



Why and When to Change Therapy

Part B Module B1
Session 8



Objectives

1. Discuss the reasons for changing therapies
2. Discuss interruption of therapy
3. Understand concept of NNRTI tail
4. Understand what limitations there may be to the selection of alternative therapy
5. Learn about choices for second-line and salvage ARV regimen

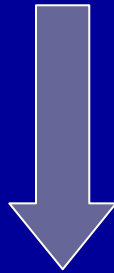


Reasons to Change a Regimen or Individual Drug

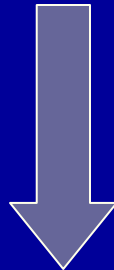
- Treatment failure
- Toxicity
- Pregnancy
- TB
- Poor adherence
- Patient choice/intolerance

Treatment failure: progressive steps

Virologic Failure



Immunologic Failure



Clinical failure



Treatment failure

- **Virologic failure:**
 - failure to achieve undetectable viral load levels after 3-6 months; repeated, continued detectable viremia indicative of incomplete viral suppression; the reappearance of a detectable viral load
- **Immunologic failure:**
 - a fall in the CD4 counts >30% from the peak value or a decline equivalent to or less than the pre-therapy baseline
- **Clinical failure:** clinical disease progression signaled by
 - the development of new symptoms
 - symptoms that do not disappear, or
 - A new OI or malignancy
 - (when the drugs have been given sufficient to induce a protective degree of immune restoration)

Treatment failure, cont'd

Note on treatment failure:

- Without viral load testing, treatment failure will not be diagnosed early
- So a suboptimal treatment regimen may be used for months before immunologic or clinical failure manifests
 - This allows for additional mutations to occur
 - Implications for resistance and cross-resistance
 - Even MORE evidence for importance of excellent adherence



Reasons for treatment failure

- Insufficient potency of the ARV regimen
- Insufficient drug levels (including cellular mechanisms)
 - Can be due to drug interactions or improper dosing
- Poor adherence
- Pre-existing viral drug resistance
- Poor prescribing or dispensing
- Inadequate/inconsistent drug supply



Reasons for non-improvement clinically despite ART

- Treatment failure
- Immune reconstitution syndrome
- Opportunistic infections
- Non-HIV related problems

What to do in the case of treatment failure

- Check treatment regimen
- Check adherence to ARV regimen
- Check for drug interactions
- Resistance test if available
- Patient and interdisciplinary team to decide on stopping ARV or changing regimen



Toxicity

- Drug causing the toxicity cannot be identified, and/or low-grade, intolerable side effects compromise adherence
- Clearly defined toxicity to a single drug:
 - This permits drug substitution without compromising the overall regimen
 - For example: d4T can be substituted for ZDV when ZDV-related symptoms or anemia appear or
 - NVP can be substituted for EFZ when EFZ-related central nervous system symptoms are unremitting



Toxicity

If an interruption in therapy is indicated to permit resolution of toxicity, the entire regimen should be suspended temporarily in order to prevent the emergence of drug resistance

