Management of The Treatment Experienced Patient

Considerations for Changing Therapy

- Clinical status of the patient
- HIV-1 RNA as determined by 2 separate, consecutive tests
- CD4 cell count
- Potential viral resistance
- Remaining treatment options
- Medication adherence
- Patient education

Treatment Regimen Failure

- Broadly includes all possible reasons for failure:
  - Baseline patient factors (pretreatment HIV-1 RNA and CD4 count; prior AIDS; drug resistance; co-morbidities)
  - Suboptimal adherence/missed appointments
  - Drug side effects/toxicity
  - Suboptimal PK (variable absorption, metabolism, and/or reservoir penetration; adverse drug-drug interactions)
  - Suboptimal regimen potency

- Often associated with virologic, immunologic, and/or clinical progression
  - Can occur independently (more often) or simultaneously

(1) Virologic Failure

- Incomplete or lack of HIV-1 RNA response:
  - Not achieving <400 copies/mL by 24 weeks or <50 copies/mL by 48 weeks on first regimen (treatment naïve patients)
  - A higher baseline HIV-1 RNA may impact the time course of the patient’s response
- Virologic rebound:
  - Repeated viremia after virologic suppression
  - Ongoing viral replication in the presence of treatment promotes selection of drug resistance mutations
  - 20-63% of patients in clinical cohort studies

(2) Immunologic Failure

- Failure to increase 25-50 cells/mm$^3$ above baseline CD4 count over 1st year of therapy
- Experiencing a decrease to below baseline CD4 count on therapy
- Lower baseline CD4 count may be associated with a reduced CD4 response
- Occurred on average 3 years after virologic failure in patients on the same PI containing regimen in clinical studies
(3) Clinical Progression

- Occurrence or recurrence of HIV-1-related events
  - Examples:
    - Thrush (oral candidiasis)
    - Weight loss
    - Night sweats
    - Headaches
    - Opportunistic infections
  - Events should take place after at least 3 months on potent therapy

Assessment of Treatment Regimen Failure

- Once identified, the cause of failure needs to be explored:
  - Physical examination
  - Medical history
    - Course of HIV-1 RNA and CD4 count changes
    - Occurrence of any HIV-1-related events
    - Antiretroviral treatment history

Management of Treatment Regimen Failure

- Distinguish among the reasons for failure
  - Examples:
    - Non-adherence with medications
    - Medication toxicities
    - Suboptimal pharmacokinetics
    - Suboptimal regimen potency
    - Development of viral drug resistance
  - Management approaches will be different

- If non-adherence is identified:
  - Address the underlying cause(s)
    - Medication-taking schedule inconvenient?
    - Forgetfulness? – reminder devices, organizers
    - Access to antiretroviral agents?
    - Depression?
    - Active substance abuse?
  - May need to simplify the treatment regimen
    - Decrease pill burden
    - Lengthen dosing interval

- If poor tolerability is identified:
  - Assess the side effects and their duration
  - Offer symptomatic treatment (ie. anti diarrheals, antiemetics)
  - Change one drug within the same class (ie. atazanavir for lopinavir/ritonavir-related lipid elevations; tenofovir for zidovudine-related anemia)
  - Change drug classes (ie. PI to NNRTI or vice versa)

- If pharmacokinetic issues are suspected:
  - Review food/fasting requirements
  - Review GI symptoms for possibility of malabsorption
  - Review concomitant medications (including OTCs and herbal supplements) for adverse drug-drug interactions
  - Measure antiretroviral drug levels (TDM) in plasma (applies to PIs and NNRTIs only)
Summary

- Treatment regimen failure involving non-adherence, poor tolerability, or PK issues does not always lead to virologic, immunologic, or clinical failure
- Often these underlying causes can be addressed without changing the entire treatment regimen

Resistance

- Ongoing viral replication in the presence of antiretroviral therapy inevitably leads to the development of drug resistant virus which can then lead to virologic, immunologic and/or clinical failure

Management of Treatment Regimen Failure

- If virologic, immunologic, and/or clinical failure is determined:
  - Thoroughly review antiretroviral treatment history and determine remaining options
  - Clarify goals: complete virologic suppression may not always be possible; depends upon the extent of prior treatment experience
  - Obtain resistance testing while the patient is still taking the failing regimen (ideal) or within 4 weeks of treatment discontinuation

