MANAGEMENT OF TREATMENT-EXPERIENCED PATIENTS WITH HIV INFECTION

Ellen Kitchell, MD
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Happily ever after?
Initiation of anti-retrovirals in 2018 for Treatment-Naïve patients

First Line Options:

- Emtricitabine/tenofovir OR Abacavir/lamivudine PLUS
  - Raltegravir OR
  - Elvitegravir/cobicistat OR
  - Dolutegravir OR
  - Bictegravir
The ideal response to antiretroviral therapy

- After initiation of antiretroviral therapy, check HIV viral load in approximately 6 weeks
- Viral load should have suppressed at least 1 log copies/mL by this time
- By 24 weeks, viral load should be below 50 copies/mL
- Should remain undetectable “ever after”
What do we do when the “ideal” doesn’t happen?
Definitions

- Virologic suppression: HIV RNA level below the limit of assay detection (usually less than 48 copies/mL)
Virologic failure

- Inability to achieve or maintain suppression of viral replication of HIV RNA to less than 50-200 copies/mL
types of virologic failure

- 1. Incomplete virologic response
  - After 24 weeks of therapy, HIV RNA remains above 50-200 copies/mL
Virologic Rebound

- Occurs after virologic suppression
- Confirmed detectable HIV RNA after virologic suppression

Example:

![HIV viral load graph](image)
Persistent low-level viremia

- Detectable HIV RNA levels <1000 copies/mL

Series 1
Virologic blip

- After virologic suppression, an isolated detectable HIV RNA level followed by return to virologic suppression
Review:
Causes of virologic failure

- Occurs when the concentration of the antiretroviral medication is not sufficient to completely suppress viral replication
- Many potential factors and causes
- Remember that virologic failure does not necessarily mean drug resistance
- Very important to explore these factors when meeting with patients experiencing virologic failure:
  - 1. Patient characteristics
  - 2. Antiretroviral regimen characteristics
  - 3. Viral characteristics
Patient Characteristics:
Risks for virologic failure

- Non-adherence!
- Higher pretreatment HIV RNA level
- Lower nadir CD4 count
- Prior AIDS diagnosis
- Co-morbidities, especially active substance abuse and depression
- Difficulties adhering to clinic appointments and obtaining pharmacy refills
Antiretroviral characteristics

- Medication side effects
- Suboptimal pharmacokinetics:
  - Absorption
  - Metabolism
  - Penetration into reservoirs
- Food/fasting requirements
- Interactions with medications/herbs
- Suboptimal virologic potency
- Prescription errors
Viral characteristics

- 1. Drug-resistant virus, either transmitted or acquired
- 2. Prior treatment failure/experience
HIV DRUG RESISTANCE
What is resistance?

- Reduced susceptibility of a patient’s viral isolate to suppression by an antiretroviral agent
- Like antibiotic resistance in bacteria, these mutations allow viral replication in the presence of medications
Resistance in HIV: Natural selection in process

- Because of HIV’s very high error rate of replication, polymorphisms are very common.
- Your patient has myriad “quasi-species” of virus, with small variations, within him- or herself.
Resistance in HIV: Natural selection in process

- In the setting of sub-therapeutic drug levels (some drug present but not enough to wipe out the virus), polymorphisms that allow the virus to replicate in the presence of drugs are favored.
- In the setting of no drugs → polymorphisms could potentially make the virus “less fit” and unable to make as many copies of itself, so drug resistance doesn’t tend to develop.
Development of HIV Resistance

- Insufficient drug level
- Viral replication in the presence of drug
- Resistant virus

Factors:
- Poor potency
- Wrong dose
- Host genetics
- Poor absorption
- Drug pharmacokinetics
- Transmitted resistance
- Drug interactions

Social/personal issues
Regimen issues
Toxicities
Poor adherence
AN INTRODUCTION TO RESISTANCE
Pretreatment Drug resistance

- Resistance mutations detected in patients prior to starting ARVs
- Results from either prior exposure to antiretroviral medications through post-exposure prophylaxis, PrEP or transmission of drug resistant variants
Transmitted Drug Resistance

