WHEN TO SWITCH?

Dr. Henry Sunpath
Head of Medicine, Mc Cord Hospital
PI SA Resistance Longitudinal Cohort Study (2005 - 2009)
Best practice guidelines to switch therapy when suspecting treatment failure on HAART

AWACC-AIDS 2009

DURBAN
OVERVIEW OF PRESENTATION

• ARV Drugs in SA
• What is ARV resistance
• Treatment failure guidelines-early vs late switch
• What to switch to -first line failures
• Second line failure-TCVF
• Concluding remarks
ARVs-HIV Inhibition

- Reverse transcriptase inhibitors
  - Maraviroc
  - Enfuvirtide
- Protease inhibitors
- Integrase inhibitors
- Maturation inhibitors
- Entry inhibitors
- Mature virus
  - Protease inhibitors
  - Maturation inhibitors
Currently five classes of ARV are available:

- Nucleoside (and nucleotide) reverse transcriptase inhibitors (N[t]RTIs);
- Non-nucleoside reverse transcriptase inhibitors
- **Protease inhibitors**
- **Entry inhibitors**, subdivided into: Attachment inhibitors (still in clinical trials), Co-receptor antagonists, Fusion inhibitors;
- **Integrase inhibitors.**
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Abbreviation</th>
<th>Brand name</th>
<th>Analog</th>
<th>Adult dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>AZT (or ZDV)</td>
<td>Retrovir®</td>
<td>Thymidine</td>
<td>300mg bid</td>
</tr>
<tr>
<td>Stavudine</td>
<td>D4T</td>
<td>Zerit®</td>
<td>Thymidine</td>
<td>30mg bid</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>3TC</td>
<td>Epivir®</td>
<td>Cytidine</td>
<td>150mg bid 300mg qd</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>FTC</td>
<td>Emtriva®</td>
<td>Cytidine</td>
<td>200mg qd</td>
</tr>
<tr>
<td>Abacavir</td>
<td>ABC</td>
<td>Ziagen®</td>
<td>Guanosine</td>
<td>300mg bid</td>
</tr>
<tr>
<td>Didanosid</td>
<td>ddI</td>
<td>Videx®</td>
<td>Adenosine</td>
<td>400mg (BW ≥ 60kg) qd 250mg (BW &lt; 60kg) qd</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>TDF</td>
<td>Viread®</td>
<td>Adenosine</td>
<td>300mg qd</td>
</tr>
</tbody>
</table>
## NNRTIs

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Abbreviation</th>
<th>Brand name</th>
<th>Adult dosages¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>EFV</td>
<td>Stocrin®, Sustiva®</td>
<td>600mg qd</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>NVP</td>
<td>Viramune®</td>
<td>200mg bid</td>
</tr>
<tr>
<td>Etravirine</td>
<td>(TMC 125)</td>
<td>Intelence®</td>
<td>200mg bid</td>
</tr>
<tr>
<td>Generic name</td>
<td>Abbreviation</td>
<td>Brand name</td>
<td>Adult dosage</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>---------------------</td>
<td>-------------------------------</td>
</tr>
<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 coreceptor</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>
<tr>
<td>“nuke backbone”</td>
<td>Combination partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT + 3TC</td>
<td>Efavirenz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF + 3TC/FTC</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC + 3TC</td>
<td>nevirapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d4T + 3TC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 2nd line

<table>
<thead>
<tr>
<th>“nuke backbone”</th>
<th>Combination drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + ddI</td>
<td>lopinavir/r,</td>
</tr>
</tbody>
</table>

### nuke backbone in first line

<table>
<thead>
<tr>
<th>“nuke backbone in first line”</th>
<th>nuke backbone in second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + 3TC</td>
<td>TNF + 3TC</td>
</tr>
<tr>
<td>TDF + 3TC/FTC</td>
<td>AZT + ddI or TDF + 3TC</td>
</tr>
<tr>
<td>ABC + 3TC</td>
<td>AZT + ddI</td>
</tr>
<tr>
<td>(d4T + 3TC</td>
<td>AZT + ddI</td>
</tr>
</tbody>
</table>
OVERVIEW OF PRESENTATION

- ARV Drugs in SA
- **What is ARV resistance**
- Treatment failure guidelines-early vs late switch
- What to switch to-first line failures
- Second line failures-TCVF
- Concluding remarks
How Does Resistance Develop?
Selective Pressure or Transmission

