Paediatric ART 6: Selecting a first-line regimen

Unit 13.1

Paediatric Antiretroviral Therapy Workshop

Institute for Human Virology-Nigeria ACTION

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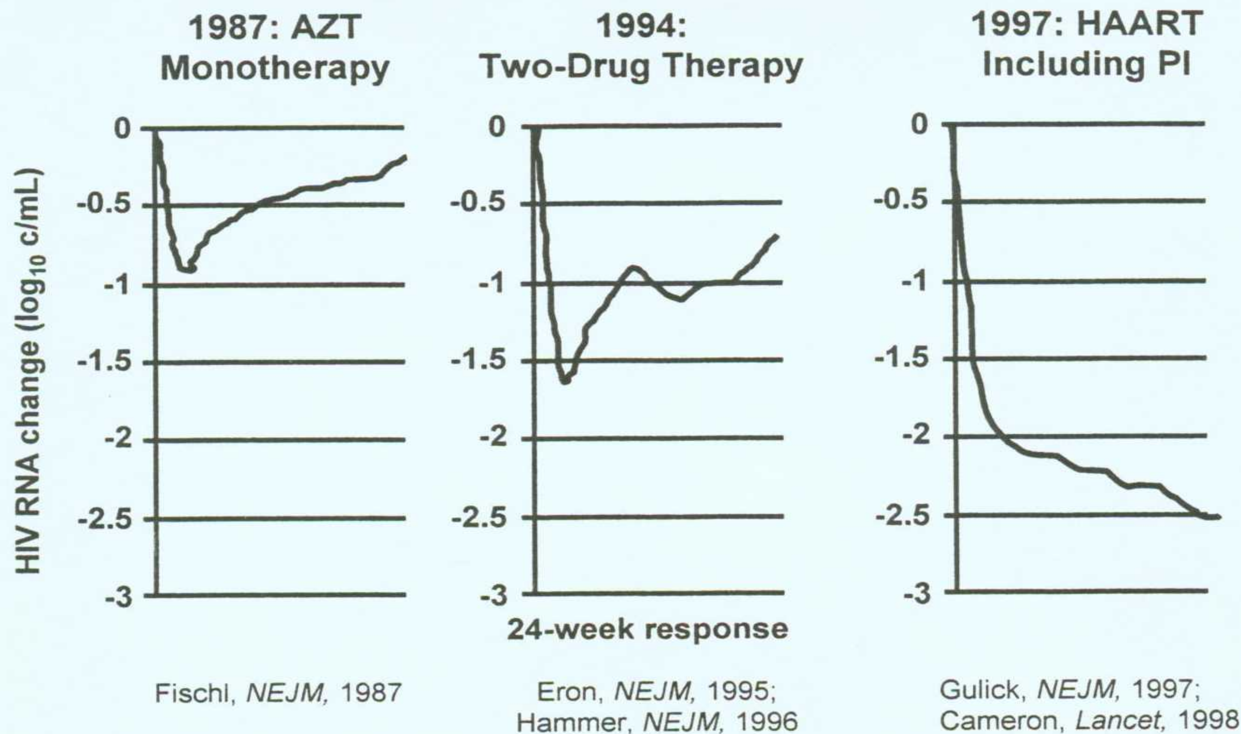
Goals

- Understand the considerations in formulating a 1st line regimen
- Compare advantages and disadvantages of available 1st line regimens in various circumstances

Origin of current ART recommendations

- Monotherapy
  - Original ART
  - Clinical benefit for about a year
- Dual therapy
  - As more NRTI developed, tested in various 2-drug combinations
  - More durable than monotherapy, but still failed

Antiretroviral Potency: Maximize Viral Suppression



Origin of HAART regimens

- By the time PIs developed, it was evident that multi-drug therapy would be necessary
- PI was added to familiar combinations of 2 NRTI
- NNRTI-based HAART: RT as sole drug target implies that it is not necessary to target 2 viral enzymes
- Other HAART regimens: NRTI/NNRTI/PI, 1-2 NRTI + 2 PI, “megahaart” (5 or more ARV), etc.
- Based on experience, clinical trials, and theoretical and practical considerations, some regimens preferred over others