- Varies by location, drug availability
- Significant increases after scale-up of antiretroviral therapy
- Meta-analysis on NNRTI resistance in low and middle income countries in 2016:
  - 11% in S Africa
  - 10% in East Africa
  - 7.2% in West and Central Africa
  - 9.4% in Latin America
  - 3.2% in Asia

Transmitted resistance

- 15.2% of all patients had >1 transmitted drug resistance mutation
  - 11% had non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations
  - 7.6% had nucleoside reverse transcriptase inhibitor (NRTI) mutations
  - 4.6% had protease inhibitor mutations
  - 3% had two-class resistance, and 0.6% had three-class resistance

Other studies in high-income countries

- 10-17% of ARV-naïve patients in Europe, US, Japan, Australia have transmitted resistance
- Recent studies show increased overall resistance: 15-19%
  - NNRTI resistance: 10-12%
  - 4-8% NTRI
  - 3-5% PI
- Rare to affect first line therapy options

Transmitted integrase inhibitor resistance

- Recent studies from European cohort, University of Washington, UNC national study in France and in Surabaya, Indonesia found low levels of transmitted integrase inhibitor resistance
  - No treatment naïve patients in their studies had major integrase inhibitor resistance
- Cohort of 339 ARV-naïve patients in California from 2013-2015
  - No integrase inhibitor resistance transmitted mutations found
- Few case reports available of transmitted resistance
- Anticipate that levels of resistance will increase over time given increased usage, especially in antiretroviral naïve patients

Swiss HIV Cohort Study

- Examined large cohort (>11000) on ARVs
- Emergence of new mutations on therapy decreased significantly from 1999-2013, from 401 to 23 patients
- Overall prevalence of drug resistance mutations from 57% to 37%
- Prevalence of 3 class resistance declined from 9 to 4.4%, <0.4% for patients who initiated therapy after 2006

How is resistance detected?

- Genotypes
- Phenotype
- Virtual phenotype
- Clinical/virologic response
When to use resistance testing

- Primary or acute infection
- Entry into care
- Prior to initiation of antiretroviral therapy
- Virologic failure
  - Usually require at least 1000 copies/mL of virus to be able to perform standard genotype and phenotype testing
- Pregnancy
Genotype: how performed

![Flowchart of genotype process]

- **Sample Preparation**: Viral RNA
- **Reverse Transcription & PCR**: PCR Product
- **Cycle Sequencing**: Purified Sequence Product
- **Automated Sequence Detection Using the 3100/3130**: Capillary Electrophoresis
- **Data Analysis Using ViroSeq Software**: Genotype & Drug Resistance Report

**Workflow Time**
- 3h
- 7h
- 5h
- 14-15h
- 1-2h

**Hands-on Time**
- 1.5–2h
- 0.75h
- 1.5h
- 1h
- ~15min/sample
genotype

- Sequences portions of your patient’s HIV RNA, including the protease gene, reverse transcriptase gene, and in some cases, the integrase enzyme
- Compares your patient’s virus to “wild-type” HIV, that does not have any resistance mutations
- Standard genotype measures mutations found in >20% of the viral population
**Genotype: results**

- Reports the sequence of base pairs coding for amino acids that comprise viral proteins
- Typically expressed as the coded amino acid, position, and the substitution after the position
- Example:
  - M184V substitution in the reverse transcriptase gene
  - Means that, in the 184\textsuperscript{th} codon of your patient’s RT gene, methionine has been replaced by valine
- Do not typically report polymorphisms or mutations that do not change the codon
Interpretation of genotypes: What does “M184V” mean to the patient?

