrEP dosing strategy comprises two PrEP pills taken 2–24 hours before anal sex; then, a third pill taken 24 hours after the first two pills, and a fourth pill taken 48 hours after the first two pills (a pill should be taken every 24 hours until having two days without anal sex).

Antiretroviral therapy refers to the use of a combination of three or more antiretroviral drugs for treating HIV infection. Antiretroviral therapy involves lifelong treatment.

[1] Event-driven PrEP data are limited in other populations, such as transgender women and people having heterosexual sex. Event-driven PrEP showed lower coverage of sex acts than daily dosing for women. Event-driven PrEP dosing is not currently recommended for these population groups.

EXECUTIVE SUMMARY

WHO recommends that pre-exposure prophylaxis (PrEP) be offered as an additional prevention choice for HIV-negative individuals at substantial risk of HIV infection (such as populations with >3% per year HIV incidence) as part of combination prevention approaches.

HIV drug resistance has been rarely reported among PrEP users who tested HIV positive in randomized controlled trials or open-label studies. However, PrEP-selected HIV drug resistance could potentially negatively impact the effectiveness of treatment options among PrEP users who acquire HIV, since there is a potential for overlapping resistance profiles between antiretroviral drugs used for both PrEP and first-line antiretroviral therapy.

WHO therefore recommends that PrEP scale-up be accompanied by surveillance of HIV drug resistance that may compromise the effectiveness of first-line antiretroviral therapy among PrEP users who acquire HIV. This technical guidance describes the methods and implementation considerations to monitor the prevalence of HIV drug resistance among PrEP users diagnosed with HIV through a cross-sectional survey. The outcomes of the survey will be used to inform the selection of maximally effective first-line combination antiretroviral therapy for PrEP users who acquire HIV.

HIV infection is expected to be an infrequent event among PrEP users, because PrEP substantially reduces the risk of acquiring HIV (especially among those who adhere to their regimen). The cross-sectional survey described in this document therefore intends that a **census of all people currently or recently taking PrEP at the time of HIV diagnosis** (subsection 4.3) will contribute information during a **defined survey period of 12 months**. This survey uses a **passive surveillance approach** with information collected at **all sites providing PrEP in a country** during the survey period (subsection 5.1). Operationally, minimal clinical and demographic information will be collected (subsection 5.3.1) and a blood specimen obtained (subsection 4.5.1) from the eligible population will be transferred to a centralized national laboratory for storage. Countries are encouraged to perform HIV drug resistance genotyping at a WHO-designated HIV drug resistance testing laboratory (subsection 4.5.2). HIV drug resistance by drug and drug class will be classified using the Stanford HIVdb algorithm. Countries are encouraged to use the WHO HIV drug resistance database for data management of surveys of HIV drug resistance in populations accessing PrEP. The annexes provide guidance for data analysis and suggest generic estimated budgets.

In countries performing HIV drug resistance testing for individual patient management of all people currently or recently taking PrEP at the time of HIV diagnosis, the prevalence of HIV drug resistance can be estimated annually leveraging routinely available data. In countries where individual HIV drug resistance testing is not routinely performed or feasible for clinical management, the survey should be repeated periodically, generally every 3–5 years.

1. INTRODUCTION

WHO recommended in 2015 that daily oral pre-exposure prophylaxis (PrEP) be offered as an additional prevention choice for HIV-negative individuals at substantial risk of acquiring HIV as part of combination HIV prevention approaches (Box 1) *(1)*. Event-driven PrEP is an alternative recommended only for cis-gender men who have sex with men *(2)*.

The recommended daily oral PrEP regimens are tenofovir disoproxil fumarate (TDF), co-formulated TDF + emtricitabine (FTC) and co-formulated TDF + lamivudine (3TC) *(1,2)*. TDF + FTC or TDF + 3TC are recommended for event-driven PrEP. TDF and FTC or 3TC (XTC) are the nucleoside reverse-transcriptase inhibitor (NRTI) backbone

Box 1. Oral pre-exposure prophylaxis to prevent HIV acquisition

WHO recommends that oral PrEP (containing TDF) be offered as an additional prevention choice for HIV-negative individuals at substantial risk of HIV infection (such as populations with HIV incidence >3% per year) as part of combination prevention approaches *(1,2)*. PrEP is described briefly as follows.

Priority populations
Individuals at substantial risk of acquiring HIV *(37)*, including, but not restricted to, men who have sex with men, serodiscordant couples (until the HIV-positive partner is receiving antiretroviral therapy and has achieved viral load suppression), sex workers, transgender women in most regions and adolescent girls and young women in high-incidence settings in southern and eastern Africa *(38)*. PrEP should be offered as part of a comprehensive HIV prevention package for HIV-negative pregnant and breastfeeding women in settings with high HIV incidence *(39)*. Harm reduction for people who inject drugs remains a critical WHO recommendation to prevent HIV and other infections. PrEP should be offered to people who inject drugs as part of HIV prevention services *(37)*.

PrEP services
WHO recommends integrating PrEP into existing health services, such as clinics that offer HIV testing services and antiretroviral therapy. Other alternatives include: sexual health and sexually transmitted infection clinics, contraception services, services for men who have sex with men and transgender people, services for sex workers, harm-reduction services and the private sector. PrEP provision could be considered in antiretroviral therapy services to protect the HIV-negative partner in a serodiscordant relationship *(38)*.

PrEP eligibility criteria
HIV-negative, no signs or symptoms to suggest acute HIV infection, substantial risk of HIV infection, no contraindications to PrEP medicines and willingness to use PrEP as prescribed *(37)*.

HIV testing
Required to confirm HIV-negative status before PrEP is initiated. HIV testing should be regularly repeated while PrEP is taken (every three months) and before PrEP is reinitiated for both daily and event-driven regimens. Individuals may be tested at the point of care and provided the results on the same day *(37,40)*. It is suggested that PrEP programmes use the WHO-recommended HIV testing strategy for retesting PrEP users. Three consecutive reactive serology test results on the first-line, second-line and third-line assays (A1+ A2+ A3+) are required to diagnose HIV infection *(41)*. Oral fluid-based rapid diagnostic tests are not ideal for conducting HIV testing among PrEP users *(40,42)*.

PrEP regimens
TDF, TDF + FTC or TDF + 3TC for daily PrEP *(37)*. TDF + FTC or TDF + 3TC for event-driven PrEP *(2)*. WHO considers FTC and 3TC interchangeable, for both HIV treatment and prevention *(43,44)*.

PrEP delivery mode
WHO recommends oral PrEP, which involves taking pills orally *(37)*. Other formulations and delivery modes (such as long-acting injectable antiretroviral drugs and intravaginal ring containing dapivirine) under development, evaluation or regulatory consideration.

PrEP dosing strategy
Daily PrEP is recommended for all people, regardless of gender, sexual orientation or sexual behaviour *(1,2)*. Event-driven PrEP is recommended only for men who have sex with men *(2)*.