Choosing drug combinations

- **Potency**
  - Combination must be potent enough to completely suppress viral replication
  - Avoid combinations that are antagonistic, e.g.
    - D4T and ZDV
    - Rifampicin and protease inhibitors
- **Durability**
  - Multiple mutations required to produce resistance
  - Avoid overlapping resistance between drugs (e.g. NVP and EFV)
  - Exploit hypersensitivity (one drug becomes more sensitive when another becomes resistant)
- **Leave options open for 2nd line therapy**
  - If 1st line therapy fails, sensitivity to alternative drugs needed

Choosing drug combinations (2)

- **Convenience**
  - Minimum number of dosings/day
  - Avoid drugs that cannot be given simultaneously (e.g. DDI with LPV/r or NFV)
  - Pills preferred over liquids
- **Toxicity & tolerability**
  - Avoid overlapping or synergistic toxicity (e.g. D4T/DDI or SQV/rifampin
- **Sustainability**
  - Use drugs with assured supply
  - Use regimen that family will continue

WHO recommendations for initial paediatric ART in resource-limited settings

2 NRTIs

ZDV/3TC *or*

D4T/3TC *or*

ABC/3TC

Plus 1 NNRTI

NVP *or*

EFV

Which 1st line NRTI to choose?

Drug	Advantages	Disadvantages
ZDV	Less long-term toxicity than D4T	Anemia Failure causes broad NRTI resistance
D4T	Well tolerated Little *early* toxicity in children	Long term toxicity Failure causes broad NRTI resistance
ABC	Most potent NRTI Failure leaves options open for 2nd line therapy	Hypersensitivity syndrome

Choice of NRTI in various circumstances

Dru g	Anaemia	Rifampicin	Renal failure	Liver disease
ZDV	Avoid if anaemic	Levels are decreased 50%, clinical significance unknown	Decrease dosage 50% in severe renal failure	Decrease dosage 33%
D4T	OK	OK	Dosage adjust	OK
ABC	OK	Levels may be decreased, clinical significance unknown	OK	OK

Which 1st line NNRTI to choose?

Drug	Advantages	Disadvantages
NVP	OK for adolescent girls Well tolerated if no hypersensitivity Dosage for children < 3 years old is defined	Hypersensitivity reactions BD dosing Lead-in dosing can be confusing Levels decrease with rifampicin Bitter taste Only 1 (scored) tablet size
EFV	Less affected by rifampicin Once daily dosing Only mild skin rash Multiple capsule/tablet sizes Opened caps easy to give	Possible 1st trimester birth defects CNS side effects Dosage for children < 3 years or 10 kg less well defined

Starting HAART after NVP PMTCT failure

- About half of infants failing SD NVP have resistance detected at 6-8 weeks
- Resistant virus declines in some children after a year, but not known if lower levels of resistant virus persist
- No data on response to therapy (trials in progress)
- WHO recommends using standard 1st line therapy after SD NVP failure
- Should consider SD NVP as relative indication for using PI in first line therapy

Comparing NNRTI versus PI-based 1st line therapy

Factor	NNRTI		PI	
	NVP	EFV	LPV/r	NFV
Potency	++	++	+++	+
Durability	0	0	+++	+
Less toxicity	+	++	0	+
Easy to give	+	+++	0	+
Tolerability	+++	++	0	++
Cost	+++	+++	0	+

NNRTI versus PI: effect of viral load monitoring

- If viral load monitoring **not available**, failure not detected until resistance to NRTIs has developed
- If viral load monitoring **available**, failure of NNRTI regimen can be detected quickly, before NRTI resistance develops
- When used in 1st regimen, LPV/r does not develop resistance
- Conclusion: NNRTI more favored if viral load monitoring available

Triple NRTI regimen: ZDV/ABC/3TC

- 3 NRTI regimen of ZDV (or D4T)/ABC/3TC has been used as HAART but failure rates are higher, particularly if viral load high
- May consider if no other option
- Consider switching later if possible
- WHO recommends ZDV/ABC/3TC with rifampicin in young children, **BUT** there may be interaction with rifampicin and young children usually have high viral load and risk of failure
- D4T/ABC/3TC not well studied