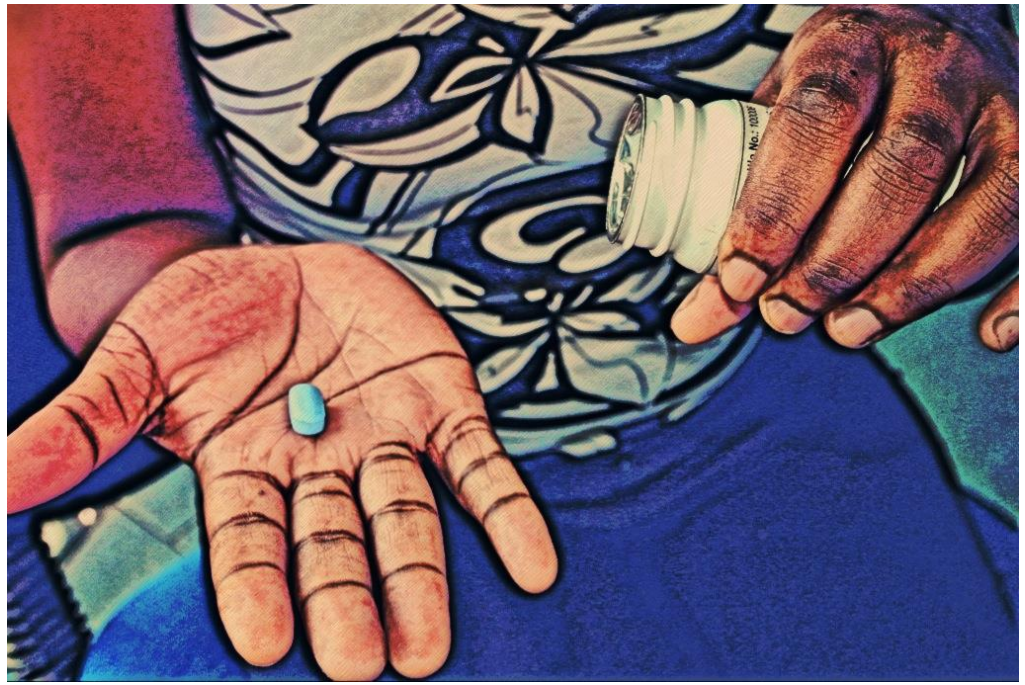

Pre-Exposure Prophylaxis (PrEP) and HIV Drug Resistance

Training materials for healthcare workers

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Training Modules

Module	Training Topic	Slide Number
I	HIV and drug resistance	3
II	Risk of drug resistance with PrEP	11
III	Drug resistance testing among PrEP seroconverters	17
IV	Dried blood spot collection steps with venipuncture	22
V	Interpreting drug resistance test results	35
VI	Counseling PrEP clients about drug resistance	49

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Module I:
HIV and Drug Resistance

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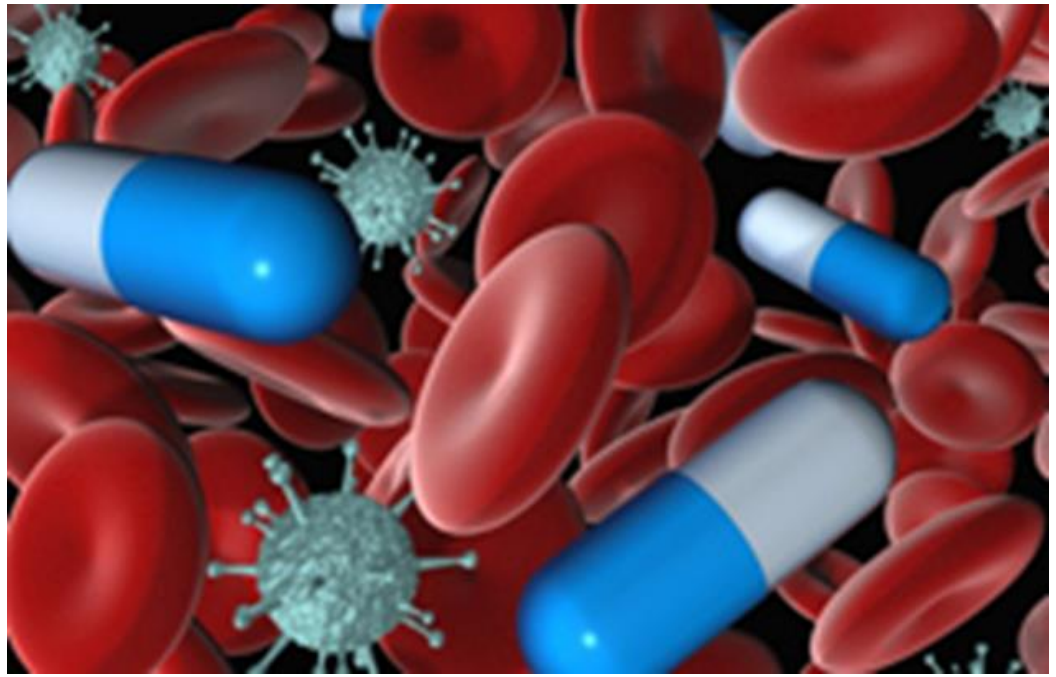
How Do ARVs Work?

- When someone becomes infected with HIV, the virus begins to make copies of itself inside the body
- Antiretrovirals (ARVs) are drugs that stop the virus from making copies of itself
- A combination of 3 ARVs is usually needed to stop the virus from making copies



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What Are Tenofovir And Truvada?

- Tenofovir (1 drug) or Truvada (tenofovir + emtricitabine = 2 drugs in one pill) are currently being used as PrEP medications
- Tenofovir and Truvada are also a part of the commonly used 3-drug ARV regimen to treat HIV
- Tenofovir and Truvada alone:
  - effectively prevent HIV infection if used correctly
  - are not effective at treating HIV; full 3-drug ARV regimen is required to treat

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What Happens When HIV Mutates?

- Sometimes, the genetic material in the virus changes; these changes are called mutations
- The mutated virus begins to make more and more copies of itself inside the person's body
- ARVs work best to treat what is called the "wild-type" (or non-mutated) virus
- Because ARVs are less effective at stopping mutated virus from making the copies of itself, the proportion of mutated virus grows, leading to treatment failure
  - this is called "acquired drug resistance"

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What Is HIV Drug Resistance?

The ability of HIV to continue making copies of itself in the presence of ARVs is called HIV drug resistance

What does this mean?

- The resistance will be to specific HIV drugs (not all types of ARVs)
- These specific drugs will not be able to stop all of the HIV viruses from making copies
- It often happens due to problems with adherence
- A different combination of 3 drugs may be needed to treat HIV
- If PrEP users develop resistance, they may have fewer choices of the ARV drugs that they can use for treatment (but they will still have options)

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Acquired Drug Resistance: Impact of Adherence

- Before a person with HIV starts ARV therapy (ART), they may have mostly “wild” type virus
- Once they start ART, the amount of virus in their body decreases
- If the person does not take their ARVs regularly, the virus in their body can mutate and become resistant to some ARVs
- If the drug resistant virus continues to grow, the current ARV regimen will no longer be effective