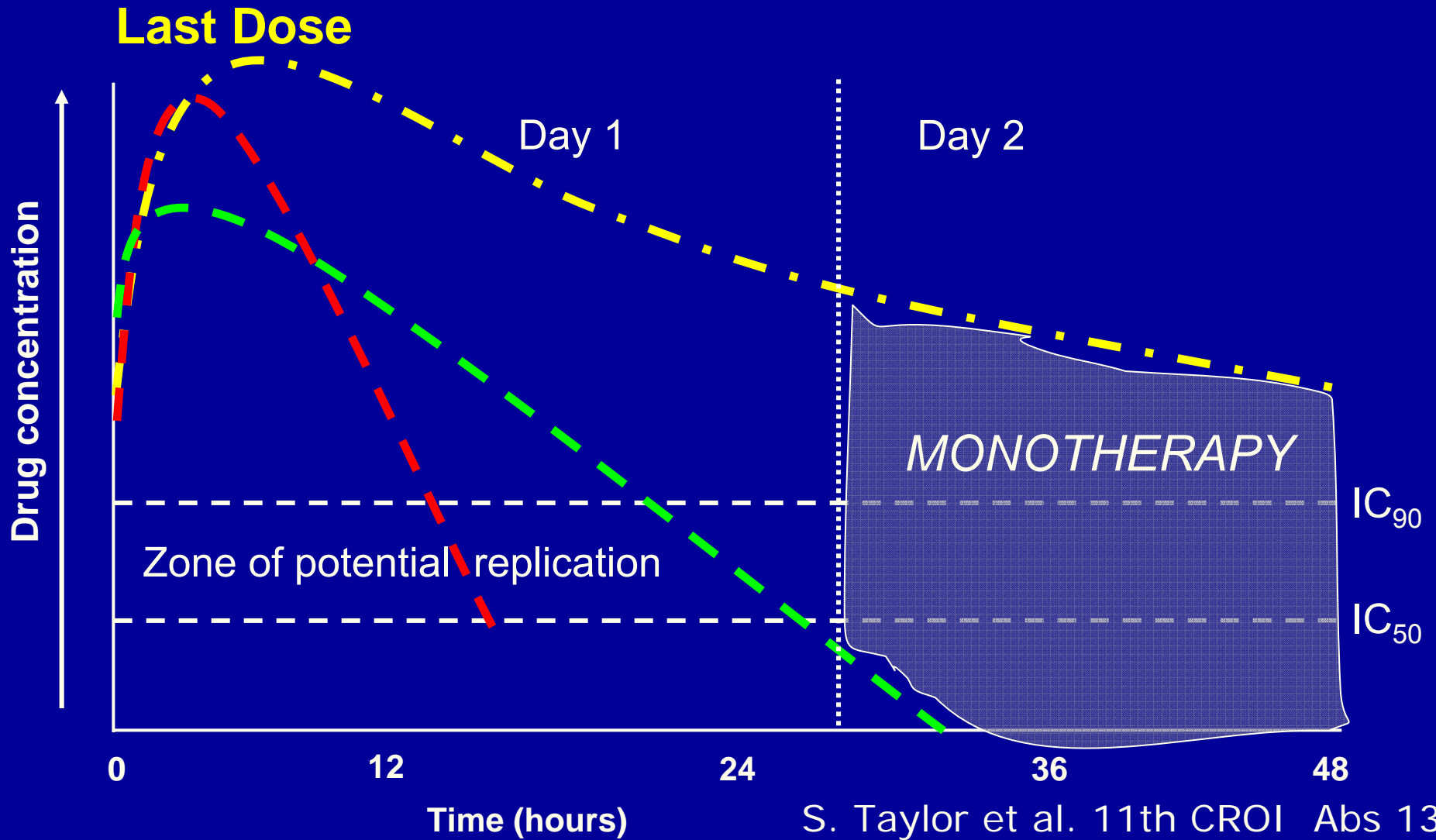
Interrupting therapy

- BY FAR, it is preferable to have a patient stay on an *effective* treatment regimen than to stop and restart therapy
- However, there may be times when interrupting therapy may be necessary
 - Travel/moving elsewhere
 - TB therapy
 - Pregnancy
 - Patient choice (upcoming life event, visitors, holiday, etc)
 - Unable to afford continuing therapy
 - Others?

Interrupting therapy, cont'd

- Let the patient know that interrupting therapy is a last option, but IF interruption is necessary, that it should be done with care and under guidance of a clinician
 - Treatment options may still be preserved
- Most treatment interruption studies have been with people who had multidrug resistance or were week on/week off, not when people want a “treatment holiday”
 - So not a lot of data on effectiveness of this
- Pt should be counseled on risks vs. benefits and monitored more closely
- Risk is higher if pt is on NNRTI because of NNRTI tail...

Stopping a Triple ARV combination when ARVs have different half lives



NNRTI tail

- Half-life of various drugs:
 - AZT 1.1 hours
 - 3TC 3-6 hours
 - d4T 1 hour
 - SQV: 1-2 hours
 - NVP: 25-30 hours
 - EFV? (look up in resource)
- Therefore, if interruption is necessary, stop EFV and NVP 3-7 days before stopping other ARVs
 - Otherwise, monotherapy will occur, and resistance may follow
 - May have implications on response to therapy once ART resumed



Caution regarding interrupting therapy

Remember:

- When ARVs are stopped, there will be an increase in viral load which leads to an increased risk of HIV transmission

