Case presentation
ART FAILURE

Presented by Dr W. Mbara
Ithembalabantu Clinic
Discussion
Dr H. Sunpath
McCord Hospital.

• Mrs Z. S.
• Age: 48yr female from Umlazi.
• Speaks Zulu and Xhosa.
• Cannot read and write.
• She lives with her family in a household of 4 at Glebe Hostel. Husband also resides in Bizana, Eastern Cape.
• Self employed, running a spaza shop.
MEDICATION ADHERENCE

- There are no symptoms related to adverse effects of ARVs making it difficult to take ARVs.
- She reports taking all doses of her ARVs, reminded by TV programmes.
- No history of pill count imbalance and no evidence of being tired from taking ARVs.
- Z.S takes ARVs before her family members without fear because she disclosed her status, but not comfortable taking these before her friends or visitors.
Z.S actively practices African traditional religion and does not affect adherence to ARVs.

She takes herbal medications and uses Immunizer for minor ailments.
She is the first wife in a customary union. Z.S has only one sexual partner and he is the second man she has been sexually involved with. She has never had a concurrent sexual relationships.

Her husband married another wife 19 years younger than him. He admits to having long term relationship with another woman; whom he did not marry. There are other two consorts identified he currently regularly has coitus with. She finds emotional support from her sister and eldest son who also provide treatment support.

She is a teetotaller, with no history of drug use.

Although she attended 5 days literacy training; she feels inadequately trained about HIV.

She was seen by adherence counsellor for the detectable viral loads.
She was referred by the local clinic to our facility for testing because she had recurrent bacterial respiratory infections, oral ulcers, shingles, prurites and skin rashes.

- Loss of weight < 10% of Initial Body Weight.
- No Pulmonary TB, HPT, DM, ASTHMA, EPILEPSY.
- Para 4. Previous Caesarean section
- Condom not used but plans to abstain.
- Genital discharge treated at local clinic.

- Medication history
  Not on Bactrim prophylaxes.
  Reports no use of traditional medications and immune boosters
  ARV naive. No sNVP for PMTCT.

- STARTED ON STAVUDINE/LAMUVIDINE/EFAVIRENZ
- BASELINE VL= 44200 AND CD4 COUNT=193
SUBSEQUENT ASSESSMENTS

- The recovery was uneventful.
- No symptoms related to ARVs were identified.
- Adherence was reportedly good and pill count always balancing.
- She reported 100% condom use
- Not disclosed to her partner yet.
<table>
<thead>
<tr>
<th>Date</th>
<th>CD4 Count</th>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/04/2005</td>
<td>193</td>
<td>44200</td>
</tr>
<tr>
<td>30/05/2005</td>
<td>26/08/2005</td>
<td></td>
</tr>
<tr>
<td>Reg 1 a initiated</td>
<td></td>
<td>&lt;40</td>
</tr>
<tr>
<td>26/08/2005</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>22/02/2006</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>25/08/2006</td>
<td></td>
<td>6500</td>
</tr>
<tr>
<td>10/04/2007</td>
<td>235</td>
<td>13000</td>
</tr>
<tr>
<td>24/08/2007</td>
<td>235</td>
<td>56000</td>
</tr>
<tr>
<td>14/02/2008</td>
<td>Reg 2 initiated: AZT/Ddi/Kaletra</td>
<td></td>
</tr>
</tbody>
</table>
### On REGIMEN 2

<table>
<thead>
<tr>
<th>Date</th>
<th>CD4</th>
<th>VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/04/2008</td>
<td>252</td>
<td>27000</td>
</tr>
<tr>
<td>19/08/2008</td>
<td>93</td>
<td>7400</td>
</tr>
<tr>
<td>12/09/2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/02/2009</td>
<td>311</td>
<td>30000</td>
</tr>
<tr>
<td>15/07/2009</td>
<td>173</td>
<td>11000</td>
</tr>
<tr>
<td>02/02/2009</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>22/07/2010</td>
<td>229</td>
<td></td>
</tr>
</tbody>
</table>
02/03/2010 ASSESSMENT
Partner was started on ARVs. He was very ill and on Reg 1a. Baseline VL was done to be repeated in 12 Weeks. He was admitted at PMMH and referred to IALCH for Empaemia and PTB. She avoided the clinic and kept sending son to collect medications for both of them.

