

Resistance

Objectives



1. Discuss factors that lead to resistance
2. Describe cross-resistance
3. Discuss ways to avoid resistance
4. Introduce resistance testing

Resistance overview



- During HIV replication, errors are made
- Errors are called mutations
- Mutations may make the virus weaker
- Mutations may make a particular ARV ineffective—the virus becomes resistant to that ARV

HIV Drug Resistance



- Refers to a reduction in the ability of a drug, or a combination of drugs, to block HIV reproduction in the body
 - This reduction occurs as a result of the changes (or mutations) in the genetic structure of HIV due to the rapid and often inaccurate reproduction of new viral copies
 - The best way to avoid the development of drug resistance is to keep HIV under control. The less virus there is in the body, the less likely that the virus will reproduce and mutate

Drug resistance, cont'd



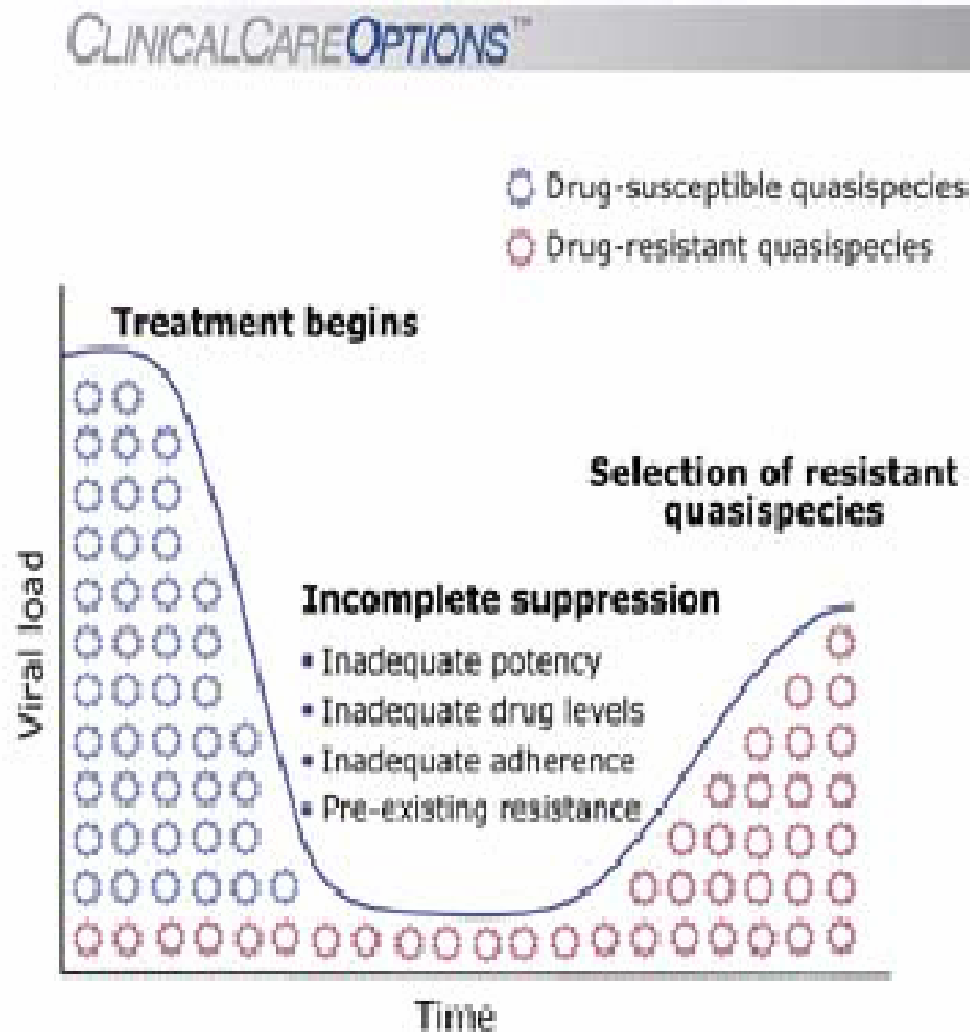
- If viral load and resistance monitoring are not used to define treatment failure, virological failure will likely have been present for an extended period by the time treatment failure has been detected
- Viral replication over time leads to the evolution of more drug resistant mutations and it will be difficult to know which drugs have been compromised without drug resistance testing

