

**KITSO AIDS Training Program**

Lecture 9:

**Treatment Failure and Its Management**

1

---

---

---

---

---

---

---

---

**Learning Objectives**

- The different types of treatment failure
- The causes of treatment failure, including ARV resistance
- The management of treatment failure.

2

---

---

---

---

---

---

---

---

**Treatment Failure**

There are three types of treatment failure:

- **Virologic:** viral load is not suppressed to < 400 copies/mL by 6 months after HAART initiation, or, after being *initially* suppressed, the viral load becomes detectable sometime later in the future.
- **Immunologic:** CD4 count/% persistently decreases or, after one year of HAART, does not increase by 25-50 cells/ $\mu$ L or 5 percentage points, respectively.
- **Clinical:** a new HIV-related illness causes clinical deterioration, e.g. a new WHO stage 3 or 4 condition, excluding IRIS.

3

---

---

---

---

---

---

---

---

### Treatment Failure (2)

- In a patient failing HAART, virologic failure usually develops first, followed by immunological failure, which then eventually leads to clinical deterioration.
- Cases of clinical and/or immunological treatment failure (as above) in which the viral load is suppressed to < 400 copies/mL *must be discussed with an HIV Specialist* before changing the regimen, since in most cases it might not be necessary to change it.
- Generally, “treatment failure” means virologic failure, and the two terms are often used interchangeably.

4

---

---

---

---

---

---

---

---

### Treatment Failure (3)

- ARV resistance reduces the ability of an ARV, or combination of ARVs, to block or reduce the replication of HIV. As a result, viral load increases, and CD4 count/% decreases.
- ARV resistance is an important cause—but *not the only cause*—of treatment (virologic) failure.
- Although a common cause of treatment failure, *ARV resistance will be the final end result of other possible causes of treatment failure*, and these other possible causes must also be considered when managing treatment failure. Addressing these non-resistance causes of failure promptly may preserve the current ARV regimen for the patient, and avoid unnecessary changing of regimens.

5

---

---

---

---

---

---

---

---

### Treatment Failure (4)

- Treatment (virologic) failure can be regarded as falling into two general categories:
  - Subtherapeutic blood/tissue levels of the ARV(s)—i.e., ARV levels are insufficient to control ongoing viral replication.
  - ARV resistance, either primary or acquired: “primary” resistance results from initial infection with an ARV-resistant HIV, and “acquired” resistance results from *prolonged and unaddressed persistence of non-resistance causes* (i.e., subtherapeutic ARV levels)

6

---

---

---

---

---

---

---

---

### Treatment Failure (5)

- The above two categories of treatment failure—suboptimal ARV levels and ARV resistance—are not always mutually exclusive, and can sometimes exist together:
  - A patient can be infected with an HIV that is already resistant to one or more ARVs (“primary resistance”), *and/or*
  - By allowing viral replication to continue, subtherapeutic ARV levels will eventually lead to development of resistance mutations and thus ARV resistance (“acquired resistance”).

7

---

---

---

---

---

---

---

---

### Treatment Failure (6)

- Correctable causes of treatment failure due to subtherapeutic blood levels of ARVs:
  - Non-adherence: the major cause
  - Drug-drug interactions (e.g., rifampicin and LPV/r)
  - Poor absorption (e.g., ddI, LPV/r food requirements)
  - Gastroenteritis (incomplete absorption of ARV due to vomiting and/or diarrhea)
  - Incorrect dose of ARV (e.g., pediatric dosing, ddI dose in adults).
  - Inadequate potency or durability of ARV regimen (e.g., weak ARV, mono/dual therapy, not refrigerating liquid d4T).

8

---

---

---

---

---

---

---

---

### Treatment Failure (7)

- Treatment failure due to non-resistance causes (i.e., from subtherapeutic ARV levels, above) may not initially be associated with HIV resistance to the ARV(s).
- However, if viral replication due to subtherapeutic ARV levels is allowed to persist, ARV resistance will eventually develop. The length of time for resistance to develop depends upon several factors—the specific ARV, the patient’s HIV, and the patient’s immunogenetics--and can be from a few days to a few months at most.
- Although other causes of treatment failure do occur, most treatment failure is due to either ARV resistance and/or non-adherence.