19/08/2010 ASSESSMENT
Discussion

- Discuss the protocols for switching treatment in cases of treatment failure. SA guidelines.
- How do we manage patients in the absence of proven genotypic resistance?
- How do we manage this patient with virological failure on Regimen 2?
CASE

CONFERENCE=management of treatment failure on ART

Dr. Henry Sunpath
Consultant HIV Unit
Dept of Internal Medicine
Mc Cord Hospital
How Does Resistance Develop?
Selective Pressure or Transmission

- Poor Adherence
  - Social/Personal Issues
  - Regimen Issues
  - Toxicities

- Insufficient Drug Level
  - Poor Potency
    - Wrong Dose
  - Host Genetics
  - Poor Absorption
    - Rapid Clearance
    - Poor Activation
    - Drug Interactions

- Viral Replication in the Presence of Drug
- Resistant Virus
- Transmission
HIV Inhibition

-**Entry inhibitors**: Maraviroc
-**Reverse transcriptase inhibitors**: Enfuvirtide
-**Integrase inhibitors**: Integrase inhibitors
-**Maturation inhibitors**: Maturation inhibitors
-**Protease inhibitors**: Protease inhibitors

Mature virus
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Abbreviation</th>
<th>Brand name</th>
<th>Adult dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>lopinavir/ritonavir</td>
<td>LPV/r</td>
<td>Kaletra®, Aluvia®</td>
<td>400mg/100mg bid</td>
</tr>
<tr>
<td>saquinavir</td>
<td>SQV</td>
<td>Invirase®</td>
<td>1000mg bid + 100mg RTV bid</td>
</tr>
<tr>
<td>indinavir</td>
<td>IDV</td>
<td>Crixivan®</td>
<td>800mg bid + 100mg RTV bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400mg bid + 400mg RTV bid</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>NFV</td>
<td>Viracept®</td>
<td>1250mg bid, or 750mg tds</td>
</tr>
<tr>
<td>fosamprenavir</td>
<td>fAMP</td>
<td>Telzir</td>
<td>700mg bid + 100mg RTV bid</td>
</tr>
<tr>
<td>atazanavir</td>
<td>ATZ</td>
<td>Reyataz</td>
<td>400mg qd or: 300mg qd + 100mg RTV qd</td>
</tr>
<tr>
<td>tipranavir</td>
<td>TPV</td>
<td>Aptivur®</td>
<td>500mg bid + 200mg RTV bid</td>
</tr>
<tr>
<td>darunavir</td>
<td>DRV</td>
<td>Prezista®</td>
<td>600mg bid + 100mg bid</td>
</tr>
<tr>
<td>ritonavir</td>
<td>RTV</td>
<td>Norvir®</td>
<td>As booster: see above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>As single PI: 600mg bid</td>
</tr>
</tbody>
</table>
## Entry inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Abbreviation</th>
<th>Brand name</th>
<th>Target</th>
<th>Adult dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td></td>
<td>Selzentry®</td>
<td>host CCR5 co-receptor</td>
<td>150mg-600mg bid</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>T-20</td>
<td>Fuzeon®</td>
<td>viral gp41</td>
<td>90mg bid s.c.</td>
</tr>
</tbody>
</table>
Intergrase inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Abbreviation</th>
<th>Brand name</th>
<th>Sub class</th>
<th>Adult dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>raltegravir</td>
<td>RGV</td>
<td>Isentress®</td>
<td>strand transfer inhibitor</td>
<td>400mg bid</td>
</tr>
</tbody>
</table>
# First line-SA guidelines (old)