HIV Drug Resistance, continued



- Factors that can prevent HIV medications from controlling the virus are
 - poor treatment adherence
 - poor drug absorption
 - varying pharmacokinetics
 - the individualized absorption, distribution, metabolism and removal of drugs from the body
 - Altered pharmacokinetics because of drug interactions

Figure 2. Selection of Resistant Viral Quasispecies



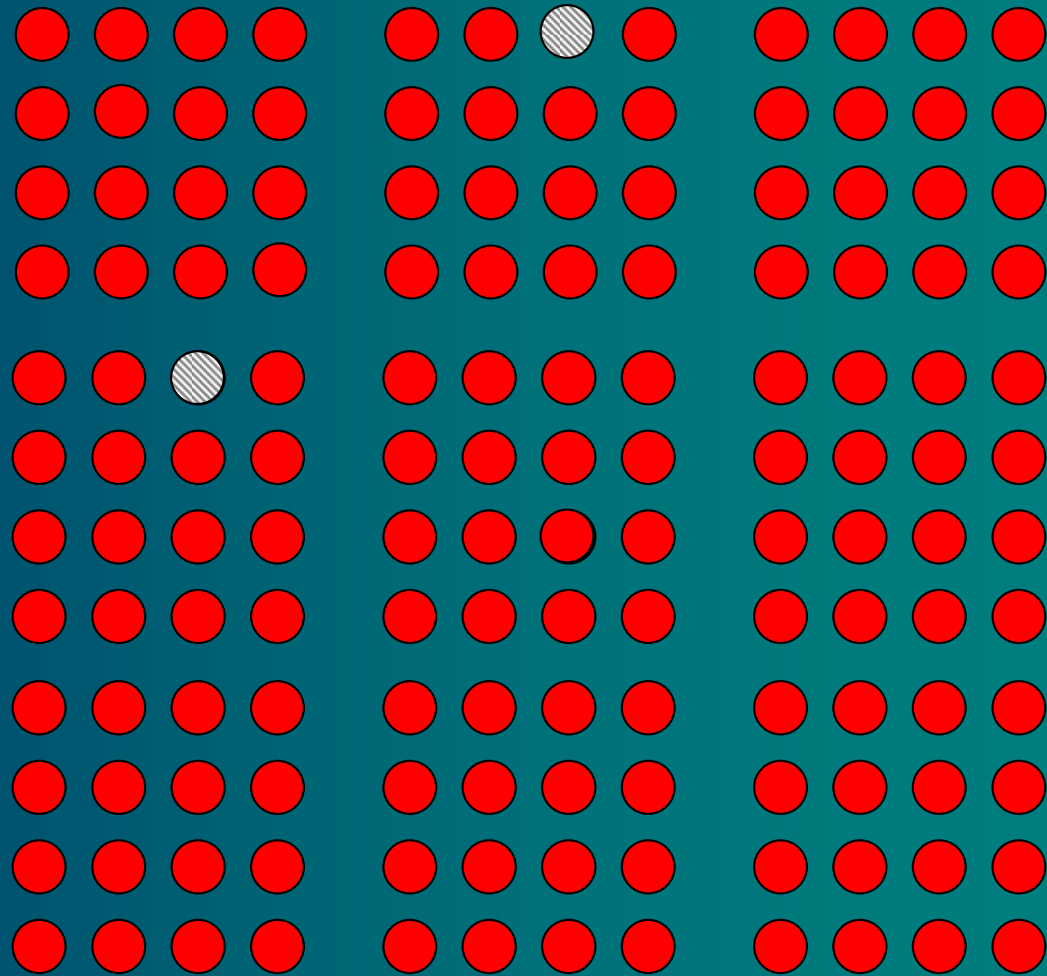
Example of how resistance may occur



Initial distribution of virus in the body

Red (solid) circles:
Wild-type virus
(drug-susceptible)