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

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

- Viral Replication in the Presence of Drug

- Resistant Virus

- Transmission
Resistance is Irreversible

- Once selected by drug pressure, resistance mutations remain in the viral population
- Resistance assays commonly detect mutations only if present in >20% of viral population
- When drug pressure is discontinued, mutations may drop below 20% and not be detected by standard assays
- Attempts to recycle the drug (or cross-resistant drugs) may result in rapid reappearance (>20%)

How Does Resistance Develop? Selective Pressure or Transmission: Case Illustration

Continuation of a failing ART regimen after early resistance has developed selects for expansion of resistance.
CHARACTERISTICS OF DRUGS THAT PREDISPOSE TO EARLY RISK OF RESISTANCE
Genetic Barrier to Resistance

Example: GB = 4

VIRAL REPLICATION

Remaining Mutations Required For Resistance

4 MU 3 MU 2 MU 1 MU 0 MU

Mutations Already Selected

0 MU 1 MU 2 MU 3 MU 4 MU
## Genetic Barrier of Approved Drug Classes

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>GB*</th>
</tr>
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<tbody>
<tr>
<td>Unboosted PI</td>
<td>1</td>
</tr>
<tr>
<td>NNRTI</td>
<td>1</td>
</tr>
<tr>
<td>NRTI</td>
<td>1*</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

Some Key Mutations for Some Antiretroviral Drugs with a Genetic Barrier of 1

<table>
<thead>
<tr>
<th>MUTATION</th>
<th>CONFERS COMPLETE RESISTANCE TO:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
</tr>
<tr>
<td>K103N</td>
<td>EFV, NVP, DLV</td>
</tr>
<tr>
<td><strong>NRTI</strong></td>
<td></td>
</tr>
<tr>
<td>M184V</td>
<td>3TC</td>
</tr>
<tr>
<td>K65R</td>
<td>TDF</td>
</tr>
<tr>
<td><strong>PI</strong></td>
<td></td>
</tr>
<tr>
<td>D30N</td>
<td>NFV</td>
</tr>
</tbody>
</table>

http://www.hivfrenchresistance.org/2006/tab2.html
Stopping Drugs with Different Half-lives: Danger of Resistance

- After a single dose or after stopping, NVP spends more time in the zone of potential replication and therefore exerts selective pressure for longer.
- With a low genetic barrier, resistance to NVP develops relatively quickly.

Last or Single Dose

Adapted from Taylor S, et al. 11th CROI, San Francisco 2004, #131. Theoretical representation does not reflect absolute values.
The role of adherence in treatment success and failure

- Taking more than 95% of the doses translates into only one missed dose for even one medication every two weeks of a twice-daily regimen.
Relationship Between Drug Adherence and Risk of PI or NNRTI Resistance

Transmitted Drug Resistance Has Been Increasing in ARV-Naïve Patients (Data from USA)

$IC_{50} > 10$-FOLD INCREASE VIA PHENOSENSE HIV (VIROLOGIC)

<table>
<thead>
<tr>
<th>Year</th>
<th>NNRTI</th>
<th>PI</th>
<th>NRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995 (n=11)</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1996 (n=56)</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1997 (n=101)</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1998 (n=97)</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1999 (n=90)</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>2000 (n=23)</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

OVERVIEW OF PRESENTATION

- ARV Drugs in SA
- What is ARV resistance
- **Treatment failure guidelines-early vs late switch**
- What to switch to -FIRST LINE FAILURE
- Second line failurep-TCVF
- CONCLUDING REMARKS
EARLY vs LATE SWITCH?
Treatment Failure
DHHS Guideline definitions

- **Virologic failure:**
  - failure to achieve VL <400 c/mL at 24 weeks
  - failure to achieve VL <50 c/mL at 48 weeks
  - confirmed virologic rebound

- **Immunologic failure**
  - failure of CD4 count to\(\uparrow\) by 25-50 cells/mm\(^3\) in 1\(^{st}\) year

- **Clinical failure**
  - HIV-related event after 3 or more months of HAART

http://www.hopkins-aids.edu/publications/report/jan05_2.html#8
### WHO Definitions for Clinical, Immunologic and Virologic Failure

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Failure</strong></td>
<td>New or recurrent WHO stage 4 condition* (some WHO stage 3 conditions may indicate treatment failure, some WHO stage 4 conditions may not indicate treatment failure)</td>
</tr>
<tr>
<td><strong>CD4 Cell Failure</strong></td>
<td>Fall of CD4 count to pre-therapy baseline (or below); or 50% fall from the on-treatment peak value (if known); or persistent CD4 levels below 100 cells/mm³</td>
</tr>
<tr>
<td><strong>Virological Failure</strong></td>
<td>Plasma viral load above 10,000 copies/ml</td>
</tr>
</tbody>
</table>

