Management of Treatment Experienced Patients with HIV Part 2

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September 26, 2017
Review from Last Week

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

- Genotypes

- Phenotypes
Common Mutations

- K103N?
- M184V?
Why do we do resistance testing?

- To assess activity of available antiretrovirals:
  - What do we have left?
How are new medications studied in treatment-experienced patients?

- Standard drug trials typically study only one medication at a time: Drug A versus placebo.
- If you just gave Drug A to (resistant) HIV, the virus would rapidly become resistant to this agent.
- Need to prove that Drug A is superior to the standard of care, currently available combination antiretrovirals.
Number of Active Agents: Optimized Background Regimen (OBR)

- Optimized background regimen: standard-of-care regimen selected by the investigator prior to randomization that is comprised of at least 2 active antiretroviral agents
Optimized Background Regimen

- Best responses of virologic suppression in patients receiving investigational drug plus an *optimized background regimen* containing at least 1 other active agent (number depends on the study)
- Over time, the “standard of care” regimen has become more active
- Our current “toolbox” of antiretrovirals provides us a great likelihood of achieving virologic suppression
Resistance Scoring: A Research Tool For Treatment-Experienced Patients

- Genotypic susceptibility score = sum of genotypic resistance scores for each drug in regimen
  - Based on rule-based algorithms using predefined drug-resistance mutations
    - 1.0: susceptible
    - 0.5: possibly resistant
    - 0: resistant

- Phenotypic susceptibility score = sum of phenotypic resistance scores for each drug in regimen
  - Based on FC in susceptibility of test sample relative to control (wild-type) isolate
    - 1: susceptible
    - 0: resistant
    - Between 0 and 1: partially susceptible
The Dawn of Salvage: Enfuvirtide in 2003
Enfuvirtide (T-20)

- Peptide that binds to region of envelope glycoprotein 41 involved in fusion of virus with membrane of CD4+ host cell
TORO (T-20 versus Optimized Regimen Only)

- Treatment-experienced patients with resistance to >3 ARV classes
- Heavily treatment experienced, many patients had NO active medications in their regimen
- Randomized to enfurvitide versus optimized background regimen alone
Results TORO

![Graph showing results of TORO study. The graph compares Enfuvirtide and Placebo groups for reductions in viral load below 50 copies/mL, below 400 copies/mL, and by more than 1 log copies/mL.](image)
The downside to enfuvirtide

- Injection site reactions in 99% of patient population
- Extremely expensive
- Rapid emergence of mutations associated with T-20 resistance in the absence of a fully suppressive antiretroviral regimen demonstrates a low genetic barrier to resistance
If your patient has never been on this medication before, it is likely effective.
If your patient has been on this medication previously, it is unlikely that this medication will work again.

gp41 envelope genotype is available commercially but not used much.
Switching Studies: EASIER, CHEER

- Patients with MDR HIV and suppressed HIV-1 RNA on enfuvirtide randomized to switch to raltegravir versus continue T-20
- Well-tolerated and continued virologic suppression
Protease Inhibitors Used in Treatment-Experienced Patients

Tipranavir/ritonavir
Darunavir/ritonavir
2006 RESIST: Tipranavir

- Highly treatment experienced patients with virologic failure (HIV RNA > 1000 copies/mL)
- Documented resistance to NRTIs, NNRTIs, and PIs
- Had received at least 2 previous protease inhibitor regimens
- Compared tipranavir to “comparator” protease inhibitor/ritonavir (lopinavir, amprenavir, saquinavir, indinavir)
RESIST Results

- 33% in tipranavir group had >1 log decrease in viral load as compared to 15% in comparison arm
- 30% had undetectable viral load as compared to 13% in comparison arm
- Increased CD4 count in tipranavir arm

Tipranavir

- High pill burden, ritonavir
- Side effects: GI, LFT abnormalities, intracranial hemorrhage
- Drug interactions (cannot use with etravirine)
- Many times “outshone” by its sister darunavir
- However, resistance patterns do not overlap completely with darunavir
- Tipranavir may be an option for patients with darunavir resistance (seen in patients previously treated with (fos)amprenavir)
POWER: Evaluation of Darunavir/ritonavir as Salvage Therapy

