Diagnosing & Managing Treatment Failure

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UKZN
Overview

• CD4 and VL as biomarkers
• Causes of treatment failure
• Mechanism of Virologic resistance
• Defining Virologic failure
• Limitations of genotypic testing
• Genetic barriers to resistance
• Mutations- rationale for stepwise regimens
• Case Discussion depending on time.
Goal of HAART

Durable Viral Suppression
Undetectable Levels

Halt disease progression
Immunological recovery
Reduce OIs
Prevent drug resistance
Reduce viral transmission
Factors that Contribute to Treatment Failure

- Sub-optimal potency of regimen
- Insufficient drug levels
  - Non-adherence
  - Malabsorption
  - Drug interactions (herbal meds, OTCs)
- Resistant virus

Note! Not all Treatment failure is due to resistance.
Bio Marker

• You can only monitor if you can measure
  – Viral load
  – CD4 count

• Need to know what to expect to interpret
Value of CD4 count

- Therapeutic decisions - antiviral treatment, prophylaxis
- Differential diagnosis of OIs
- Predicting prognosis
CD4 count - 500-1400/µL

- 3 analytic steps ⇒ total WCC, % LC, % CD4
- ⇒ wide analytic variation
- Seasonal variation, diurnal variation.
- Inter-current illness
- Corticosteroids.
- Splenectomy.
- Age in adults, gender, psychological stress, physical stress, pregnancy ⇒ no effect

Trend needs to be monitored
Viral load

- Plasma HIV RNA load ⇒ most representative and sensitive test for monitoring:
  - Risk of progression.
  - Response to ART
  - Failure of ART.
- VL change >0.3 log (2 fold) is signif.
Measuring Viral Load → Earliest & most sensitive Marker of Rx Failure

- CD4 Count
  - VL $10^3$ cpm
  - VL 25 cpm

Virologic Failure
Immunologic Failure
Clinical Failure

Losina E et al, 15th CROI 2008, #823
Pillay D, et al. 14th CROI, Los Angeles 2007, #642
Viral Load Response

Expected decay in VL in ART naïve patients on potent ART:

- 0.75 - 1 $\log_{10}$ in one week
- 1.5 - 2 $\log_{10}$ in 4 weeks (<5000 cpm)
- <500 cpm in 8-16 weeks
- <50 24-48 weeks
Virologic/Treatment failure

2 consecutive viral loads >1000cpm
Treatment failure

- Check for:
  - Adherence
  - Tolerability
  - Dosing schedule
  - Drug interactions
- Repeat VL in 2 months >1000 ⇒ change regimen
Factors that contribute to the Development of Resistance

- Poor Adherence
- Insufficient Drug Level
  - Poor Potency
  - Wrong Dose
  - Drug Interactions
- Insufficient Drug Level
  - Rapid Clearance
  - Poor Activation
  - Host Genetics
  - Viral Replication in the Presence of Drug
  - Resistant Virus
- Resistant Virus
  - Transmission
- Social/Personal Issues
  - Regimen Issues
  - Toxicities
How Resistance Mutations Arise

- HIV replication $\Rightarrow$ error prone:
  - DNA Replication $1:10^9$
  - HIV Replication $1:10^4$
  - RNA Synthesis $1:10^4$
  - Airline Baggage Loss $1:200$
  - Good Typist $1:100$

- $10^9$ viral particles produced/day
  - All possible mutations emerge daily

- Persistence of mutant depends on fitness

Modified from http://hivinsite.ucsf.edu
Growth in the absence of inhibitory pressure

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

- As it proliferates, HIV undergoes spontaneous mutations in random genes due to error prone RT enzyme.
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

- The mutated HIV grows and multiplies, even in the presence of ARVs.

This virus is now RESISTANT and will continue to replicate albeit at a slower rate due to reduced fitness.
Growth in the absence of ARVs
Treatment Interruption

- Wt. - replicative advantage
- Wt. - dominant species
Resistance is Irreversible

- Once selected resistance mutations remain archived in mononuclear cells
- When drug pressure is discontinued, mutations \(\downarrow\) below 20\% \(\Rightarrow\) not detected
- Recycling drugs \(\Rightarrow\) rapid reappearance (>20\%)
  – history of drug use is critical.

Palmer et al. PNAS 103 (no. 18) 2006: 7094-7099
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 viruses selected by previous treatments that are “archived”
- Important to obtain comprehensive past drug history & outcome of past regimens
Facts on resistance testing

- Tells you what will not work, not what will work.
- Most reliable for indicating Ω to drugs pt is currently on or recently discontinued.