*Some Stage 3 conditions may indicate treatment failure. Some Stage 4 conditions may not indicate treatment failure.*

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Immunological failure
Persistently low or declining CD4 count
 approx 30% drop
Clinical failure
New or recurrent clinical events despite ARVs
- Pulmonary TB may not represent clinical failure as the incidence of TB in South Africa is high

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).
SAHIV CLINICIANS GUIDELINES

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.
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
The NORA Substudy of the DART Study

- 600 patients with CD4<200 randomized to AZT/3TC/ABC vs AZT/3TC/NVP
- Further randomized to be monitored by clinical monitoring alone or clinical and immunologic monitoring
- Viral loads were assessed retrospectively
- At baseline, median CD4 count was 99 cells/mm3
- At 48 weeks, of the 300 patients randomized to NVP:
  - 23% had viral loads >50 copies/ml ("Virologic Failure")

Walker S, et al. 14th CROI 2007, Los Angeles, #506
Incomplete Virologic Suppression is Associated With Less Robust Gains in CD4 Count at 24 Months

- 1667 patients in South Africa, mean CD4 count at ART initiation was 106/μL, followed for 24 months

<table>
<thead>
<tr>
<th>SUPPRESSION (COPIES/ML)</th>
<th>% ACHIEVED OR ΔCD4/μL (95% CI)</th>
<th>24 MONTHS SINCE ART INITIATION N=482</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full (≤ 400)</td>
<td>% achieved Δ CD4</td>
<td>74.5 (70.3-78.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>306 (287-325)</td>
</tr>
<tr>
<td>Partial (401-100,000)</td>
<td>% achieved Δ CD4</td>
<td>3.9 (2.4-6.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>186 (122-250)</td>
</tr>
<tr>
<td>Not suppressed (&gt; 100,000)</td>
<td>% achieved Δ CD4</td>
<td>21.6 (18.0-25.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (55-69)</td>
</tr>
</tbody>
</table>

Losina, et al. 15th CROI 2008, Boston, # 823
Viremia on Therapy Associated with Increased Risk of Clinical Progression

- Analysis of 3023 patients in ICONA cohort study, enrolled when antiretroviral naive and monitored after initiation of HAART
  - Median, 3.8 years of follow-up*
- Increased risk of disease progression including

<table>
<thead>
<tr>
<th>VL AFTER &gt; 6 MONTHS ON HAART (COPIES/ML)</th>
<th>RR OF CLINICAL PROGRESSION (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>501-10,000</td>
<td>1.77 (0.90-3.51)</td>
<td>.09</td>
</tr>
<tr>
<td>10,000-100,000</td>
<td>2.79 (1.43-5.44)</td>
<td>.003</td>
</tr>
<tr>
<td>&gt; 100,000</td>
<td>5.34 (2.83-10.08)</td>
<td>.0001</td>
</tr>
</tbody>
</table>

*Noted as a limitation by author

Consequences of Staying on a Virologically Failing Regimen

- Virologic Failure
- Immunologic Failure
- Clinical Failure

CD4 Count
Viral Load
Drug Resistance

Losina E et al, 15th CROI 2008, #823
Pillay D, et al. 14th CROI, Los Angeles 2007, #642
Consequences of Staying on a Virologically Failing Regimen

In resource-limited settings, where adequate virologic or CD4 monitoring is not always available, waiting until clinical failure or even immunologic failure ensues means that the patient is unknowingly viremic in the presence of subtherapeutic ARV concentrations.

This is the perfect setup for drug resistance to occur*

*Brun S et al., 8th ECCATH, Athens, October 2001, #7
Consequences of a delay in switch..

- Consequences of waiting to switch from first-line to second-line regimens until immunologic or clinical failure ensues may include:
  - Increased risk of morbidity/mortality
  - Increased cost to patient (illness, hospitalization, stigma)
  - Increased resistance with potential of cross-resistance to regimen components used in second-line and therefore reduced options in second-line regimen
- Switching therapy soon after virologic rebound may decrease the likelihood of high-grade resistance to NRTIs used in second-line treatment
OVERVIEW OF PRESENTATION

- ARV Drugs in SA
- What is ARV resistance
- Characteristics of drugs that predispose to risk of early resistance
- Treatment failure guidelines-early vs late switch
- **What to switch to -FIRST LINE FAILURE**
- Second line failurep-TCVF
- CONCLUDING REMARKS
Deciding Which Drugs to Add/Remove From a Regimen