Special situations
People who have been exposed to HIV in the preceding 72 hours should be offered post-exposure prophylaxis for 28 days. PrEP can be initiated without a gap after post-exposure prophylaxis if the HIV serology test result is non-reactive (negative) and there is ongoing risk of acquiring HIV. PrEP initiation should be deferred for people with suspected acute HIV infection until HIV-negative status is confirmed. People with signs or symptoms of acute HIV infection should delay PrEP initiation and have further HIV testing after four weeks *(37,45)*.

Stopping PrEP
PrEP is needed during periods of risk rather than for life. PrEP can be discontinued if an individual taking PrEP is no longer at risk and when lack of risk is likely to be sustained *(37)*. The health-care personnel who counsel PrEP users may support them to plan for effective PrEP use, including education and support for safely stopping and reinitiating PrEP *(46)*.

Managing HIV infection
If a PrEP user tests positive for HIV, antiretroviral therapy can be started immediately after discontinuing PrEP *(37)*. A dolutegravir-based regimen is recommended as the preferred first-line regimen for people initiating antiretroviral therapy *(3,45,47)*.

of the WHO-recommended first-line antiretroviral therapy regimen *(3)*; since these antiretroviral drugs are used for both PrEP and first-line antiretroviral therapy, resistance generated by the use of PrEP could potentially adversely affect the effectiveness of first-line antiretroviral therapy for PrEP users who acquire HIV.

A systematic review and meta-analysis of oral TDF-containing PrEP trials concluded that PrEP significantly reduces the risk of acquiring HIV when adherence is optimal *(4)*. Indeed, most PrEP users who test HIV positive are non-adherent to PrEP or have unrecognized HIV infection when they initiate PrEP *(4,5)*.[1]

Although the risk of acquiring HIV is substantially reduced among PrEP users, individuals who become infected are at risk of having a virus carrying resistance to XTC, TDF or both drugs.

HIV drug resistance may be detected among PrEP users diagnosed with HIV as a consequence of three situations (Box 2) *(5,6)*.

1) Individuals initiating PrEP during undiagnosed acute HIV infection can select for HIV drug resistance.

2) Individuals taking PrEP can acquire XTC + TDF–susceptible HIV, most likely when adherence is suboptimal, and select for drug-resistant virus.

3) Individuals taking PrEP can be infected with XTC-resistant virus, TDF-resistant virus or both.

Concern over HIV drug resistance should not be a reason to limit the use of PrEP. HIV drug resistance has rarely been reported in randomized controlled trials of oral TDF-containing PrEP or open-label studies *(7–20)*, although some trials have observed low levels of PrEP adherence. Resistance to XTC and/or TDF was infrequent (3.5%, 11 of 315) if HIV was acquired after PrEP initiation. Resistance was more frequent (33.3%, 13 of 39) if PrEP was inadvertently initiated during undiagnosed acute HIV infection (Box 2 and Table 1). Taking all reasonable steps to exclude acute HIV infection before initiating or reinitiating PrEP is therefore imperative.

Next-generation PrEP products are under development, evaluation or regulatory consideration *(21,22)*. The European Medicines Agency approved the monthly intravaginal ring containing dapivirine (DPV, a non-nucleoside reverse-transcriptase inhibitor (NNRTI)) for PrEP after demonstration of its efficacy against HIV-1 acquisition in two independent randomized clinical trials involving African women *(23–25)*. A multinational clinical trial demonstrated daily oral tenofovir alafenamide (TAF) + FTC non-inferior PrEP efficacy compared with TDF + FTC *(26)*. The United States Food and Drug Administration approved daily TAF + FTC for PrEP among adults and adolescents at higher risk for sexually acquired HIV, excluding cis-gender women *(27)*. The efficacy of the long-acting injectable cabotegravir (an integrase inhibitor (INI)) to reduce the risk of HIV acquisition is currently being evaluated *(28)*. The preclinical studies of islatravir (a novel reverse transcriptase–translocation inhibitor) demonstrates its potential as a long-acting next-generation PrEP agent *(29)*. Other PrEP agents in development include broadly neutralising HIV-1 monoclonal antibodies, topical products and multipurpose prevention technologies for HIV and other sexually transmitted infections, with or without contraception *(22)*.

There is a potential for overlapping resistance profiles between next-generation antiretroviral drug–based PrEP regimens and the antiretroviral drugs used for first-line antiretroviral therapy. For example, TAF and TDF share the same drug resistance profile *(30)*. There are also concerns regarding the prolonged low-level concentrations of cabotegravir (an analogue of dolutegravir (DTG)) after the long-acting injectable cabotegravir discontinuation, which could potentially exert selective pressure for INI

Box 2. HIV drug resistance among PrEP users who test HIV positive

Twelve randomized controlled trials and open-label PrEP studies *(7–20)* measured and reported cases of TDF or XTC drug resistance (Table 1). Within these studies, 6.8% (24 of 354) of PrEP users who had tested HIV positive had infection with mutations conferring resistance to TDF and/or XTC. Specifically, resistance to TDF or XTC was infrequent (3.5%, 11 of 315) if PrEP was initiated before HIV was acquired, and resistance was more likely (33.3%, 13 of 39) when PrEP was inadvertently initiated during undiagnosed acute HIV infection.

XTC resistance in the form of the M184V/I mutation occurred more frequently than TDF resistance in the form of K65R or K70E mutations among PrEP users who tested HIV positive and had taken a fixed-dose combination of TDF + FTC for PrEP *(6)*. To date, at least five cases of breakthrough HIV infection caused by a virus with drug resistance mutations to TDF and/or XTC have been reported that appear to have occurred despite optimal adherence to oral PrEP containing TDF + FTC *(48–52)*.

[1] Less frequently, HIV infection with drug resistance virus appear to have occurred despite optimal adherence to oral TDF-containing PrEP. Other proposed mechanisms of HIV acquisition while taking oral TDF-containing PrEP are: high burden of viral inoculum, disruption and inflammation of the mucosal barrier, variable pharmacokinetics of PrEP in mucosal tissue and potential parenteral transmission.