<table>
<thead>
<tr>
<th>“nuke backbone”</th>
<th>Combination partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + 3TC</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>TDF + 3TC/FTC</td>
<td>+</td>
</tr>
<tr>
<td>ABC + 3TC</td>
<td>nevirapine</td>
</tr>
<tr>
<td>(d4T + 3TC)</td>
<td></td>
</tr>
<tr>
<td>&quot;nuke backbone in first line&quot;</td>
<td>nuke backbone in second line</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>AZT + 3TC</td>
<td>TNF + 3TC</td>
</tr>
<tr>
<td>TDF + 3TC/FTC</td>
<td>AZT + ddl or TDF + 3TC</td>
</tr>
<tr>
<td>ABC + 3TC</td>
<td>AZT + ddl</td>
</tr>
<tr>
<td>(d4T + 3TC)</td>
<td>AZT + ddl</td>
</tr>
</tbody>
</table>
South African Guidelines
Adult, PMTCT, Paediatrics.

Dr N Dlamini
NDOH
February 2010
### Regimens. Adults

<table>
<thead>
<tr>
<th><strong>1st line</strong></th>
<th><strong>Regimen</strong></th>
<th><strong>Note</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts eligible for treatment</td>
<td>NEW TDF + 3TC/ FTC + NVP/EFV</td>
<td>1a</td>
</tr>
<tr>
<td>Current 1&lt;sup&gt;st&lt;/sup&gt; line.</td>
<td>OLD D4T + 3TC + NVP/EFV</td>
<td>1b To remain on this old regimen if tolerated</td>
</tr>
<tr>
<td>Contraindication to TDF. Kidney disease</td>
<td>AZT + 3TC + EFV/ NVP</td>
<td>New 1c</td>
</tr>
</tbody>
</table>
### Regimens

<table>
<thead>
<tr>
<th></th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Line</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Failing D4T or AZT</td>
<td>TDF + 3TC + LPV/r</td>
<td>2a</td>
</tr>
<tr>
<td>Failing TDF</td>
<td>AZT + 3TC + LPV/r</td>
<td>2b</td>
</tr>
<tr>
<td>Salvage</td>
<td>In discussion</td>
<td></td>
</tr>
</tbody>
</table>
Optimal virologic response to therapy:
- VL < 400 after 24 weeks
- VL < 50 after 48 weeks
• In patients with sub-optimal VL reduction, perform drug-resistance testing while the patient is taking ARVs
• Genotypic testing is preferred in patients with suboptimal virologic responses or virologic failure while on 1st or 2nd line regimens
• Add phenotypic testing to genotypic testing in persons with known or suspected complex drug resistance mutations, particularly to PIs
When to Switch ART

- Where available, use VL to confirm treatment failure
  - Strong recommendation, low quality of evidence
- Where available, use VL every 6 months to detect HIV replication
- Persistent VL $>5,000$ c/mL confirms treatment failure
  - Conditional recommendation, low quality of evidence
- When VL not available, use immunologic criteria to confirm clinical failure

WHO. Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents, November 2009
Second-line ART

• Boosted PI (PI/r) + 2 NRTIs

• Which boosted PI?
  • ATV/r and LPV/r are preferred

• Which NRTI?
  • If d4T or AZT has been used in 1st-line, use TDF + 3TC or FTC
  • If TDF has been used in 1st-line, use AZT + 3TC in 2nd line.
  • Important that monitoring and early switching take place to avoid resistance to 2nd line NRTI

WHO. Rapid Advice: Antiretroviral therapy for HIV infection in adults and adolescents, November 2009
GUIDELINES FOR RESISTANCE TESTS (in discussion)

1. Failing multiple regimens
2. Second line virological failures despite good adherence? Time
3. First line failures despite adherence interventions? Time
4. ?? PEP
5. ?? Known cases of drug resistance in partners
DOH = TREATMENT FAILURE (2007)

Virological failure
VL remains persistently detectable or rebounds.
VL > 5000 as a guideline

Immunological failure
Persistently low or declining CD4 count
approx 30 % drop

Clinical failure
New or recurrent clinical events despite ARVs

The standard six month gap between viral load tests should only be shortened to three months if the viral load is > 5 000 copies/ml. The regimen should only be changed if the viral load is > 5 000 copies/ml on two consecutive occasions. (Dept of Health, 2004).
Change regimen if VL is persistently above 1000 copies/ml irrespective of CD4 and/or clinical criteria

If the viral load is above 1,000 copies/ml on ART then the test may be repeated after 1-3 months. If the VL was two times >1,000 copies/ml the patient should be changed to a second line regimen (SAHIVSOC, 2008).