- Patient drug history
- Scientific and medical literature
- Outside opinions
- Toxicity profile
- Drug resistance testing
  - Genotypic and Phenotypic
Choice of 2\textsuperscript{nd} Line Regimen
Local Guidelines - KwaZulu-Natal\textsuperscript{1}

Regimen 2

Patients who continue to fail virologically despite demonstrated adherence may be changed to schedule 2. Before changing to schedule 2, the patient should go through the treatment readiness and education process again.\textsuperscript{1}

\textsuperscript{1}KZN ART Site Manual, 1\textsuperscript{st} Edition, 2004
Treatment options for drug-resistant virus

- Following failure of a regimen containing 2 NRTI and a NNRTI, consider 2 new NRTI + a protease inhibitor
- BUT IN THE PRESENCE OF A/E THE OPTIONS MAY BE
  - AZT/3TC/Kaletra (able to recycle 3TC if needed)
  - ?3TC/DDI/Kaletra OR 3TC/Kaletra only (options rarely used)
- AWAITING FOR TDF AND ABC TO BE MORE READILY AVAILABLE.
Prevalence of HIV-1 Drug Resistance after Virologic Failure of First-line Antiretroviral Therapy (ART) in South Africa

Marconi VC², Sunpath H¹, Tarin M³, Kuritzkes DR⁴
McCord Hospital¹, Wilford Hall Medical Center, Texas², University of KZN³, Harvard Medical School/Brigham and Women’s Hospital⁴
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
Discussion

- Resistance was found predominantly to: NRTI and NNRTI mutations-first line
- Major risk factors for viral failure with drug were found to be:
  - Recent opportunistic infections
  - Viral loads between 5000 and 100 000 copies/ml
  - **NB. Patients with REPEAT VL BETWEEN 1000 -5000 also showed genotypic resistance**
98 patients in Thailand failing first-line ART (fixed-dose combination stavudine, lamivudine, nevirapine) got genotypic resistance testing; median duration of ART was 20 months.

- 92% had >1 mutation conferring NNRTI resistance
- 95% had >1 mutation conferring NRTI resistance

Authors concluded that second-line options for 48% of patients were limited.

The limited options for second-line decreased to 8% of patients in settings where TDF and ABC were available.

Strategies for prevention of HIV-1 resistance are crucial.

Early detection of virologic failure may provide more options and better treatment outcomes.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184V</td>
<td>89%</td>
</tr>
<tr>
<td>TAMs</td>
<td>37%</td>
</tr>
<tr>
<td>K65R</td>
<td>6%</td>
</tr>
<tr>
<td>Q151M</td>
<td>8%</td>
</tr>
</tbody>
</table>

## Impact of First-Line NRTI Mutations On Second-Line NRTI Options

<table>
<thead>
<tr>
<th>First-Line NRTI</th>
<th>Second-Line NRTI</th>
<th>Resistance</th>
<th>Active Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT/d4T/3TC</td>
<td>M184V + TAMS</td>
<td>3TC, FTC, ZDV, d4T ± ABC, ± ddl, ±TDF</td>
<td>?ABC, ?ddl, ?TDF</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>M184V + L74V</td>
<td>3TC, FTC</td>
<td>ZDV, d4T, TDF ABC ± ddl</td>
</tr>
<tr>
<td>TDF/XTC</td>
<td>M184V + K65R</td>
<td>TDF, 3TC, FTC, RP ABC, RP ddl</td>
<td>ZDV, d4T</td>
</tr>
</tbody>
</table>

Choosing the Next Regimen

Principles

- Goal should continue to be viral suppression to <50 c/mL
- Resistance testing should guide choice when available
- If no testing is available, knowledge of resistance patterns should guide new regimen choice
- New regimens should contain 3 active drugs
- Be aware of cross-resistance in new drug choices
- Better response to salvage therapy associated with:
  - lower viral load at the time of treatment switch
  - use of a drug class to which the patient is naïve
  - use of ritonavir-boosted PI
RECOMMENDATIONS...first line

- There is seldom an indication to test 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.
Uses OF RESISTANCE TESTS

- RESISTANCE TESTING WILL HELP DETERMINE IF A HIGH VL IS DUE TO NON ADHERENCE OR DRUG RESISTANCE.
- PTS WHO HAVE BEEN ON SUBOPTIMAL REGIMENS
- MULTIPLE REGIMENS PRIOR TO FAILURE
- Stopped ARVs on their own due to adverse events
- BEEN ON FAILING FIRST LINE FOR MORE THAN SIX MONTHS
**Patient 1**