Types of Resistance Testing

(1) Genotyping

- Detects drug resistance point mutations in specific HIV genes (PRO, RT)
- ↓ ability of an ARV to bind to its target enzyme
- Mutations are detected by sequencing genes
- Turnaround time: 1-2 weeks
- Interpretation of resulting point mutations and cross-resistance can be complex
- Consultation with specialist is recommended

(2) Phenotyping

- Measures the ability of viruses to grow in various concentrations of single antiretroviral drugs
- Turnaround time: 2-4 weeks
- More expensive than genotyping
- Ratio of IC₅₀ for the patient’s virus to IC₅₀ for the reference virus reported as a fold change in IC₅₀
- Interpretation can be complex
- Consultation with specialist is recommended
Resistance Testing: Limitations

- Assays lack uniform quality assurance
- Insensitive for minor (<10-20%) viral species in the patient's viral population
- Difficult to conduct on HIV-1 RNA < 1000
- Correlation is often poor between genotype and phenotype reports
- Interpreting an absence of resistance must be considered along with treatment history

Initial Regimen Failure

<table>
<thead>
<tr>
<th>Initial Regimen</th>
<th>Change To:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI + 2 NRTIs</td>
<td>PI ± RTV + 2 new NRTIs*</td>
</tr>
<tr>
<td>PI ± RTV + 2 NRTIs</td>
<td>new PI* + RTV or NNRTI + 2 new NRTIs*</td>
</tr>
<tr>
<td>3 NRTIs</td>
<td>PI ± RTV or NNRTI + 2 new NRTIs*</td>
</tr>
<tr>
<td></td>
<td>NNRTI + PI + RTV + new NRTI(s)*</td>
</tr>
</tbody>
</table>

*Guided by resistance testing results

Limited to Intermediate Prior Treatment

<table>
<thead>
<tr>
<th>Clinical Reason</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance Test</td>
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</tr>
<tr>
<td>No Response</td>
<td>Single Drug Regimen</td>
</tr>
<tr>
<td>Multi-Drug Resistance</td>
<td>Multi-Drug Regimen</td>
</tr>
<tr>
<td>Off Therapy? Non-adherence</td>
<td>Change Single Drug or Change Entire Regimen</td>
</tr>
<tr>
<td>Change Single Drug or Change Entire Regimen</td>
<td>Change Entire Regimen</td>
</tr>
<tr>
<td>Change Enzyme Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Resume Same Regimen</td>
<td></td>
</tr>
<tr>
<td>Change Entire Regimen</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the DHHS treatment guidelines.

Extensive Prior Treatment

<table>
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<th>Clinical Reason</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance Test</td>
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</tr>
<tr>
<td>No Response</td>
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</tr>
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<td>Multi-Drug Resistance</td>
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<td>Change Single Drug</td>
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</tr>
<tr>
<td>Change Entire Regimen</td>
<td>Resume Same Regimen</td>
</tr>
<tr>
<td>Change Entire Regimen</td>
<td>Change Same Regimen</td>
</tr>
<tr>
<td>Change Enzyme Inhibitor</td>
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<td></td>
</tr>
<tr>
<td>Change Entire Regimen</td>
<td></td>
</tr>
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Treatment Experienced Patients: Goals of Therapy

- Limited to intermediate prior treatment:
  - Re-establish maximal viral suppression
  - Consider changing therapy early to prevent further development of resistance mutations
- Extensive prior treatment:
  - Re-establish maximal viral suppression
  - Preservation of immune function
  - Prevention of clinical progression
  - Balance benefits of partial viral suppression with risk of additional resistance mutations
General Considerations

- Use treatment history, past and current resistance tests to identify ≥ 2 active ARVs.
- If unavailable, consider PK enhancement and/or re-cycling ARVs with partial activity.
- Try to add a drug with activity against drug-resistant virus (PI + RTV) and one with a new mechanism of action (enfuvirtide) to an optimized background regimen.
- Avoid adding only 1 active ARV → resistance.
- Drug potency is more important than # of drugs.