- Based on clinical experience, in vitro studies, and computer algorithms
- Constantly updated based on new data
- For example, multiple studies have shown that M184V is a signature mutation that develops rapidly in patients treated with lamivudine, conferring resistance to that medication
Significance of resistance mutations

- Genetic mutations may cause conformational changes in the viral structure
  - Can cause the patient’s virus to become less susceptible to certain medications
    - This includes changes that can affect multiple medications in the same class
  - Can cause the patient’s virus to become more susceptible to certain medications
  - Sometimes the mutations can “cancel each other out”
  - Need to account for all mutations noted in the genotype
Interpretation of genotypes

- Company interprets genotype for you – figure 1
Other resources for interpretation of genotypes

- http://hivdb.stanford.edu/
phenotypes

- Removes genetic information from your patient’s virus, inserts it into a resistance testing vector
- Creates a “pseudovirus”
- Assayed for ability to complete a cycle of replication in the presence of varying concentrations of different antiretroviral agents in vitro
Phenotypes

- Compares how much drug is required to reduce the concentration of a wild-type virus by 50% (50% inhibitory concentration, or IC50) to the amount of drug required to do the same thing to your patient’s virus.

- Reports a “fold change” → ratio of the IC50 of the patient’s sample as compared to the IC50 of the wild-type virus.

- For example, if twice as much drug is needed to reduce viral replication by 50% in your patient’s virus compared to wild-type virus, then your patient’s virus is said to have a 2-fold reduced susceptibility to the drug.
**Understanding Phenotypic Testing: Fold Change and Cutoffs**

| Proteinase Inhibitor | Drug Name | Fold Change | Sensitive | Resistant | | | | |
|----------------------|-----------|-------------|-----------|-----------| | | | |
| Darunavir            | Prezista  | 1.71        | Y         | Y         | Sensitive |
| Lopinavir            | Kaletra   | 2.36        | Y         | N         | Sensitive |
| Tipranavir           | Aptivus   | 0.70        | Y         | Y         | Sensitive |

**Fold change:** ratio of IC$_{50}$ of patient viral isolate to IC$_{50}$ of wild-type virus

- Measures degree of resistance to a specific antiretroviral
- The higher the fold change, the greater the loss of susceptibility
- Fold change required to reduce response to a particular drug varies from drug to drug

**Pl Mutations:** L10F, I13V, D30N, L33F, I54M, L63P, A71V, T74S, V77I, N88D
Understanding Phenotypic Testing: Fold Change and Cutoffs

- **Cutoff**: fold change in susceptibility associated with reduced likelihood of clinical response to a particular drug
  - Cutoffs differ from drug to drug
  - Optimally, determined by results from clinical trials
  - Lower cutoff: fold-change at which there is a reduction in antiviral activity compared with a fully susceptible virus
  - As fold change increases, the degree of drug activity progressively decreases
  - Upper cutoff: fold change above which there is minimal antiretroviral activity of a drug

### Table: Phenotypic Testing Results

<table>
<thead>
<tr>
<th>NRTI Mutations</th>
<th>Stavudine</th>
<th>Zerit</th>
<th>(1.7)</th>
<th>1.90</th>
<th>N</th>
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NRTI Mutations: M41L, V118I, M184V, T215Y
### Phenotype Interpretation

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<tr>
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<td>0.70</td>
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</table>

**PI Mutations**

Viral fitness and replication capacity

- Replication capacity: ability to infect target cells *in vitro* without drug pressure
- Viral fitness: ability to reproduce in defined environment *in vivo* with drug and immunologic pressures
Replication capacity

- Ability of patient’s virus to replicate relative to median of wild-type population of viruses
- Median RC value of wild-type population of viruses defined as 100%
**Virtual phenotype**

- **No longer available** (but you might see this in the paper chart)
- Predicts HIV-1 drug susceptibility from a viral genotype
- Virus from the patient is sequenced and software then searches database for previous samples with the same patterns of resistance mutations.
- Phenotypes for these matching samples are then retrieved from the database and an average resistance figure (change in IC50) calculated for each drug in turn.
## Virtual Phenotype