There must be increased adherence counselling between the two measurements of the viral load. This may include assisting with disclosure, providing memory aids and performing pill counts if possible.
NDOH GUIDELINES-(2010)
without resistance tests-using virological criteria only

- First raised VL ->1000 copies/ml
- Do adherence interventions for first three months
- REPEAT VL AFTER 3 MONTHS
- If VL REMAINS>1000 COPIES/ML = apply for COR
Clinical Failure is Just the Tip of the Iceberg

Virologic Failure can lead to Immunologic Failure which can lead to Clinical Failure.

Losina E et al, 15th CROI 2008, #823
Consequences of Staying on a Virologically Failing Regimen

CD4 COUNT

VIRAL LOAD

VIROLOGIC FAILURE
IMMUNOLOGIC FAILURE
CLINICAL FAILURE

DRUG RESISTANCE

Losina E et al, 15th CROI 2008, #823
Pillay D, et al. 14th CROI, Los Angeles 2007, #642
Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial

Methodology and Results presented by:
Eric Shamo
Final year medical student at Ohio State Univ.

Discussion presented by:
Henry Sunpath, M.D.
Clinical Head of Medicine at McCord Hospital
Durban, South Africa
Exclusion Criteria

- <= 18 years old
- CD4 > 200 cells per uL
- Prior ART exposure (except to prevent mother-to-child transmission)
- Cannot or unlikely to attend regular follow-up (usual residence to far from study center)
- Likelihood of poor compliance
- Presence of acute infection
- On an intensive phase of antituberculosis therapy
- Contraindications to starting ARV’s
  - Hgb <80 g/L
  - Neutrophils <0.5 x10^9/L
  - ALT or AST > 5x normal
  - Cr >360 umol/L
  - Urea > 5x upper limit of normal
  - Pregnant
  - Breastfeeding
Discussion

- Given the results, the authors state that ART can be safely delivered without routine laboratory monitoring for toxic effects, but recommend CD4 monitoring starting in the 2nd year to guide the switch to second-line treatment.

- The authors postulate that only the CD4 count, and not the FBC/LFT’s, is needed to reduce the incidence of WHO Stage 4 events occurring in the CDM by recognizing ARV failure earlier and initiating 2nd line treatment earlier.
Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis

Ravindra K Gupta, Andrew Hill, Anthony W Sawyer, Alessandro Cozzi-Lepri, Viktor von Wyl, Sabine Yerly, Viviane Dias Lima, Huldrych F Günthard, Charles Gilks, Deenan Pillay
Antiretroviral-therapy rollout in resource-poor countries is often associated with limited, if any, HIV-RNA monitoring.

The effect of variable monitoring on the emergence of resistance after therapy with commonly used drug combinations was assessed by systematic review of studies.

Studies reported resistance in patients infected with HIV with a CD4 count of fewer than 200 cells per μL treated with two nucleoside analogues (including a thymidine analogue) and a non-nucleoside reverse transcriptase inhibitor.
Results

8376 patients from eight cohorts and two prospective studies were analysed.

Resistance at virological failure to non-nucleoside reverse transcriptase inhibitors at 48 weeks was 88.3% (95% CI 82.2–92.9) in infrequently monitored patients, compared with 61.0% (48.9–72.2) in frequently monitored patients (p<0.001).
Conclusions..

Lamivudine resistance was 80.5% (72.9–86.8) and 40.3% (29.1–52.2) in infrequently and frequently monitored patients, respectively (p<0.001);
The prevalence of at least one thymidine analogue mutation was 27.8% (21.2–35.2) and 12.1% (5.9–21.4), respectively (p<0.001).
Genotypic resistance at 48 weeks to lamivudine, nucleoside reverse transcriptase inhibitors (thymidine analogue mutations), and non-nucleoside reverse transcriptase inhibitors appears substantially higher in less frequently monitored patients.
RECOMMENDATIONS...first line

There is seldom an indication to test for genotypic resistance for **first-line failure**. As the first-line regimen is usually a NNRTI based regimen with 3TC, the mutations will most likely be M184V and K103N (or another NNRTI mutation). In general the only information gleaned from this test will be the number of TAMS or other mutations to the third drug in the regimen.