**ART Regimens:**

<table>
<thead>
<tr>
<th>Date Range</th>
<th>1/10/06 – 10/4/07</th>
<th>10/4/07 – 8/1/08</th>
<th>8/1/08-5/5/08</th>
<th>5/5/08-present</th>
</tr>
</thead>
<tbody>
<tr>
<td>D4T</td>
<td>D4T</td>
<td>AZT</td>
<td>AZT</td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>→</td>
<td>3TC</td>
<td>→</td>
<td>DDI/3TC</td>
</tr>
<tr>
<td>NVP</td>
<td>EFV</td>
<td>EFV</td>
<td>PN</td>
<td>Kaletra</td>
</tr>
</tbody>
</table>

**OIs:**

TB lymphnodes (1/1/95 – 1/7/95)
PTB (1/10/06)

**CD4/VL:**

<table>
<thead>
<tr>
<th>Date</th>
<th>4/9/06</th>
<th>22/2/07</th>
<th>10/4/07</th>
<th>17/7/07</th>
<th>8/1/08</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>16</td>
<td>259</td>
<td>------</td>
<td>119</td>
<td>233</td>
</tr>
<tr>
<td>VL</td>
<td>------</td>
<td>-------</td>
<td>490000</td>
<td>530</td>
<td>5300</td>
</tr>
</tbody>
</table>

**Other Meds:**

Takes epilim for epilepsy
Bactrim (PCP prophylaxis)
Took muthi in December 2007
Patient 1 (continued)

Adverse Events:
Epilepsy since 1989
PN- 1/11/06
Rash during TB treatment

Resistance Mutations:
**NRTI:** D67N, K70R, M184V, K219Q
- High-level resistance: 3TC, FTC
- Intermediate resistance: AZT
- Low-level resistance: ABC, D4T,
- Potential low-level resistance: DDI

**NNRTI:** K101E, V106M, G190A
- High-level resistance: DLV, EFV, NVP
- Intermediate resistance: ETR

No significant resistance to PI's
Patient 2

ART Regimens:

23/08/06 – 4/05/07
D4T, 3TC

6/7/07 – 5/5/08
AZT → 3TC
EFV

5/5/08 - PRESENT
DDI → 3TC
EFV → Kaletra

Lactic Acidosis
Resistance to NVP, EFV, 3TC, AZT

OIs:
PTB (2/1/06-19/7/06)
Cryptococcal Meningitis (29/8/07)

CD4/VL:

<table>
<thead>
<tr>
<th>Date</th>
<th>21/11/07</th>
<th>16/1/08</th>
<th>12/3/08</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>231</td>
<td>155</td>
<td>119</td>
</tr>
<tr>
<td>VL</td>
<td>-------</td>
<td>10000</td>
<td>15389</td>
</tr>
</tbody>
</table>

Other Meds:
Amphateracin
Fluconazole
Bactrim
Adverse Events:
Stopped ARV’s for four months in 2007
Mild PN
Lactic Acidosis 7/07

Resistance Mutations:
NRTI: D67N, K70KR, M184V, T215IT, K219Q
- High-level resistance: 3TC, AZT, FTC
- Intermediate resistance: ABC, D4T
- Low-level resistance: DDI, TDF
NNRTI: V106M, G190A, M230L
- High-level resistance: DLV, EFV, NVP
- Intermediate resistance: ETR

No significant resistance to PI’s
Patient 3

ART Regimens:

<table>
<thead>
<tr>
<th>Period</th>
<th>ART Regimen</th>
<th>Date</th>
<th>ART Regimen</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/04 – 2/11/06</td>
<td>DDI</td>
<td>2/11/06 – 6/8/07</td>
<td>D4T</td>
<td>6/8/07-15/04/08</td>
</tr>
<tr>
<td></td>
<td>3TC → DDI</td>
<td></td>
<td>3TC → D4T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Prescribed by GP)</td>
<td></td>
<td>EFV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/5/08 - present</td>
<td>Kaletra</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3TC</td>
<td></td>
</tr>
</tbody>
</table>

New service provider
(McCord)

Resistance

Opportunistic Infections:
PTB (2005) took 9 mo. Meds
PTB (27/06/07) +VE, AFB, ATB; took ciprobay, ethambutol
Oral thrush 29/10/07
Diss TB (10/03/08)

CD4/ VL:

<table>
<thead>
<tr>
<th>Date</th>
<th>CD4</th>
<th>VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/1/08</td>
<td>8</td>
<td>26000</td>
</tr>
<tr>
<td>12/3/08</td>
<td>9</td>
<td>42850</td>
</tr>
</tbody>
</table>
Patient 3 (continued)

Other Meds:
PCP Prophylaxis
2007 – took herbs with ARV’s for 2 mo.
Bactrim

Adverse Events:
PN

Resistance Mutations:
NRTI: D67DN, T69NT, K70KR, L74IL, M184V, T215FIST, K219EK
• High Level Resistance: 3TC, AZT, ABC, D4T, DDI, FTC
• Low-level Resistance: TDF
NNRTI: K101E, Y181DFVY, Y188L, G190A
• High-level Resistance: DLV, EFV, ETR, NVP

No significant resistance to PI’s
HIV Drug Resistance-NRTI

- Look for key mutations=M184V /TAMS of two pathways
  - K65R (TDF)
  - 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
Dichotomous Pathways in the Evolution of TAMs

ZIDOVUDINE OR STAVUDINE

<table>
<thead>
<tr>
<th>41L</th>
<th>215Y</th>
<th>210W</th>
</tr>
</thead>
<tbody>
<tr>
<td>67N</td>
<td>70R</td>
<td>219Q/E</td>
</tr>
</tbody>
</table>

- Higher-level AZT and d4T resistance
- More NRTI cross-resistance
- Common with dual-NRTI therapy (ie, AZT/ddC or AZT/ddI)

- Lower-level AZT and d4T resistance
- Less NRTI cross-resistance
- Common with AZT monotherapy

“ARV mutations” presentation: http://www.clinicaloptions.com/HIV.aspx
K65R...

- In subtype C, 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.
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.
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
  - F227C,
  - or the combination K103N + L101I,
  - or combination of 3 mutations out of V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S.
How good are the next options?
Boosted PI regimens

1. Adequate despite NRTI backbone after access to genotypic resistance testing
2. Good outcomes whether switch is made after access to immunological or virological monitoring
3. Excellent outcomes when used without prior exposure to PIs
4. Local data supports efficacy
Lopinavir/ritonavir (LPV/r) + Two Nucleoside Analogues as Second-Line ART in Protease-Inhibitor Naïve Adults in South Africa: Outcomes and Adverse Effects

Virologic Response to Second-Line Therapy with LPV/r in South Africa

- 3365 patients initiating ART since 2004 in Durban, 192 (6%) have required LPV/r-based 2nd-line ART, majority (72%) due to virologic failure of 1st line
- Median CD4 count at switch = 143/mm3
- NRTI backbone: AZT/DDI (47%), AZT/3TC (29%), d4T/3tC (15%)
- After 6 months, 82% achieved virologic suppression (<50 copies/ml):
  - No significant difference by:
    - NRTI backbone used
    - Indication for 2nd-line ART
    - Number of prior 1st-line regimens
    - Concurrent TB therapy
  - Significant differences were found by gender:
    - Women (89%) vs. men (71%); p = 0.01

R. Murphy et al, 15th CROI 2008, #831
NRTI backbones used with LPV/r were: AZT/DDI (47%), AZT/3TC (29%), D4T/3TC (15%), and other (9%).

number of prior first-line regimens [1 (78%) vs. ≥2 (89%), p = 0.08], or

After 6 months, 82% achieved virologic suppression to <50 c/mL.
Immunologic and Virologic Response to Second-Line ART with LPV/r in Cambodia

- 113 patients failing first-line ART
  - Majority were resistant to NNRTI and NRTI (92% M184V)
- Switched to LPV/r-based second-line ART
  - 30% switched on basis of CD4 alone
    - Median CD4 at switch: 68 cells/ml
  - 70% switched on basis of CD4 and VL
    - Median VL 4.8 log10 c/ml
- After median 10.2 months on LPV/r-based ART:
  - Median CD4 increase +105 cells/ml at 6 months and +180 cells/ml at 12 months
  - VL undetectable in 89%
  - No resistance to LPV/r detected
Clinical Outcomes on Second-line Antiretroviral Therapy in a Large Urban HIV Clinic in Johannesburg, South Africa

Matthew Fox\textsuperscript{€¥}, Prudence Ive\textsuperscript{Γ}, Lawrence Long\textsuperscript{¥}, Ian Sanne\textsuperscript{£Γ}

\textsuperscript{€} Center for International Health and Development
\textsuperscript{¥} Health Economics Research Office, South Africa
\textsuperscript{£} Right to Care, South Africa
\textsuperscript{Γ} Clinical HIV Research Unit, South Africa
ART