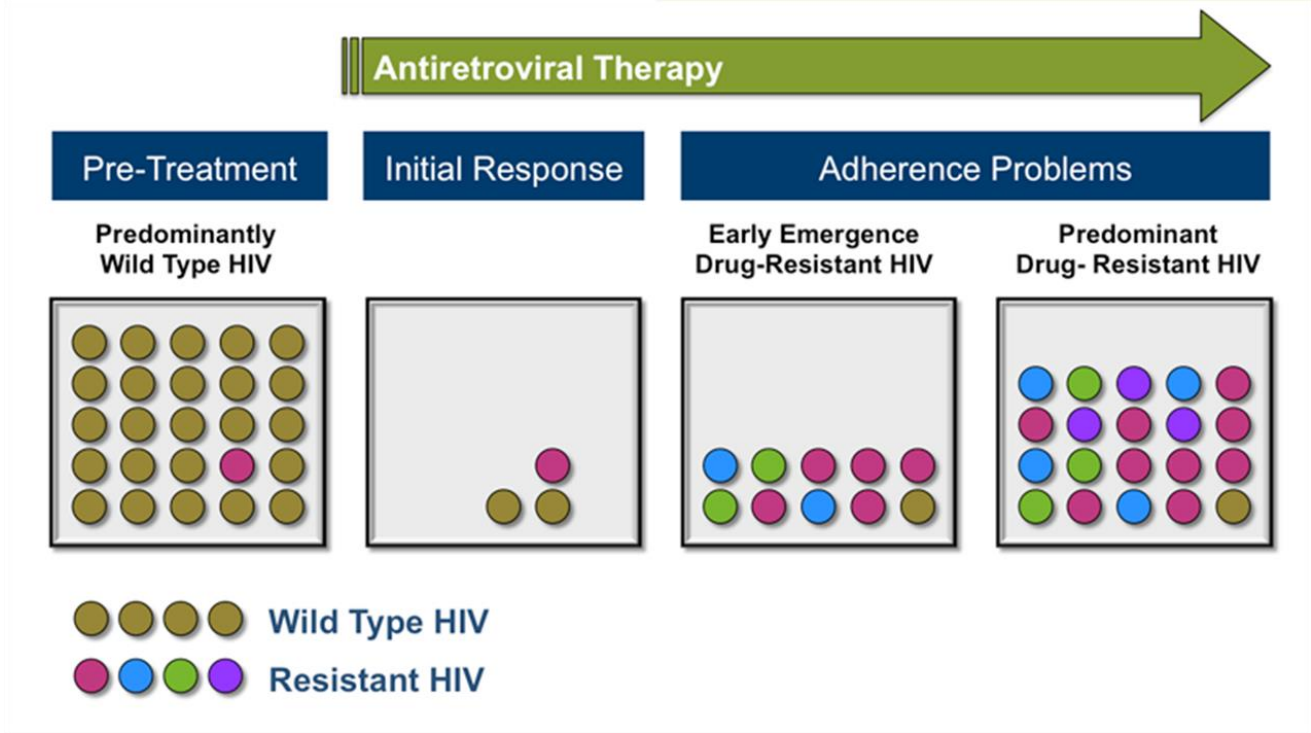

*Figure from www.hivwebstudy.org

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Are There Other Ways To Get Drug Resistant Virus?

The person can get HIV from someone whose virus already mutated and became resistant to one or more ARVs. This is called "transmitted drug resistance."

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Why Is HIV Drug Resistance A Concern With PrEP?

- Tenofovir and Truvada that are used for PrEP are also used in the “first-line” ARV treatment regimen — that is providers’ first choice of ARV drugs for treating HIV (commonly two NRTIs and a NNRTI).
- If an HIV-positive client develops resistance to tenofovir or Truvada, the provider has to:
  - find another first-line combination of ARVs that may be effective against the mutated virus OR
  - switch to a second-line regimen (commonly 2 NRTIs and a ritonavir-boosted PI)

It is important to reassure clients with resistant virus that there are still treatment options

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Module II:

Risk of Drug Resistance with PrEP

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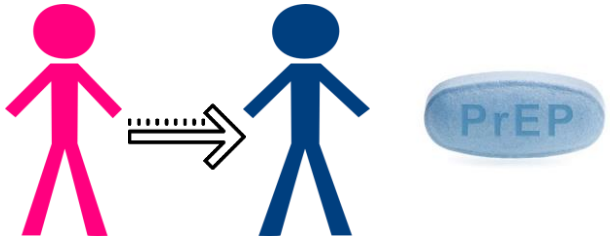
Drug Resistance Scenarios While On PrEP



- A person with HIV transmits drug resistant virus to HIV-negative partner who takes PrEP
- PrEP does not protect against the resistant virus
- PrEP user becomes infected with drug resistant HIV

- A person starts taking PrEP during acute HIV infection (before HIV test turns positive)
- Keeps taking PrEP until she/he gets a positive rapid test result
- HIV becomes drug resistant

- HIV-negative person takes PrEP
- Becomes infected with HIV, but keeps taking PrEP until she gets a positive rapid test result
- HIV becomes drug resistant

Less likely scenario (if PrEP is taken correctly)

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How Could Someone Take PrEP And Not Know They Were Infected?

1. By not getting tested for HIV, a PrEP user may not be aware that she/he has become infected

   - This is why it is important for PrEP users to get tested at the frequency recommended by the program

2. If a person was recently infected, the HIV test might not have detected the infection because of the window period of the test

   - This is why it is important for providers to assess for symptoms of acute HIV infection before providing PrEP

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PrEP and Drug Resistance: Scenario

A client is taking Truvada as PrEP. Because she was very busy for the last few months, she had a hard time remembering to take PrEP regularly and became infected with HIV.

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PrEP and Drug Resistance Scenario: Outcome #1

- She returns to the clinic for her routine HIV test within a month of her seroconversion. She learns right away that she is positive, so the PrEP provider informs her to stop using the PrEP medications.
- Because she stopped using the PrEP medication so quickly, the HIV virus did not become resistant to Truvada, as confirmed by her resistance test result.
- She is referred to the ART clinic and initiates first-line ARV treatment regimen, which includes Truvada.

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PrEP and Drug Resistance Scenario: Outcome #2

- She misses her next clinic visit and continues taking Truvada as PrEP inconsistently. She returns to the clinic for PrEP refill and an HIV test approximately 6 months after her seroconversion. Her resistance test results show high levels of resistance to Truvada.
- Because she continued using the PrEP medication after seroconversion, the virus became resistant to Truvada.
- She is referred to the ART clinic and initiates 2nd line treatment regimen, which doesn't include Truvada.

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Module III:

Drug Resistance Testing Among PrEP Seroconverters

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Drug Resistance Testing Rationale

For the individual client and provider:

- Drug resistance test results will guide treatment options, including recommendations to initiate 2nd line regimen if needed

For the policy maker:

- Analyzing drug resistance test results across all PrEP users who become HIV infected will provide important information about:
  - the effectiveness of the national PrEP program and whether additional client support may be needed for PrEP adherence and/or routine HIV testing
  - whether the frequency of HIV testing is adequate to capture seroconversions as quickly as possible
  - changes in overall rates of HIV drug resistance in the country

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Drug Resistance Testing In PrEP Seroconverters

What

- Blood for a dried blood spot (DBS) sample will be collected using venipuncture
- Client's demographic and adherence data will be collected using a brief data collection form

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Drug Resistance Testing In PrEP Seroconverters

When

- Blood for DBS will be collected upon identification of seroconversion
- If blood is not collected on the day of seroconversion confirmation, clients should be asked to return as soon as possible to complete the procedure
- Results will be returned to the clinic as soon as possible (time will vary based on location)

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Drug Resistance Testing In PrEP Seroconverters

Where

- DBS sample collection will be done at the clinic
- Drug resistance testing will be done at a centralized laboratory
- The centralized laboratory will not have any identifying information about the client
  - the sample and results will be tracked only by a barcode
- Results will be provided to the clinic that collected the sample in a form of the report listing identified mutations and affected drugs

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Module IV:

Dried Blood Spot Collection with Venipuncture

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Step 1: Obtain Informed Consent *[if required by program]*

- After confirming HIV infection with PrEP client, review consent for DBS collection.
- If consent is obtained, continue.