Resistance testing must be done when the patient is on the failing regimen.
Designation of Mutations

- 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
All drugs are not equally susceptible to resistance: **Genetic Barrier to \( \Omega \)**

- The genetic barrier to resistance describes:
  - The number of mutations the genome has to undergo to make the virus resistant to the drug.
Pharmacokinetic & Genetic Barriers to Resistance

NNRTIs
High drug levels
Large change per mutation

BOOSTED PIs
Small change per mutation
High drug levels

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

*Up to 3 for thymidine analog mutations

Potency vs. Genetic barrier

Genetic barrier to resistance
(approximate no. of mutations needed to fail)
Summary: GB to Resistance

- GB of 1 = 1 specific mutation for the drug to lose all activity
- GB of 6 = 6 mutations required for the drug to lose all activity
- Ritonavir boosted PI have a high GB
- NNRTI have a low GB
- A high GB implies there is far less selection of resistance when on a boosted PI based regimen compared to NNRTI based regimen
ABC of HIV Mutations
Effects of M184V

- High-level resistance to 3TC / FTC
- AZT, d4T activity enhanced
- TDF activity may be enhanced.
- Decreases ‘viral fitness’ – decrease VL by about 0.5Log$_{10}$
Thymidine Analog Mutations TAMs

- Selected for by AZT and d4T
- 3-6 such mutations $\Rightarrow$ reduces AZT susceptibility by 100 fold
- Accumulation of several mutations causes cross-resistance to other NRTIs
Two Pathways in the Evolution of Thymidine Analog Mutations (AZT/d4T)

TAM 1 Pathway

41L
215Y
210W

Higher-level Ω
More cross Ω within Class
Less likely to be sensitized by M184V

TAM 2 Pathway

67N
70R
219Q/E

Lower-level Ω
Less Cross Ω within Class
Likely to be sensitized by M184V

“ARV mutations” presentation: http://www.clinicaloptions.com/HIV.aspx
K65R Mutation (Non-TAM)

- Selected by ABC, ddI, TDF, d4T.
- Decreases susceptibility to ABC, ddI, TDF & 3TC.
- Increases susceptibility to AZT in the presence of few TAMS.
- Rarely occurs with TAMS & L74V.
- Does not affect susceptibility to d4T.
- Reduces viral replication esp. with M184V.
L74V Mutation (Non-TAM)

- Selected by ddI and ABC,
- Results in resistance to both drugs either alone (ddI) or together with other mutations (ABC)
- HIV quasi species expressing L74V are more sensitive to AZT and TDF
Summary - NRTI Mutations to Remember

• M184V - 3TC
• K65R – TDF, ddI, ABC, 3TC
• L74V – ddI and ABC
NNRTIs Resistance Mutations

- NNRTI mutations common at failure
- Often occurs as 1\textsuperscript{st} Ω mutation.
- Most mutations $\Rightarrow$ high level cross-Ω to other NNRTIs
- Mutations do NOT $\downarrow$ replicative fitness
- Do not continue NNRTI if VL not suppressed $\Rightarrow$ additional mutations will compromise 2\textsuperscript{nd} generation NNRTIs

Gallant J., Topics in HIV medicine
NNRTI Resistance Mutations

• K103N ⇒ high level resistance EFV & NVP
• Y181C - high level resistance to NVP & low level resistance to EFV, sensitizes to AZT
• New generation NNRTI- have higher genetic barrier to resistance – main mutation is Y181C, active against K103N mutants
• Etravirine is more robust active against most strains resistant to 1st generation NNRTIs

Johnson et al, 2007
PI Mutations

- Resistance most complex.
- 2 groups of mutations major and minor
- Major mutations develop first.
- Minor are usually compensatory mutations

### Major Protease Inhibitor (PI) Resistance Mutations

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</table>

**ATV/r**
- I
- IL
- V
- VM
- L
- VTALM
- ATFS
- V
- S
- M

**DRV/r**
- I
- IL
- VA
- V
- LM
- V
- F
- V

**FPV/r**
- I
- IL
- VA
- V
- VTALM
- V
- ATSF
- V
- S
- M

**IDV/r**
- I
- IL
- V
- VTALM
- V
- AFTS
- V
- S
- M

**LPV/r**
- I
- IL
- VA
- VM
- V
- VTALM
- V
- AFTS
- V
- S
- M

**NFV**
- N
- IL
- V
- VM
- VTALM
- AFTS
- V
- DS
- M

**SQV/r**
- VM
- VTALM
- AT
- V
- S
- M

**TPV/r**
- I
- IL
- VA
- VAM
- TL
- V
Don’t have to know mutations

HIV Drug Resistance Database Stanford

http://hivdb.stanford.edu/
Early Warning Indicators
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)
Case 1

39yr ♀ diagnosed HIV in pregnancy in 2007 CD4<200, sdNVP at delivery. 09/2010 initiated TDF/3TC/EFV. She attended every each clinic visit on time, knew names & dosages of her ART, disclosed to family Counseling ⇒ no specific barriers to adherence. History revealed a diagnosis of epilepsy on phenobarbitol 30mg dly x ~20yrs & asthma on budesonide & salbutamol inhalers.
Case 1: Clinical chart