- ART initiated according to DOH guidelines
  - Majority of patients on d4T/3TC/EFV 1\textsuperscript{st} line
  - Standard second line with AZT/ddI/LPV\textsubscript{r} after virological failure (2VL’s >1000)
- Analysis included all patients on standard second line April 04 - June 08
- Cohort analysis of data collected prospectively as part of routine HIV care
给他们拉鲁诊所- 第二线ART

- Alive and in care:
  - 78% (95% CI: 73-82%)
  - Of 70 with a negative outcome
    - 17 (24%) died
    - 53 (76%) were LTFU

- Suppressed viral load:
  - 77% (95% CI: 72-82%)
Outcomes 24 Weeks After Virologic Failure and HIV-1 Drug Resistance Testing in KwaZulu Natal, South Africa

- The South African Resistance Cohort Study (SARCS)

Presented at CROI 2009 by the SARCS team
METHODS

The SARCS study enrolled patients with virologic failure during initial ART (plasma HIV-1 RNA viral load (VL) >1000 copies/mL). Second-line ART was determined by results of GART.

A historical control (HC) group consisted of patients with virological failure who received empirical Lop/r based second line before GART was available through the primary study.
Results...

Among patients in whom no major drug resistance mutation was detected at first ART failure, we observed inferior 24-week outcomes. This group (N=19) had a lower rate of 24-week viral suppression of 37% ($P=0.001$), and an elevated 24-week mortality of 21% ($P=0.02$).
Conclusions

An advantage of VL monitoring in sub-Saharan Africa is the potential for regimen failure to be identified early. In this study, surveillance with viral monitoring was linked with:

- a preserved CD4 count at virologic failure (median 173 cells/mm³) and
- a rapid immunological recovery with a median 24-week follow-up CD4 cell count 249 cells/mm³.
Virological monitoring combined with potent second-line ART may help patients with first-line regimen failure avert life-threatening clinical events during a vulnerable period prior to immune reconstitution.

POORLY ADHERENT PATIENTS ARE AT HIGHER RISK FOR FAILURE IN SUBSEQUENT REGIMENS

Controlled studies will be needed to determine how GART can be best utilized in resource-poor settings.
OVERVIEW OF PRESENTATION

- ARV Drugs in SA
- What is ARV resistance
- Characteristics of drugs that predispose to risk of early resistance
- Treatment failure guidelines-early vs late switch
- What to switch to -FIRST LINE FAILURE
- **Second line failure**-TCVF
SECOND LINE FAILURES

TRIPLE CLASS

VIROLOGICAL FAILURE
TCVF

Defined as failure of multiple nucleoside reverse-transcriptase inhibitors (RTIs), of a nonnucleoside RTI, and of a ritonavir-boosted protease inhibitor (PI)
Case Presentation

- 35 yr Female with H/O
- Previous multiple regimens/Was Non Naïve
- Started on AZT/3TC/EFV, then Kaletra/DDI/AZT/boosted ritonavir.
- H/O TB x2 episodes
  - Disseminated TB adenitis: Sept 2006-June 2007
- CD4: 102-baseline and 114 six months after starting at SKT. May 2008. Then 221 and 242 at 12 and 18 months resp.
- VL=61000 at baseline, then 56 000/100 000/7400
Pt was enrolled into Study in June 2008 and bloods for genotype resistance study done.

GENOTYPE RESULTS: Intermediate resistance to DDI/Liponavir and high level resistance to AZT.

Patient was then changed to 3TC/DDI/Kaletra in August 2008.

Her subsequent visits showed that patient was well, with no problems and tolerating meds well with no evidence of new OI.
Pt was reviewed in March 2009. Was well. Good wt gain, no evidence of new OI, no clinical problems. No history of adherance issues, sober habits. CD4=280 [Feb 2009] VL=3200 [Feb 2009] Pt was re genotyped on 08/03/09.
**PI Major Resistance Mutations:**  M46I, I54L, L76V, I84V  
**PI Minor Resistance Mutations:**  L10F  
**Other Mutations:**  I15V, L19I, K20R, M36I, R41K, D60E, I62IV, L63P, H69K, L89M

<table>
<thead>
<tr>
<th>Medication</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>atazanavir/r (ATV/r)</td>
<td>Intermediate resistance</td>
</tr>
<tr>
<td>darunavir/r (DRV/r)</td>
<td>Intermediate 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>Intermediate resistance</td>
</tr>
<tr>
<td>tipranavir/r (TPV/r)</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>
NRTI Resistance Mutations:  
T69N, K70KR, L74V, M184IMV, T215F, K219Q

NNRTI Resistance Mutations:  
L100I, K103NS, H221Y, M230L

Other Mutations:  
MULTI DRUG RESISTANCE = TRIPLE CLASS FAILURE

MDR = HIV
What next? No treatment options?

