Management of Treatment Experienced Patients

Roger Bedimo, MD
VA North Texas Health Care System
UT Southwestern Medical Center
Faculty and Planning Committee Disclosures
Please consult your program book or the Conference App.

Off-Label Disclosure
There will discussion of off-label uses of approved agents.

Learning Objectives
Upon completion of this segment, learners should be able to:

- Identify comorbid conditions and concomitant medications that might require modification of antiretroviral regimens in the setting of virologic suppression
- Optimize antiretroviral therapy to enhance tolerability and mitigate drug-drug interactions
- Manage virologic failure in patients receiving antiretroviral therapy
Outline

- Virologic Failure (When the going gets tough…)
  - Define the Problem → Establish Goals → Analyze its Cause(s) → Determine Strategy (Ask for Help…)
  - Clinical Scenarios; Key Considerations
- Poor CD4 Count Recovery: No targeted Interventions recommended
- Optimizing ART in Setting of Virologic Suppression
  - Why?: Simplification, Tolerability, Interactions, Food, Fertility (STIFF)
  - How?: General Principles and Recommended Strategies
- Discontinuation or Interruption of ART: Just Don’t Do It…Please

Managing Patients with Virologic Failure

- Define the Problem: Is this failure?
- Establish the Goals:
- Analyze the Causes: How to identify the cause(s) of failure?
- Determine the Strategy: Based on failing regimen
Case 1: 30-Yr-Old MSM Experiencing Virologic Failure

- 30-yr-old MSM with h/o polysubstance abuse, previously virologically suppressed on EFV/FTC/TDF
  - Baseline labs: HIV-1 RNA was 630,000 copies/mL, CD4+: 200 cells/mm³; No baseline RAM, HLA-B*5701 negative; HBsAb positive.
  - No previous virologic failure; on EFV/FTC/TDF, VL<50 copies/mL, CD4 =600
- Struggling with multiple life stressors: family, work, housing insecurity; Lapsed adherence for past 3 weeks.
- Upon return to clinic, HIV-1 RNA was 4500 copies/mL and CD4+ cell count 450 cells/mm³
  - K103N, M184V, and K65R mutations detected

The patient is ready to restart ART. What do you recommend?

A. Boosted PI + 2 NRTIs
B. INSTI + 2 NRTIs
C. Boosted PI + INSTI
D. DTG + 3TC
E. DTG + RPV
F. Investigational ART regimen
G. Something else
Managing Patients with Virologic Failure

- Define the Problem: Is this failure? When should something be done?
  - The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.
  - HIV RNA levels of <200 copies/mL not predictive of subsequent rebound (but controversial); consider monitoring for 3 months…

- Establish the Goals:
  - To establish virologic suppression (i.e., HIV RNA levels below the lower limits of detection of currently used assays)
  - If not feasible (highly experienced patients), preserve CD4 gains, minimize toxicity, delay clinical progression.
  - Avoid DTG if pregnant ≤12 wks, childbearing potential w/o contraception

Impact of Low-level Viremia on Virological Outcomes

Same approach as for patients with high level viremia. Caveat: resistance testing might not be successful with VL<1000. Consider empirical change on case-by-case, based on ARV history and resistance.

Kaplan–Meier survival estimates

Log-rank test: $P < 0.001$
Analyzing Causes of Virologic Failure

#1: THE PATIENT
- Challenges to adherence: co-morbidities, psychosocial factors
- Poor access to care, cost
- Adverse effects, tolerability

#2: THE VIRUS
- Persistence resistant strains, prior failures
- Innate resistance
- Higher pre-treatment RNA

#3: THE TREATMENT
- Suboptimal PK/PD
- Suboptimal potency
- Low genetic barrier
- DDIs with non-ARVs

Virologic Failure: Confirm Identify Cause(s) Determine Strategy

Determine the Strategy: General Principles in Management of Virologic Failure

- In new regimen, at least two, and preferably three fully active drugs: based on patient’s ART history, current AND PAST drug-resistance test results.
  - Adding single drug to failing regimen is NOT recommended.
- When resistance mutations identified with:
  - NRTIs, PIs: Possibility of partial activity and could be retained in regimen.
  - NNRTIs, RAL: Likely need to discontinue to avoid further resistance, and jeopardizing future options in same class.
  - DTG or DRV/r might need to be given BID
- Resistance testing while still on failing regimen (or w/in 4 wks of D/C)