- At 6/12 and 12/12 suboptimal viral suppression
# Case 1: Mutations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations</th>
<th>Description</th>
<th>Level</th>
<th>GSS</th>
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<tr>
<td>zidovudine</td>
<td>184V</td>
<td>Susceptible</td>
<td>1</td>
<td>1.0</td>
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<tr>
<td>zalcitabine</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>didanosine</td>
<td>184V</td>
<td>Susceptible</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>lamivudine</td>
<td>184V</td>
<td>High-level resistance</td>
<td>5</td>
<td>0.0</td>
</tr>
<tr>
<td>stavudine</td>
<td>184V</td>
<td>Susceptible</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>abacavir</td>
<td>184V</td>
<td>Potential low-level resistance</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>emtricitabine</td>
<td>184V</td>
<td>High-level resistance</td>
<td>5</td>
<td>0.0</td>
</tr>
<tr>
<td>tenofovir</td>
<td>184V</td>
<td>Susceptible</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>nevirapine</td>
<td>103N 108I 225H</td>
<td>High-level resistance</td>
<td>5</td>
<td>0.0</td>
</tr>
<tr>
<td>delavirdine</td>
<td>103N 108I 225H</td>
<td>High-level resistance</td>
<td>5</td>
<td>0.0</td>
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<tr>
<td>efavirenz</td>
<td>103N 108I 225H</td>
<td>High-level resistance</td>
<td>5</td>
<td>0.0</td>
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<tr>
<td>etravirine</td>
<td>103N 225H</td>
<td>Low-level resistance</td>
<td>3</td>
<td>0.5</td>
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</tbody>
</table>
Case 1: Interpretation

- Pt. failing for a short time
- Only NNRTI resistance (K103N, P225H, V108I) and the M184V mutation
- AZT & TDF remain viable options.
- Both std. 2nd line regimens (AZT/3TC/LPVr and TDF/3TC/LPVr) are genotypically susceptible
Case 1: Recommendations

• Should do well on a standard second-line
• Can use AZT if Hb>10 g/dl and does not have a high risk of metabolic complications.
• Test for HBV- if has active HBV use TDF.
• Intensive adherence support needed
• Use of alternative remedies & social deterrents to adherence must be explored.
• Monitor for IRIS
• Montior renal function at baseline & 3mnths – more frequently if risk factors for renal Dx
Case 1: Question

• Can you give 2 reasons why this patient might have developed ART resistance?

• Would you make any other changes to her medication?
Case 1

- sdNVP
- Phenobarbitone
- Switch antiepileptic Rx
Case 2

• 17yr ♀ on d4T/3TC/EFV since age 14 (2005).
• Baseline CD4 77cells/μl
• At initiation she severe wasting wt 23.4kg
• It was discovered there was poor disclosure to her by her family until 2010 with poor understanding of HIV and ART
Case 2: Clinical Chart

- 1\textsuperscript{st} yr good response. The VL was never fully suppressed. Yr later VL $\uparrow$ & CD4 $\downarrow$
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutations</th>
<th>Description</th>
<th>Level</th>
<th>GSS</th>
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<tbody>
<tr>
<td>zidovudine</td>
<td>41L 44D 69N 74V 118I 184V 210W 215Y</td>
<td>High-level resistance</td>
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<td>zalcitabine</td>
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<td>N/A</td>
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<td>didanosine</td>
<td>41L 44D 69N 74V 118I 184V 210W 215Y</td>
<td>High-level resistance</td>
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<td>stavudine</td>
<td>41L 44D 69N 118I 184V 210W 215Y</td>
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<tr>
<td>abacavir</td>
<td>41L 44D 69N 74V 118I 184V 210W 215Y</td>
<td>High-level resistance</td>
<td>5</td>
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<td>emtricitabine</td>
<td>41L 44D 69N 118I 184V 210W 215Y</td>
<td>High-level resistance</td>
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<tr>
<td>tenofovir</td>
<td>41L 44D 69N 118I 184V 210W 215Y</td>
<td>Intermediate resistance</td>
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<td>delavirdine</td>
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<td>efavirenz</td>
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<td>etravirine</td>
<td>103N 106M 227L 230L</td>
<td>Intermediate resistance</td>
<td>4</td>
<td>0.5</td>
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</table>
Case 2: Recommendation

- Pt. failing for long time ⇒ complex resistance pattern
- Durable suppression on std 2nd line regimen likely limited.
- Need new class of ARV ⇒ best combination integrase inhibitor, TDF/3TC & LPVr.
Case2: Questions