Table 1. Summary of HIV drug resistance prevalence among PrEP users who tested HIV positive in TDF-containing PrEP randomized controlled trials or open-label studies

Study	Acute HIV infection at study enrolment				HIV infection occurred during the study			
	HIV cases	HIV drug resistance to TDF and/or XTC	K65R/K70E	M184IV	HIV cases	HIV drug resistance to TDF and/or XTC	K65R/K70E	M184IV
Bangkok Tenofovir Study *(7)*	0	–	–	–	17[b]	0	0	–
FEM-PrEP *(8)*	1	0	0	0	33	4	0	4
iPrEx *(9,18)*	2	2	0	2	48	0	0	0
Partners PrEP *(10,19)*	12	3	1	2	51	4	1	4
TDF2 *(11)*	1	1	1	1	9	0	0	0
VOICE *(12)*	14	2	0	2	113	1	0	1
IPERGAY *(13)*	3[a]	Not reported	Not reported	Not reported	2	0	0	0
PROUD *(14)*	3	2	0	2	3	0	0	0
iPrEx OLE *(15)*	0	–	–	–	28	1	0	1
USA DEMO *(16)*	3	1	0	1	2	0	0	0
HPTN-067 *(17)*	3	2	1	1	9	1	1	1
Prevenir Study *(20)*	0	–	–	–	2	0	0	0
Total	**39**	**13**	**3**	**11**	**315**	**11**	**2**	**11**
%		**33.3**	**7.7**	**28.2**		**3.5**	**0.6**	**3.5**

[a] The three cases were excluded from the total number of HIV cases because HIV drug resistance data were not reported.
[b] Two of the 17 cases were excluded from the total number of HIV cases because HIV drug resistance testing was not successful.

resistance among those who acquire HIV during this period *(31)*. With respect to the intravaginal ring containing DPV, there was no significant difference in NNRTI resistance virus between the placebo and DPV groups in the two efficacy clinical trials *(23,24)*. Pharmacokinetic studies of an intravaginal ring containing DPV showed low systemic DPV concentrations *(32,33)*, suggesting a low risk of DPV-resistant virus selection if this PrEP regimen is initiated during undiagnosed acute HIV infection. However, selection of DPV-resistant virus in the genital tract has not been excluded in the context of suboptimal DPV use. In vitro studies showed cross-resistance between DPV and other NNRTI drugs *(34–36)*. Whether DPV could be effective against NNRTI-resistant virus was evaluated in vitro, with the results suggesting that the high genital tract DPV concentration from intravaginal DPV-containing ring use could inhibit the replication of most NNRTI-resistant virus *(35)*. However, the DPV concentration needed in the vaginal fluid and tissue to provide full protection against NNRTI-resistant virus infection remains uncertain.

2. SURVEY PURPOSE

There is a consensus among mathematical models that antiretroviral therapy in association with PrEP will decrease HIV prevalence, compared with antiretroviral therapy alone, but will increase the prevalence of HIV drug resistance among those infected with HIV despite PrEP *(47,53)*. HIV drug resistance caused by antiretroviral therapy is predicted to far exceed that resulting from PrEP *(53)*. However, resistance generated by the use of PrEP could potentially compromise treatment options among PrEP users who acquire HIV, since TDF and XTC are used for both PrEP and as a component of WHO-recommended first-line antiretroviral therapy: TDF + XTC + DTG *(3,45)*. Limited evidence supports the use of DTG as first-line antiretroviral therapy in combination with an NRTI backbone whose activity is compromised by the presence of resistance-associated mutations *(54,55)*. Maintenance monotherapy with DTG can be associated with failure of viral suppression and accumulation of INI resistance-associated mutations *(56–58)*.

In addition, there is potential for overlapping resistance profiles between the antiretroviral drugs used for first-line antiretroviral therapy and the novel PrEP regimens under development or undergoing regulatory review.

Since HIV drug resistance may compromise the effectiveness of first-line antiretroviral therapy among PrEP users who acquire HIV, WHO recommends that PrEP scale-up be accompanied by surveillance of HIV drug resistance *(59,60)*.

This technical guidance describes survey methods to assess the prevalence of HIV drug resistance among PrEP users diagnosed with HIV. The survey findings will be used to inform the selection of maximally effective first-line combination antiretroviral therapy for PrEP users who acquire HIV.

3. SURVEY OUTCOMES

3.1 Primary survey outcome

The primary survey outcome is the prevalence of predicted TDF and/or XTC resistance among individuals diagnosed with HIV during the survey period who have taken oral TDF-containing PrEP at any time in the three months prior to the HIV diagnosis and who have a HIV drug resistance genotype available for analysis.

As new PrEP regimens become available, the primary outcome of the survey will be expanded to include the prevalence of resistance by drug and drug class relevant to the drugs included in the PrEP regimen (such as the prevalence of DPV resistance among people exposed to the DPV vaginal ring).

3.2 Secondary survey outcome

The secondary survey outcome is the prevalence of predicted drug resistance by drug and drug class to antiretroviral drugs other than TDF or TDF + XTC among individuals diagnosed with HIV during the survey period who have taken oral TDF-containing PrEP at any time in the three months prior to the HIV diagnosis (such as the prevalence of NNRTI resistance among people exposed to TDF or TDF + XTC for PrEP). This outcome will account for potential transmitted resistance and will inform optimal regimen selection among people exposed to PrEP and infected with HIV.

As new PrEP regimens become available, the secondary outcome of the survey will be expanded to include the prevalence of drug resistance to antiretroviral drugs and drug class other than those included in the PrEP regimen taken (such as the prevalence of XTC or TDF resistance among individuals exposed to the DPV vaginal ring for PrEP).

4. OVERVIEW OF METHODS

In countries performing HIV drug resistance testing for clinically managing all people currently or recently taking oral TDF-containing PrEP at the time of HIV diagnosis, the prevalence of resistance can be estimated annually by aggregating results from HIV drug resistance genotypes *(61)*. In countries where individual HIV drug resistance testing for clinical management is not routinely performed or feasible, a cross-sectional survey is recommended to estimate the prevalence of resistance among individuals who have taken PrEP at any time during the previous three months and who are diagnosed with HIV (Fig. 1).

4.1 Cross-sectional survey approach

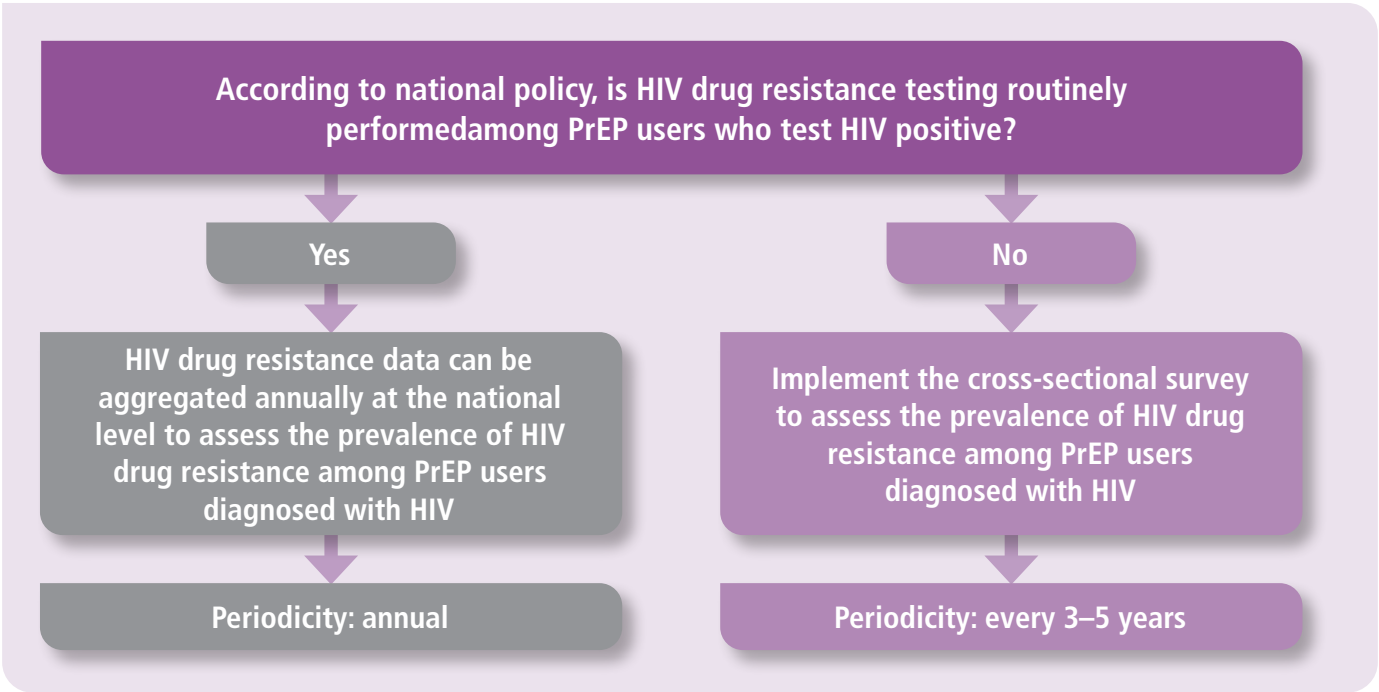
HIV infection is expected to be infrequent among PrEP users, because PrEP substantially reduces the risk of acquiring HIV, especially among those who adhere to their regimen *(4)*. The survey therefore intends that a census of all eligible individuals (subsection 4.3) will contribute information and specimens during a defined survey period of 12 months. This cross-sectional survey uses a passive surveillance approach with information collected at all sites providing PrEP in a country during the survey period (subsection 5.1).