9

---

---

---

---

---

---

---

---

### Treatment Failure (8)

- **Treatment failure must be addressed promptly:**

- Unless addressed promptly, non-resistance causes of treatment failure, e.g., nonadherence or poor ARV absorption, will eventually lead to development of ARV resistance.
- Once resistance develops to one ARV, cross resistance to other ARVs can develop quickly, thus limiting future treatment options for the patient.
- *Patients must not be kept on a failing regimen for much more than a month at most.*

10

---

---

---

---

---

---

---

---

### How Does ARV Resistance Develop?

- HIV drug resistance is a consequence of viral replication *in the presence of ARV drugs*. Subtherapeutic ARV levels favor, or “select for,” the resistant HIV species, which can replicate freely to become the predominate species, while the ARV-sensitive wild type HIV remains suppressed.
- Reverse transcriptase is a very error-prone enzyme and thus causes many mutations (on average, 1 mutation per life cycle).
- These mutations are completely random and by chance.

11

---

---

---

---

---

---

---

---

### Effects of HIV Mutations

- Mostly of no consequence
- Increased or decreased viral fitness (ability of a virus to replicate in competition with the original infecting strain, i.e., the “wild type” virus)
- Increased or decreased viral replication capacity (number of virions produced per life cycle)
- Viral infectivity or pathogenicity increased or decreased
- Escape from immune control
- **ARV drug resistance**

12

---

---

---

---

---

---

---

---

### How Does ARV Resistance Develop? (2)

- Higher viral replication leads to a higher chance of random HIV mutations, some of which can cause resistance to the ARV drugs.
- Once mutations render HIV resistant to one ARV, it can then quickly develop other related mutations, which can cause resistance to related ARVs, including an entire class of drugs. For example, if replication is allowed to persist—i.e., *if treatment failure is not promptly addressed*--resistance to **AZT** can extend to other N[t]RTIs, and thus limit future treatment options.

13

---

---

---

---

---

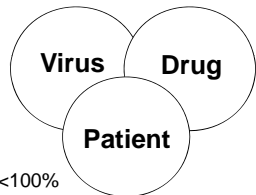
---

---

---

### Factors Leading to Resistance

- High replication rate
- High mutation rate
- Latent reservoirs of HIV



- Inadequate potency
- Inadequate durability
- Drug-drug interactions
- Incorrect dosage
- Poor tolerability
- Inconvenience

- Adherence <100%
- Toxicity or inconvenience
- Gastroenteritis, food requirements of ARVs

14

---

---

---

---

---

---

---

---

### Virus-Related Factors Leading to Resistance

15

---

---

---

---

---

---

---

---

### Virus related Factors

- High replication rate of HIV
  - Turnover of tens of billions of virions daily
- Frequent errors made during replication
- High mutation rate
  - Billions of mutations daily
- Latent reservoirs of HIV
  - Enable drug-resistant HIV to “hide” for 20-30 years, inaccessible to ARV drugs.

16

---

---

---

---

---

---

---

---

### Latent Reservoirs and Resistance

- ARV resistance, once it develops, is probably life-long, since resistant HIV persists in latent cellular reservoirs, which can then become activated many years to decades later.
- Once a patient is resistant to an ARV drug, that drug will probably be ineffective in the future. HIV does not “forgive” treatment errors or non-adherence.

17

---

---

---

---

---

---

---

---

### Drug-Related Factors Leading to Resistance

18

---

---

---

---

---

---

---

---

### Drug-Related Factors

- Inadequate potency of ARV's
- Drug interactions leading to suboptimal drug levels, e.g., rifampicin and LPV/r
- Incorrect ARV dosage (e.g., pediatric dosing)
- Inadequate durability of ARV regimen (e.g., mono/dual therapy)
- Incorrect ARV storage (e.g., Kaletra, liquid d4T)
- Poor tolerability
- Inconvenience of regimen

19

---

---

---

---

---

---

---

---

### Potency

- Inadequate potency (e.g. mono/dual therapy, intrinsically weak ARV) will allow increased viral replication, which will eventually allow resistance mutations to develop.
  - All ARVs in the Botswana national program are potent.
  - Mono/dual therapy is forbidden under the National Program.
  - With a more potent regimen, there is decreased replication and decreased chance to develop ARV resistance mutations.

20

---

---

---

---

---

---

---

---

### Virus- and Drug-Related Factors Leading to Enhanced Resistance

21

---

---

---

---

---

---

---

---

### Mutations and Resistance

- For certain ARVs, only one single-point mutation is required to render the ARV ineffective.
- For other ARVs, multiple, step-wise mutations must occur before the drug loses effect.