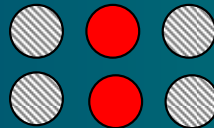
White (hashed) circles:
Resistant virus



Incomplete suppression via ART



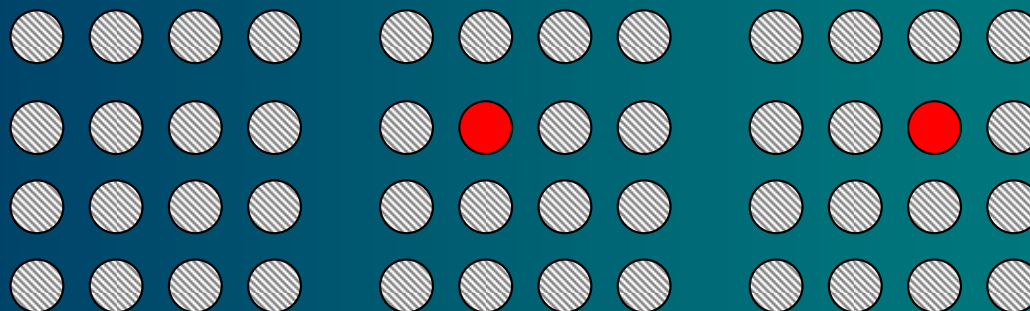
- In the case of incomplete suppression of the virus, the amount of drug-susceptible virus has been reduced dramatically, but is still present, while the drug resistant virus is also still present.



Resistance



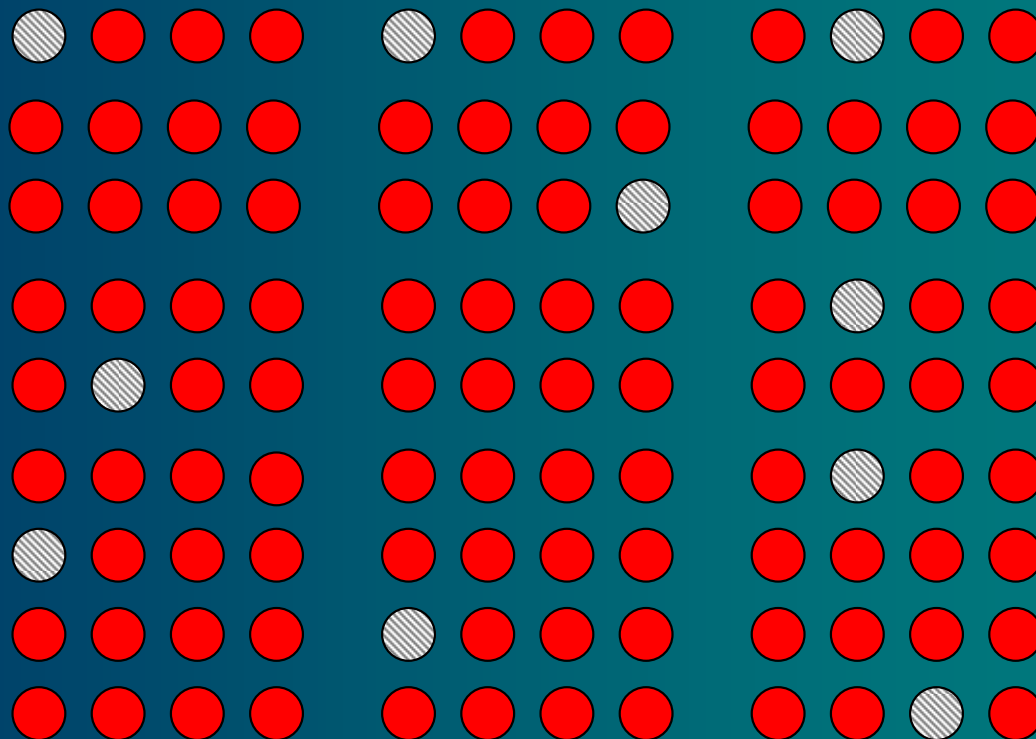
- Because the patient had incomplete suppression, yet there is still medication in the body, it may be enough to stop the wild-type (drug-susceptible) virus from replicating, but now the resistant virus is replicating and becomes the dominant virus