### Patient/Sample Details

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### Physician Details

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### SUMMARY REPORT

#### DROPS

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## Notes

1. Potentially important advice (e.g., adherence counseling, lifestyle modifications)
2. Cut-off values: fold change (FC) and cut-off (C) values are used for interpretation of resistance.
3. Resistance interpretation: resistance is reported as either "susceptible," "reduced response," or "resistant." "Susceptible" indicates the virus is not resistant to the drug. "Reduced response" indicates a potential decrease in drug efficacy. "Resistant" indicates a high level of resistance, which may require alternative treatment options.
4. Important: the additional clinical notes on page 2 provide important information about the specific genotype analyzed and should be considered in combination with the information on this Summary Page.
WHEN TO PERFORM RESISTANCE TESTING
Choosing a resistance test for your patient

- **Genotype preferred for**
  - Treatment naive: acute or chronic infection
  - Early virologic failure
  - Patient no longer receiving therapy

- **Phenotype or combined phenotype/genotype preferred for**
  - High-level resistance to NRTIs or PIs on genotype
  - Multiple regimen failure with limited treatment options
  - More expensive, complicated, takes longer
  - Can account for more complex interactions between genotypic changes
When to perform resistance testing

- Off of medications, the most fit viruses make the most copies of themselves
- Sub-population that has resistance may decrease in relation to wild-type virus
- Our resistance tests may not be able to find these small sub-populations if the patient is not experiencing drug pressure
“Archived” virus

- Resistant virus can be “hiding,"
- “tucked away for a rainy day”
- And start to be seen again when drug pressure is resumed
When to perform resistance testing

- Ideally when patient is still taking failing antiretroviral regimen to evaluate for resistance mutations, or within 4 weeks of being off of medications.
- If you perform resistance testing when the patient is not on medications, it may appear normal despite archived mutations.
- Take into account all previous resistance tests, as these mutations are likely archived and will re-emerge if drug pressure is reintroduced.
Real-life example

- Patient with long history of HIV, resistant to almost all antiretrovirals
- Moves to another state, off of medications
- Presents to new provider
- New genotype is wild-type (previous genotypes, medical records, treatment history etc. not requested)
- New provider places patient on Atripla (previous genotypes demonstrated resistance to this regimen)
- This regimen does not work, as the resistant viral population quickly re-emerges on this therapy
Sequencing Archived Viruses—New Technology

- Analyzes archived proviral HIV-1 DNA in host cells
- Amplifies cell-associated HIV-1 DNA
- Uses next-generation sequencing, which performs millions of parallel sequencing reactions

- Example: Genosure Archive from Monogram

- Caveat: “Longer follow-up is needed to determine the clinical relevance of NGS in routine clinical practice and eventually define a clinically relevant mutations' prevalence.”

PATTERNS OF NON-NUCLEOSIDE REVERSE-TRANSCRIPTASE INHIBITOR RESISTANCE
# Resistance Consequences of Initial NNRTI-Based Regimen Failure

**DHHS Preferred Regimens**

<table>
<thead>
<tr>
<th>DHHS Preferred Regimens</th>
<th>HIV-1 RNA &lt; 50 copies/mL at Wk 48, %</th>
<th>Detectable Resistance at VF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV, TDF, FTC</td>
<td>80 (n = 244)[1]</td>
<td>NRTI M184V/I Other NNRTI</td>
</tr>
<tr>
<td></td>
<td>82 (n = 230)[2]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90† (n = 464)[3]</td>
<td></td>
</tr>
<tr>
<td>EFV, TDF, 3TC</td>
<td>76 (n = 299)[4]</td>
<td></td>
</tr>
</tbody>
</table>

*For patients with available baseline and postfailure genotypes.
†96 wks.

Clinical implications of resistance to first-generation NNRTIs

- Common after failure: K103N and Y181C
- Do NOT affect replication capacity/viral fitness
- NO benefit to continuing efavirenz or nevirapine in the setting of these mutations
- Extensive cross-resistance between first-generation drugs
- Also very common mutation seen transmitted
Clinical implications of NNRTI Resistance

- Any previous NNRTI resistance compromises subsequent responses to first-generation NNRTI.
- Failing NNRTI should be stopped as soon as possible to prevent accumulation of mutations that can impair response to second-generation NNRTIs (etravirine, rilpivirine).
- Among patients failing a reverse transcriptase inhibitor-based regimen, 3-month delay until treatment modification was associated with increased risk of mortality.
  - Not true of protease-inhibitor-based regimens.