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Step 2: Complete Data Collection Form

Complete the data collection form to record client's demographic and adherence data.

Resistance Data Collection Form			
Date of Specimen Collection (DD/MM/YYYY) _____			**Client ID/Barcode Sticker _____**
Date of First Positive HIV Test (DD/MM/YYYY) _____			**Date of PrEP Initiation (DD/MM/YY) _____**
Sex	**Male _____ Female _____ Other _____**		
Date of Birth: _____			
Was the client adherent?	☐ **Yes, usually used medication as instructed**	☐ **Somewhat adherent, used medication but not daily**	☐ **No, mostly did not use medication as instructed**
Please insert the completed form, along with the dried DBS card, in the envelope for shipment			

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Step 3: Affix Barcode Labels

Remove barcode labeled stickers and affix stickers to:

- Two DBS cards
- Data collection form
- Client's medical file
- Blood collection tube

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Step 4: Wash Hands And Put On Gloves

- The clinician will wash his/her hands with soap and water, and then put on well-fitting gloves
  - non-sterile gloves are sufficient

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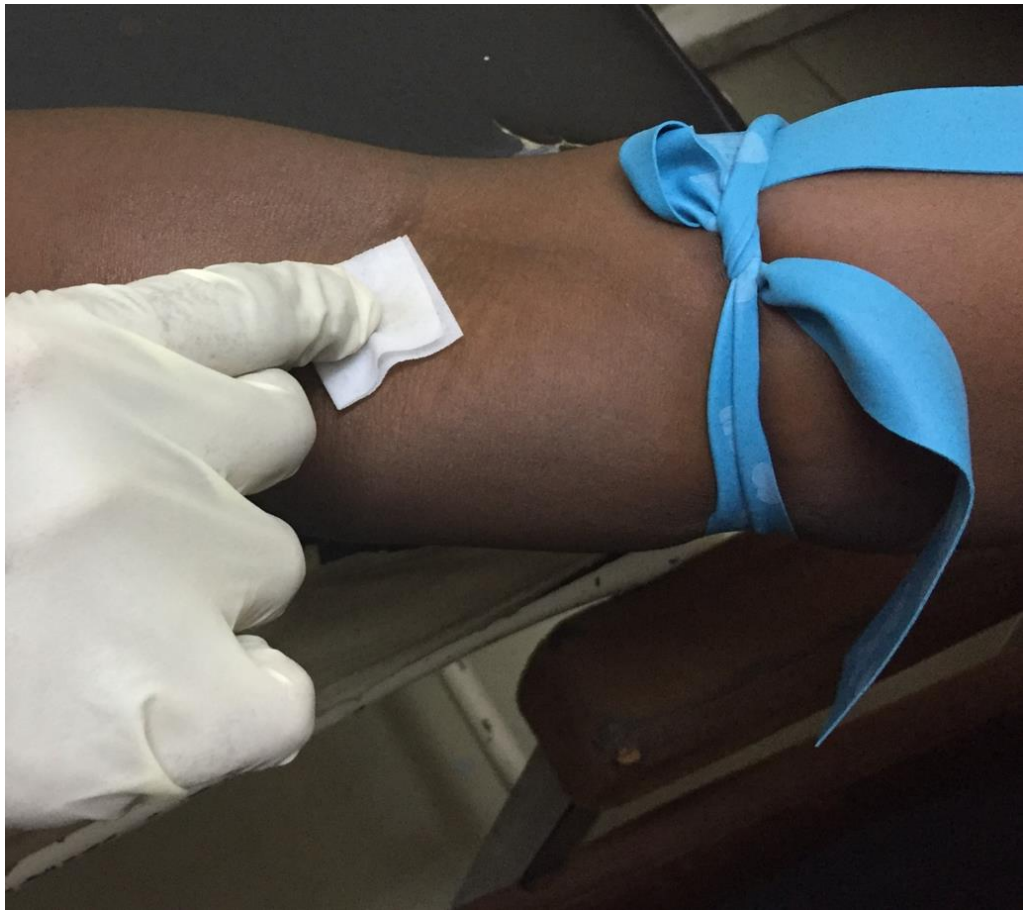
Step 5: Apply Tourniquet And Wipe Puncture Site



- Apply a tourniquet 3-4 inches (8-10 cm) above the puncture site
- Wipe the puncture site with the alcohol wipe. Allow the site to air dry for 30 seconds

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Step 6: Collect Blood

- Anchor the vein by placing a thumb BELOW the venipuncture site
- Guide the needle into the vein at a 30 degree angle and fill the connected EDTA blood collection tube
- Once done:
  - release tourniquet
  - withdraw needle
  - apply a gauze pad to site
  - apply Band-Aid as needed

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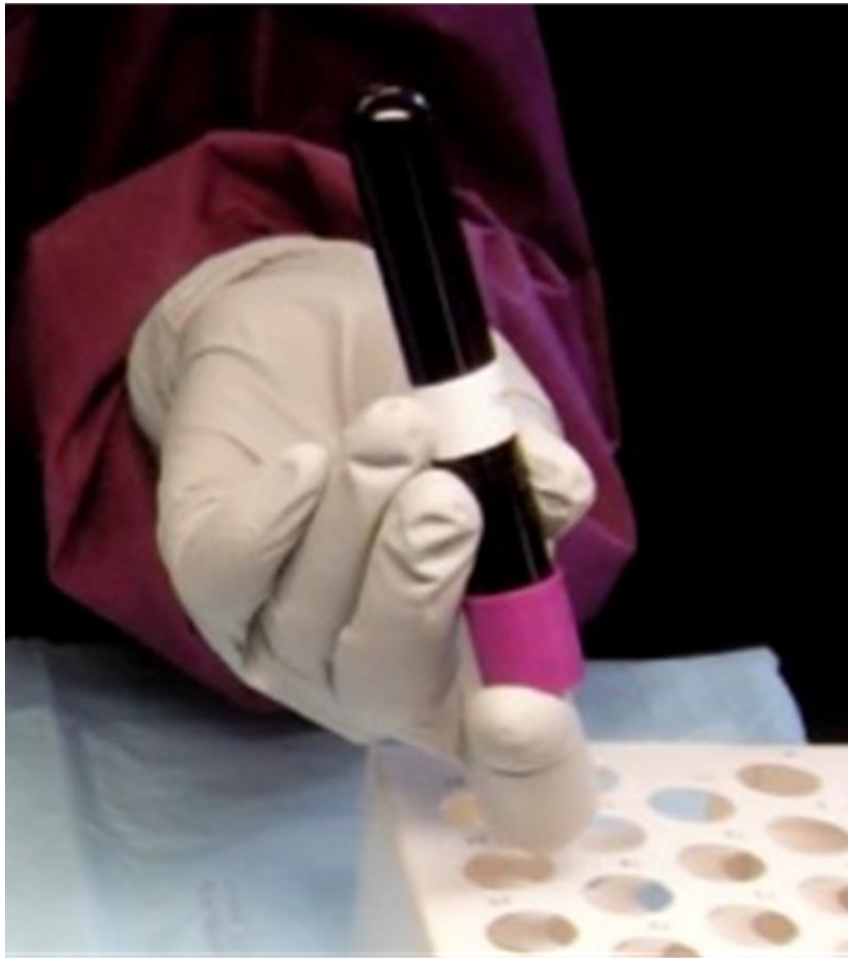
Step 7: Invert The Tube



- Gently invert the blood collection tube gently 2 to 4 times to mix anti-coagulant (EDTA) additive with the blood
- Then open the stopper carefully