22

---

---

---

---

---

---

---

---

### Single Mutations and Resistance

- Certain single mutations will result in HIV having complete resistance to an ARV, or even to an entire class of ARVs (eg., NNRTIs).
- Drugs in which such single mutations cause complete resistance are said to have a **LOW GENETIC BARRIER** to the development of resistance.

23

---

---

---

---

---

---

---

---

### ARVs with Low Genetic Barrier

- **3TC** and **FTC**
- All NNRTI drugs (**NVP** and **EFV**)
  - Intra-class resistance mutations can appear with just one mutation, which renders all NNRTIs ineffective.
  - Resistance to **NVP** causes resistance to **EFV**, and vice versa.
- Regimens containing ARV's with low genetic barriers to resistance can be very potent and durable, but they are also very vulnerable to factors causing low drug levels (e.g., non-adherence, drug interactions, etc.).

24

---

---

---

---

---

---

---

---

### Multiple Mutations and Resistance

- Other ARVs require multiple, step-wise mutations for HIV to become resistant to the ARV. For these drugs resistance is not “all or nothing,” but instead is gradual: e.g., one or two mutations affecting AZT activity will usually not completely abolish AZT’s anti-HIV activity, but will still lessen its ability to suppress HIV replication, whereas three or more mutations will render AZT completely ineffective.
- ARVs which require multiple mutations for resistance have a **High Genetic Barrier** to the development of resistance.

25

---

---

---

---

---

---

---

---

---

---

### ARVs with High Genetic Barrier

- Most protease inhibitors, e.g., **LPV/r**
- All NRTIs except **3TC** and **FTC**
- *However*, the longer a failing regimen is continued, the greater the number of mutations which can accumulate, and which can lead to greater resistance, including resistance across an entire ARV class, thus limiting future treatment options.
  - For example, if viral replication—i.e., treatment failure—persists in the presence of AZT, then gradual accumulations of AZT resistance mutations will render not only AZT ineffective, but also alternative ARVs such as d4T and TDF.

26

---

---

---

---

---

---

---

---

---

---

### Summary of Drugs Based on Genetic Barrier

Barrier type	Low	High
Mutations required	Single*	Multiple, stepwise
Drugs	<b>3TC, FTC, EFV, NVP</b>	PIs and NRTIs – but not <b>3TC</b> and <b>FTC</b>

\*Note: The 3TC/FTC resistance mutation is different from the NNRTI resistance mutation.

27

---

---

---

---

---

---

---

---

---

---

**Patient-Related  
Factors Leading  
to Resistance**

28

---

---

---

---

---

---

---

---

- Patient Factors**
- Lack of adherence to potent regimens
  - Intolerance
  - Toxicity
  - Inconvenience
  - Not taking ARV properly (food requirements, adequate liquid)
  - Missing doses
  - Drug holidays

29

---

---

---

---

---

---

---

---

**Clinical Management of  
Treatment Failure**

Treatment failure should be approached in a step-by-step manner.

30

---

---

---

---

---

---

---

---

### Clinical Management of Treatment Failure

- First, recognize and address treatment failure as early as possible by monitoring the patient clinically and through recommended laboratory testing, i.e., CD4 cell count and viral load. Prompt follow-up of elevated viral loads is crucial to early recognition of treatment failure.
- Determine whether the treatment failure is virologic, immunologic, and/or clinical. If virologic and/or immunologic, repeat the viral load and/or CD4 count/% as *priority laboratory tests*, to confirm the initial result.
  - If the repeat test(s) does not return within 2 weeks, *do not delay* any indicated action.
- While waiting for repeat monitoring labs to return, investigate for various causes of the treatment failure:
  - Subtherapeutic ARV levels (non-adherence, drug interactions, poor absorption, incorrect dosage, etc.)
  - ARV resistance

31

---

---

---

---

---

---

---

---

### Management of Treatment Failure (2)

- Correct any identified non-resistance cause: e.g., adherence counseling, ARV dose adjustment, treatment of gastroenteritis, correction of drug interaction.
- Mild gastroenteritis, minor non-adherence, easily corrected drug interaction, or correction of ARV dose do not require HAART discontinuation while the non-resistance cause of failure is being addressed.
- Severe non-adherence, defaulting, or severe gastroenteritis may require holding HAART until the non-resistance cause of failure is corrected.

