Antiretroviral therapy in treatment-experienced patients

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At the conclusion of this interactive session, participants should be able to:

- Implement strategies for managing treatment-experienced patients with particular attention to addressing drug resistance
- Design treatment regimens based on an assessment of treatment toxicity and its influences on later regimen redesign and the incorporation of newer agents

Outline

- Approach to treatment failure
- Selecting PIs in salvage
- How to use newer agents (maraviroc, etravirine, raltegravir)
- Resistance to newer agents
- Switching regimens in patients who are suppressed: recent studies

Changing Treatment Goals for Treatment-Experienced Patients

<table>
<thead>
<tr>
<th>2003: Moderately Well-Tolerated and Effective Drugs</th>
<th>2009: Well Tolerated and Effective Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full viral suppression is an achievable goal</td>
<td>Preserving immune function</td>
</tr>
<tr>
<td>- Newer drugs in old classes</td>
<td>- Prevent new AIDS-defining events</td>
</tr>
<tr>
<td>- Drugs in newer classes</td>
<td>- Maximize reduction in plasma HIV RNA levels</td>
</tr>
<tr>
<td>Use multiple active drugs to achieve full suppression</td>
<td>- Minimize toxicity</td>
</tr>
<tr>
<td>Minimize toxicity (NRTIs, T-20)</td>
<td>“switch out” old drugs which are effective virologically but which are causing low-grade symptoms or toxicities</td>
</tr>
</tbody>
</table>

Antiretroviral Treatment Failure

- Often associated with virologic failure, immunologic failure, and/or clinical progression
- Factors associated with an increased risk of treatment failure:
  - Baseline CD4 and HIV RNA
  - Unrecognized baseline resistance (archived) not identified by resistance testing
  - Incomplete medication adherence and missed clinic appointments
  - Drug adverse events and toxicity
  - Suboptimal pharmacokinetics
  - Occult dual-tropic or X4-tropic HIV when CCR5 antagonists are used


General Approaches to the Management of Virologic Failure

- Goal is to achieve plasma HIV RNA <50 copies/mL
- Identify fully active agents
  - Add at least two fully active new drugs and at least one agent from a new class
  - Residual activity of NRTIs useful in maintaining potency of salvage regimen
  - Drug potency and susceptibility more important than number of drugs (try to preserve treatment options for the future)
  - Adding a single active drug is not recommended
- Discontinuing or briefly interrupting therapy is not recommended
  - Increases risk of clinical progression

Picking PIs in treatment-experienced patients

- Use all prior genotypic and phenotypic resistance tests
- Generally darunavir/r and tipranavir/r most active
- Tolerability (pill burden) and toxicity (hyperlipidemia, transaminitis) generally favor darunavir/r
- Sometimes ritonavir intolerance leads to use of unboosted PIs (atazanavir, fosamprenavir)

Level of evidence: expert opinion

Weighing the mutations associated with a diminished response to darunavir

<table>
<thead>
<tr>
<th>Estimated increase in FC</th>
<th>&lt; 2</th>
<th>2 to 3</th>
<th>3 to 4</th>
<th>&gt; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations</td>
<td>V11I</td>
<td>V32I</td>
<td>L33F</td>
<td>I50V</td>
</tr>
<tr>
<td></td>
<td>I54L</td>
<td>I47V</td>
<td>L76V</td>
<td>I84V</td>
</tr>
<tr>
<td></td>
<td>G73S</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Determined by multiple regression analyses of the 1,465 screening samples from the POWER 1, 2 and 3 studies

P Flandre et al. XV Int Drug Resist Workshop, Sitges, Spain, Abstract 73, 2006

TPV and DRV Mutations and Phenotypic Cut-offs

<table>
<thead>
<tr>
<th>Assay/Cutoff</th>
<th>Phenosense TC for Reduced Activity</th>
<th>Phenosense TC for No Response</th>
<th>VircoTYPE TC for Minimal Response</th>
<th>VircoTYPE TC for Maximal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPV</td>
<td>≥ 2</td>
<td>≤ 3</td>
<td>≤ 1.2</td>
<td>≥ 4</td>
</tr>
<tr>
<td>DRV</td>
<td>&gt; 10</td>
<td>≥ 90</td>
<td>&lt; 3.4</td>
<td>≥ 96.9</td>
</tr>
</tbody>
</table>