Second line and salvage regimens



Limitations to selection of alternative therapy

- **Drug resistance**

- 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

Recommended second-line regimen*

First line	Second line
AZT or d4T + 3TC + NVP or EFV* *if on Rifampicin for TB treatment	TDF or ABC + ddl+ IDV/r or SQV/r

**This may change with guideline revision*

Salvage therapy

Second line treatment failure

- Choice of salvage therapy difficult without resistance testing
- Should determine why patient has failed two lines of therapy
 - If regimen was too complex, will likely not respond to a more complex regimen
- Meds available for salvage therapy:
 - TDF, ABC, IDV/r, SQV/r, LPV/r, enfuvirtide (fusion inhibitor)
- May consider GIGA HAART: 6 or more drugs



Tenofovir/Viread(TDF)

- First nucleotide RTI with durable activity against some nucleoside-resistant strains of HIV
- Favorable safety profile
- Tenofovir and/or nevirapine may be used in cases of high cholesterol and triglyceride levels
- Dose: 300 mg OD

Didanosine/Videx/Videx EC (ddl)

- Chewable buffered tablets:
 - 25 mg, 50 mg, 100 mg, 150 mg, 200mg
- 10 mg/ml white suspension
- Videx EC:
 - 125mg, 200mg, 250mg, 400mg
 - Not available in Nigeria



Didanosine/Videx (ddl)

- Adolescent/Adult dosing
 - 400 mg OD if ≥ 60 kg
 - 250 mg OD if:
 - < 60 kg
 - combined with tenofovir (TDF)
- Give on an **empty stomach** at least 1 hour before or 2 hours after meals
- **Buffered tablets**, give 2 tablets to ensure adequate buffering
 - EXAMPLE: if the dose is 400 mg, give two 200 mg tablets, **NOT** one 400 mg tablet
- Buffered tablets not suitable for once daily dosing except in patients with renal failure

Didanosine/Videx (ddl)

- When combined with tenofovir (TDF)
 - Decrease dose to 250 mg OD

Abacavir/Ziagen (ABC)

- Tablet: 300 mg
- 20 mg/ml yellow oral solution



Abacavir/Ziagen (ABC)

- Adolescent/Adult dosing
 - Oral: 300 mg twice daily
- Give with or without food
- Store at room temperature
- Teach the signs and symptoms of hypersensitivity reaction
- Instruct patients/care givers to telephone immediately if rash occurs
- Provide medication guide and warning card

Protease Inhibitors (PIs)

- NFV, Nelfinavir (Viracept)
 - LPV, lopinavir (Kaletra)
 - SQV, Saquinavir (Fortovase)
 - APV, Amprenavir (Agenerase)
 - IDV, Indinavir (Crixivan)
 - RTV, Ritonavir (Norvir)
 - As pharmacoenhancer
-
- NAFDAC approval pending or absent:
 - Atazanavir (Reyataz)
 - Lopinavir/ritonavir



Protease inhibitors (PIs)

- HIV protease enzyme
 - cleaves various polyproteins in the process of producing mature infectious virions
- Protease Inhibitors or PIs
 - interfere with the production of HIV protease
 - lead to reduction of the virus in the body
 - reduction is sometimes significant enough to lead to undetectable levels of virus
 - do not use PIs alone (monotherapy) because rapid resistance will develop—they should be used in combination with other drugs

- PIs are associated with multiple drug interactions because of their inhibition of cytochrome P450 enzymes

For example: PIs increase the metabolism of rifampicin and decrease its effectiveness in treating TB

- Indinavir should be taken with plenty of water to prevent kidney stones
- If a patient develops diabetes during PI treatment, it is best to stop the PIs if there is another alternative

Nelfinavir/Viracept (NFV)

- Tablets: 250 mg blue, capsule shaped
- Powder: 50 mg/scoop white powder (200 mg/one level teaspoon)

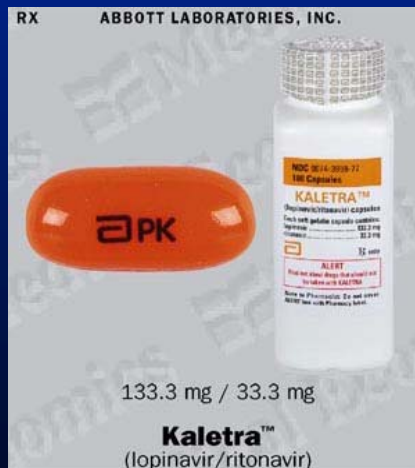


Nelfinavir/Viracept (NFV)

- Adolescents and adults
 - 1250 mg (5 tablets) BD or
 - 750 mg (3 tablets) TDS
- Can administer with meal or light snack
- Tablets can be crushed or dissolved in water and mixed with pudding
- Do not mix with acidic food or juice -> poor taste!