32

---

---

---

---

---

---

---

---

### Management of Treatment Failure (3)

- Once the non-resistance cause has been corrected, reinstitute the original regimen (if it had been discontinued, as above), and recheck *priority* viral load after 6 weeks (for both adults and pediatric patients).
  - If 6 week viral load is < 400 copies/mL, then continue regimen and repeat in 3 months. If still suppressed, adult viral load monitoring may return to every 6 months (continue every 3 month monitoring indefinitely for pediatric patients).
  - For adult patients, if 6 week viral load is not < 400 copies/mL, then reassess the patient. If a correctable cause of failure is found, then address it, continue the regimen, and repeat *priority* viral load in another 6 weeks. If viral load is still not suppressed, then assume resistance has occurred. If no correctable cause of failure is found at first 6 week determination, then assume that resistance has developed and change the regimen accordingly.

33

---

---

---

---

---

---

---

---

**Management of Treatment Failure (4)**

(6 week viral load determination after adherence interventions, continued)

- Pediatric patients may require longer periods for complete suppression. If the viral load 6 weeks after adherence intervention is not < 400 copies/mL, then reassess the patient for any correctable causes of failure, and address them. Regardless of whether or not correctable causes of failure have been identified, continue HAART, and repeat *priority* viral load in 6 weeks. If this second follow-up viral load is not < 400 copies/mL, a pediatric HIV Specialist must be consulted.

34

---

---

---

---

---

---

---

---

**Management of Treatment Failure (5)**

- If initial evaluation of of treatment failure fails to find causes due to subtherapeutic ARV levels—i.e., nonadherence, gastroenteritis, incorrect doses, drug interactions--then assume that ARV resistance has developed, and is the cause of the treatment failure.
  - More than one visit may be necessary to determine with certainty that non-resistance causes of failure are not present.
- For treatment failure due to resistance, the failing regimen must be replaced with three new ARVs, at least two of which must be fully active against HIV.

35

---

---

---

---

---

---

---

---

**Management of Treatment Failure (6)**

- For second line treatment failure, obtain a genotypic resistance assay while the patient is on the failing regimen.
- *Do not wait for more than 4 weeks for the resistance assay to return before switching to a new empiric regimen under HIV Specialist guidance. Contact the lab for estimated return of assay.*
- Pediatric treatment failure (e.g., viral load not < 400 copies/mL after 6 months of HAART) must be discussed with an HIV Specialist.

36

---

---

---

---

---

---

---

---

**2008 Guidelines Mandate Prompt Management of Treatment Failure**

- At every clinic there must be ongoing, “real time” review of all returning viral loads. Waiting to review a patient’s viral load at the next 3 month follow-up visit is a serious lapse of clinical responsibility, and will allow treatment failure to persist for up to 3 months before even being identified and addressed.
- Every returning viral load will be on a patient on HAART, and thus must always be < 400 copies/mL. Thus, **clinicians must promptly identify all returning viral loads > 400 copies/mL for prompt follow-up for possible treatment failure.**

37

---

---

---

---

---

---

---

---

---

---

**2008 Guideline Mandates (2)**

- Viral load must be < 400 copies/mL no later than 6 months after HAART initiation (or change), but most patients will suppress to undetectable levels by 3 months after initiation.
- Adult patients whose viral loads are not undetectable by 3 months do not strictly meet the definition of treatment failure (yet), but because they may be at increased risk of eventual failure at 6 months, they must be carefully evaluated for any correctable causes of potential failure, especially non-adherence.
  - Pediatric patients may require longer, up to 6 months, for full virologic suppression.

38

---

---

---

---

---

---

---

---

---

---

**2008 Guidelines Mandates (3)**

- Management of treatment failure must, of necessity, be a “team effort,” involving many different staff and clinical cadres in the ARV clinic.
- *Every ARV clinic must have an established, ongoing Failure Management Clinic and a corollary Failure Management Team*, to address failure management in a comprehensive, methodical manner.
- The complete 2008 guidelines document, also available at [www.moh.gov.bw](http://www.moh.gov.bw), outlines the details of the Failure Management Team and Clinic.

39

---

---

---

---

---

---

---

---

---

---

### 2008 Guidelines Mandates (4)

- An HIV Specialist Panel has been established, both to monitor implementation of the 2008 guidelines, and to serve as a consultative resource to clinicians in all aspects of HIV/AIDS care, including management of treatment failure. The contact numbers of these HIV Specialists are in the 2008 guidelines document, and will be periodically updated in the guidelines document at [www.moh.gov.bw](http://www.moh.gov.bw).
- Failure to promptly follow up treatment failure is the most serious threat to the long-term integrity of Botswana's National HIV/AIDS Program.