- Highly-treatment experienced patients (average 6 NRTIs, 1 NNRTI, 5 PIs)
- High level of protease inhibitor resistance
- Compared darunavir (new agent) versus investigator-selected protease inhibitor (included lopinavir, amprenavir, saquinavir, atazanavir)
- Open-label trial
POWER: Criteria for Entry

- Prior failure of PI-containing regimen
- Prior NNRTI, NRTI experience
- ≥ 1 primary PI mutation
- HIV-1 RNA > 1000 copies/mL
POWER

- Optimized background regimen and comparator PI(s) selected by the investigator based on genotype resistance testing and prior ARV history
- OBR consisted of $\geq 2$ NRTIs $\pm$ ENF
- Approximately 47% of all patients used enfurvitide
POWER- Combined Results

- Response to darunavir/ritonavir was reduced in patients with ≥ 10 baseline PI mutations
- Darunavir has high binding affinity to HIV protease (100x higher than comparator PIs) and slow dissociation rates (>240 hrs as compared to minutes)
TITAN: Darunavir/rit versus Lopinavir/rit in Treatment-Experienced Patients

- DRV- and LPV-naive patients with HIV-1 RNA > 1000 c/mL and on current regimen for ≥ 12 weeks randomized to
  - DRV/RTV 600/100 mg BID plus OBR or LPV/RTV 400/100 mg BID plus OBR

<table>
<thead>
<tr>
<th>Previous ARV Experience, %</th>
<th>DRV/RTV (n = 440)</th>
<th>LPV/RTV (n = 443)</th>
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<tr>
<td>≥ 4 NRTIs</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>≥ 1 NNRTI</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>0 PI</td>
<td>32</td>
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<tr>
<td>≥ 2 PIs</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>3-class experienced</td>
<td>46</td>
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</table>
TITAN Results: 48 Weeks

- HIV RNA <400 copies/mL
- HIV RNA <50 copies/mL

- Darunavir
- Lopinavir
TITAN Results

- Darunavir met criteria for superiority to Lopinavir/ritonavir in proportions with HIV-1 RNA < 400 c/mL and < 50 c/mL
- DRV/RTV also met criteria for superiority to LPV/RTV in proportions with HIV-1 RNA < 400 c/mL at Week 96
- Reduced susceptibility to darunavir noted at >3 mutations to darunavir or more
ODIN: Once-Daily Darunavir/Ritonavir Noninferior

Use of darunavir in “lightly” treatment-experienced patients
ODIN

Stratified by baseline HIV-1 RNA ≤ and > 50,000 copies/mL

Wk 48

Once-daily Darunavir/Ritonavir
800/100 mg + OBR*
(n = 294)

Twice-daily Darunavir/Ritonavir
600/100 mg + OBR*
(n = 296)

Treatment-experienced adults on a stable HAART regimen for ≥ 12 wks with HIV-1 RNA > 1000 copies/mL, CD4+ count > 50 cells/mm³, no darunavir RAMs
(N = 590)

*OBR contained ≥ 2 active NRTIs. Activity based on previous antiretroviral use and resistance testing.
Darunavir RAMs

- Patients with the following mutations were excluded from the study:
  - V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V
  - Forget the mutations? Always available in Stanford Resistance Database
ODIN

- Even if patients are “protease-inhibitor experienced”
- Can use once daily darunavir IF no documented resistance to darunavir
NNRTIs Used in Treatment-Experienced Patients

Etravirine
Etravirine

- Second-generation NNRTI
- Twice daily medication
- Not approved for use in naïve patients at this time
- Drug interactions
DUET-1 and -2

- Treatment-experienced patients with HIV-1
- Patients with virologic failure on current HAART, at least 5000 copies/mL
- Had to have at least 1 NNRTI resistance-associated mutations (RAMs) and ≥ 3 primary protease inhibitor RAMs
- Randomized to:
  - Darunavir/ritonavir + Optimized Background Regimen + etravirine OR
  - Darunavir/ritonavir + Optimized Background Regimen + placebo
DUET Results