NNRTI Hypersusceptibility

- first described in association with high level AZT/3TC resistance (Whitcomb, 7th CROI, 2000)
- found in 20% of highly drug-experienced patients (Haubrich, 4th Intl Workshop on HIV Drug Resistance)
- Has been associated with superior virologic responses in various clinical trials (Haubrich, AIDS 2002; 16:F33-40)
- Is most clinically meaningful if new classes of drugs are still available at time of switch (PI's, entry inhibitors)
- Etravirine hypersusceptibility has also recently been commonly documented in association with high level NRTI resistance

DUET Studies: Etravirine in Treatment-Experienced Patients

- Two phase 3, 96-week studies
  - Treatment-experienced patients with evidence of resistance to current NNRTIs
  - Stratified by baseline enfuvirtide use, previous darunavir use, and HIV RNA (<30K, ≥30K copies/mL)
- Treatment arms
  - Etravirine 200 mg bid or placebo
  - All patients received optimized background therapy
  - Darunavir + RTV plus optimized NRTIs and optional enfuvirtide

### DUET Studies: Combined 48-Week Analysis

#### Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>HIV RNA &lt;50 Copies/mL</th>
<th>CD4 Cell Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine</td>
<td>61%</td>
<td>48%</td>
</tr>
<tr>
<td>Placebo</td>
<td>40%</td>
<td>73%</td>
</tr>
</tbody>
</table>

#### CD4 Cell Gain (cells/mm³)

<table>
<thead>
<tr>
<th></th>
<th>Etravirine (n=599)</th>
<th>Placebo (n=604)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>61%</td>
<td>40%</td>
</tr>
</tbody>
</table>

### DUET 1 and 2: Virologic response (<50 c/mL) in etravirine arms by BL mutations at Week 24

- 13 BL resistance-associated mutations (RAMs) associated with a decreased response to ETR:
  - V90I
  - K101E/P
  - A98G
  - V179D/F
  - L100I
  - G190A/S
  - V106I
  - Y181C/I/V

#### Notes:
- If >3 mutations present, response similar to PBO
- Note: 14% had >2 ETR RAMs

### DUET: Combined Effect of ETR and DRV FC on Virologic Response at Week 24 (TLOVR)

- ETR-treated patients; not de-novo ENF (n=406)

### Updated list of etravirine RAMs: weight factors for 2008 etravirine RAMs

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Prevalence in the panel of 4,246 HIV-1 clinical isolates, %</th>
<th>Weight factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y181T</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Y181T</td>
<td>0.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Y181C</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Y181C</td>
<td>0.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Y181C</td>
<td>0.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Y181C</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Y181C</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Y90I</td>
<td>0.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Y90I</td>
<td>0.6</td>
<td>1.5</td>
</tr>
<tr>
<td>A98G</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>A98G</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>V179D</td>
<td>0.9</td>
<td>1</td>
</tr>
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<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>V179D</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>V106I</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
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<td>0.9</td>
<td>1</td>
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</tr>
<tr>
<td>V106I</td>
<td>0.9</td>
<td>1</td>
</tr>
</tbody>
</table>

*V179F was never present as single etravirine RAM (always with Y181C)
**BENCHMRK Studies**

- **Two phase 3, 156-week studies**
  - Treatment-experienced patients with triple-class resistance
  - Stratified by baseline HIV RNA, enfuvirtide and darunavir use in optimized background therapy (OBT)
- **Treatment arms**
  - Raltegravir 400 mg twice daily + OBT
  - Placebo + OBT


**BENCHMRK Combined Analysis: 96-Week Virologic Failure and Safety**

<table>
<thead>
<tr>
<th>CD4 cell gain (cell/mm³)</th>
<th>OBT Alone (n=377)</th>
<th>Raltegravir 400 mg bid (n=385)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median CD4 (cell/mm³)</td>
<td>123</td>
<td>119</td>
</tr>
<tr>
<td>Mean HIV RNA (log₁₀ copies/mL)</td>
<td>4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>AIDS (%)</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>OBT (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New enfuvirtide</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>New darunavir</td>
<td>36</td>
<td>36</td>
</tr>
</tbody>
</table>

CD4 cell gain: *P*<0.001 versus OBT alone. Virologic failure:

1) >1 log₁₀ decrease in HIV RNA from baseline and HIV RNA >400 copies/mL at week 16
2) >1 log₁₀ increase in HIV RNA above nadir or HIV RNA >400 copies/mL from nadir after response of HIV RNA <400 copies/mL.