RESIST Entry Criteria

- ≥3 consecutive months’ experience with 3 ARV classes (NRTIs, NNRTIs, PIs).
- ≥2 PI-based regimens for ≥3 mos.
- Any CD4 count.
- HIV-1 RNA (VL) ≥1000 copies/mL.
- Viral isolate with ≥1 1st protease mutation at 30N, 46I/L, 48V, 50V, 82A/F/L/T, 90M.
- Viral isolate carrying <3 mutations at codons 33, 82, 84, 90.

RESIST-1 (R-1) and RESIST-2 (R-2): 48 week meta-analyses demonstrate superiority of protease inhibitor (PI) tipranavir + ritonavir (TPV/r) over an optimized comparator PI (CPI/r) regimen in antiretroviral (ARV) experienced patients.

P. Cahn¹ and C. Hicks² for the RESIST-1 and RESIST-2 Study Teams
1. Fundacion Huesped, Buenos Aires, Argentina
2. Duke University, Durham, NC, USA

48 Week Results:

<table>
<thead>
<tr>
<th></th>
<th>TPV/r</th>
<th>CPI/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-1</td>
<td>R-2</td>
<td>R-1</td>
</tr>
<tr>
<td>pts randomized</td>
<td>311</td>
<td>435</td>
</tr>
<tr>
<td>baseline median VL</td>
<td>4.81</td>
<td>4.78</td>
</tr>
<tr>
<td>baseline median CD4</td>
<td>123</td>
<td>175</td>
</tr>
<tr>
<td>treatment response (≥1 log¹⁰ decrease at 48 weeks)</td>
<td>33.8%*</td>
<td>15.3%*</td>
</tr>
<tr>
<td>median time to failure</td>
<td>113 days*</td>
<td>9 days*</td>
</tr>
<tr>
<td>mean change in VL (LOCF)</td>
<td>-1.14</td>
<td>-0.94</td>
</tr>
<tr>
<td>V&lt;400</td>
<td>30.4%*</td>
<td>13.8%*</td>
</tr>
<tr>
<td>V&lt;50</td>
<td>22.8%*</td>
<td>10.2%*</td>
</tr>
<tr>
<td>V&lt;50 ENF naïve taking ENF</td>
<td>35.8%*</td>
<td>14.4%*</td>
</tr>
<tr>
<td>mean change in CD4 (LOCF)</td>
<td>44.8%*</td>
<td>21.1%*</td>
</tr>
</tbody>
</table>

*p<0.0001

Efficacy of TMC114/r in 3-Class–Experienced Patients with Limited Treatment Options: 24-Week Planned Interim Analysis Two 96-Week Multinational Dose-Finding Studies.


10th European AIDS Conference, Dublin, Ireland Nov 17-20, 2005
12th CROI, Boston MA, Feb 22-25, 2005
**TMC114 Dose-Finding Studies: Design**

- Two dose-finding studies (TMC114-C213/C202)
  - Partially blinded (doses, not schedule of TMC114)
  - Patients randomized equally to 1 of 4 TMC114 doses (given with or without RTV) or investigator-selected PI regimen in combination with optimized background regimen
  - 400/100 mg q.d.
  - 400/100 mg b.i.d.
  - Control: Investigator-selected PI regimen
- Total treatment duration of 96 weeks
- Multinational, multicentre
  - 14 countries
  - 90 participating sites
- Primary objective/end point
  - To evaluate the relationship between dose of TMC114 and antiviral response (change in HIV RNA) at 24 weeks

**Change From Baseline in HIV RNA at Week 24: ITT NC=F**

**HIV RNA <50 at Week 24: ITT NC=F (Cont’d)**

<table>
<thead>
<tr>
<th>T-20 Used (Valve)</th>
<th>16% (n=25)</th>
<th>87% (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-20 Not Used</td>
<td>37% (n=27)</td>
<td></td>
</tr>
<tr>
<td>Primary PI NRTi</td>
<td>48% (n=40)</td>
<td></td>
</tr>
<tr>
<td>TMC114 FC+4</td>
<td>49% (n=58)</td>
<td></td>
</tr>
<tr>
<td>No Sensitivity</td>
<td>51% (n=18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0% (n=13)</td>
<td></td>
</tr>
</tbody>
</table>