![Graph showing the percentage of patients with HIV-1 RNA <50 copies/ml over time for Etravirine plus BR (n=599) compared to Placebo plus BR (n=604). The graph indicates a significant difference with a P-value of <0.0001.]
DUET-1 and -2: Predictors of Etravirine Response and Resistance at Failure

- Resistance associated mutations
- Scoring system created
  - 3.0: Y181I/V
  - 2.5: L100I, K101P, Y181C, M230L
  - 1.5: V106I, V179F, E138A, G190S
  - 1.0: V90I, A98G, K101E/H, V179D/T, G190A

HIV-1 RNA < 50 copies/mL

<table>
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<tr>
<th>Weighted Score Category</th>
<th>0-2.0</th>
<th>2.5-3.5</th>
<th>&gt; 3.5</th>
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<tr>
<td>HIV-1 RNA (copies/mL)</td>
<td>74.4</td>
<td>52.0</td>
<td>37.7</td>
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TMC125-C227: Etravirine vs Protease-Inhibitor in NNRTI-Experienced Patients

HIV-infected, PI-naive patients with failure of a first-line NNRTI-based regimen with ≥ 1 NNRTI resistance mutation, HIV-1 RNA > 1000 copies/mL

- HIV-1 RNA declined by 1.3 log_{10} copies/mL in etravirine arm at Week 8 but rebounded
  - By contrast, continual HIV-1 RNA decline in protease inhibitor arm
- Lack of sustained response to etravirine most likely associated with both baseline NRTI and NNRTI resistance mutations
- Unexpectedly large numbers of baseline resistance mutations in this first-line failure population

Failure of an NNRTI-Based Regimen

- Patients randomized to PI-based therapy had much better virologic suppression than those who received etravirine.
- Strategy of using etravirine plus 2 NRTIs after initial NNRTI failure is inferior to selecting an agent from a new class.
Integrase Inhibitors in Treatment-Experienced Patients

Raltegravir
Dolutegravir
BENCHMRK: Methods

- Treatment-experienced patients with virologic failure, HIV RNA > 1000 copies/mL
- Documented resistance to at least 1 drug in the NRTI, NNRTI, PI classes
- Randomized to raltegravir vs. placebo + OBR
BENCHMRK 1 & 2

HIV-1 RNA Level < 50 copies/mL (%)

No. of Patients

RAL                  462       458      458      461     453      458      459
Placebo             237       236      236      237     237      237      237

P < .001 at Week 16 and Week 48

SAILING: Dolutegravir vs Raltegravir in ART-Exp’d, Integrase Inhibitor–Naive Pts

Stratified by number of fully active background agents, use of DRV, screening HIV-1 RNA ≤ vs > 50,000 copies/mL

Treatment-experienced, integrase inhibitor–naive patients with HIV-1 RNA > 400 copies/mL and ≥ 2 class resistance (N = 715)

Dolutegravir 50 mg QD + OBR (n = 354)

Wk 24 interim analysis

Raltegravir 400 mg BID + OBR (n = 361)

Wk 48

SAILING: Results

- Dolutegravir superior in efficacy to raltegravir in treatment experienced patients
- Lower incidence of integrase resistance at VF with DTG
- Both regimens well tolerated with similar AE profiles

• Open-label trial
• Treatment-experienced patients with virologic failure, integrase resistance
• Documented resistance to >1 compound in >2 drug classes
VIKING Results

• Used 50 mg BID dosing
• Virologic suppression noted in most patients despite resistance to raltegravir

• *J Infect Dis.* 2013 Mar 1;207(5):740-8
Entry Inhibitors

Maraviroc
- CCR5 co-receptor antagonist
- Binds selectively to human chemokine receptor CCR5 on cell membrane
- Prevents interaction of HIV’s gp120 and CCR5 necessary for CCR5-tropic virus to enter the cell
CCR-5 Tropic Virus

- Virus using CCR-5 to enter the cell are called “CCR-5 tropic”
- Most important co-receptor during initial infection
- Able to replicate in macrophages and CD4 T-cells
CXCR-4 Co-Receptor Tropism

- As the natural history of HIV progresses, patients’ virus tends to become CXCR-4 tropic over time (but not always!)
- Associated with faster disease progression, clinical progression to AIDS and greater decreases in CD4 count
What co-receptor does your patient’s virus use?