On failure of the **second line**, there is a stronger case to be made. However, this should be done with expert advice.
Prospective analysis of HIV-1 Drug Resistance after Virologic Failure on Antiretroviral Therapy (ART): Initial Results from a Paediatric Cohort Study from KZN, South Africa

H. Sunpath¹, H. France¹, J Kamihara², N Chelin¹, M Tarin³, MVC Marconi⁴, D Kuritzkes²,⁵, B Crotty²,⁶

¹ Dept. of Medicine, McCord Hospital, Durban SA; ²Harvard Medical School, Boston MA; ³ Dept. of Virology, Albert Luthuli Hospital & University of KwaZulu-Natal, Durban SA; ⁴HIV Research Unit, University of Texas San Antonio; ⁵ Dept. of Medicine, Brigham & Women’s Hospital, Boston MA; ⁶ Dept of Medicine, Beth Israel Deaconess Medical Center, Boston MA
Drug resistance mutations-Durban cohort (SARCS)
Lopinavir/ritonavir (LPV/r) + Two Nucleoside Analogues as Second-Line ART in Protease-Inhibitor Naïve Adults in South Africa: Outcomes and Adverse Effects

Of 3365 patients initiating ART since 2004, 192 (6%) have required second-line ART. We report outcomes for 135 patients.

Indications for second-line ART were virologic failure (72%), prior adverse effect (25%), and other (3%).

NRTI backbones used with LPV/r were: AZT/DDI (47%), AZT/3TC (29%), D4T/3TC (15%), and other (9%). After 6 months, 82% achieved virologic suppression to <50 c/mL.
RESULTS

We did not find a large difference in the percentage achieving suppression

- by NRTI backbone used with LPV/r [AZT/DDI (83%) vs. non-DDI containing backbones (82%), p=0.9),
- indication for second-line ART [virologic failure (79%) vs. adverse reaction /other indication (89%), p=0.2],
- number of prior first-line regimens [1 (78%) vs. ≥2 (89%), p= 0.08),
- or concurrent use of tuberculosis (TB) therapy during second-line ART (concurrent TB therapy (82%) vs. no concurrent TB therapy (82%), p=0.9).
No Primary Protease Resistance has been Observed in 698 Patients Initiating Therapy with LPV/r in Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Duration (Weeks)</th>
<th>VL &lt; 400 (ITT)</th>
<th>VL &lt; 50 (ITT)</th>
<th>Primary PRO Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>720¹</td>
<td>100</td>
<td>360</td>
<td>62%</td>
<td>59%</td>
<td>0/19</td>
</tr>
<tr>
<td>056³</td>
<td>38</td>
<td>72</td>
<td>N/A</td>
<td>74% OD</td>
<td>0/5</td>
</tr>
<tr>
<td>418⁶</td>
<td>190</td>
<td>96</td>
<td>N/A</td>
<td>57% OD</td>
<td>0/15 OD</td>
</tr>
<tr>
<td>940⁵ (Peds)</td>
<td>44</td>
<td>72</td>
<td>89%</td>
<td>N/D</td>
<td>0/13</td>
</tr>
<tr>
<td>863²</td>
<td>326</td>
<td>96</td>
<td>74%*</td>
<td>64%*</td>
<td>0/51</td>
</tr>
</tbody>
</table>

0/698 ARV-naive patients treated for up to 24 to 360 weeks demonstrated PI resistance (95% CI: 0 to 0.9%)

*60 week data

NFV resistance = D30N, L90M and/or M46I/L or M46I/L with confirmed reduced phenotypic susceptibility
LPV/r resistance = any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 82, 84, and 90)