Second-generation NNRTIs: etravirine and rilpivirine

- In the same class but (somewhat) morphologically dissimilar
- Mutation profile distinct from that of first-generation NNRTIs
  - Key mutations: L100I, Y181C, Y188L. Unique to rilpivirine: E138K
- However, failure of first-generation NNRTI may generate mutations that can impair fitness of second-generation NNRTIs
- Etravirine has been studied extensively in treatment-experienced patients, may maintain activity
- Rilpivirine has not been studied much in treatment-experienced patients
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR DRUG RESISTANCE
The “M184V” Mutation

- Signature mutation for emtricitabine/lamivudine
- High level resistance to emtricitabine/lamivudine
- Can decrease susceptibility to abacavir and didanosine a little
- However, this mutation:
  - Decreases viral fitness
  - Also, increases the susceptibility of the virus to zidovudine, stavudine and tenofovir
  - Can counteract other mutations to maintain activity of tenofovir
M184V Mutation

- Studies have shown that continuing lamivudine monotherapy in the setting of M184V results in:
  - Impaired replication capacity of the virus
  - Results in 0.5 log reduction in viral load (despite viral “resistance” to the medication)
  - CD4 decline not as abrupt in patients treated with lamivudine monotherapy
M184V Mutation

- Often lamivudine or emtricitabine is continued in a regimen of patients with M184V mutation to maintain selection pressure
- Reduces viral fitness and improves susceptibility of other medications
- Lamivudine/emtricitabine have minimal side effects and often in combination with other products
Thymidine-analog mutations (TAMs)

- Mutations that commonly emerged in patients treated with thymidine analogues: zidovudine and stavudine
- Affect the susceptibility to all NRTIs except lamivudine/emtricitabine
- Additive in nature
- Does affect replication capacity of virus
TAM Pathways

- Tend to emerge in one of 2 main pathways
  - M41L-L210W-T215Y (the “bad” TAM pathway) OR
  - D67N-K70R-T215F-K219Q/E (the “not so bad” pathway)

- Additive in nature:
  - If only one TAM, not so bad
  - But more TAMs (3-4), decreased susceptibility of zidovudine, stavudine, abacavir, didanosine, tenofovir
TAM + 184V

- M184V mutation can mitigate drug resistance from TAMs, especially from tenofovir, and especially in the “not so bad” TAM pathway
**K65R**

- Signature resistance mutation in patients treated with tenofovir
- High-level resistance to tenofovir, didanosine, abacavir, lamivudine/emtricitabine, stavudine
- Increases susceptibility to zidovudine
L74V

- Signature resistance mutation for abacavir
- Cross-resistance to didanosine
- Abacavir and didanosine have very similar resistance profiles
PROTEASE INHIBITOR RESISTANCE
Resistence Consequences of Initial PI-Based Regimen Failure

 embroidery (30%)  Less likely (10% to 30%)  Rare (< 10%) or none

<table>
<thead>
<tr>
<th>DHHS “Preferred” and/or IAS-USA “Recommended” Regimens</th>
<th>HIV-1 RNA &lt; 50 copies/mL at Wk 48, %</th>
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<tbody>
<tr>
<td>ATV/RTV, TDF/FTC</td>
<td>78 (n = 440)[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>89 (n = 465)[2]†</td>
<td></td>
</tr>
<tr>
<td>DRV/RTV, TDF/FTC</td>
<td>84 (n = 340)[3]</td>
<td></td>
</tr>
<tr>
<td>LPV/RTV, TDF/FTC</td>
<td>76 (n = 443)[1]</td>
<td></td>
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<tr>
<td></td>
<td>78 (n = 346)[3]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>67 (n = 345)[4]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64 (n = 170)[5]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>77 (n = 664)[6]</td>
<td></td>
</tr>
<tr>
<td>SQV/RTV, TDF/FTC</td>
<td>65 (n = 167)[5]</td>
<td></td>
</tr>
</tbody>
</table>