**Determine the Strategy: Resistance Testing in Treatment Experienced Patients**

- Perform if VL>1000; could be successful at VL b/w 500 & 1000
- Genotypic testing preferred w/ 1st & 2nd line regimen failure / expected non-complex resist.
- INSTI resist testing separately
- Phenotyping or combined phenotype/genotype preferred for
  - Known or suspected complex drug-resistance mutation patterns
  - Multiple regimen failures with limited treatment options

**Impact of ARV Discontinuation in Virologic Failure**

Discontinuation or temporary interruption NOT recommended ...

Treatment Strategies in First Line Regimen Failure. Based on Failing Regimen

- **Failing Boosted PI + NRTIs**
  - Enforce adherence
  - Modify for toxicity, DDI, or resistance concerns

- **Failing NNRTI + NRTIs**
  - Boosted PI + NRTIs (≥ 1 active NRTI)
  - Boosted PI + INSTI
  - INSTI + NRTIs
    - If only 1 NRTI fully active or if adherence a concern, DTG preferred vs. EVG or RAL


- **Randomized trial of with virologic failure on NNRTI + 2 NRTIs treated with LPV/RTV + RAL, LPV/RTV + 2-3 NRTIs, or LPV/RTV monotherapy (N = 1277)**

  | Patients (%) | HPV-1 RNA < 50 copies/mL, Wk 96
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<tbody>
<tr>
<td>LPV/RTV + RAL (n = 428)</td>
<td>74</td>
</tr>
<tr>
<td>LPV/RTV + RAL (n = 433)</td>
<td>44</td>
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<tr>
<td>LPV/RTV monotherapy (n = 418)</td>
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*Pts had no prior PIs; pts receiving monotherapy received 12 wks of LPV/RTV + RAL.


- **Randomized trial of patients with virologic failure on NNRTI + 2 NRTIs treated with DTG + 2 NRTIs or LPV/RTV + 2 NRTIs (N = 624). Required to have ≥ 1 active NRTI)**

  | Patients (%) | HIV-1 RNA < 50 copies/mL, Wk 48 (ITT-E)
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<tr>
<td>DTG + 2 NRTIs</td>
<td>84</td>
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<tr>
<td>LPV/RTV + 2 NRTIs</td>
<td>84</td>
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</tbody>
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Treatment Strategies in First Line Regimen Failure. Based on Failing Regimen

- **Failing Boosted PI + NRTIs**
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- **Failing NNRTI + NRTIs**
  - Boosted PI + NRTIs (≥ 1 active NRTI)
  - Boosted PI + INSTI
  - INSTI + NRTIs
    - If only 1 NRTI fully active or if adherence a concern, DTG preferred vs. EVG or RAL

- **Failing INSTI + NRTIs**
  - Boosted PI + NRTIs or DTG + NRTIs
    - (If no INSTI resistance, ≥ 1 active NRTI.)
  - Boosted PI + active INSTI
    - If EVG or RAL resistant but DTG susceptible, use boosted PI + NRTIs (≥ 1 active), BID DTG + NRTIs (2 active), or BID DTG + boosted PI.


Treatment Strategies in Failure of Second Line Regimen and Beyond

- **Drug resistance with active treatment options**
  - Use past and current genotypic +/- phenotypic resistance testing and ART history in designing new regimen
  - At least 2, and preferably 3, fully active agents
  - Partially active drugs may be used when no other options are available
  - Consider using an ARV with a different mechanism of action

- **Multiple or extensive drug resistance with few treatment options**
  - Use past and current genotypic and phenotypic resistance testing
    - Identify as many partially active drugs as possible
  - Consider viral tropism assay if use of MVC is considered
  - Consult an expert
  - Consider enrollment into clinical trials or expanded access progr.

