# Pharmacokinetics and Pharmacodynamics
# A primer for HIV prevention advocates

*Pharmacokinetic (PK) and pharmacodynamic (PD) research is a central aspect of the search for ARV-based prevention including oral PrEP and topical microbicides. As advocates follow and influence the ARV-based research agenda, it's useful to understand some of the basic terms, aims and objectives of PK and PD studies.*

## Defining the terms

**Pharmacokinetics (PK)** is the study of *what happens to a drug* when it is taken into the body. Pharmacokinetic studies explore:

- Absorption (the process by which the drug enters the blood stream);
- Distribution (the process by which the drug moves throughout the body, including into specific tissues like vaginal and rectal tissue for example);
- Metabolism (the process by which the drug is broken down into various components or "metabolites"); and
- Excretion (the elimination of the drug and its metabolites from the body).

**Pharmacodynamics (PD)** is the study of *what happens to the body and/or microorganisms or parasites within the body* when a drug is taken. Pharmacodynamic studies look at the mechanisms of drug action and the relationship between drug concentration and drug effect.

## How do PK and PD relate to ARV-based prevention research like PrEP and microbicides?

*Get the right amount of the right product to the right place at the right time.* This is the guiding principle for ARV-based prevention in HIV-negative people. Pharmacokinetic and pharmacodynamic studies help define these parameters: What is the right amount of drug? How long does that drug need to be present in the right place? How soon before and/or after potential HIV exposure does the drug need to be present to reduce risk of infection?

Simply put, PK studies provide information about how the drug moves around, accumulates in, and leaves the body. PD studies provide information on how much drug is needed in a given place to provide protection.

For example, if you take an antimalarial tablet to treat malaria, a PK study would tell you how much time elapsed between when you swallowed the antimalarial and when it was detected in the blood. PK studies would also tell you how the concentrations of antimalarial changed in your blood over time. A PD study would tell you how much antimalarial needed to be detected in your blood to be sure that you effectively treated your illness.

Here is another example, this one tied to prevention research. PD studies help define the goal—e.g., vaginal tissue concentrations at or above X to achieve protection. PK studies point to how to achieve this goal—e.g., how long after taking a pill orally will a woman have vaginal tissue concentrations of X percent for drug Y; how long will these levels last; and so on.

*Pharmacokinetic studies related to ARV-based HIV prevention provide information on*:

- How long it takes for the drug in an oral pill (e.g., TDF/FTC) to be detected in the genital tract;
- How long it takes the drug concentration to reach a "steady state" (steady state is a term which means that the drug has been given long enough so that the plasma concentrations will remain the same with each subsequent dose);
- How long the drug is detected in blood or tissue and how concentrations of the drug change over time;

- How concentrations of drug in the blood relate to concentrations detected in genital tract tissue since these are different compartments of the body;
- How absorption, metabolism and excretion are affected by other drugs or food;
- How "forgiving" a regimen is—i.e., can a person miss a dose and still maintain the right level of drug in the right place?

*Pharmacodynamic studies related to ARV-based HIV prevention provide information on*:

- The concentration of a drug needed to inhibit HIV replication or block infection in cells

## What do we know about PK and PD for ARV-based prevention?

There are a range of PK studies related to PrEP and microbicides that have looked at the relationship between blood and tissue concentrations of different antiretroviral drugs. These studies can tell us things like: how much drug is detectable in the blood, and for how long, after a person applies a topical formulation of 1% tenofovir gel; if there is a blood level of x percent, is the level detected in the vagina or rectal tissue higher or lower; how much drug is delivered to the genital tract following oral use, versus topical application.

Information from research to-date includes:

- For 1% tenofovir gel – levels of tenofovir in vaginal tissue are about 1,000-times those detected in plasma; levels of tenofovir inside rectal cells (study in men and women) shown to be 100-times higher after single rectal gel dose as compared to single oral dose
- For oral TDF – levels in the vaginal tissue are similar to those in the plasma; levels in rectal tissue are 100-times those of plasma.
- For oral FTC – the levels of FTC in the vagina and rectum is about 10 and 5 times the plasma level, respectively

## What do we still need to learn?

- What is the threshold drug level in vaginal or rectal tissue for reducing risk of HIV infection?
- Is there a blood or a mucosal fluid level that can be reliably used as an indicator of protective drug levels in genital tract tissues?

## Special considerations for TDF and TDF/FTC

- TDF and FTC are processed within the body's cells and the intracellular concentration of these drugs is a central determinant of both HIV prevention and toxicity—however, measuring intracellular concentrations is more complex than looking at blood levels. Researchers working on PK and PD studies related to current PrEP drugs are also interested in the relationship between intra- and extracellular concentrations, which will allow us to identify surrogate markers for protection.
- Drug-specific toxicities including potential renal and bone changes are related to concentrations of the drug in blood and tissues. PK and PD studies are helping researchers add detail to the risk-benefit balance of using TDF and TDF/FTC in HIV-negative people.

*Please note that this document is a work in progress. Send any questions or comments to* avac@avac.org.