- Maraviroc will only work in patients with CCR-5 tropic virus

- **Q:** What happens if a CCR5 antagonist is administered to a patient with a virus that does not use CCR-5 as a co-receptor?

- CCR-5 antagonists do not show antiviral activity in CXCR4-using strains.
- Clinical trial exploring the use of maraviroc in patients who had D/M virus showed that addition of maraviroc to optimized background therapy (OBT) did not reduce viral load further than OBT alone
Phenotypic Tropism Assay

- Need >1000 copies/mL HIV RNA
- Patient’s sample taken
- Genes encoding HIV env gene extracted
- Recombined with lab strain of HIV
- Used to infect CD4-expressing cells co-expressing either CCR5 or CXCR4
- If the virus can get into the cell and replicate, it produces luciferase (light) gene
Confirmatory Assay
Potential Results

- CCR5-tropic HIV-1: a virus strain that can only use the CCR5 co-receptor to infect CD4 cells.
- CXCR4-tropic HIV-1: a virus strain that can only use the CXCR4 co-receptor to infect CD4 cells.
- Dual-tropic HIV-1: a virus strain that can use either the CCR5 or CXCR4 co-receptor to infect CD4 cells.
- Mixed-tropic HIV-1: mixture of the above types in a single patient.
Trofile DNA

- Trofile® DNA is recommended for patients with undetectable serum HIV RNA viral loads
- Uses gp160 coding region of HIV-1 to evaluate tropism
- Instead of using HIV-1 RNA isolated from patient plasma, uses cell associated viral DNA taken from whole blood cells infected with HIV
- HIV-1 envelopes encoded by the viral DNA are tested in a cell-based viral infectivity assay in order to determine which co-receptor the HIV-1 virus population is capable of using
Genotype Tropism Testing

- Sequencing of the V3 loop region of viral gp120 envelope protein
- Sequences interpreted using web-based algorithm
Why Use Genotype Testing?

- Cost
- Turn-around time
- Availability
Studies Involving Genotype Testing

- Retrospective analysis using samples from prior maraviroc trials
- Patient responses to maraviroc similar to those observed with Trofile testing (viral load decreases, undetectable viral load)
- Not as well studied
MOTIVATE

- Included patients with R5 tropic HIV-1 only
- Had treatment history including at least 3 ARV classes and had resistance to >3 classes of medications
- Patients randomized to maraviroc versus placebo + optimized background regimen

MOTIVATE results

![Graph showing HIV-1 RNA Suppression](image-url)
If you want to use maraviroc at Parkland...

- Need results of tropism testing
- Either Trofile or Trofile DNA
- Very expensive tests, >$2000
- Parkland will pay once in patient’s lifetime
- Patient assistance program offer other methods
- However, only order this test if you are seriously considering using maraviroc at the time (if you wait too long, your patient’s virus may have switched tropism)
- Remember drug interactions
In the future...

- Investigational HIV attachment inhibitor fostemsavir (BMS-663068)
- Prevents viral entry by binding to gp120 and blocking viral attachment to host CD4 receptor
- Phase IIb study comparing this to atazanavir/ritonavir in combination with raltegravir and tenofovir
- Phase III trial ongoing

*Antivir Ther.* 2017;22(3):215-223
In the future...

- GS-CAI
- Interferes with assembly and disassembly of p24 capsid protein
- Inhibits multiple steps involved in capsid assembly necessary for late-stage maturation, functions occurring after entry into host cell
- Potent, long-half life, may be suitable for long-acting injectables
- Effective against viral mutants resistant to all approved antiretroviral classes

In the future...