Treatment Strategies in Failure of Second Line Regimen and Beyond

- Multiple or extensive drug resistance with few treatment options
  - Use past and current genotypic and phenotypic resistance testing
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Case 2: 54-Yr-Old Man Virologically Suppressed on RPV/FTC/TDF

- 54-yr-old man diagnosed with HIV infection 10 years ago.
- Baseline laboratory values:
  - CD4+ cell count 120 cells/mm³, HIV-1 RNA 85,000 copies/mL
  - HIV genotype: wild type; HLA-B*5701 negative
  - HBsAb positive, HCV Ab positive, HCV RNA negative
- Has received RPV/FTC/TDF since diagnosis
- Current laboratory values:
  - HIV-1 RNA levels < 50 copies/mL with rare “blips”; current CD4+ cell count 650 cells/mm³; Creatinine clearance: 80 mL/min
Case 2: Current Presentation

- Comorbidities: HTN, CAD s/p AMI, Asthma, GERD
- Multiple new health problems in the past few months:
  - He sustains a wrist fracture. Undergoes DXA scan showing osteoporosis. Prescribed Calcium, Vitamin D and Alendronate
  - Worsening asthma attacks and heartburn: His PCP prescribes omeprazole and inhaled fluticasone.
- The patient is generally satisfied with his ART regimen but does not always like that she must take her medication with meals

What changes would you recommend to this patient’s antiretroviral regimen?

A. Continue current regimen: RPV/FTC/TDF
B. Switch to BIC/FTC/TAF
C. Switch to DTG/ABC/3TC
D. Switch to RPV/FTC/TAF
E. Switch to DTG/RPV
F. Switch to DRV/COBI/FTC/TAF
G. Switch to EVG/COBI/FTC/TAF
General Principles for Optimizing ART in the Setting of Viral Suppression

- Maintain Viral Suppression: without jeopardizing future options…
- Review the ARV History: Failures? Toxicities? Resistance Testing?
  - Assume resist. to EFV, 3TC/FTC, RAL, EVG if previous failure on them
- Assess Prior Resistance Before Switch:
  - Once selected, resistance mutations are “archived”; With h/o Xple failures or prior regimens, proviral DNA genotypic testing may be useful.
- Consider HBV co-Infection:
  - Maintain 2 HBV-active drugs in new regimen. 3TC or FTC as sole HBV-active drug NOT recommended. Important: HBV flares…
- Consider DDIs and Potential for Pregnancy

Evidence-Based Antiretroviral Therapy Modification in Suppressed Patients

- **Within-Class Switches**
  - TDF or ABC → TAF
  - RAL to EVG/c → DTG
  - DTG, EVG/c, or RAL → BIC
  - EFV → RPV
  - PI/r → PI/c
  - ATV/c or ATV/r → unboosted ATV (when used with ABC/3TC)

- **Between-Class Switches**
  - Boosted PI → INSTI
  - Boosted PI → RPV
  - NNRTI → INSTI
  - Boosted PI → Maraviroc (MVC) (w/ CCR5 virus).


Reasons for Regimen Switch During Virologic Suppression: “STIFF Cost”

- **Simplification:** To reduce pill burden and/or dosing frequency
- **Tolerability:** To enhance tolerability and/or decrease toxicity
- **Interactions:** To prevent or mitigate drug-drug interactions
- **Food/Fluids:** To eliminate food or fluid requirements
- **Fertility:** To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur
- **Cost:** To reduce costs
**Simplification: Switching From Suppressive ART to an STR: Key Studies With Contemporary Regimens**

- Noninferior efficacy for all switch regimens vs baseline regimen; all FDA approved to treat virologically suppressed patients.

