Preparing for Third Line Agents

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Overview

- Factors contribute to resistance
- Pathogenesis of resistance
- Definition of treatment failure
- Critical facts - genotyping
- Genetic barriers to resistance
- Local data
- Review of third line agents
- DOH Process
Factors that contribute to the Development of Resistance

- Poor Adherence
- Insufficient Drug Level
- Viral Replication in the Presence of Drug
- Resistant Virus
- Transmission

Factors influencing resistance:

- Social/Personal Issues
- Regimen Issues
- Toxicities
- Host Genetics
- Poor Potency
- Wrong Dose
- Drug Interactions
- Poor Absorption
- Rapid Clearance
- Poor Activation
Pathogenesis of $\Omega$

- Error prone RT enzyme
- Mistakes $\Rightarrow$ mutant forms of the virus
- Mutations $\Rightarrow$ occur randomly in the genome altering structural proteins, regulatory proteins or enzymes.
Growth in the absence of inhibitory pressure

- HIV multiplies freely taking the most optimum form for rapid growth → wt.

- As it proliferates ⇒ spontaneous random mutations
Growth in the presence of ARV pressure

ARVs kill all of the original wild type organisms

but

The mutated virus which is RESISTANT survives.
Growth in the presence of ARV pressure

- Mutated HIV grows & multiplies, even in the presence of ARVs.
- This virus is now RESISTANT & will continue to replicate albeit at a slower rate due to reduced fitness.
- Note resistant virus are “archived” in long lived cells - may fade but not disappear when drug stopped.
Treatment Failure VL - Early & Sensitive

- Virologic Failure
- Immunologic Failure
- Clinical Failure

CD4 Count

Viral Load

VL $10^3$ cpm

VL 25 cpm

Losina E et al, 15th CROI 2008, #823
Pillay D, et al. 14th CROI, Los Angeles 2007, #642
Clinical Failure is Just the Tip of the Iceberg

Virologic failure leads to Immunologic failure leads to Clinical failure

Losina E et al, *15th CROI* 2008, #823
Definition of Virologic failure

2 consecutive viral loads >1000cpm after adequate exposure to ART
Facts on resistance testing

- Minimum VL required 1000 cpm
- Measures dominant HIV strains (>20%)
- Does **not** detect virus in sanctuary sites
- Does **not** detect mutant “archived” viruses selected by past treatment
- Important to obtain comprehensive past drug history & outcome of past regimens
- Most reliable for detecting Ω to current or recently discontinued
To Decide on a Third Line Regimen

Need to know all ARVs patient has experienced in the past

Need to know reasons for discontinuation

Need to know regimen patient is on at time of resistance testing

Resistance testing must be done when the patient is on the failing regimen
How do we identify a resistance mutation?

- “M” = amino acid in “wild type”
- “184” is the amino acid position in the protein
- “V” = amino acid in mutant

Designation of Mutations
Important Property of ARVs - Genetic Barrier to $\Omega$

- Number of mutational steps the virus must undergo for clinically significant drug resistance
- High genetic barrier means the virus needs to undergo many mutations to become resistant.
Pharmacokinetic & Genetic Barriers to Resistance

**NNRTIs**
- High drug levels
- Large change per mutation

**BOOSTED PIs**
- Small change per mutation
- High drug levels

**IC$_{50}$**
- Low drug trough level

**Loss in Susceptibility**
- Increasing number of mutations

Brun S et al., 8th ECCATH, Athens, October 2001, #7
## Genetic Barrier of Drug Classes

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>GB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unboosted PI</td>
<td>1</td>
</tr>
<tr>
<td>NNRTI</td>
<td>1</td>
</tr>
<tr>
<td>NRTI</td>
<td>1/2/3 *</td>
</tr>
<tr>
<td>Fusion Inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>3–8</td>
</tr>
</tbody>
</table>

*Up to 3 for thymidine analog mutations

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Local Study

- Second line treatment for $\geq 6/12$
- Clinician **convinced** patient adherent:
  - Direct questions
  - Pill counts
  - Clinic attendance
  - Adherence to script refills