- Ibalizumab
- Monoclonal antibody that targets CD4 protein on T-cells
- Unique resistance profile
- Small phase 3 trial of very treatment experienced patients on a failing regimen (at least 1 drug resistant from 3 classes)
- Long-acting injectable

- Lalezari J et al. Primary efficacy endpoint and safety results of ibalizumab (IBA) in a phase 3 study of heavily treatment-experienced patients with multi-drug resistant (MDR) HIV-1 infection. IDWeek, New Orleans, abstract LB-6, 2016.
Putting things together: TRIO
Combination therapy for treatment-experienced patients
TRIO

- Combined multiple new agents to which the patient was susceptible rather than just one new agent
- Treatment experienced patients with >3 PI resistance mutations (but <3 darunavir RAMs), >3 NRTI mutations, predicted susceptibility to etravirine
- Patients treated with: raltegravir, etravirine, darunavir/ritonavir + optimized background regimen
TRIO

- 90% had undetectable HIV viral load (<50 copies/mL) at 24 weeks
- 86% had undetectable HIV viral load at 48 weeks

Clin Infect Dis. 2009 Nov 1;49(9):1441-9
Putting it All Together: Choosing the Best Regimen for Your Patient
Choosing a Regimen for Treatment Experienced Patients

1. Assess barriers to previous treatment failure—what has changed to ensure success with this regimen?

2. Review current and prior resistance testing, as well as previous treatment history

   1. How many active medications do you have available, and how many do you need?
Assessing Active Agents

• Genotypic and/or phenotypic resistance testing
  ◦ Assess susceptibility to approved agents
  ◦ Review previous tests to identify any archived resistance

• Integrase inhibitors and ENF presumed fully active in previously unexposed patients

• Tropism testing to assess activity of CCR5 antagonists
Number of Active Agents

- Prefer to treat with at least 2, and preferably 3 active agents
- Trend toward greater benefit with 3 vs 2 fully active agents in studies of treatment-experienced patients
- Some clinicians argue that if 2 fully active agents are included in the regimen with high potency, 3 active agents are not needed
- Adding more agents than what is “necessary” can increase the pill burden, cost, potential for adverse effects, loss of future options, drug interactions
- However, if you suspect that a drug will only be partially active, would err on side of “overtreating” rather than “undertreating”
- Contribution of “partially active” agents (eg, lamivudine) difficult to calculate
- No added benefit from using 4 vs 3 fully active agents
Management of First Regimen Failures
NRTI + 3TC/FTC + Boosted PI Effective Second-Line Regimen in Pts With M184V

- Retrospective analysis of patients who failed first-line NNRTI-based regimen
- Pts with M184V ± NNRTI RAMs but no PI or other NRTI RAMs
  - 1. Ritonavir-boosted PI + lamivudine/emtricitabine + another NRTI
  - 2. Ritonavir-boosted PI + lamivudine/emtricitabine + another NRTI + another active agent
  - 3. Ritonavir-boosted PI + NRTIs sparing lamivudine/emtricitabine +/- another active agent
- No significant difference in likelihood of HIV-1 RNA suppression between 3 types of second-line regimen → No advantage to adding another agent

Recommendations: Patients With Initial NNRTI Failure

- Assess and address cause(s) of failure
- Boosted PI regimens well studied, expected to be effective
- Few comparative data in initial failure
- Backbone: 2 NRTIs likely sufficient if no NRTI resistance or M184V alone
- If more complex NRTI mutations, combinations of novel agents and boosted PIs may be preferable
Patients with virologic failure on NNRTI + 2 NRTIs
No previous PI or INSTI use
Randomized patients to lopinavir/ritonavir + raltegravir versus lopinavir/ritonavir + 2NRTIs versus lopinavir/ritonavir alone
Similar efficacy in the first two arms

Strategies to Avoid/Use With Caution With Compromised NRTIs

- 2 NRTIs + etravirine
  - TMC125-C227 study demonstrated etravirine inferior to PI in patients with first-line NRTI + NNRTI failure and resistance

- 2 NRTIs + raltegravir
  - SWITCHMRK suggests previous virologic failure (NRTI resistance) associated with increased risk of rebound on 2 NRTIs + raltegravir
  - Patients were more treatment experienced in SWITCHMRK

Recommendations: Patients With Initial Boosted PI Failure

- PI resistance rare with virologic failure of initial boosted PI
  - Different boosted PI should be fully active but address any shortcomings of initial PI, eg, tolerability, dosing
- NRTI resistance also rare with virologic failure of initial boosted PI
  - Presence of (limited) NRTI resistance unlikely to affect outcomes of subsequent NRTIs + boosted PI regimen
- Data support QD dosing of DRV/RTV in experienced patients with little/no PI resistance
- No clear data on whether the addition of a new agent in a new class adds benefit
Recommendations: Patients With Initial Raltegravir Failure