- Why so many resistance mutations?
- Outcomes in adolescents vs. older adults?
- What interventions would you put in place for this patient before switching her antiretroviral therapy?
Case2: Answers

- On failing regimen for a very long time, probably in the presence of suboptimal adherence- allowed virus to replicate in the presence of drug ⇒ multiple mutations.
- Adolescents well known for poorer treatment outcomes
- Intensive adherence support by a counselor, adolescent support group.
Case 4

- 45 yr ♀ with extensive ARV resistance.
- D4T/3TC/EFV - 03/03/2006 - 02/01/2009.
- AZT/ddI/LPV/r- 02/01/2009- 25/7/2011

Adherence has always been good except when admitted to hospital in 2008 ⇒ claims ARVs were not given to her.

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<th>1/08</th>
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Case 4: Genotype: 06/2011

- Major PI: M46I, I54V, L76V, V82C, I84V
- Minor PI: Q58E
- NRTI: M41L, D67N, K70R, V75M, T215F,K219Q

27th July 2011 Started on TDF/3TC/DRV/r
600/100mg BD
## Drug Resistance Interpretation: PR

<table>
<thead>
<tr>
<th>PI Major Resistance Mutations:</th>
<th>M46I, I54V, L76V, V82C, I84V</th>
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<tbody>
<tr>
<td>PI Minor Resistance Mutations:</td>
<td>None</td>
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<tr>
<td>Other Mutations:</td>
<td>None</td>
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</tbody>
</table>

**Protease Inhibitors**

- atazanavir/r (ATV/r) | High-level resistance
- darunavir/r (DRV/r)  | Intermediate resistance
- fosamprenavir/r (FPV/r) | High-level resistance
- indinavir/r (IDV/r)  | High-level resistance
- lopinavir/r (LPV/r)  | High-level resistance
- nelfinavir (NFV)     | High-level resistance
- saquinavir/r (SQV/r) | High-level resistance
- tipranavir/r (TPV/r) | High-level resistance

**PR Comments**

PIMajor

- M46I/L are nonpolymorphic PI-selected mutations that reduce susceptibility to IDV/ATV when present with other mutations. M46L also reduces susceptibility to TPV.
Case 4: progress

- 4\textsuperscript{th} August 2011 (1/52 into 3\textsuperscript{rd} line Rx) developed cough/night sweats/fever. Went to local clinic $\Rightarrow$ diagnosed smear negative TB$\Rightarrow$ Rifafour.

- 10\textsuperscript{th} August 2011 returned for follow up:

What would you do at this point?
Case 4: Progress

• 24th August patient still on rifafour and 3rd line agents despite suggestion to stop rifampicin.
• Counseled and now on H/E/Z
• 21 Sept 2011- MDR TB diagnosed and referred to KGV for MDR treatment
## Case 4: Progress

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<tbody>
<tr>
<td>310 11.2%</td>
<td>-</td>
<td></td>
<td>363 15%</td>
</tr>
<tr>
<td>15123 (log value)</td>
<td>62160</td>
<td></td>
<td>60584</td>
</tr>
<tr>
<td>Reg 3 and MDR TB tx</td>
<td>Reg3 MDR TB Tx</td>
<td>Reg3 and MDR TB tx</td>
<td></td>
</tr>
</tbody>
</table>
Case 4: Genotype: 03/2013

- Major PI: V32I, M46I, I54V, L76V, V82C, I84V
- Minor PI: L10F, L33F, Q58E
- NNRTI: K103S, V106M, F227L
**Drug Resistance Interpretation: PR**

<table>
<thead>
<tr>
<th>PI Major Resistance Mutations:</th>
<th>V32I, M46I, I54V, L76V, V82C, L84V</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI Minor Resistance Mutations:</td>
<td>L10F, L33F, Q58E</td>
</tr>
<tr>
<td>Other Mutations:</td>
<td>None</td>
</tr>
</tbody>
</table>

**Protease Inhibitors**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Resistance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>atazanavir/r (ATV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>darunavir/r (DRV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>fosamprenavir/r (FPV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>indinavir/r (IDV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>lopinavir/r (LPV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>nelfinavir (NFV)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>saquinavir/r (SQV/r)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>tipranavir/r (TPV/r)</td>
<td>High-level resistance</td>
</tr>
</tbody>
</table>

**PR Comments**

PIMajor

[Table continues with more detailed information]
Reasons for failure

- Drug drug interactions
- Poorly potent regimen
- Considering etraverine, maraviroc, Raltegravir, DRV/r, tenofovir, 3TC
Conclusion

• Monitor treatment with VL
• All treatment failure is not due to viral resistance
• Must exclude other causes of treatment failure
• Genotypic resistance testing has limitations
• Early detection of resistance and early switch to suppressive regimen imp to prevent amplification of resistance