40

---

---

---

---

---

---

---

---

### Resistance Assay

- A blood test which assesses a patient's resistance profile, to assist with selection of subsequent ARV regimen
- Very expensive
- Per Botswana guidelines, must be obtained if the patient is failing second line regimen
- Consultation with an HIV specialist for interpretation is required, but *do not wait for return of the assay* before consulting the Specialist for advice about empiric regimen change, pending return of the assay.

41

---

---

---

---

---

---

---

---

### Resistance Assay (2)

- The assay should be drawn while the patient has a viral load greater than 1,000 copies/mL and *is still on the failing ARV regimen*. Consult HIV Specialist if viral load is between 400 and 1000 copies/mL.
- At best, the assay can only predict which ARVs will not be effective, not which ARVs will work.
- The assay cannot replace careful treatment history and expert opinion.

42

---

---

---

---

---

---

---

---

### Case Discussion:

A 40 year-old patient has had VL<400 copies/mL for 18 months since initiation of **AZT + 3TC + EFV** in early 2006. Now, after 18 months of successful therapy, the VL is 15,000 copies/ ml (confirmed by repeat VL). CD4 count has increased from a baseline of 54 cells/ $\mu$ L to a recent value of 376 cells/ $\mu$ L. Over the past 18 months the patient has improved clinically, with increase in weight from a baseline of 48 kg to a recent weight of 65 kg. He feels well, and is without complaints.

Is this treatment failure? If so, what kind?  
How should this case be managed?

43

---

---

---

---

---

---

---

---

### Case Discussion (2)

- Identify the type and cause of treatment failure.
- Evaluate for sub-optimal drug levels (non-adherence, drug interactions, poor absorption, etc), and address such problems, if present.
  - Once problems have been corrected, restart or continue original regimen and repeat VL in 6 weeks.
  - If 6 week VL is < 400 copies/mL, continue the regimen and repeat in 3 months. If still suppressed, then resume every 6 month VL monitoring.
  - If 6 week VL is > 400 copies/mL, reassess for any correctable causes, and if found and addressed, repeat VL in another 6 weeks. If still not suppressed, then assume resistance has developed.
- If non-resistance causes have been ruled out initially, or if VL is not <400 copies/ml 6 weeks after non-resistance causes have been addressed, then assume ARV resistance is present.
  - HIV mutations affecting **3TC** and **EFV** are probably present (low genetic barrier). **AZT** will probably have not been affected significantly (high genetic barrier).

44

---

---

---

---

---

---

---

---

### Case Discussion (3)

- The current regimen should be changed as quickly as possible to three new ARVS per 2008 guidelines—i.e., **TDF + FTC + LPV/r**--to avoid accumulation of additional NRTI mutations which could further compromise future regimens (e.g., accumulation of **AZT** resistance mutations could render **TDF** ineffective).
- Because of class cross-resistance, **EFV** cannot be replaced with **NVP**.
  - **AZT** may still retain potency for future treatment options, if the second line regimen fails. Resistance assay at time of second line failure may clarify this question.

45

---

---

---

---

---

---

---

---

### Treatment Failure: Key Points

- ARV resistance is an important cause of treatment failure, but correctable non-resistance causes--i.e., subtherapeutic ARV levels due to a variety of causes, listed earlier--must also be considered and either ruled out or addressed.
- If viral replication due to non-resistance causes is allowed to continue in the presence of subtherapeutic levels of ARVs, resistance will eventually develop.

46

---

---

---

---

---

---

---

---

### Treatment Failure: Key Points (2)

- ARV resistance is a consequence of viral replication in the presence of drug, and can be minimized by suppressing viral load below the limits of detection.
- Never replace one NNRTI for another within a failing regimen: resistance to **NVP** causes resistance to **EFV**, and *vice versa*.
- A resistance assay and discussion with an HIV Specialist is required for second line treatment failure.

47

---

---

---

---

---

---

---

---

### Treatment Failure: Key Points (3)

- **Clinicians must review all viral load results as soon as they return from the laboratory, and must promptly follow up any viral load > 400 copies/mL.**
- Do not keep a patient on a failing regimen for more than a month or so: treatment failure must be addressed **PROMPTLY!**

48

---

---

---

---

---

---

---

---