After a predefined survey start date, any individual meeting the eligibility criteria will be offered informed consent. Upon consent, minimal clinical and demographic information will be collected (subsection 5.3.1) and a blood specimen obtained (subsection 4.5.1). Information on recent PrEP exposure can be obtained using a screening questionnaire.

Operationally, a blood specimen from an enrolled individual is collected for HIV drug resistance testing on the same day that the HIV diagnosis is made and before antiretroviral therapy is initiated (subsection 4.5.1). Specimens should be collected, processed, handled and shipped following WHO HIV drug resistance laboratory guidance *(62)*. Basic clinical and demographic information (subsection 5.3.1) is obtained at the time of specimen collection.

HIV drug resistance testing can be performed in batches for all survey specimens at the end of the survey period; alternatively, to enable HIV drug resistance results to be timely reported to the patients, individual specimens can be genotyped as soon as they are received at the genotyping laboratory. Countries are encouraged to perform HIV drug resistance genotyping at a WHO-designated HIV drug resistance testing laboratory

Fig.1. Framework for HIV drug resistance surveillance in countries scaling up PrEP



(subsection 4.5.2). The reverse-transcriptase region of the HIV-1 *pol* gene will be sequenced using standard sequencing methods. Other regions of the HIV-1 *pol* gene will need to be sequenced as novel PrEP regimens become available (such as the integrase region for long-acting injectable INI).

A unique PrEP survey identifier (subsection 5.2) should be used to identify participants' basic clinical and demographic information, the blood specimen and the HIV sequence generated by the genotyping assay.

4.2 Survey population

HIV infection is expected to be infrequent among PrEP users, because PrEP substantially reduces the risk of acquiring HIV (especially among those who adhere to their regimen) *(4)*. The survey population is therefore a census of all eligible individuals during the defined survey period.

4.3 Survey eligibility criteria

4.3.1 Survey inclusion criteria

The inclusion criteria are:

- individuals providing written informed consent;
- have taken PrEP at any time during the three months prior to HIV diagnosis,[1] regardless of the PrEP regimen, dosing strategy and levels of PrEP adherence; and
- newly diagnosed with HIV during the survey period in accordance with the WHO recommendations *(40–42)* and national testing policy.[2]

4.3.2 Survey exclusion criterion

PrEP users diagnosed with HIV who have already initiated antiretroviral therapy at the time of specimen collection should be excluded.

4.3.3 Expected number of eligible individuals

For survey budgeting and planning purposes, countries may want to anticipate the number of eligible individuals requiring HIV drug resistance testing. This can be calculated considering the expected number of PrEP users during the survey period, the most likely HIV incidence rate among PrEP users and the average time of continuation on PrEP (Annex 1).

4.4 Survey participating sites

Ideally, all sites providing PrEP services in a country should participate in the survey. Many countries are generating demand and uptake of PrEP at sites outside of the public sector. The survey should therefore not be limited to the sites within the public health-care system and should include PrEP sites run by nongovernmental, community-based organizations and in the private sector to the extent possible.

4.5 Laboratory methods

4.5.1 Specimen collection, handling, shipment and storage

The blood specimen – either dried blood spot or plasma – should be collected from the enrolled individual on the same day that the HIV diagnosis is made and before antiretroviral therapy is initiated. Dried blood spot has been shown to be a reliable specimen type for HIV drug resistance genotyping *(63,64)*. The dried blood spot specimen should be collected, handled, shipped and stored according to the WHO guidance for dried blood spot specimen collection and handling for HIV drug resistance testing *(65)*. It is critical that no more than 14 days passes between the date the specimen is collected and the time of freezing. Countries using plasma specimens for this survey should refer to the WHO HIV Drug Resistance Network (HIVResNet) recommendations on standards for specimen collection, handling, shipment and storage for HIV drug resistance testing *(62)*.

4.5.2 HIV drug resistance genotyping and quality assurance of sequences

The reverse-transcriptase region of the HIV-1 *pol* gene will be sequenced using standard sequencing methods. Other regions of the HIV-1 *pol* gene will need to be sequenced as novel PrEP regimens become available and are incorporated as part of the PrEP programme (for example, using long-acting injectable INI as a PrEP regimen will require integrase region sequencing).[3]

HIV drug resistance testing can be performed in batches for all survey specimens at the end of the survey period; alternatively, to enable HIV drug resistance results to be timely reported to the patients, individual specimens can be genotyped as soon as they are received at the genotyping laboratory.[4]

[1] Individuals are not required to have been taking PrEP continuously during the past three months nor are they required to be taking PrEP at the time of HIV diagnosis.

[2] It is suggested that PrEP programmes use the WHO HIV testing strategy for retesting PrEP users. Three consecutive reactive serology test results on the first-line, second-line and third-line assays (A1+ A2+ A3+) are required to diagnose HIV infection. Oral fluid-based rapid diagnostic tests are not ideal for conducting HIV testing among PrEP users.

[3] To simplify the survey implementation and to avoid tailored genotyping, all specimens should be genotyped for both reverse transcriptase and integrase regions if INI are recommended and available in the country PrEP programme. At present, it is anticipated that most countries will not opt to genotype the integrase region.

[4] The WHO website lists the currently designated HIV drug resistance genotyping laboratories: http://www.who.int/hiv/topics/drugresistance/en.