Study PI: Dr. M. Gordan
Mutations Requiring Third line Agents

- No Significant PI pressure: 92
- Triple Class: 22
- PI + NRTI: 14

N = 144

27/119 = 23%
Most drug failures occur without significant mutations $\Rightarrow$ non-adherence

Resistance testing is effective but expensive means to determine adherence

Cost benefit favors resistance testing
HIVDR Early Warning Indicators (EWI)

- Pharmacy refill
- Clinic visits
- Pill counts – self reported adherence
- Clinical risk factors
- Psychosocial risk factors

*WHO recommends (http://www.who.int/hiv/topics/drugresistance/indicators/en/index.html)
Drugs for Third-line

- Lamivudine
- Tenofovir
- Raltegravir
- Boosted Darunavir
- Etravirine
Why recycle 3TC

- Well tolerated - no mito toxicity
- Low pill burden
- M184V decreases viral fitness
- Antagonizes development of TAMs, K65R, and Q151M.
- Enhances activity against AZT, d4T, TDF resistant virus
Raltegravir- **Integrase Inhibitor**

- Dose is 400 mg bd. With or without food
- Metabolized by glucuronidation
- No dose adjustment in hepatic or renal impairment. No data in severe disease.
- RAL does **not** use, induce or inhibit CYP
- Significant interaction with rifampicin 40% reduction in AUC →↑ to 800mg bid
- Overall, raltegravir was well tolerated - N, V, D, fatigue, H/A, increased CPK ? significance.
Etravirine

- 200mg bid with food.
- No dosage adjustment in renal disease.
- No dosage adjustment mild/moderate liver disease.
- N, V, D, abd pain, rash
- Hepatotoxicity- HBV/HCV
- Lipid abnormalities
- Pregnancy Category B drug
Etravirine

- Active against NVP & EFV resistant virus
- Depends on no. & type of mutations
- Prevent accumulation of NNRTI mutation.

Drug interactions
- Substrate & inducer of CYP.
- No dose adjustment DRV/r, RAL, TDF.
- Do not use with RIF.
Darunavir

- potent PI activity vs. MDR
- Always boosted with RTV (14x↑)
- Bioavailability ↑ed ~30% with food
- Rx experienced DRV/r 600/100 bd
- Rx naïve DRV/r 800/100 mg OD
- Is SA recommended in Rx-experienced
Darunavir

- Metabolized by the CYP3A4
- Mild to moderate liver disease no dosage adjustment, C/I in severe hepatic
- No does adjustment in RF

Toxicity:
- Hepatotoxicity - 0.5%
- Rash - 7%
- Glucose intolerance, lipodystrophy
- GI intolerance - N, V, D, abd pain
- Headache
Activity against PI Resistant Strains

- High genetic barrier to resistance
- ≥3 DRAMS on background of ⇒14 PI RAMS

Factors associated with high risk of DRAMs
- No. of PI experienced in past
- Duration on a failing PI
Principals Providing Third line Agents

- Decentralize - allow wide accessibility

- Doctor/ ± nurses:
  - know the drugs, drug interactions/toxicity
  - ensure adherence, regular attendance,
  - Treat “special” - maintain control, Pt. education,

- Pharmacist:
  - monitor, evaluate,
  - Supply chain/storage/accountability
  - Patient education
  - Active patient follow-up
Process to follow

Clinic

Genotyping

Central Pharmaceutical services

Central Coordinator
Motivation Forms

- Patients details
- Facility details
- Past ART - drugs/duration/ why discontinued
- Concomitant medication
- Serial recent CD$_4$/VL/ Safety bloods (ALT, Cr, WCC)
- Genotype
Contact Numbers

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Conclusion

- Third line agents are here
- Adherence - cause of failure
- Critical to detect resistance early for optimum effect of third-line agents.
- Genotypic analysis has limitations
- Consider drug interactions of third line agents.
- Engage third line process responsibly
- Use third line agents prudently
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