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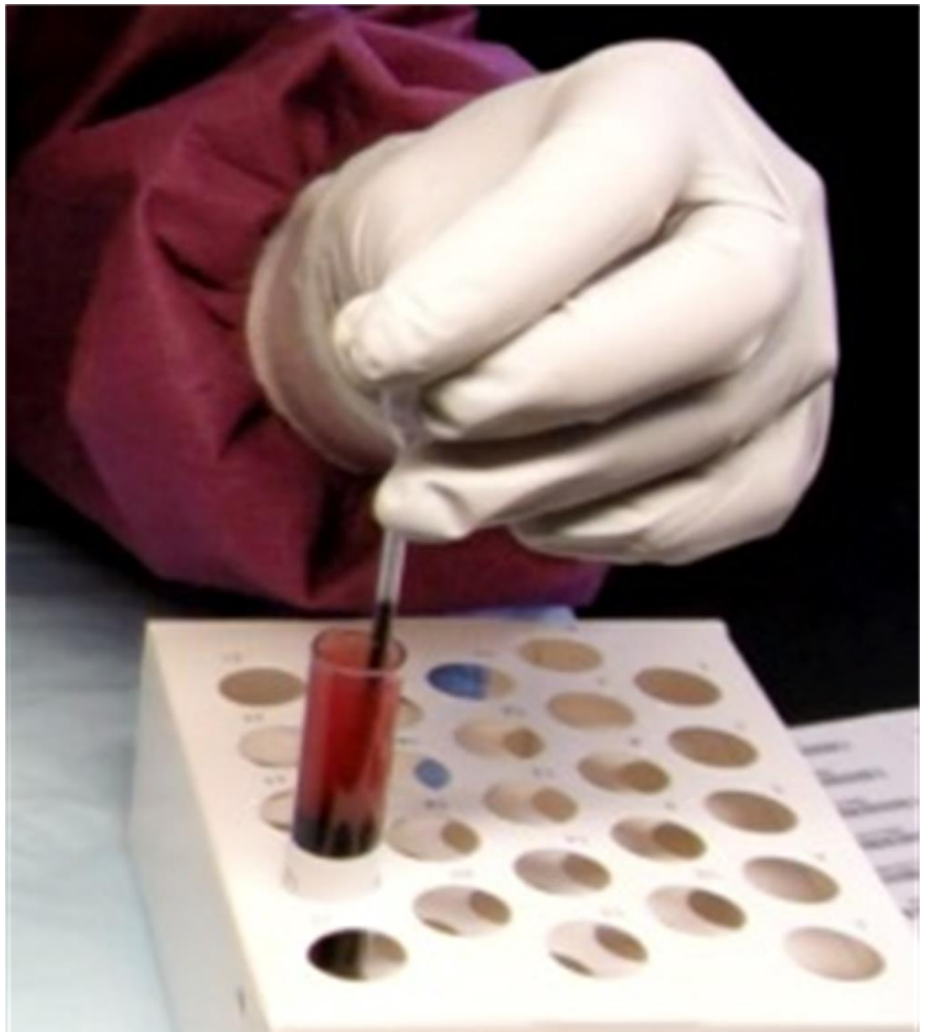
Step 8: Aspirate Blood



- Aspirate whole venous blood using a transfer pipette
  - avoid air bubbles
- It takes 1 to 2 drops of blood per circle (or 50µL–100 µL)

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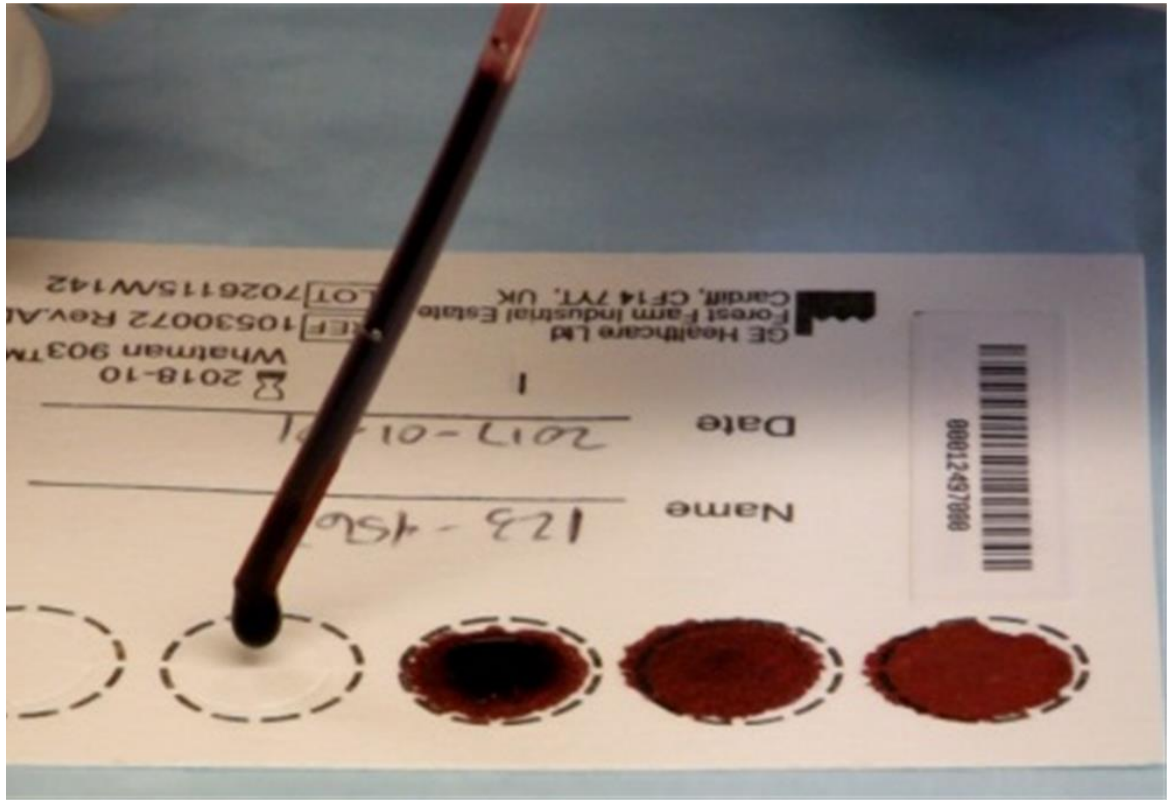
Step 9: Transfer Blood To Two DBS Cards

- Transfer 1-2 drops of the blood to the center of each circle without touching the filter paper directly with the tip of the pipette
- Fully saturate the entire circle
- Complete all five circles on each of the two DBS cards
- Avoid touching and smearing the blood spots