Questions

- IS THIS SUCH A MAJOR ISSUE IF THEY ARE GOING ON TO SECOND LINE WITH BOOSTED LOPINAVIR?
- THE ONLY RISK EXISTS FOR INCREASED MORBIDITY AND MORTALITY WITH IMMUNLOGICAL FAILURE AT TIME OF VIROLOGICAL FAILURE...IF WE AWAIT “TOO LONG “TO SWITCH.
- THE MAJOR PROBLEM IS TO ADDRESS THEIR RISK FOR FAILURE IN THE FIRST LINE AND PROVIDE ONGOING ADHERENCE SUPPORT AFTER COMMENCING SECOND LINE.
Issues in second line failure

- Adherence
- OI’s
- Tolerability and absorption
- Rifampin use with Kaletra,
- RTV USE WITH NNRTI
- Active ARVs vs New ARVs
- Use of 3TC in all regimens
- Kaletra +/- 3TC alone
- NRTI-sparing regimens for salvage
- Add another new agent and keep on a holding regimen vs wait for RAL/ETV/DRV
TCVF=MANAGEMENT

Defined as failure of multiple nucleoside reverse-transcriptase inhibitors (RTIs), of a nonnucleoside RTI, and of a ritonavir-boosted protease inhibitor (PI)
Look for key mutations = M184V/TAMS of two pathways

K65R/L74V (ddI, ABC resistance, AZT still active)

Get a sense of resistance “density” = Classify as none, low-level, moderate, or high level resistance

Low level: M184V alone (all commonly used NRTIs have some activity)

Moderate: M184V with <3 TAMS

High level: M184V with 3 or more TAMS (esp. with 210) OR K65R

Continue 3TC/FTC - yes, why not?
TAMs:

Thymidine analogue associated mutations

6 TAMs: M41L; D67N; K70R; L210W; T215Y/F; K219Q/E/N/R

The presence of these confer cross-resistance to all NRTIs, with degree of cross-resistance increasing as number of TAMs increase

TAMs are PREVENTABLE, if patients with a failing regimen is not left on a thymidine analogue based regimen (d4T/AZT)
Dichotomous Pathways in the Evolution of TAMs

**ZIDOVUDINE OR STAVUDINE**

- **215Y**
  - **41L**
  - **215Y**
  - **210W**
  - Higher-level AZT and d4T resistance
  - More NRTI cross-resistance
  - Common with dual-NRTI therapy (ie, AZT/ddC or AZT/ddI)

- **70R**
  - **67N**
  - **70R**
  - **219Q/E**
  - Lower-level AZT and d4T resistance
  - Less NRTI cross-resistance
  - Common with AZT monotherapy

“ARV mutations” presentation: http://www.clinicaloptions.com/HIV.aspx
L74V

L74V = This mutation is selected by ddI and ABC, causing resistance to both drugs either alone (ddI) or together with other mutations (ABC). HIV quasi species expressing L74V are more sensitive to AZT and...
K65R

- **K65R**: This mutation is selected by TDF, ABC d4T and ddI. It results in an intermediate resistance against TDF, ABC, ddI, 3TC/FTC but does not cause cross-resistance to AZT.

- In subtype C however, this mutation can develop due to exposure to d4T. In an observational cohort on Malawi, where d4T was used in the first line and the regimen was changed on clinical criteria, 25% of the participants had the k65R mutation.
K65R...

- K65R very rarely occurs together with TAMs and almost never with L74V.
- K65R sensitizes to AZT or re-sensitizes AZT if there are already (few) TAMs present.
- K65R also reduces the viral replication, especially if together with M184V.
- AZT prevents the formation of K65R.
NNRTI mutations (most common K103N) are common at the time of virologic failure. They may occur as the first resistance mutation. Most mutations are associated with high level cross-resistance to other drugs in the class. These mutations do NOT reduce replicative fitness of the virus. Currently it is advisable to use NNRTIs only in fully virologically suppressed patients, as continued use during a non-suppressive regimen allows additional NNRTI mutations – important to think about for future use of 2nd generation NNRTIs now in development.
HIV Drug Resistance-NNRTIs

Mutations affecting NNRTIs:

Extensive cross-resistance between efavirenz, nevirapine, and delavirdine

Remember K103N (EFV) and Y181C (NVP)