Patient stopped drug altogether



Now that the patient has stopped the drug, the wildtype virus, which is more “fit” to reproduce, and the overall viral load continues to go up. However, there is still resistant virus around, at a much higher concentration than prior to therapy



Nevirapine resistance



- Whereas most NRTIs usually need several mutations to occur before resistance occurs, only one mutation to reverse transcriptase is required to confer resistance to NNRTI
- Keep in mind that when pts are not adherent to therapy on NNRTI-containing regimen
 - * there will essentially be monotherapy on the NNRTI
 - * Resistance can occur relatively easily
 - All the more reason adherence on first line regimen needs to be stressed
- HIVNET 012: Significant number of pregnant women who received just one dose of NVP exhibited resistance to NVP, as did infants who became infected.
- Women who had nevirapine resistance after PMTCT were more likely to not respond to HAART.
 - * Most of these women deserved full HAART during pregnancy
 - * Integration of PMTCT and ART programs may address this concern

Cross-resistance



- Many mutations will cause resistance to more than one ARV
- Resistance to one drug may make the entire class ineffective for a patient
- Resistance to nevirapine causes resistance to efavirenz, so entire class is rendered useless
- Cross-resistance may occur in all drug classes

Viral Suppression



- ARVs suppress viral replication
- Suppression of viral replication also suppresses the development of mutations
- Incomplete suppression increases the chances of the virus developing resistance to medications

Avoiding drug resistance



- Choose potent ART regimen
- Address potential barriers to adherence in counseling
- Optimal adherence
 - Taking correct dose at the right time
 - Adhering to food requirements
 - Consider interrupting therapy or stopping a regimen altogether if adherence is poor
 - It is generally *worse* to continue a patient on a failing regimen than to stop the drug, work on adherence issues, and restart medications later

Avoiding drug resistance



- Monitor for treatment failure
- Avoid drug interactions that may lead to decreased concentrations in blood
- Switch all ARVs (at least two) in the case of treatment failure
 - NNRTI tail if stopping nevirapine or efavirenz
- Consider possibility of cross-resistance when choosing a new regimen when a patient has previous ARV experience

Testing for resistance



There are two ways to test for HIV drug resistance:

- Genotypic testing:
 - Identifies mutations that are linked to the reverse transcriptase and protease genes of a person's HIV
- Phenotypic testing:
 - Measures the growth of HIV in the presence of HIV drugs

Weaknesses/drawbacks of resistance testing



- The tests measure only the dominant HIV strains that exist at the time of testing, not “minority” strains or strains that may be “hiding” in, for example, resting cells
- The tests should be performed when the patient is taking ARVs and no later than 3 weeks from stopping treatment (otherwise, the virus will likely have reverted to “wild type”)
- The tests are difficult to interpret and often present conflicting results, particularly in patients who have had multiple regime failures
- The tests are costly, not feasible in Nigeria at this time

Major implications of resistance



- Not enough antiretroviral choices because of cross-resistance
- Leads to increased morbidity and mortality
- Second-line and salvage regimens have higher pill burden, complex nutritional requirements, more side effects
- Potential for spread of resistant virus

Summary



- The lower the viral load, the less likely that replication will occur
- Many errors occur during replication of HIV, so the more the virus is replicating, the greater the chance for mutations to occur.
- Occasionally this may lead to decreased effectiveness of an ARV to HIV
- Resistance to one ARV may lead to resistance across all drugs in the same class.
- Resistance can lead to worsening morbidity and mortality as well as transmission of resistant virus to others