- Order integrase genotype
- Prolonged failure on a raltegravir regimen may lead to more complex resistance patterns and decreased likelihood of activity of second-generation integrase inhibitors
- Risk of NRTI resistance similar to initial NNRTI failure
Management of Heavily-Treatment Experienced Patients
Heavily Treatment-Experienced Patients

1. Obtain complete treatment history, including all previous resistance testing
2. Consider phenotype testing, as well as Trofile testing
3. Try to come up with 2-3 active agents involving multiple classes, especially novel agents
4. If you cannot come up with an active regimen, consider referral to study (but few active novel antiretrovirals coming up)
Management of Heavily Treatment Experienced Patients

- Ask for help!
- Under SA MEDICINE context in EPIC, add patients to “Interesting HIV Patient” List
- Will have management discussions throughout the coming year of tough cases
SWITCHING ART
My Opinion:

- “If it’s not broken, why fix it?”
- If a patient is tolerating an “older” regimen with no toxicities, excellent virologic and immunologic control, I tend to keep the regimen going
But Is It Broken?

- Evaluate whether your patient is experiencing toxicity even in stable patients.
- E.g. metabolic issues from protease inhibitors, neuropathy from zidovudine, body changes from stavudine/didanosine etc.
- Is the patient having difficulty adhering to complicated, multi-pill regimens?
- Are there new options since the patient started on their current regimen that would offer advantages?
SWITCH STUDIES
SWITCHMRK

Switching from a suppressive PI-based regimen to raltegravir
Patients currently being treated with lopinavir/ritonavir successfully (undetectable viral load for >3 months)

Half of the patients were switched to raltegravir while continuing background therapy

Lipids looked great– however, more patients in the raltegravir switch group developed virologic failure (80% suppressed vs. 88% in lopinavir group)
 Patients whose first regimen was the lopinavir-containing regimen or patients without history of virologic failure had similar virologic responses

Those who had history of previous virologic failure were more likely to fail with the switch
Why did this happen?

- Theorized that, in treatment experienced patients with high levels of resistance to NRTIs, patients in this study may have been receiving functional monotherapy.
- Because ritonavir-boosted protease inhibitors have high genetic barrier to resistance, PI monotherapy may be more effective than integrase inhibitor monotherapy.
Randomized stable patients on boosted-PI regimen with undetectable viral load >6 months

Switched PI to raltegravir versus continued boosted PI

Similar rates of virologic suppression between the groups

OTHER SWITCH STUDIES
STRATEGY-PI

- Evaluated patients on stable ritonavir-boosted protease inhibitor + emtricitabine/tenofovir with undetectable HIV viral load for >6 months
- Excluded patients with history of virologic failure or resistance to emtricitabine or tenofovir
- Randomized patients to elvitegravir/cobicistat/emtricitabine/tenofovir versus continuing same regimen
STRATEGY-PI

- Rates of continued virologic suppression <50 copies/mL:
  - EVG/COBI/FTC/TDF: 94%
  - RTV-boosted PI plus FTC/TDF: 87%
  - Elvitegravir group actually had statistical superiority
STRATEGY-NNRTI

• Evaluated patients on stable NNRTI + tenofovir/emtricitabine who were virologically suppressed for >6 months
• No history of resistance to emtricitabine or tenofovir
• Randomized to continuing same regimen versus switching to elvitegravir/cobicistat/tenofovir/emtricitabine
Results

- 93% in elvitegravir arm remained undetectable
- 88% in NNRTI arm
- Statistically non-inferior
SPIRIT: Switch to Rilpivirine From Boosted PI Regimens in Suppressed Pts

Pts with HIV-1 RNA < 50 copies/mL on stable RTV-boosted PI + 2 NRTIs for ≥ 6 mos, no previous NNRTI use (N = 476)

Switch to RPV/TDF/FTC (n = 317)

