Case Presentation

Demographics

- 41 year-old Caucasian male
- HIV+ since March of 2002
- Allergies: NKDA
- PMH: HPV infection, seasonal allergies
- Social: small business owner; lives with HIV negative partner
Demographics
- Initiated care at Fairview University Medical Center HIV Clinic in April of 2002
- Baseline laboratory data:

<table>
<thead>
<tr>
<th>Date</th>
<th>HIV-1 RNA (RT-PCR)</th>
<th>CD4 count</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/29/02</td>
<td>32,208</td>
<td>331</td>
</tr>
<tr>
<td>05/20/02</td>
<td>30,312</td>
<td>333</td>
</tr>
</tbody>
</table>

Question 1
- According to the DHHS treatment guidelines, should this patient be started on antiretroviral therapy?

Adapted: Mellors JW et al., Ann Int Med 1997;126:946-54
Case Scenario

- After much discussion with his doctor, the patient decides that he is ready to start antiretroviral therapy.
- Treatment concerns identified: fat accumulation and facial fat loss
- Concomitant medications: multivitamin; Claritin D

Question 2

- Which of the following treatment regimens is the best first regimen for this patient?
  - zidovudine + lamivudine + abacavir
  - lopinavir/ritonavir + zidovudine + lamivudine
  - nevirapine + stavudine + lamivudine
  - efavirenz + zidovudine + lamivudine

Question 3

- After 10 days of treatment the patient develops a severe rash with hives. Which of the following drugs is most likely responsible for this patient’s adverse drug reaction?
Question 4

Which of the following regimens is the best next regimen for this patient?

- nevirapine + zidovudine + lamivudine
- zidovudine + lamivudine + abacavir
- lopinavir/ritonavir + zidovudine + lamivudine
- nelfinavir + stavudine + didanosine

Case Scenario

The patient started ? in June of 2002

Follow-up laboratory data:

<table>
<thead>
<tr>
<th>Date</th>
<th>HIV-1 RNA</th>
<th>CD4 count</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/02</td>
<td>301</td>
<td>428</td>
</tr>
<tr>
<td>08/19/02</td>
<td>&lt; 50</td>
<td>505</td>
</tr>
<tr>
<td>11/21/02</td>
<td>&lt; 50</td>
<td>561</td>
</tr>
<tr>
<td>05/05/03</td>
<td>&lt; 50</td>
<td>581</td>
</tr>
<tr>
<td>11/29/03</td>
<td>&lt; 50</td>
<td>727</td>
</tr>
</tbody>
</table>

Management of The Treatment Experienced Patient
Treatment Regimen Failure

- Broadly includes all possible reasons for failure:
  - Baseline patient factors (i.e., pretreatment HIV-1 RNA and CD4 count, prior AIDS; drug resistance; co-morbidities)
  - Suboptimal adherence/missed appointments
  - Drug side effects/toxicity
  - Pharmacokinetics (absorption, metabolism, food/fasting, drug-drug interactions, penetration into reservoirs)
  - Potency of the regimen
- Often associated with virologic, immunologic, and/or clinical failure
- These failures do not occur 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)
  - 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
- Mean increases $\approx$ 150 cells/mm$^3$ over first year on first regimen (treatment naïve patients)
- Lower baseline CD4 count may be associated with a reduced CD4 response
(3) Clinical Failure

- 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 therapy

Assessment of Treatment Regimen Failure

- Once identified, the cause of failure needs to be explored:
  1. Physical examination
  2. Medical history
     - Course of HIV-1 RNA and CD4 count changes
     - Occurrence of HIV-1-related events
     - Antiretroviral treatment history
     - Medication-taking behavior
     - Medication tolerability
     - Pharmacokinetics
     - Concomitant medications

Management of Treatment Regimen Failure

- Distinguish among the reasons for failure
  - Examples:
    - Non-adherence
    - Poor tolerability
    - Suboptimal pharmacokinetics
    - Suboptimal regimen potency
    - Development of drug resistance
  - Management approaches will be different
Management of Treatment Regimen Failure

- 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
    - Increase dosing interval

Management of Treatment Regimen Failure

- If poor tolerability is identified:
  - Assess the side effects and their duration
  - Offer symptomatic treatment (ie. antidiarrheals, antiemetics)
  - Change one drug within the same class (ie. nevirapine for efavirenz-related CNS side effects)
  - Change drug classes (ie. PI to NNRTI)

Management of Treatment Regimen Failure

- 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 drug interactions
  - Measure antiretroviral drug levels in plasma (therapeutic drug monitoring)
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.