**How many active drugs are needed?**

- **BENCHMRK subset analysis based on use of raltegravir, darunavir, and enfuvirtide**

Cooper D and Steinhagle R, et al, 15th CROI; Boston, MA (2008), Abstracts 788 and 789

**BENCHMRK 1 & 2: Evolution From N155 to Q148 Mutations Over Time**

Evolution of high level integrase inhibitor resistance in treatment experienced patients at SFGH and SFVAMC

H. Hatano et al, 16th CROI, Montreal, 2009, Abstract 621

Darunavir/r, etravirine and raltegravir in treatment-experienced patients in TRIO: proportion of patients with VL <50 copies/mL at Week 24 (M=F)


Tropism Profile in SCOPE and HOMER Cohorts are Influenced by CD4 Counts and by Treatment Status

Hunt et al., JID, 2006, 194:926-30

Sensitivity of Enhanced Trofile - X4 Minor Variant Detection

J Reeves et al, 17th Drug Resistance Workshop, Sitges, Spain, 2008, Abstract 118

TRIO study: combining raltegravir, darunavir and etravirine

24 week, phase II, non-comparative, multicenter trial

- N = 103 pts viremic on current regimen
  - HIV RNA > 1000 mL, any CD4 count
- Documented multidrug-resistant virus
  - ≥ 3 NRTI mutations (2006 IAS list)
  - ≥ 3 major PI mutations (2006 IAS list)
  - Susceptible to DRV (≤ 3 DRV mutations*)
- Previous virologic failure on NNRTIs
- Susceptible to ETR (< 3 ETR NNRTI mutations)

- All initiate raltegravir, darunavir/r and etravirine (naïve to all)
- Additional ARVs allowed: NRTIs and ENF (based on clinical judgment)

* V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V

Yazdanpanah, et al. 17th IAC; Mexico City, Aug 3-8, 2009; Abstract THAB0406.
MOTIVATE Studies

- Combined analysis of two 48-week phase 2b/3 trials
  - Triple-class experienced (≥ triple-class resistance)
  - R5-only virus
  - Stratified by baseline HIV RNA (<100K, ≥100K copies/mL) and enfuvirtide use
  - R-optimized background therapy (OBT)

- Treatment arms
  - Maraviroc 150 mg once daily
  - Maraviroc 150 mg twice daily
  - Placebo


Patients receiving a PI (except tipranavir) and/or delavirdine in their OBT received maraviroc 150 mg; all others received 300 mg.

<table>
<thead>
<tr>
<th></th>
<th>Maraviroc</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Once Daily</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>Median CD4 (cells/mm$^3$)</td>
<td>171</td>
<td>167</td>
</tr>
<tr>
<td>Mean HIV RNA (log$_{10}$ copies/mL)</td>
<td>4.85</td>
<td>4.80</td>
</tr>
<tr>
<td>OBT (%)</td>
<td>64%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Maraviroc

OBT Alone

Maraviroc

CD4 cell gain (cells/mm$^3$)

Treatment failure (%)

CD4 gain at time of failure (cells/mm$^3$)

Remaining R5

RS to X4


MOTIVATE Combined Analysis: Immunologic Outcomes at Week 48

HIV RNA <50 Copies/mL

Week: 48

Maraviroc + OBT

Maraviroc

OBT Alone

Week: 48

Morning dose

Evening dose

Concomitant treatment

- Includes a potent CYP3A4 inhibitor (→ Cmax and AUC)
  - For example: Efavirenz, Rifampin, phenytoin, carbamazepine, phenobarb