Continue RTV-Boosted PI* + 2 NRTIs (n = 159)

Continue RPV/TDF/FTC (n = 317)

Switch to RPV/TDF/FTC (n = 159)


*PIs: ATV/RTV, 37%; LPV/RTV, 33%; DRV/RTV, 20%; FPV/RTV, 8%; SQV/RTV, 2%.
SPIRIT Results

- Switch to rilpivirine-containing regimen non-inferior to continuing boosted-PI regimen
- This was regardless of pretreatment HIV-1 RNA
- Remember that rilpivirine does not perform as well in patients with HIV viral load >100k
- But if you are switching from someone with an undetectable viral load, you should be ok
STRIIVING: Switch to Dolutegravir/abacavir/lamivudine

- Patients who had undetectable viral load, stable for >6 months
- No history of previous virologic failure
- At baseline, 42% on PI, 31% on NNRTI and 26% on INSTI
- Patients randomized to switch immediately, or after 24 weeks
STRIVING at Week 24-48

- 5-6% in each arm removed due to protocol violations
- When cases reviewed, some patients had baseline resistance
- 85% in dolutegravir arm and 88% in control arm had virologic success (defined as being on therapy on protocol and suppressed)
- When removed protocol violations, virologic nonresponse was 1% in each arm
- More discontinuation on treatment change arm
OLE Trial

- Randomized patients on lopinavir/ritonavir + lamivudine or emtricitabine + one other nucleos(t)ide that had undetectable viral load for >6 months
- Half of the patients discontinued the third ARV, half continued same regimen
- Non-inferior virologic suppression after 6 months

Other Dual-Therapy Trials

- ATLAS-M, SALT:
  - Patients receiving atazanavir/ritonavir with 2 NRTIs

- DUAL GESIDA
  - Patients receiving darunavir/ritonavir with 2 NRTIs

- Studies dropped the 3rd drug and found similar virologic suppression in both arms with dual versus triple therapy

Dual-Therapy Trials with Dolutegravir

- SWORD-1 and SWORD-2
  - Open-label, phase III non-inferiority trials
  - Treatment-experienced, virologically suppressed patients receiving stable therapy
  - No previous virologic failure
  - Randomized to continue previous HAART versus switch to dolutegravir + rilpivirine
  - Similar virologic efficacy between the arms, 95% of patients had continued virologic suppression
  - Larger number of patients in the switch arm discontinued treatment for adverse events
  - Llibre JM, Conference on Retroviruses and Opportunistic Infections; February 13-16, 2017; Seattle, Washington. Abstract 44LB.
Other NRTI-Sparing Regimens

- MONET: switch to darunavir/ritonavir monotherapy showed similar efficacy as continuing standard ART
- PIVOT: switch to PI monotherapy but could switch back if developed detectable viremia, did note higher rates of virologic failure but improved after restarting NRTIs
- MONOI: patients switched to darunavir/ritonavir/2 NRTIs, then randomized to stop the NRTIs
  - Per protocol was noninferior but in intention-to-treat analysis did not meet noninferiority

Darunavir + Dolutegravir

- Observational cohort of treatment-experienced patients
- Proportion of patients who developed undetectable viral load went from 36% to 73%
- Open-label clinical trial currently recruiting patients in Germany (DUALIS)

Antivir Ther. 2017;22(3):257-262
Remember the Failures...

- NEAT001/ANRS143, ACTG5262, RADAR
  - Treatment-naïve patients randomized to darunavir/ritonavir +
    - raltegravir OR
    - tenofovir + emtricitabine
  - Similar rates of virologic suppression in overall population
  - Increased risk of virologic failure in dual versus triple therapy, increased resistance in patients with HIV viral load >100k, CD4<200
Strategic Simplification

- Heavily treatment experienced patients with at least 2 treatment failures, >2 class resistance
- No integrase resistance
- No Q151M, T69ins, or darunavir resistance
- Changed to Stribild + darunavir
- At week 48, no difference in virologic efficacy
If you do switch:

Need to know:
- Previous ARV history
- All previous genotypes/phenotypes,
- Including potential drug resistances
  - Patient may have been on regimen prior to use of genotypes, has archived virus