Countries are encouraged to perform HIV drug resistance genotyping at a WHO-designated HIV drug resistance testing laboratory. As members of the WHO HIVResNet, these laboratories undergo a rigorous inspection process and participate in annual proficiency panel testing. WHO-designated HIV drug resistance testing laboratories perform extensive quality assurance of sequences and follow the WHO laboratory standard operating procedures for post-testing quality assurance of HIV sequence data. The use of WHO-designated laboratories promotes quality-assured results for the purpose of public health surveillance. If a country does not have a WHO-designated laboratory for HIV drug resistance testing, it is encouraged to send specimens to a WHO-designated regional or specialized laboratory.

4.6 Survey limitations

The survey methods cannot account for HIV testing sites non-reporting or underreporting HIV being acquired among individuals who have taken PrEP during the survey period. By not including all HIV testing sites, the survey may miss PrEP-exposed individuals who test HIV positive at a non-PrEP site. Further, since PrEP use may be self-reported, there is potential for underreporting; however, this is likely to be low when providers explain the potential for underreporting. In addition, the individuals with informal access to PrEP (such as via the Internet or acquaintances) who acquire HIV may not be enrolled in the survey if they do not seek clinical care and regular HIV testing at PrEP sites participating in the survey. Because of these potential biases, the survey results may not be nationally representative of PrEP users who acquired HIV.

A cross-sectional study cannot distinguish acquired (PrEP-selected) and transmitted HIV drug resistance to the prescribed PrEP regimen. The primary survey outcome should therefore be interpreted as levels of drug resistance among PrEP users who acquired HIV instead of levels of PrEP-selected drug resistance.

5. IMPLEMENTATION CONSIDERATIONS

5.1 Duration of the survey and enrolment procedure

Operationally, after the survey start date is chosen, PrEP providers in a country should screen all individuals attending the PrEP clinics for the eligibility criteria (subsection 4.3).

Eligible individuals should be consecutively enrolled throughout a period of 12 months. Survey enrolment should proceed in three steps:

- step 1: obtain informed consent;
- step 2: abstract or obtain basic clinical and demographic information (subsection 5.3.1); and
- step 3: collect a specimen for HIV drug resistance testing (subsection 4.5.1).

After an eligible individual is identified and consent is obtained, a survey identifier should be assigned to the individual following the guidance provided in subsection 5.2. The data abstracted by clinic personnel should not include identifying information.

Information on recent PrEP exposure can be obtained using a screening questionnaire.

5.2 Convention for assigning survey identification numbers

Individuals enrolled in the survey are assigned a unique survey identifier. This is used to identify the basic clinical and demographic data collected, the blood specimen and the sequence generated by the genotyping assay. It comprises the following five elements delimited by a hyphen ("-"):

- country abbreviation: the standard three-letter abbreviation, as defined by the International Organization for Standardization (ISO 3166):[1]
- survey type: PREP;
- the year the survey started;
- the clinic ID: site abbreviation (a three-letter abbreviation for the site, unique within the country; by default, the first three letters of the site name unless this is not unique); and
- a four-digit unique number: a consecutive unique number assigned to an eligible individual enrolled at that site.

For example, if the University HIV Clinic was a site that participated in a national survey of HIV drug resistance among PrEP users diagnosed with HIV in South Africa in 2020, the survey identifier for the first case specimen would be: ZAF-PREP-2020-UHC-0001.

5.3 Data collection

5.3.1 Minimum set of individual-level information

Clinical and demographic information

This section describes the minimal set of individual-level information that should be captured once eligible individuals have been identified and enrolled. These variables can be collected using a questionnaire administered at the time of enrolment or obtained from clinical records.

1. Survey ID (survey identifier)
2. Clinic ID
3. Date of survey enrolment (DD-MM-YYYY)
4. Gender (female, male or other)
5. Date of birth (DD-MM-YYYY); if not available, age in years
6. Risk group (multiple response question: men who have sex with men, serodiscordant couple, sex worker, transgender women, adolescent girls and young women, pregnant and breastfeeding women, people who inject drugs, other. If other, specify)
7. PrEP delivery mode during the previous three months (multiple response question: oral PrEP, other. If other, specify the delivery mode (such as a DPV vaginal ring))
8. PrEP regimen during the previous three months (multiple response question: TDF, TDF + XTC, other. If other, specify the antiretroviral drugs)
9. PrEP dosing strategy during the previous three months (multiple response question: daily PrEP, event-driven PrEP, other. If other, specify the dosing strategy)

[1] Country codes – ISO 3166 are available at: https://www.iso.org/obp/ui/#search/code.

10. Date PrEP was initiated for the first time (DD-MM-YYYY)
11. Date PrEP was last taken (DD-MM-YYYY)
12. Date of the most recent HIV negative test (DD-MM-YYYY)
13. Date of HIV diagnosis (DD-MM-YYYY)

Laboratory information

This section describes the minimal set of individual-level information that should be provided by the WHO-designated HIV drug resistance testing laboratory.

1. Survey ID (survey identifier)
2. Laboratory name
3. Reverse-transcriptase region of the HIV-1 *pol* gene successfully sequenced? (successful, unsuccessful, not attempted, unknown)[2]
4. Integrase region of the HIV-1 *pol* gene successfully sequenced? (successful, unsuccessful, not attempted, unknown, not applicable)[3]
5. HIV drug resistance genotypes in FASTA file format

5.3.2 Survey-level information

This section describes the minimal set of information that should be captured at the national level.

1. Country abbreviation (three-letter ISO 3166 code)
2. Survey type: PREP
3. Survey start date (date when the screening of eligible individuals starts; DD-MM-YYYY)
4. Survey end date (date when the screening of eligible individuals ends; DD-MM-YYYY)
5. Number of sites providing PrEP services in the country during the survey period (disaggregated by public, nongovernmental, community-based organizations and private sector)
6. Number of sites participating in the survey (disaggregated by public, nongovernmental, community-based organizations and private sector)
7. Number of sites enrolling eligible individuals and contributing specimens for genotyping to the survey (disaggregated by public, nongovernmental, community-based organizations and private sector)

5.4 Data management

Countries are encouraged to use the WHO HIV drug resistance database for managing data for surveys of HIV drug resistance in populations accessing PrEP *(66)*. The WHO HIV drug resistance database supports countries and genotyping laboratories in the quality assurance of epidemiological and sequence data for the purpose of generating high-quality country reports.

Survey data are entered into a standardized Excel-based data upload template. This Excel file and the HIV drug resistance genotypes in FASTA file format are uploaded into the WHO HIV drug resistance database.[4] The WHO HIV drug resistance database is a web interface that joins survey-level and participant-level epidemiological and sequence information and prepares it for analysis by performing automated quality assurance checks on both epidemiological and sequence information. In addition, the platform provides standardized HIV drug resistance interpretations by linking to the most recent Stanford HIV drug resistance interpretation algorithm. Quality-assured participant and sequence information from the WHO HIV drug resistance database is used as the source of information when surveys are analysed.