For experts: L100I, V106A, V108I, Y188L, G190S, P225H

More are being discovered all the time

Delavirdine: K103N, V106M, Y181C, Y188L, P236L

Efavirenz: L100I; **K103N**; V106M; V108I; Y181C/I;
Y188L;G190S/A; P225H

Nevirapine: L100I; K103N; V106A/M; V108I; **Y181C/I**; Y188C/L/H;
G190A

**Multi-NNRTI resistance**: K103N; V106M; Y188L

**Multi-NNRTI resistance (accumulation of mutations)**: L100I; V106A;
V181C/I; G190S/A; M230L

Adapted from Gallant J., Topics in HIV medicine Dec 2005-Jan 2006
NEW NNRTIs

- The new NNRTI, etravirine, is more robust against mutations in the RT enzyme compared to NVP or EFV. Etravirine still works if L100I, K103N, Y188L or G190A/S are present as a single mutation.

- Mutations associated with etravirine resistance are F227C, or the combination K103N + L101I, or a combination of 3 mutations out of V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S.
Major mutations affecting PIs:

- **Atazanavir**: I50L; **I84V**; N88S
- **Fosamprenavir**: I50V; **I84V**
- **Indinavir**: M46I/L; V82A/F/T; **I84V**
- **Lopinavir/ritonavir**: V32I; I47V/A; V82A/F/T/S
- **Nelfinavir**: D30N; L90M
- **Ritonavir**: V82A/F/T/S; **I84V**
- **Saquinavir**: L90M
- **Tipranavir/ritonavir**: L33F; V82L/T; **I84V**
- **Darunavir**---

Adapted from Gallant J., Topics in HIV medicine Dec 2005-Jan 2006
PI resistance

Important PI mutations

- Resistance to PI is the most complex. Two groups of mutations can occur: major and minor. Major mutations develop first.
- In subtype C there are number of naturally occurring polymorphism that are minor PI mutations that seem to have little clinical effect.
PRAMS and hi-level PI resistance

- All PIs will have activity reduced by the presence of substitutions at 46, 54, 82, 84, and 90
- More mutations (including minor mutations) = more resistance
- Resistance to boosted PIs (LPV/r, IDV/r, SQV/r, ATV/r) is relative, not absolute
Lopanivar/ritonavir

- Studies of LPV/r used in initial therapy have not yet selected for phenotypic resistance; NRTI resistance invariably emerges first.
- In salvage therapy, 5 or more key PI mutations diminishes response to LPV/r.
- **LPV/r will select for typical PI mutations when used in PI-experienced patients.**
TCVF=MANAGEMENT

Defined as failure of multiple nucleoside reverse-transcriptase inhibitors (RTIs), of a nonnucleoside RTI, and of a ritonavir-boosted protease inhibitor (PI)
TRIO Study: RAL + ETR + DRV/RTV
Highly Effective as 3 Active Agents

- Multicenter, phase II study of darunavir/ritonavir + etravirine + raltegravir (N = 103); addition of NRTIs, enfuvirtide at discretion of physician
  - Inclusion criteria included susceptibility to darunavir and ETR based on ≤ 3 darunavir and ≤ 3 ETR RAMs
  - 59% of patients had < 1 active agent in OBR, as assessed by GSS

- HIV-1 RNA < 50 copies/mL at Week 24 in 90% (95% CI: 85% to 96%) of patients
  - Of 10 patients with detectable HIV-1 RNA at Week 24, only 3 confirmed at > 400 copies/mL
- Median CD4+ cell count increase from BL to Week 24: 99 cells/mm³ (IQR: 32-147)
- Two possibly drug-related grade 4 AEs; only 1 led to treatment discontinuation

Principles for Use of Raltegravir in ARV-Resistant Patients

- Greater likelihood of achieving virologic suppression if raltegravir introduced earlier rather than later
- Regimen containing raltegravir + 2 other active agents appears more effective than regimen containing raltegravir + 1 other active agent
- High rates of integrase resistance at virologic failure highlights importance of prescribing raltegravir with other active agents

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