*For patients with available baseline and postfailure genotypes. †96 weeks

References:
- Daar E, et al. CROI 2010 59 LB
- Smith K, et al. AIDS. 2009;23:1547-1556
“Genetic barrier to resistance”

- Ritonavir-boosted protease inhibitors have a high genetic barrier to resistance
- Very unlikely to develop mutations to protease inhibitors despite ongoing viral replication
Selection of protease inhibitor resistance

- When “unboosted” protease inhibitors, used alone without ritonavir, common to see protease inhibitor resistance
- Examples: nelfinavir, atazanavir, amprenavir, indinavir
- D30N = signature nelfinavir mutation, does not affect any other PIs
- I50L = signature atazanavir mutation, increases other PIs
Ritonavir-Boosted Protease inhibitor regimens

- Virologic failure of initial ritonavir-boosted PI based regimen typically not associated with emergence of PI resistance
Virologic failure of Protease inhibitor based regimen

- Usually occurs in patients with extensive previous protease inhibitor resistance
- Accumulation of multiple mutations
INTEGRASE INHIBITOR RESISTANCE
## Resistance Consequences of Initial RAL-Based Regimen Failure

<table>
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<tr>
<th>DHHS “Preferred” Regimens</th>
<th>HIV-1 RNA &lt; 50 copies/mL at Wk 48, %</th>
<th>Detectable Resistance at VF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL, TDF/FTC*</td>
<td>78 (n = 440)[1]</td>
<td>M184V/I Other IN</td>
</tr>
</tbody>
</table>

*For patients with available baseline and postfailure genotypes.

Integrase inhibitor resistance

- First generation integrase inhibitors: elvitegravir and raltegravir
- Low-to-moderate genetic barrier to resistance
- Single mutations sufficient to confer high-level resistance
- Accessory mutations emergence
- Extensive cross-resistance between elvitegravir and raltegravir
- Second-generation integrase inhibitor: dolutegravir
  - Often active against raltegravir and elvitegravir resistant strains (but not always)
Main Pathways for First-generation integrase inhibitors (Raltegravir and elvitegravir)

- Q148K/R/H*
- N155H
- Y143C/R (raltegravir mainly)

- All of the above mutations significantly impact susceptibility of HIV to the medication
- Most mutations lead to cross-resistance between first-generation integrase inhibitors.
- No therapeutic advantage to continue raltegravir or elvitegravir in setting of these mutations, as further mutations to integrase inhibitors tend to develop, including “compensatory mutations” that restore viral fitness
Pathways for integrase inhibitor resistance

- If patient continued on a non-suppressive integrase inhibitor, can start developing secondary mutations within these pathways
- Can lead to decreased susceptibility to second-generation integrase inhibitors (dolutegravir)
- Mutations on the **Q148** pathway are more potent against second-generation drugs:
  - **Q148K/E138K, Q148R/N155H, Q148R/G140S** + further secondary mutations
dolutegravir resistance

- Closer bond to viral DNA than raltegravir/elvitegravir
- Slower dissociation constant
- Selection of drug resistance on treatment less common
- Accumulation of multiple mutations required to cause resistance
- Q148 mutation pathway in combination with additional mutations
Review

- Virologic failure is related to subtherapeutic drug levels, which can have multiple etiologies
- Resistance develops in the setting of subtherapeutic drug levels
- Perform resistance testing ideally while the patient is still taking the failing regimen
- Remember archived mutations, and take into account past resistance testing
Resistance to antiretrovirals

- With first-generation NNRTIs and integrase inhibitors, continuation of the regimen can lead to resistance to second-line agents.
- Virologic failure on a ritonavir-boosted protease-inhibitor based regimen is often NOT associated with resistance mutations to the protease inhibitor.
- Resistance for NRTIs is more complicated, with mutations that can increase or decrease susceptibility to medications.
Next time...

- Lessons from clinical trials in antiretroviral-experienced patients ("salvage")
- Use of novel antiretroviral agents in treatment-experienced patients
- Putting everything together to create new regimens for patients with virologic failure due to antiretroviral resistance