5.5 Frequency of the survey

In countries performing HIV drug resistance testing for individually managing all people currently or recently taking PrEP at the time of HIV diagnosis, the prevalence of resistance can be estimated annually.

In countries where individual HIV drug resistance testing for individual management is not routinely performed or feasible, the survey should be repeated periodically, typically every 3–5 years, to enable the assessment of trends of HIV drug resistance among PrEP users who acquire HIV. The survey should be repeated earlier if the PrEP programme changes the target population or implements different PrEP regimens and dosing strategies.

[2] A specimen is considered to be successfully sequenced only when it passes the appropriate quality assurance as recommended by WHO.

[3] Genotyping of the integrase region should be considered if novel PrEP regimens become available (such as long-acting injectable INI) and are incorporated as part of the PrEP programme. At present, it is anticipated that most countries will not opt to genotype this region.

[4] The WHO HIV drug resistance database is available at: https://www.who.int/hiv/topics/drugresistance/hiv-drug-resistance-database/en.

6. DATA ANALYSIS

Once all data have been collected and genotyping is complete, unweighted point prevalence estimates are calculated. Annex 2 provides guidance on data analysis.

For this survey, the Stanford HIVdb algorithm *(67)* is used to predict HIV drug resistance. It classifies HIV sequences in five categories for each antiretroviral drug: susceptible, potential low-level, low-level, intermediate or high-level drug resistance. Sequences classified as susceptible or as having potential low-level resistance are classified as susceptible. Sequences classified as having low-, intermediate- or high-level drug resistance are classified as resistant.

6.1 Primary survey outcome

The prevalence of predicted HIV drug resistance to TDF and/or XTC among individuals diagnosed with HIV during the survey period who have taken oral TDF-containing PrEP at any time during the three months prior to HIV diagnosis is calculated:

- numerator: number of individuals in the denominator who have an HIV sequence classified as having resistance to TDF and/or XTC; and
- denominator: number of individuals who have taken oral TDF-containing PrEP at any time during the three months prior to HIV diagnosis and have successful HIV drug resistance genotyping performed.

The drug resistance analysis should be disaggregated by dual NRTI resistance (resistance to both TDF and XTC) and by drug. The outcome should be disaggregated by gender, age band, PrEP regimen (TDF, TDF + XTC) and dosing strategy (daily PrEP, event-driven PrEP).

As novel PrEP regimens become available and are implemented, the prevalence of resistance by drug and drug class will be calculated according to the type(s) of PrEP regimen exposure.

The frequency of drug resistance mutations associated with TDF + XTC will also be reported using the Stanford HIVdb algorithm *(60)*.

6.2 Secondary survey outcome

The secondary outcome is the prevalence of predicted drug resistance by drug and drug class to antiretroviral drugs other than TDF or TDF + XTC among individuals diagnosed with HIV during the survey period who have taken oral TDF-containing PrEP. For example, the prevalence of NNRTI resistance among people exposed to TDF or TDF + XTC for PrEP is calculated:

- numerator: number of individuals in the denominator who have an HIV sequence classified as having resistance to NNRTI; and
- denominator: number of individuals who have taken oral TDF-containing PrEP at any time during the three months prior to HIV diagnosis and have successful HIV drug resistance genotyping performed.

As new PrEP regimens become available, the secondary outcome of the survey will be expanded to include the prevalence of drug resistance to antiretroviral drugs other than those included in the PrEP regimen taken (such as the prevalence of XTC or TDF resistance among individuals exposed to a DPV vaginal ring for PrEP).

The frequency of drug resistance mutations for all drugs and drug classes will also be reported using the Stanford HIVdb algorithm *(60)*.

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ANNEX 1. EXPECTED NUMBER OF ELIGIBLE INDIVIDUALS REQUIRING HIV DRUG RESISTANCE TESTING

Countries can estimate the number of eligible individuals requiring HIV drug resistance testing, for budgeting and logistics purposes, by multiplying the most likely HIV incidence rate (number of people acquiring HIV per 100 person-years) among PrEP users, the expected number of PrEP users during the 12-month survey period and the average time of continuation on PrEP.

n=HIV incidence × (number of PrEP users × average time of continuation on PrEP)

For example, if a country expects 15 000 PrEP users during the survey period, assuming an HIV incidence rate of 0.25 people acquiring HIV per 100 person-years and an average of one year of continuation on PrEP, the anticipated number of eligible individuals is 38.

$$n = \left(\frac{0.25\ HIV\ infections}{100\ person-years}\right) \times (15\,000 \times 1\ \text{year}) = 38\ HIV\ infections$$

The anticipated number of eligible individuals will be lower if the average time of continuation on PrEP is less than one year:

$$n = \left(\frac{0.25\ HIV\ infections}{100\ person-years}\right) \times (15\,000 \times 0.5\ \text{year}) = 19\ HIV\ infections$$

The calculation of this proxy number of eligible individuals will be affected by the characteristics of the different risk groups accessing PrEP within the country, including the population relative size, HIV incidence per risk group and length of time on PrEP per individual.

Table A1 shows examples of the expected number PrEP users diagnosed with HIV during a 12-month period, based on different scenarios of number of PrEP users, HIV incidence rates and an average of one year of continuation on PrEP.

Table A1. Expected number of PrEP users diagnosed with HIV during a 12-month period

Expected number of PrEP users	Expected HIV incidence rate per 100 person-years among PrEP users			
	0.25	0.50	0.75	1.00
1 000	3	5	8	10
2 000	5	10	15	20
3 000	8	15	23	30
4 000	10	20	30	40
5 000	13	25	38	50
10 000	25	50	75	100
15 000	38	75	113	150
20 000	50	100	150	200
25 000	63	125	188	250
30 000	75	150	225	300
35 000	88	175	263	350
40 000	100	200	300	400
45 000	113	225	338	450
50 000	125	250	375	500

ANNEX 2. DATA ANALYSIS PLAN

It is recommended to enter data in Excel. Instructions are provided below for unweighted data analysis in Stata. The simple proportion is calculated with associated confidence interval adjusted for clustering without finite population correction.

An example is provided for data analysis of 109 individuals enrolled in 56 sites.

Step 1: create a table summarizing the necessary clinical and demographic information for each individual enrolled

In Excel, create a spreadsheet summarizing the necessary clinical and demographic information for each individual enrolled (see Table A2 for an example).[1]

1. List the unique participant survey ID in a column labelled SID.
2. List the clinic ID in a column labelled SITE_ID (the three-letter abbreviation for the site).
3. List the date of survey enrolment in a column labelled ENROLMENT_DATE (DD-MM-YYYY format).
4. List the gender in a column labelled GENDER (female = 0; male = 1; other = 2).
5. List the date of birth in a column labelled BIRTH_DATE (DD-MM-YYYY format).
6. List the age in years in a column labelled AGE (number of years between the date of birth and the date of enrolment).
7. List the type of PrEP dosing strategy used during the previous three months in a column labelled PREP_DOSING (daily PrEP = 0; event-driven PrEP = 1; both dosing strategies = 2).
8. List the PrEP regimen taken during the previous three months in a column labelled PREP_REGIMEN (TDF =0 ; TDF + FTC = 1; TDF + 3TC = 2).
9. List the date PrEP was last taken in a column labelled PREP_STOP_DATE (DD-MM-YYYY format).
10. List the date of the most recent HIV negative test in a column labelled HIV_NEG_DATE (DD-MM-YYYY format).
11. List the date of HIV diagnosis in a column labelled HIV_POS_DATE (DD-MM-YYYY format).
12. In a column labelled GENOTYPE_BN indicate whether the participant has or has not had successful HIV drug resistance genotyping performed (unsuccessful genotype = 0; successful genotype = 1).
13. Save data in a spreadsheet, with a file name such as PrEP_PT_DATA.xlsx.