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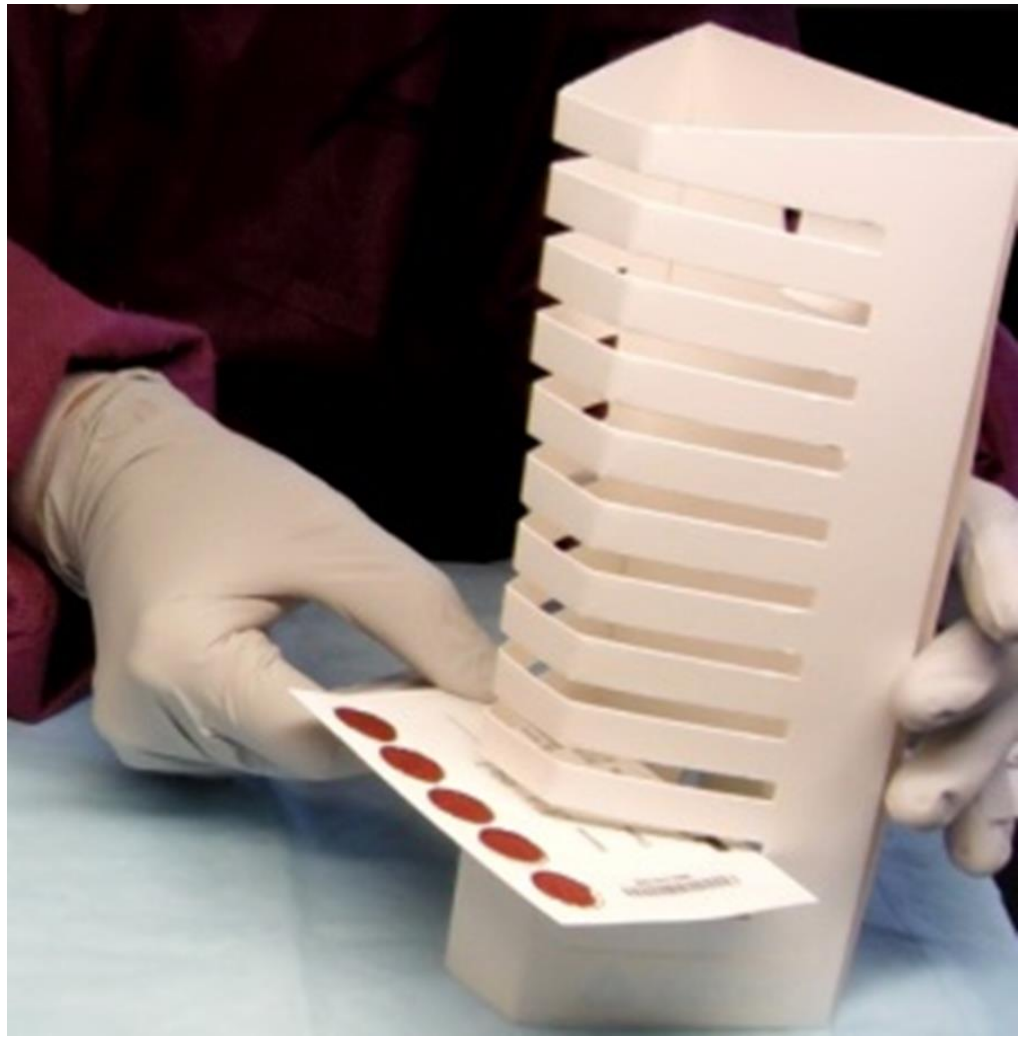
Step 10: Drying DBS Cards



- Do not stack or allow DBS to touch other surfaces during the drying process
- Keep away from direct sunlight
- Dry DBS cards, with the blood facing up, on the drying rack at room temperature for a minimum of 3 hours (preferably overnight)
- The blood color on the DBS cards will change from bright red to dark red as it dries

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Step 11: Packaging DBS Cards

- After the DBS cards dry, insert both into the sealable plastic bag with the desiccant pack(s) and humidity indicator
  - up to 5 desiccant packs may be needed, depending on environmental conditions
- Avoid using bags that are too big as the cards will shuffle inside the bag

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Step 12: Prepare For Shipment

- Place a label on the outside of the sealable plastic bag indicating bio-hazardous contents
- Put the sealable plastic bag and data collection form into a rip-resistant envelope and then into brown shipping envelop and seal for shipment.
- Mail the envelope as soon as possible, but within 3 days

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Module V:

Interpreting Drug Resistance Test Results

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Getting The Result Back From The Lab

- Drug resistance test results take on average 2 weeks, but the time it gets to the clinic may vary depending on setting
- By the time test results are available, the client may or may not have started ART
- Clinic staff will retrieve the result and confirm client identification using the barcode sticker
- The clinician or other trained staff will either:
  - counsel the client on his/her results and their implications for future treatment
  - forward the results to the client's ART provider

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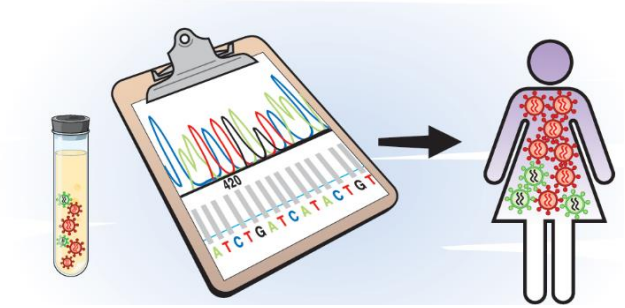
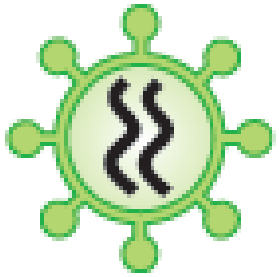
What Does a Drug Resistance Test Measure?





HIV

Drug resistant HIV

A drug resistance test identifies presence of ***HIV mutations*** that have been linked to resistance to ARVs

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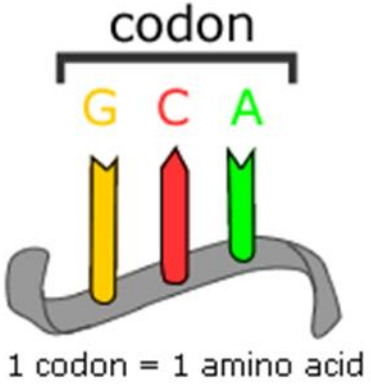
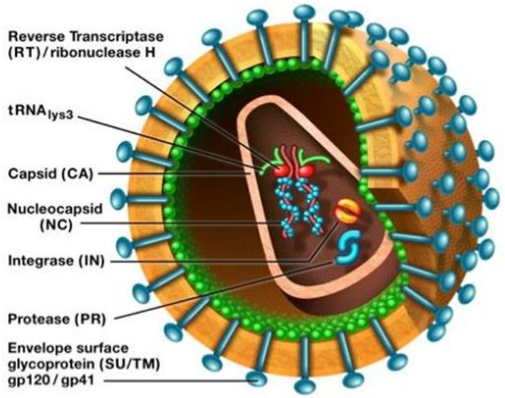
Understanding Terminology: Codon, RT and PR

- Codon: a sequence of three building blocks (nucleotides) that corresponds with a specific amino acid. A “chain” of codons makes up viral genetic code



- Reverse transcriptase (RT) and protease (PR): viral enzymes, in which genetic code is analyzed in order to detect mutations that are known to result in drug resistance.



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Understanding Terminology: Major vs. Minor Mutations

Major mutations:

- Commonly occur during virologic failure (when ART fails to adequately suppress a viral load)
- Located at structurally important parts of a viral protein
- Reduce susceptibility to one or more ARV

Minor mutations:

- Commonly occur in untreated patients as natural variants
- Are rare or emerge later, after other drug-resistance mutations occurred
- Have little or no effect on susceptibility to ARVs