Residence

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

Types of Drug Resistance

- Genotypic
  - Acquisition of drug-resistance point mutations in the targeted HIV genes
  - Decreased ability of an antiretroviral to bind to its target

- Phenotypic
  - Increase in the drug concentration needed to inhibit viral replication by 50% or 90% (IC₅₀ or IC₉₀)
  - Assays are available to detect both types
  - Guides selection of drugs for a new regimen
Management of Treatment Regimen Failure

- If virologic, immunologic, and/or clinical failure is determined:
  - Review detailed antiretroviral treatment history
  - Distinguish limited and extensive prior experience
  - Confirm a single HIV-1 RNA increase with at least 2 determinations
  - Confirm CD4 count trends with at least 3 determinations
  - Obtain resistance testing while the patient is still taking the failing regimen

First Regimen Failure

<table>
<thead>
<tr>
<th>Initial Regimen</th>
<th>Change To:</th>
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<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</td>
</tr>
<tr>
<td></td>
<td>NNRTI + PI + 1 new NRTI</td>
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</table>

Limited Prior Treatment

Virologic Failure

[Diagram]

First Regimen Failure

- NNRTI + 2 NRTIs
- PI ± RTV + 2 new NRTIs
- new PI + RTV or NNRTI + 2 new NRTIs
- PI ± RTV or NNRTI + 2 new NRTIs
- NNRTI + PI ± RTV
- NNRTI + PI + 1 new NRTI

Limited Prior Treatment

- Virologic Failure
- [Diagram]

[Note]: Resistance Testing
Extensive Prior Treatment

Virologic Failure

- Change Problematic Drug
- Intensification
- Resume Same Regimen
- Change Entire Regimen
- Off Therapy?
- Non-adherence?
- No Resistance

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Change Regimen If Possible
No Options - Continue Current Regimen
Clinical Trials Await New Antiretroviral Agents

Case Presentation

Demographics
- 33 year old African-American male
- HIV+ since 1993
- AIDS diagnosis
- Allergies: NKDA
- Intolerances: indinavir - kidney stones
- PMH: PCP, oral candidiasis
- Social: flight attendant; lives with HIV negative partner
Case Scenario

- Transferred care to Fairview University Medical Center HIV Clinic in October of 2002
  - HIV RNA = 351,808; CD4 cell count = 6
- Current ARVT regimen (4 to 5 months)
  - stavudine 40 mg po bid
  - abacavir 300 mg po bid
  - nelfinavir 1250 mg q12h

Case Scenario

- Per patient, HIV RNA > 75,000 x 3-5 years; CD4 counts < 50 x 2 years
- Reports missing doses on past and current treatment regimens
  - Forgetfulness; difficult work schedule
- Previous ARV exposures:
  - AZT, 3TC, ddi, EFV, SQV, IDV, APV
- Concurrent medications:
  - TMP/SMX, azithromycin

Viral Resistance Testing 10/15/02

- Genotype:
- Phenotype:
  - susceptibility to all available antiretrovirals
  - Higher drug concentrations are needed to inhibit viral replication by 50% (overcome IC50)
Assessments

- Chronic HIV-1 infection
- Unsuppressed HIV-1 RNA in a severely immunocompromised patient
- Evidence of multi-drug resistant HIV-1
- Non-adherence with likely contributions to resistance
- Potent salvage regimen needed

Plan

- Discontinue current treatment regimen
- New treatment regimen (11/02)
  - lamivudine 300 mg po qd
  - didanosine EC 250 mg po qd
  - tenofovir 300 mg po qd
  - lopinavir/ritonavir 400/100 mg po q12h
  - amprenavir 600 mg po q12h
- Extensive adherence counseling with pt and partner; loperamide prescription given

Clinical Progress

<table>
<thead>
<tr>
<th>Date</th>
<th>HIV RNA</th>
<th>CD4</th>
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<tbody>
<tr>
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* In February, 2003 hospitalized for ocular herpes zoster outbreak
Assessments

- Initial significant reduction in HIV RNA
- Patient reported 100% adherence
- Refill records demonstrated consistency
- Diarrhea controlled on loperamide
- Persistent viremia does indicate virologic failure of salvage regimen
- No clinical progression of patient’s disease however weight loss is noted

Viral Resistance Testing 07/01/03

- Genotype

- Phenotype
  - Further susceptibility to all available antiretrovirals

Clinical Progress

- Between July and September of 2003, R.S. elected to stop ARVT and went on to develop symptomatic HIV-1
  - Fevers, night sweats, MAIC bacteremia, oral candidiasis, marked weight loss
  - Multiple hospitalizations for recurrent cellulitis of right lower extremity

- Evaluated for treatment with enfuvirtide in September of 2003
Plan

- Given limited treatment options, an optimized background regimen + enfuvirtide was designed using medical history and resistance testing data:
  - zidovudine + lamivudine (Combivir) 300/150 mg po bid
  - tenofovir 300 mg po qd
  - lopinavir/ritonavir 533/133 mg po q12h
  - amprenavir 750 mg q12h
  - enfuvirtide 90 mg SC bid

- Patient and partner received thorough education and instruction.

Clinical Progress

<table>
<thead>
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<th>Date</th>
<th>HIV RNA</th>
<th>CD4</th>
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<td>02/12/04</td>
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- Started new salvage regimen on 10/10/03

Case Conclusions

- New drug classes benefit patients with highly resistant HIV-1 strains.
- Resistance information aids in treatment selection and optimizing new regimens.
- Therapy goals in patients with highly resistant HIV-1 strains differ from those set for treatment naïve patients.