[1] At the analysis stage, all variable names should be indicated with capital letters.

In Table A2:

- Participant ZAF-PREP-2020-ABC-0001 (from Site ABC) is a man who has taken daily PrEP during the previous three months, and the PrEP regimen was TDF + FTC. This participant has had successful HIV drug resistance genotyping performed.
- Participant ZAF-PREP-2020-ABC-0003 (from Site ABC) is a woman who has taken daily PrEP during the previous three months, and the PrEP regimen was TDF + FTC. This participant has had successful HIV drug resistance genotyping performed.
- Participant ZAF-PREP-2020-BCD-0001 (from Site BCD) is a man who has taken event-driven PrEP during the previous three months, and the PrEP regimen was TDF + FTC. This participant has had successful HIV drug resistance genotyping performed.
- Participant ZAF-PREP-2020-ZAB-0004 (from Site ZAB) is a woman who has taken daily PrEP during the previous three months, and the PrEP regimen was TDF + FTC. This participant has not had successful HIV drug resistance genotyping performed.

Table A2. Example of clinical and demographic data

SID	SITE_ID	GENDER	PREP_DOSING	PREP_REGIMEN	GENOTYPE_BN
ZAF-PREP-2020-ABC-0001	ABC	1	0	1	1
ZAF-PREP-2020-ABC-0002	ABC	1	0	1	1
ZAF-PREP-2020-ABC-0003	ABC	0	0	1	1
ZAF-PREP-2020-ABC-0004	ABC	1	0	1	1
ZAF-PREP-2020-BCD-0001	BCD	1	1	1	1
…					
ZAF-PREP-2020-ZAB-0003	ZAB	0	0	1	1
ZAF-PREP-2020-ZAB-0004	ZAB	1	0	1	0

Step 2: create a table summarizing the necessary HIV drug resistance information for each individual enrolled

In Excel, create a spreadsheet summarizing the necessary HIV drug resistance[2] information for each individual enrolled (see Table A3 for an example).[3]

1. List the unique participant survey ID in a column labelled SID.
2. List a binary variable indicating whether a participant had detectable resistance to XTC in a column labelled XTC_HIVDR_BN (HIV drug resistance = 1, no HIV drug resistance = 0; missing if no data are available).
3. List a binary variable indicating whether a participant had detectable resistance to TDF in a column labelled TDF_HIVDR_BN (HIV drug resistance = 1, no HIV drug resistance = 0; missing if no data are available).
4. List a binary variable indicating whether a participant had detectable resistance to TDF or XTC in a column labelled TDF_OR_XTC_HIVDR_BN (HIV drug resistance = 1, no HIV drug resistance = 0; missing if no data are available).
5. List a binary variable indicating whether a participant had detectable resistance to TDF and XTC in a column labelled TDF_AND_XTC_HIVDR_BN (HIV drug resistance = 1, no HIV drug resistance = 0; missing if no data are available).
6. Save the data in a spreadsheet with the file name PrEP_HIVDR_DATA.xlsx.

In Table A3:

- Participant ZAF-PREP-2020-ABC-0001 has detectable resistance to TDF and XTC.
- Participant ZAF-PREP-2020-ABC-0002 has no detectable resistance to TDF or XTC.
- Participant ZAF-PREP-2020-ABC-0003 has no detectable resistance to XTC and no detectable resistance to TDF.
- Participant ZAF-PREP-2020-ZAB-0004 has no HIV drug resistance data available (unsuccessful genotype).

Table A3. Example of HIV drug resistance data

SID	XTC_HIVDR_BN	TDF_HIVDR_BN	TDF_OR_XTC_HIVDR_BN	TDF_AND_XTC_HIVDR_BN
ZAF-PREP-2020-ABC-0001	1	1	1	1
ZAF-PREP-2020-ABC-0002	0	0	0	0
ZAF-PREP-2020-ABC-0003	1	0	1	0
ZAF-PREP-2020-ABC-0004	1	0	1	0
ZAF-PREP-2020-BCD-0001	0	0	0	0
…				
ZAF-PREP-2020-ZAB-0003	0	0	0	0
ZAF-PREP-2020-ZAB-0004				

[2] For this survey, the Stanford HIVdb is used to classify HIV drug resistance. This algorithm classifies HIV drug resistance into five categories: susceptible, potential low-level, low-level, intermediate or high-level drug resistance. Sequences classified as being susceptible or having potential low-level resistance are considered susceptible (no resistance). Sequences classified as having low-, intermediate- or high-level resistance are classified as resistant.

[3] At the analysis stage, all variable names should be indicated with capital letters.

Step 3: import the data into Stata

1. Import the clinical and demographic data using the import data option (FILE/IMPORT/EXCEL SPREADSHEET).[4] Use the BROWSE button to identify the spreadsheet (PrEP_PT_DATA.xlsx). Select the option to import the first row as variable names. Change the variable case to upper to preserve variable names.
2. Save data as a .dta file using the save option (FILE/SAVE). In this example, we save the data as PrEP_PT_DATA.dta.
3. Import the HIV drug resistance data using the import data option (FILE/IMPORT/EXCEL SPREADSHEET). Use the BROWSE button to identify the spreadsheet (PrEP_HIVDR_DATA.xlsx). Select the option to import the first row as variable names. Change the variable case to upper to preserve variable names.
4. Save the data as a .dta file using the save option (FILE/SAVE). In this example, we save the data as PrEP_HIVDR_DATA.dta. Press YES to overwrite the data currently in memory.
5. Merge the two datasets using the merge option (DATA/COMBINE DATASETS/MERGE TWO DATASETS). Select the ONE-TO-ONE option. Select or type in SID as the key variable. Use the BROWSE button to select PrEP_PT_DATA.dta. Press OK.
6. Save the data as a .dta file using the save option (FILE/SAVE). In this example, we save the data as PrEP_DATA.dta.

