APPROPRIATE MEDICINES: OPTIONS FOR PRE-EXPOSURE PROPHYLAXIS

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Ioannis Hodges-Mameletzis (WHO) prepared the meeting report. He also served as rapporteur during the meeting along with Praneel Kumar (WHO).

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ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
3TC-TP	lamivudine−triphosphate
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
CDC	United States Centers for Disease Control and Prevention
dATP	deoxyadenosine triphosphate
dCTP	deoxycytidine triphosphate
DXA	dual energy x ray absorptiometry
EC_{90}	drug concentration associated with a 90% reduction in HIV acquisition
FDA	United States Food and Drug Administration
FTC	emtricitabine
FTC-TP	emtricitabine−triphosphate
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
LBW	low birth weight
LPV/r	lopinavir/ritonavir
MR	meta-regression
NMRA	national medicines regulatory authority
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PEP	post-exposure prophylaxis
PEPFAR	United States President's Emergency Plan for AIDS Relief
PK	pharmacokinetics
PMTCT	prevention of mother-to-child HIV transmission
PrEP	pre-exposure prophylaxis
PTD	preterm delivery
RCT	randomized clinical trial
RR	relative risk or risk ratio
RF	rectal fluid
sdNVP	single-dose nevirapine
SHIV	simian/human immunodeficiency virus
SIV	simian immunodeficiency virus
SRA	stringent regulatory authority
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	TFV-diphosphate
UNAIDS	Joint United Nations Programme on HIV/AIDS
VF	vaginal fluid
VPTD	very preterm delivery
WHO	World Health Organization

DEFINITION OF KEY TERMS

Age brackets: The following definitions for adults, adolescents, children and infants are used to ensure consistency within these guidelines. Other agencies may use different definitions.

- An **adult** is a person older than 18 years.
- An **adolescent** is a person 10–19 years old inclusive.
- A **child** is a person younger than 10 years old.
- An **infant** is a child younger than 1 year old.

AUC (area-under-the-curve) refers to the systemic exposure to a drug following dosing by a route of administration, used as a measure of the quantity of drug in the body.

Breakthrough infection: refers to HIV infection occurring in an individual who is taking pre-exposure prophylaxis (PrEP). Note: Most infections occurring in persons who have been prescribed PrEP appear to be related to lack of adherence to the PrEP regimen and are not explicitly breakthrough infections.

Combination HIV prevention: a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

Direct evidence: evidence on the safety and/or efficacy of (pre-exposure prophylaxis) drugs generated from studies whose aim is to directly assess these outcomes of interest. This includes randomized clinical trials and meta-analyses of studies. For example, the United States Centers for Disease Control and Prevention study of TDF provides direct evidence of the safety of TDF alone in men who have sex with men and indirect evidence on efficacy (see "Indirect evidence" below).

Elimination half-life: the amount of time it takes for a drug concentration in the blood to decline by half. The half-life can be a critical pharmacokinetic parameter for how often a drug should be dosed (for example, once a day or twice a day).

HIV: human immunodeficiency virus, of which there are two types: **HIV-1** and **HIV-2. HIV-1** is responsible for the majority of HIV infections globally.

Indirect evidence: evidence on the safety and/or efficacy of (pre-exposure prophylaxis) drugs inferred from studies whose primary aim is not to directly assess these outcomes of interest.

Interchangeability: refers to when a biological product, in addition to meeting the bio similarity standard, has the same clinical result as the reference product in any given patient.

Public health approach: addresses the health needs or collective health status of a population, rather than focusing primarily on individual case management. This approach aims to ensure the widest possible access to high quality services at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings. For HIV key elements of a public health approach include simplified treatment algorithms; large-scale use of fixed-dose combinations for first-line treatment for adults, adolescents and children; care and treatment provided free at the point of service delivery; decentralization and integration of services, including task shifting; and simplified approaches to clinical monitoring.

Pre-exposure prophylaxis (PrEP): oral pre-exposure prophylaxis for HIV infection is the use of antiretroviral drugs by HIV-uninfected people before potential exposure to block the acquisition of HIV.

Serodiscordant couple: a couple in which one partner is living with HIV and the other is HIV-negative. A couple refers to two people in an ongoing sexual relationship; each of these persons is referred to as a partner in the relationship. How individuals define their relationships will vary according to their cultural and social context.

Substantial risk of HIV infection: defined, based on the WHO 2015 recommendation on PrEP, by an incidence of HIV infection in the absence of PrEP that is sufficiently high (>3% incidence) to make offering PrEP potentially cost-saving (or cost-effective). Offering PrEP to people at substantial risk of HIV infection maximizes the benefits relative to the risks and costs. People at substantial risk of HIV infection are present in most countries, including some (but not all) people identified within key and vulnerable populations.

Technical Group: the group of scientific, technical and programmatic experts convened by WHO and UNAIDS for this review of PrEP drug regimens, whose contribution, insight and expertise contributed to decision-making, including decisions on this technical report. The term “technical group” does not include observers at the March 2016 meeting in Geneva, who had a very limited role observing specific discussion points.

EXECUTIVE SUMMARY

In March 2016, WHO and UNAIDS jointly convened a technical group of experts in antiretroviral (ARV) pharmacology and HIV pre-exposure prophylaxis (PrEP) clinical research to provide clarifications related to three specific implementation concerns for countries regarding the appropriate use of PrEP drug regimens:

(1) possible use of lamivudine (3TC) as an alternative to emtricitabine (FTC) for oral PrEP containing tenofovir disoproxil fumarate (TDF),
(2) possible use of TDF alone for oral PrEP, and
(3) safety of PrEP during pregnancy and breastfeeding, in terms of both maternal and fetal/newborn outcomes.

The technical consultation reviewed a spectrum of evidence, including animal studies, human pharmacology and randomized clinical trials (RCTs) on PrEP as well as indirect evidence from HIV treatment studies.

In 2015 WHO recommended that oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches. This recommendation was based on a systematic review and meta-analysis of the clinical trial evidence available at the time. All these trials investigated either TDF/FTC and/or TDF alone. Since the release of that recommendation, countries and civil society have requested that WHO provide additional clarification on the safety and efficacy of PrEP drugs, including the potential role of TDF/3TC. Country ownership is a guiding principle for WHO, for the uptake of new recommendations. WHO recognizes that countries face many practical considerations with regards to PrEP implementation, including cost and feasibility.

This report presents direct and indirect evidence for each of the three regimens (TDF alone, TDF/FTC, TDF/3TC), which can be considered by countries as they look towards adopting WHO guidelines on PrEP and introducing PrEP as a service to individuals at substantial risk of HIV acquisition. Most clinical trial evidence on the safety and efficacy of oral PrEP has been generated by studies that examined TDF/FTC in men who have sex with men, and heterosexual populations. Two major RCTs (Partners PrEP and Bangkok Tenofovir Study) looked at the efficacy of TDF alone in heterosexual and drug-using populations. There are some limited data for TDF alone in men who have sex with men, from one small safety study. No clinical trials have been conducted to assess the safety and efficacy of TDF/3TC for PrEP in any of the population groups, although there have been two clinical studies on TDF/3TC for prevention of mother-to-child transmission (PMTCT), which provide indirect evidence for the use of TDF/3TC and serve as proof of principle. The expert group suggested that off-label use of TDF/3TC could be appropriate in countries where TDF/FTC is not available or accessible.