- Better to continue on ARVs even if virologic failure and tx options limited by resistance testing
- For patients with “no treatment options”, a boosted PI (LPV/r) should generally be at least part of the regimen
- Likely because mutated virus is less fit (ie less virulent) and higher drug levels can overcome resistance
PI resistance

- 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
Antiretroviral drug resistance and resistance testing

- 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**

Adapted from Gallant J., Topics in HIV medicine Dec 2005-Jan 2006
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>N/A</td>
<td>0/5</td>
</tr>
<tr>
<td>418⁶</td>
<td>190</td>
<td>96</td>
<td>N/A</td>
<td>N/A</td>
<td>0/15 QD 0/8 BID</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-naïve 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)

Case Summary-Durban.
During 27,441 person-years of observation,

1. Extensive TCVF developed in 167 patients.
   2. 90% already experienced failure with 7 drugs,
   3. 58% had experienced failure with two different ART regimens.
   4. developed resistance to multiple agents because of sequential monotherapy or dual therapy.
By 10 years of therapy, the cumulative risk for extensive TCVF was 9%.

TCVF = lower in patients who initiated ART in more-recent years and higher in patients who had experienced previous virologic failure on combination ART.
Patients who started ART with CD4 counts <200 cells/mm$^3$ had a higher rate of TCVF than did those who started at counts 200/mm$^3$ (12% vs. 6%).

The death rate by 5 years from the time of TCVF was about 10%, even in patients initiating ART at CD4 counts <200 cells/mm$^3$.

These findings suggest that current classes of antiretroviral medications will allow successful treatment of most patients for many years;

This prospect is particularly important in resource-scarce settings, where the number of drugs available is limited.
OVERVIEW OF PRESENTATION

- ARV Drugs in SA
- What is ARV resistance
- Characteristics of drugs that predispose to risk of early resistance
- Treatment failure guidelines: early vs late switch
- What to switch to - FIRST LINE FAILURE
- Second line failure - TCVF

CONCLUDING REMARKS
Conclusions

- Second-line ART should be considered a priority for patients failing first-line ART in resource poor settings.
- Change of regimen after virological failure will prevent drug resistance developing to drugs in the same class and enable longer use of second line.
- Third line may not be needed if changes are made earlier with newer drugs.
Proposals for new DOH recommendations

- IF VL >1000 copies/ml at least 6 months after initial HAART or change in regimen

A) If CD4 decrease >30 % from baseline or previous record, even in the absence of signs of clinical failure

- Confirm VF after one month of adherence intervention and if VL still >1000, apply for regimen 2

If any pt has signs of clinical failure, do VL AND CD4 count and apply steps above
DOH recommendations...proposal

B) IF CD4 COUNT INCREASING

- CONDUCT INTENSE ADHERENCE COUNSELING AND REPEAT CD4 COUNT AND VL AFTER THREE MONTHS
- IF CD4 DECREASES .30 % FROM PREVIOUS RECORD AND VL > 1000, CONSIDER REGIMEN CHANGE
- Repeat procedure 3 months later if CD4 is stable and poor adherence still suspected by VERY HIGH/CONSIDERABLE INCREASE IN VL
References...


References...


Hoffmann C et al. The rate of developing ART resistance during HIV viraemia on HAART in South Africa. *Poster 656 CROI*, Feb 2009, Montreal

Acknowledgements

- South African Resistance Cohort Study (SARCS) Group: Henry Sunpath3, Zhigang Lu6, Douglas Ross4, Elena Losina6, Bruce D. Walker6, Daniel R. Kuritzkes1 Vincent C. Marconi1,2*, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; 2Tri-Service AIDS Clinical Consortium, Wilford Hall USAF Medical Center, Lackland AFB, TX, USA; 3McCords Hospital, Durban, KZN, SA; 4St. Mary’s Hospital, Mariannhill, KZN, SA; 5Inkosi Albert Luthuli, Nelson Mandela School of Medicine, Durban, KZN, SA; 6Massachusetts General Hospital, Harvard Medical School, Boston, USA
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- The South African National ARV Rollout Plan
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1. FPD COURSEWORK BOOK-
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2. PEER TO PEER REVIEW ABBOTT MANUAL
   (Sibtaiam/Sunpath)