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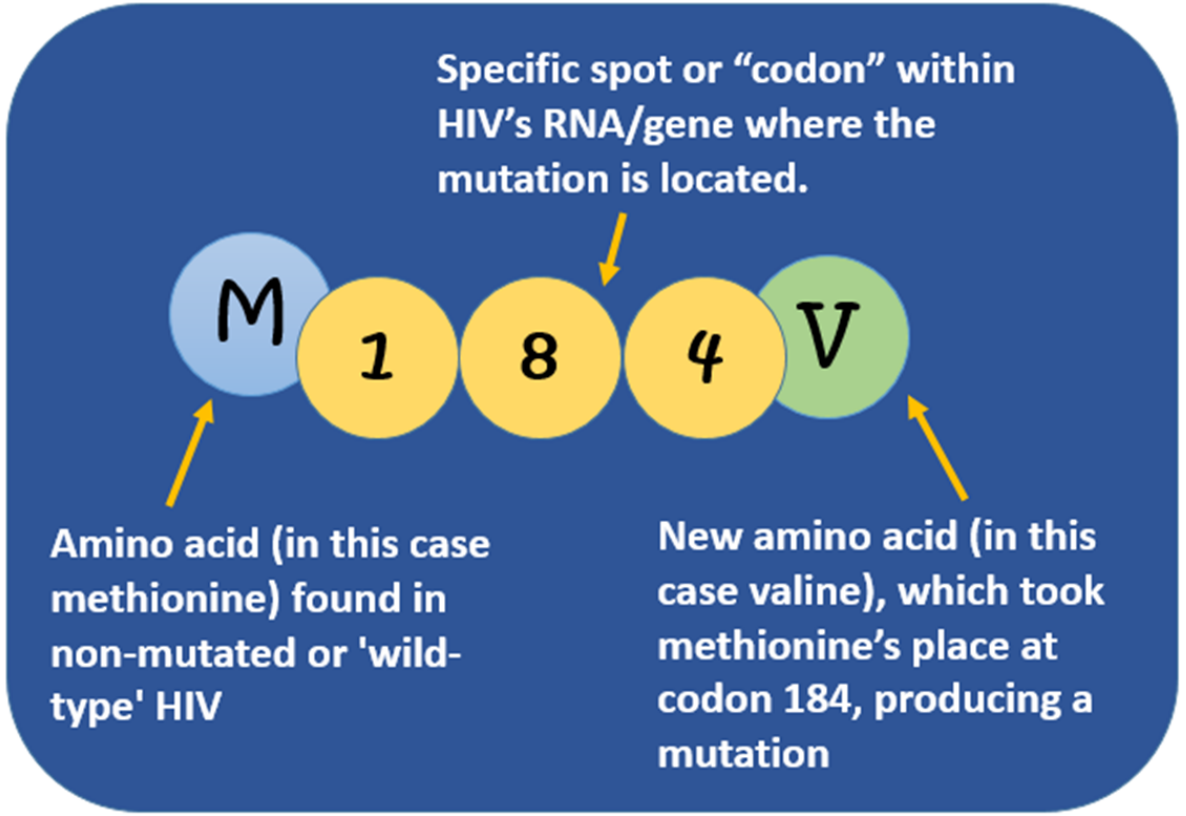
Understanding How To Read Mutations

- Scientists use a letter and number to describe HIV's genetic material
- The **NUMBER** shows where the mutation occurred.
- The **LETTER** shows how it changed.



M184V -- a mutation in the reverse transcriptase (RT) gene that causes resistance to 3TC (lamivudine)

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Why Is This Terminology Important?

HIV that has the mutation…	Makes this drug less effective
K103N	Nevirapine, Efavirenz
M184V	3TC, FTC
K65R	Tenofovir

- These letters and numbers will be on the client's drug resistance report
- The mutation pattern will:
  - —let the healthcare workers know which drugs the client is resistant to
  - —help the ART provider to decide which drugs to prescribe to the client to treat his/her HIV infection

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Can HIV Have More Than One Mutation?

YES

NO

HIV can be resistant to one drug or multiple drugs

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How To Interpret HIV Drug Resistance Results

- The results will indicate which ARVs have reduced effectiveness
- Each HIV drug has its own resistance result, which can be:

SUSCEPTIBLE

INTERMEDIATE RESISTANCE

HIGH LEVEL RESISTANCE

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What Do The Drug Resistance Results Mean?

SUSCEPTIBLE	There is no evidence of resistance to this ARV
INTERMEDIATE RESISTANCE	There is some evidence of resistance but it may not have been validated or clinically verified
HIGH LEVEL RESISTANCE	This ARV's effectiveness is significantly reduced

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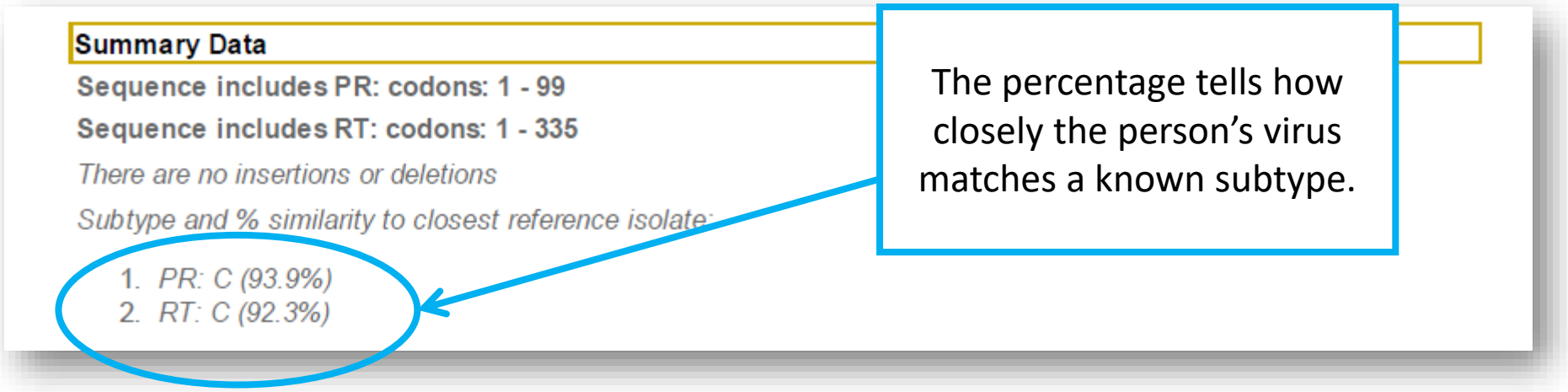
What Is In The Drug Resistance Report?



The Summary Data identifies the subtype.
This client is infected with **SUBTYPE C** HIV-1.

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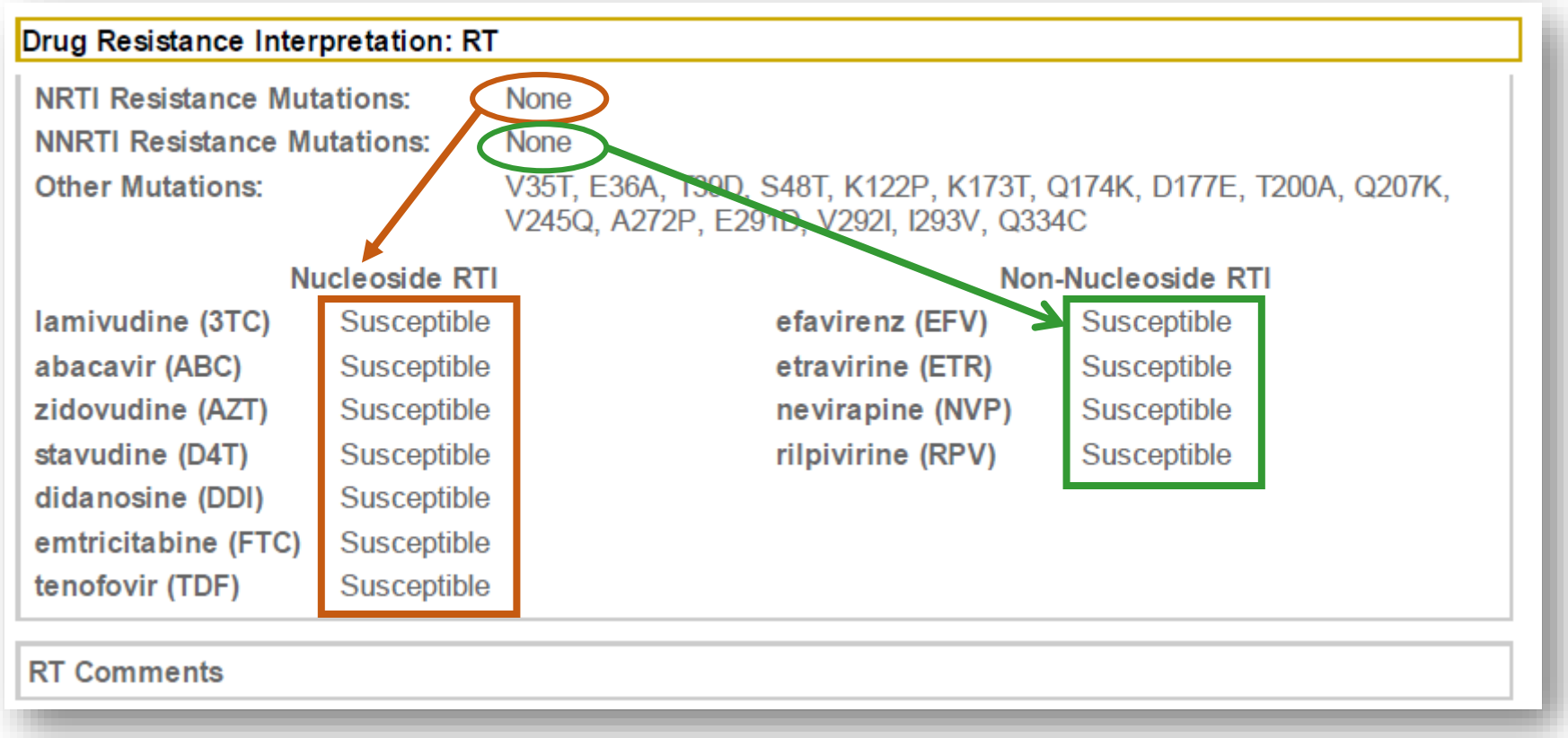
What Is In The Drug Resistance Report (continued)?



Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	None
Other Mutations:	V35T, E36A, T39D, S48T, K122P, K173T, Q174K, D177E, T200A, Q207K, V245Q, A272P, E291D, V292I, I293V, Q334C

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	efavirenz (EFV)	Susceptible
abacavir (ABC)	Susceptible	etravirine (ETR)	Susceptible
zidovudine (AZT)	Susceptible	nevirapine (NVP)	Susceptible
stavudine (D4T)	Susceptible	rilpivirine (RPV)	Susceptible
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

RT Comments

- RT mutations affect resistance to drugs in the **NRTI** and **NNRTI** class (first-line ART)
- The report shows this client does not have RT-based drug resistance and can be treated with the first-line ARV regimen.

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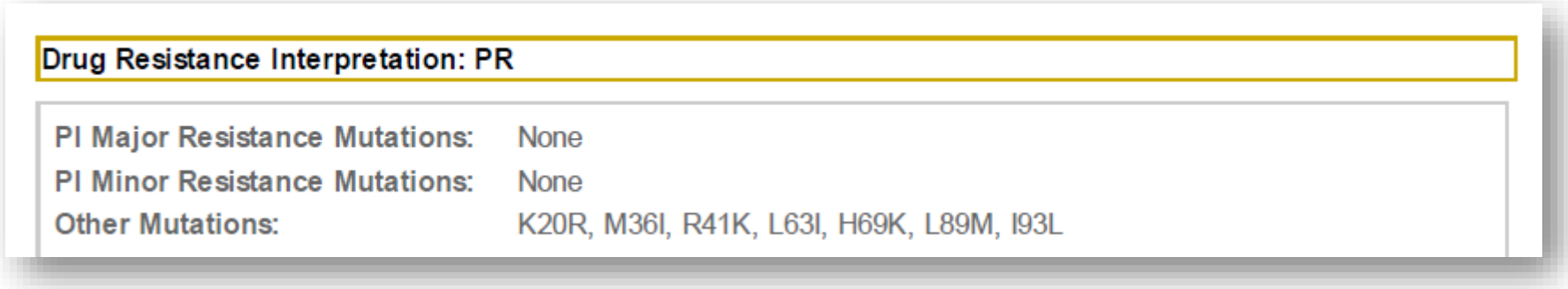
What Is In The Drug Resistance Report (continued)?



Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	None
PI Minor Resistance Mutations:	None
Other Mutations:	K20R, M36I, R41K, L63I, H69K, L89M, I93L

- Protease Inhibitors (PR) are usually part of the second-line ARV treatment regimen
- PR mutations may not be relevant as long as there are valid options for the first-line treatment regimens
- Knowing both, RT and PI mutations is important when making a decision if/when switching to a second-line ARV regimen is warranted

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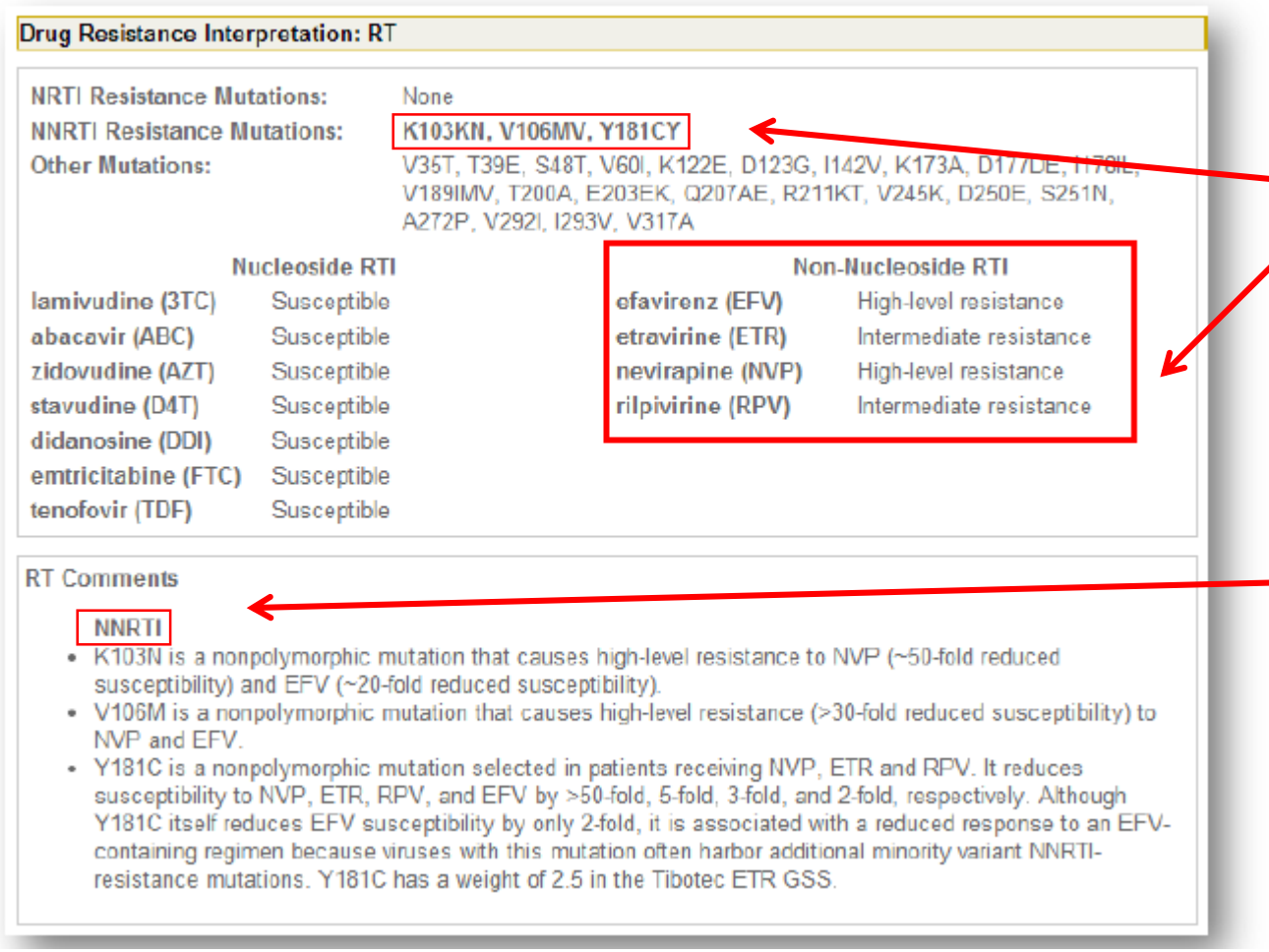
What If There Is Resistance Found?



Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	K103KN, V106MV, Y181CY
Other Mutations:	V35T, T39E, S48T, V60I, K122E, D123G, I142V, K173A, D177DE, I178IL, V189IMV, T200A, E203EK, Q207AE, R211KT, V245K, D250E, S251N, A272P, V292I, I293V, V317A

Nucleoside RTI	
lamivudine (3TC)	Susceptible
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Susceptible
emtricitabine (FTC)	Susceptible
tenofovir (TDF)	Susceptible

Non-Nucleoside RTI	
efavirenz (EFV)	High-level resistance
etravirine (ETR)	Intermediate resistance
nevirapine (NVP)	High-level resistance
rilpivirine (RPV)	Intermediate resistance

RT Comments

NNRTI

- K103N is a nonpolymorphic mutation that causes high-level resistance to NVP (~50-fold reduced susceptibility) and EFV (~20-fold reduced susceptibility).
- V106M is a nonpolymorphic mutation that causes high-level resistance (>30-fold reduced susceptibility) to NVP and EFV.
- Y181C is a nonpolymorphic mutation selected in patients receiving NVP, ETR and RPV. It reduces susceptibility to NVP, ETR, RPV, and EFV by >50-fold, 5-fold, 3-fold, and 2-fold, respectively. Although Y181C itself reduces EFV susceptibility by only 2-fold, it is associated with a reduced response to an EFV-containing regimen because viruses with this mutation often harbor additional minority variant NNRTI-resistance mutations. Y181C has a weight of 2.5 in the Tibotec ETR GSS.

The specific mutations causing the resistance and what drugs are affected will be shown.

The comments may help the doctor who is prescribing therapy to have more information about the specific kind of resistance.

Only the client's clinician can decide which ARVs the client should take

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Module VI:

Counseling PrEP Clients About Drug Resistance

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GLOBAL EVALUATION OF MICROBICIDE SENSITIVITY

Client Counseling

- Maintain respectful attitude and show acceptance
- Avoid:
  - being judgmental
  - arguing, confronting, and pressuring the client into action
- Employ good counseling skills, such as asking simple open-ended questions, using active listening, paraphrasing and reframing

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Client Counseling (continued)

- Provide counseling on the outcome of client's resistance test and explain:
  - —what test shows
  - —impact on treatment
  - —next steps

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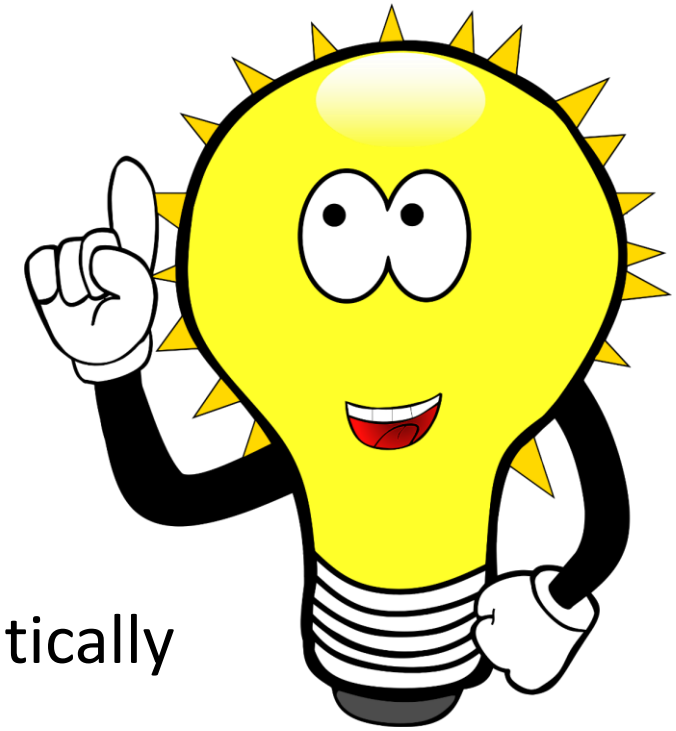
Tips for Resistance Counseling When Providing Results

- Resistance can be hard to understand. It is important to:
  - assess client's understanding
  - encourage client to ask questions
- If a client's test results show resistance, explain:
  - there are different degrees of resistance
  - resistance to a certain ARV does not automatically mean that one can no longer use it
  - even when a certain ARV is not effective due to resistance, other treatment regimens exist



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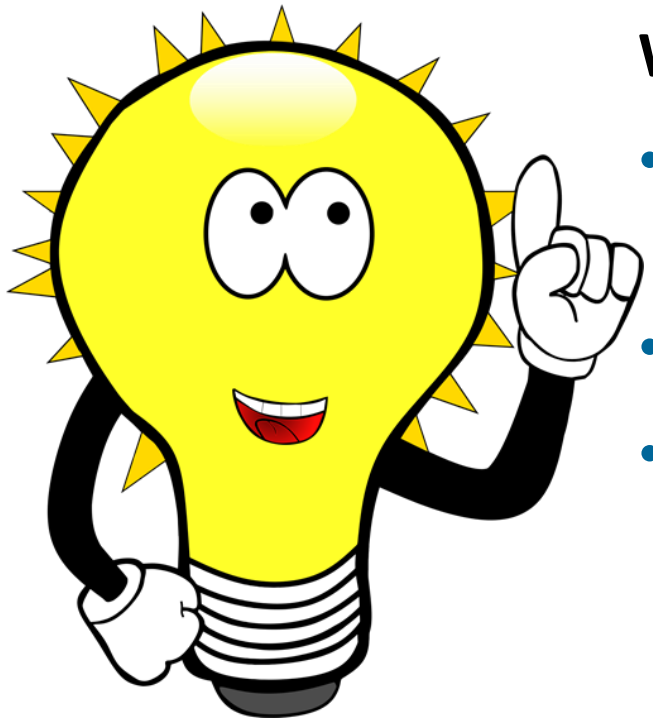
Additional Tips for Resistance Counseling



While on PrEP:

- Emphasize the importance of taking medication as instructed
- Explain importance of adherence in preventing resistance
- Build client's skills for adherence to PrEP:
  - identifying approaches to improve adherence
  - discuss a realistic, doable plan

In case of seroconversion:

- Provide referrals and explain their importance
- Follow up on referral completion

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Minimizing Risk of Resistance: Key Counseling Points

AVOID

Avoid Getting HIV: Use PrEP consistently and correctly while at-risk of acquiring HIV. Resistance to ARV drugs cannot occur in a person who does not have HIV.

ATTEND

Attend Clinic Visits: HIV testing will be done quarterly. If testing shows that a person has become infected with HIV, PrEP should be stopped immediately to avoid developing drug resistance.

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Minimizing Risk of Resistance: Key Counseling Points

DO NOT SHARE

Do Not Share PrEP: Sharing PrEP with other people, even with a partner, could be harmful. They could have HIV, and not know it. If a person with HIV use PrEP, this could cause resistance to ARV drugs.

PrEP WORKS!

PrEP works if you use it: The benefits of PrEP are greater than the risk of resistance. But minimizing the risk will help to limit the potential impact on HIV treatment.

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What If I Need Help?

For help with DBS collection procedures, counseling messages, or interpreting the drug resistance outcome report, contact: *(insert appropriate contact information here)*

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