- Includes a CYP3A4 inducer (↓ Cmax and AUC)
  - For example: Rifampin, phenytoin, carbamazepine, phenobarb

Maraviroc drug interactions and dose modifications

YES

NO

Regardless of other agents in the regimen

SWITCHMRK: Study Design

- Identical, multicenter, double-blind, randomized studies
- Enrolled patients with HIV RNA < 50 c/mL on LPV/r BID regimens in combination with at least 2 NRTIs
  - No limit on number of prior ART regimens
  - Prior virologic failure not an exclusion
  - No lipid lowering therapy for at least 12 weeks
- Randomized (1:1) to continue LPV/r or switch to RAL
- Endpoints:
  - Lipids
  - Virologic failure

Eron J, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 79aLB.
SWITCHMRK 1 & 2: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SWITCHMRK 1</th>
<th>SWITCHMRK 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAL (N=174)</td>
<td>LPV/r (N=174)</td>
</tr>
<tr>
<td>HIV RNA ≤ 50 copies/mL</td>
<td>94.3%</td>
<td>92.5%</td>
</tr>
<tr>
<td>Mean CD4 count (cells/mm³)</td>
<td>478</td>
<td>508</td>
</tr>
<tr>
<td>LPV/r ≤ 1 yr</td>
<td>16.7%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Median yrs of prior ART (min, max)</td>
<td>3.3 (0.3, 22.3)</td>
<td>3.6 (0.5, 20.2)</td>
</tr>
<tr>
<td>Median # of prior ART (min, max)</td>
<td>5.0 (4.0, 16.0)</td>
<td>5.0 (2.0, 15.0)</td>
</tr>
</tbody>
</table>

Eron J, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 70aLB.

SWITCHMRK 1 and 2: Virologic Outcomes (NC = F)

<table>
<thead>
<tr>
<th></th>
<th>SWITCHMRK 1</th>
<th>SWITCHMRK 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL</td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td>Number of Contributing Patients</td>
<td>174</td>
<td>174</td>
</tr>
</tbody>
</table>

Eron J, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 70aLB.

ANRS 138: Enfuvirtide to Raltegravir Switch in Highly Experienced Patients

- Patients with triple-class resistance and HIV RNA <400 c/mL
- Randomized to continue ENF (n=85) or switch to RAL (n=84)
  - Median of 13.6 years prior ART and 2.3 years on ENF
- Week 24 Results:
  - 89% <50 c/mL in both arms
  - Virologic Failure: 1 in each arm (P = 0.01%, 95% CI 4.4, 4.5)
  - No significant CD4 changes in either arm
  - Grade 3/4 AE: 11% ENF arm, 19% RAL arm (P=0.12)
- Conclusion: Raltegravir maintains suppression when substituted for ENF in suppressive regimens

De Castro N, et al. 16th CROI; Montreal, Canada; February 8-11, 2009. Abst. 572.

New ARV choices for salvage therapy: conclusions (1)

- most patients should be able to be suppressed with simultaneous approval of many new agents, but resistance to each of these new agents is possible
- the availability of maraviroc, etravirine, and raltegravir is a "great moment" for our patients but there won't be another moment like this in a long time
- our understanding of resistance to the newer agents continues to be refined (etravirine, integrase inhibitors)
- ritonavir-boosted PIs remain the backbone of most salvage regimens and most patients in studies of new agents (MOTIVATE, BENCHMRK, DUET, TRIO) received them in these studies. The SWITCHMRK study suggests this class should only be discontinued/switched with caution

Level of evidence: expert opinion
New ARV choices for salvage therapy: conclusions (2)

- use at least 2 new agents in failure, one new class and one fully susceptible drug in previously used classes; recycled NRTIs are likely to have residual activity and may be continued
- poor adherence may have disastrous consequences as patients are exposed to the new classes (especially for integrase inhibitors)
- new choices allow us to discontinue older agents if associated with toxicity or intolerance (NRTI sparing, r/PI sparing, discontinuation of T-20)

THANK YOU FOR YOUR ATTENTION!!

Level of evidence: expert opinion