Lopinavir/Ritonavir/Kaletra (LPVr)

- Orange, soft gelatin capsule
 - 133.3 mg lopinavir/33.3 mg ritonavir
- Light, yellow/orange oral solution
 - 80 mg Lopinavir/ 20 mg ritonavir/ml



Lopinavir/Ritonavir/Kaletra (LPVr)

- Without Nevirapine or Efavirenz
 - 400 mg LPV/100 mg RTV twice daily with food
(3 capsules or 5 ml)
- With Nevirapine or Efavirenz
 - 533 mg LPV/133 mg RTV twice daily with food
(4 capsules or 6.5 ml)

Lopinavir/Ritonavir/Kaletra (LPVr)

- Should be administered with food
- High fat meals increase absorption of LPVr
- If coadministered with ddl, ddl should be given 1 hour before or 2 hours after LPVr
- Oral capsules and solution should be refrigerated, but can be kept at room temperature up to 77° (25°C) if used within 2 months
- Need “cold chain”: drug should be refrigerated during transport and in storage

Kaletra Press Release

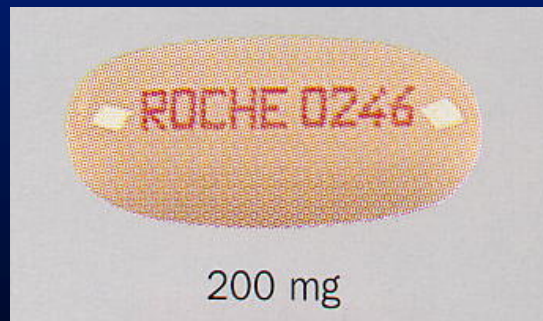
- “. . .no patient taking . . .protease inhibitor Kaletra demonstrated evidence of PI resistance through the five year(252 week) period of the study.”
- 94% patients had HIV RNA < 50 copies/ml
- 99% patients had HIV RNA < 400 copies/ml

Abbott Laboratories, 9th European AIDS Conference, Warsaw,
October 27, 2003

Saquinavir/Fortovase (SQV)

- Soft gel beige capsule: 200 mg
- Hard gel capsule(Saquinavir-HGC, Invirase) : 200 mg*

Not recommended except with Ritonavir



Saquinavir/Fortovase (SQV)

- Adolescent/Adult dosing
 - 1200 mg TDS
 - 1000 mg + 100 mg ritonavir BD

Saquinavir/Fortovase (SQV)

- Administer within 2 hours of a full meal to increase absorption
- Avoid grapefruit juice – increases Saquinavir levels
- Sun exposure can cause photosensitive reactions – sunscreen and protective clothing are recommended

Ritonavir/Norvir (RTV)

- White soft gelatin Capsule: 100 mg
- 80 mg/ml orange colored solution



Ritonavir/Norvir (RTV)

- Stand-alone dosing
 - Initiate:
300 mg twice daily
 - Increase over 5 days:
600 mg twice daily
- Usually used as pharmacoenhancer (“boosted PI regimen”) because of its effect on P450
 - Take advantage of its inhibition of CYP 3A4 to increase levels of other PIs
 - Taken in combination with all PIs except NFV

Ritonavir/Norvir (RTV)

- Nausea/vomiting are major side effects because of poor taste and gastrointestinal upset
- Administer with food to decrease gastrointestinal side effects and increase absorption
- Can be refrigerated or stored at room temperature for 30 days
- Gradually increasing the dose minimizes the nausea

Summary

- Virologic failure precedes immunologic failure, which precedes clinical failure
- Without viral load testing, it is even more imperative to ensure good adherence
- Poor adherence is the foremost reason for treatment failure, but other factors should be considered
- It is preferable to have a patient continue on an *effective* regimen than interrupting therapy, but it is preferable to stop a regimen when adherence is poor, before resistance becomes a major problem