Step 4: analyse the data

1. Calculate the prevalence of HIV drug resistance to TDF and/or XTC (STATISTICS/SUMMARIES, TABLES AND TESTS/SUMMARY AND DESCRIPTIVE STATISTICS/PROPORTIONS).
   a. In the MODEL tab, select XTC_HIVDR_BN, TDF_HIVDR_BN, TDF_OR_XTC_HIVDR_BN and TDF_AND_XTC_HIVDR_BN as the VARIABLES.
   b. In the WEIGHTS tab, select NONE.
   c. In the SE/CLUSTER tab, select CLUSTER in the STANDARD ERROR TYPE, and select SITE_ID as CLUSTER VARIABLE. Press OK.
   d. In the REPORTING tab, select 95 as the CONFIDENCE LEVEL, and select LOGIT as the CONFIDENCE INTERVAL TYPE. Press OK.

[4] (Menu/Option/Sub-option) indicates using the drop-down menus to select an option.

. proportion XTC_HIVDR_BN TDF_HIVDR_BN TDF_OR_XTC_HIVDR_BN TDF_AND_XTC_HIVDR_BN, vce(cluster SITE_ID)

Proportion estimation
Number of observations = 108
Standard error adjusted for 56 clusters in SITE_ID

	Proportion	Robust standard error	Logit [95% confidence interval]	
XTC_HIVDR_BN				
0	0.6203704	0.0638503	0.486952	0.7377767
1	0.3796296	0.0638503	0.2622233	0.513048
TDF_HIVDR_BN				
0	0.8425926	0.0331571	0.7643436	0.8983158
1	0.1574074	0.0331571	0.1016842	0.2356564
TDF_OR_XTC_HIVDR_BN				
0	0.5925926	0.0625537	0.4639241	0.709703
1	0.4074074	0.0625537	0.290297	0.5360759
TDF_AND_XTC_HIVDR_BN				
0	0.8703704	0.031026	0.7946432	0.9209504
1	0.1296296	0.031026	0.0790496	0.2053568

2. Calculate the prevalence of HIV drug resistance to TDF and/or XTC disaggregated by demographic characteristics. In this example, the proportion of HIV drug resistance to TDF and XTC is disaggregated by gender (STATISTICS/ SUMMARIES, TABLES AND TESTS/SUMMARY AND DESCRIPTIVE STATISTICS/PROPORTIONS).

   a. In the MODEL tab, select TDF_AND_XTC_HIVDR_BN as the VARIABLE.

   b. In the IF/IN/OVER tab, select GENDER in the GROUP OVER SUBPOPULATIONS.

   c. In the WEIGHTS tab, select NONE.

   d. In the SE/CLUSTER tab, select CLUSTER as the STANDARD ERROR TYPE, and select SITE_ID as the CLUSTER VARIABLE. Press OK.

   e. In the REPORTING tab, select 95 as the CONFIDENCE LEVEL, and select LOGIT as the CONFIDENCE INTERVAL TYPE. Press OK.

. proportion TDF_AND_XTC_HIVDR_BN, over(GENDER) vce(cluster SITE_ID)

Proportion estimation
Number of observations = 108
_prop_1: TDF_AND_XTC_HIVDR_BN = 0 _prop_2: TDF_AND_XTC_HIVDR_BN = 1
0: GENDER = 0 1: GENDER = 1
Standard error adjusted for 56 clusters in SITE_ID

	Proportion	Robust standard error	Logit [95% confidence interval]	
_prop_1				
0	0.9090909	0.0498809	0.7489513	0.9710313
1	0.8533333	0.0343196	0.7705549	0.9097453
_prop_2				
0	0.0909091	0.0498809	0.0289687	0.2510487
1	0.1466667	0.0343196	0.0902547	0.2294451

ANNEX 3. GENERIC BUDGETS

The tables below provide generic estimated budgets to assess the prevalence of HIV drug resistance among PrEP users diagnosed with HIV for countries using survey methods (Table A4) described in this document and for countries performing HIV drug resistance testing as part of routine monitoring and individual patient management (Table A5). All figures should be adapted to reflect the local context and costs. The cost of HIVDR test can vary from laboratory to laboratory (ranging from 50 to 300 US dollars per test). To develop a more realistic budget, countries are therefore encouraged to contact the laboratory they are willing to work with to obtain a quotation and adjust the budget accordingly in the planning phase. All costs are given in US dollars.

Table A4. Estimated budget for HIV drug resistance survey among PrEP users diagnosed with HIV

Number of regions: 40
Expected number of PrEP users diagnosed with HIV: 100

Protocol development and training					
	Number of personnel per region	**Transport costs**	**Per diem cost**	**Number of nights**	**Total**
Training of regional personnel (one-day training)	1	200.00	150.00	1	14 000.00
Production of: a) protocol and b) training and implementation materials					10 000.00
				Subtotal	**24 000.00**
Survey coordination					
		Number of personnel	**Cost per person per month**	**Number of months**	**Total**
Regional staff incentive		40	50.00	12	24 000.00
National coordination and data management		1	1 000.00	14	14 000.00
				Subtotal	**38 000.00**
Laboratory					
				Cost per unit	**Total**
Blood collection				3.00	300.00
Dried blood spot preparation and storage				5.00	500.00
Genotyping				150.00[a]	15 000.00
Laboratory labour cost for genotyping				5.00	500.00
Shipment of specimens (US$ 100 per month for national shipping, US$ 250 for one international shipment)					1 450.00
				Subtotal	**17 750.00**
Technical support					
					Total
Consultant (US$ 500 daily fee, US$ 200 per diem, 10 days) and flight					10 000.00
Support for analysis and interpretation					5 000.00
				Subtotal	**15 000.00**
Report production, printing and distribution					
					Total
Report production and distribution					10 000.00
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)					10 500.00
				Subtotal	**20 500.00**
				Total	**115 250.00**

[a] The cost of HIVDR test should be adapted based on the laboratory quotation (ranging from USD 50 to 300 US dollars per test).

Table A5. Estimated budget for routine monitoring of HIV drug resistance among PrEP users diagnosed with HIV[a]

Number of regions: 40
Expected number of PrEP users diagnosed with HIV: 100

Training					
	Number of personnel per region	Transport costs	Per diem cost	Number of nights	Total
Training of regional personnel (one-day training)	1	200.00	150.00	1	14 000.00
Production of training and implementation materials					5 000.00
				Subtotal	**19 000.00**
Laboratory					
				Cost per unit	Total
Blood collection				3.00	300.00
Dried blood spot preparation and storage				5.00	500.00
Genotyping				150.00[b]	15 000.00
Laboratory labour cost for genotyping				5.00	500.00
Shipment of specimens (US$ 100 per month for national shipping)					1 200.00
				Subtotal	**17 500.00**
Technical support					
					Total
Support for analysis and interpretation					5 000.00
				Subtotal	**5 000.00**
Report production, printing and distribution					
					Total
Report production and distribution					10 000.00
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)					10 500.00
				Subtotal	**20 500.00**
				Total	**62 000.00**

[a] Countries performing HIV drug resistance testing for clinical management of PrEP users diagnosed with HIV can analyse the HIV drug resistance genotypes annually at the national level and estimate the prevalence of HIV drug resistance.
[b] The cost of HIVDR test should be adapted based on the laboratory quotation (ranging from USD 50 to 300 US dollars per test).

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