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<thead>
<tr>
<th>Switch to</th>
<th>Switch From</th>
<th>Key Studies</th>
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<tbody>
<tr>
<td>BIC/FTC/TAF</td>
<td>Boosted PI + 2 NRTIs</td>
<td>Daar. Lancet HIV. 2018</td>
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<tr>
<td></td>
<td>DTG/ABC/3TC</td>
<td>Molina. Lancet HIV. 2018</td>
</tr>
<tr>
<td>DTG/RPV</td>
<td>Third agent + 2 NRTIs</td>
<td>SWORD 1 &amp; 2. Libre. Lancet. 2018</td>
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<tr>
<td>DTG/ABC/3TC</td>
<td>Third agent + 2 NRTIs</td>
<td>STRIVIVING Trottier. Antivir Ther. 2017</td>
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<tr>
<td>DRV/COBI/FTC/TAF</td>
<td>Boosted PI + FTC/TDF</td>
<td>EMERALD Orkin. Lancet HIV. 2018</td>
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<tr>
<td>EVG/COBI/FTC/TAF</td>
<td>TDF-based regimen</td>
<td>GS-109 Mills. Lancet HIV. 2018</td>
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<tr>
<td>RPV/FTC/TAF</td>
<td>RPV/FTC/TDF</td>
<td>Orkin. Lancet HIV . 2017</td>
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<tr>
<td></td>
<td>EFV/FTC/TDF</td>
<td>DeJesus. Lancet HIV. 2017</td>
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- Most recent FDA approvals: for BIC/FTC/TAF and DTG/RPV, must have no history of treatment failure and no resistance to regimen components; for DRV/COBI/FTC/TAF, must have no resistance to DRV, TFV.

References in slidnotes.

**Slide credit:** clinicaloptions.com

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**Simplification: Switch From Suppressive ART to DTG + RPV in Patients With No Previous VF - SWORD-1&2**

- Randomized, open-label phase III trials in which virologically suppressed patients with no previous virologic failure:
  - Continued with baseline ART for 52 wks, then switched to DTG + RPV (delayed switch) or
  - Immediately switched to DTG + RPV (early switch) (N = 1024)\(^1,2\)
  - High rates of virologic response in both arms.

**Simplification**: Switch to EVG/COBI/FTC/TAF + DRV in Treatment-Experienced Patients with H/o Failures

Multicenter, open-label, randomized phase III trial

- Treatment-experienced patients, HIV-1 RNA < 50 c/mL for ≥ 4 mos
- Resistance to ≥ 2 ARV classes, including ≤ 3 thymidine analogue mutations and/or K65R, but no INSTI or DRV resistance
- 39% patients receiving ≥ 6 pills/day at baseline


**Tolerability**: Look for Ways to Enhance Tolerability and Limit Toxicity

- Special attention to older patients, polypharmacy.
- Low BMD / History of Fractures:
  - TDF → TAF, ABC: Increases in BMD; Clinical significance unclear
- High CVD Risk
  - ABC → TAF, TDF: High CVD risk with ABC; Impact of switch?
  - RTV or COBI-boosted PI → INSTI: High CVD risk with DRV; Improved lipids with switch; impact on CVD risk unclear.
- CKD / Proximal Tubulopathy
  - TDF → TAF, ABC
  - ATV/RTV → DTG, BIC, RAL, or NNRTI
**Tolerability: Look for Ways to Enhance Tolerability and Limit Toxicity**

Gallant. Lancet 2016

Additional Considerations:
- ↑ LDL; Potential for weight gain.


**Interactions and Food: Selected Concomitant Drugs to Watch for with Switching to INSTI-based Regimen**

- Polyvalent cations (Al, Mg, Ca):
  - ↓ INSTI exposure – space dosing; Do not co-administer Al/Mg w/ RAL:
- Direct-acting anticoagulants: Exposure ↑ by EVG/c. Caution…
- Anti-seizure: Carbamazepine & Phenytoin ↓ INSTI exposure: Can use DTG BID with Carbamazepine
- Metformin: Increases BIC and DTG exposure. Caution with DTG BID
- Rifamycins: ↓ INSTI exposure. Can use Rifabutin with DTG
- Steroids: Exposure increased by EVG/c (Beclomethasone inh OK)

Consult DHHS Guidelines: [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines)
Liverpool HIV Drug Interactions Website: [https://www.hiv-druginteractions.org/](https://www.hiv-druginteractions.org/)
The Cost-effectiveness and Budget Impact of 2-Drug Dolutegravir-Lamivudine Regimens for the Treatment of HIV Infection in the United States

Michael P. Girouard,1,2 Paul E. Sax,3,4 Robert A. Parker,1,4,5 Babafemi Taiwo,6 Kenneth A. Freedberg,1,2,4,7,8 Roy M. Gulick,9 Milton C. Weinstein,5,11 A. David Palitiel,12 and Rochelle P. Walensky1,2,3,4,7

– Potential savings: >$500 million in ART costs in the US over 5 y

Fertility (Pregnancy) : Neural Tube Defects and DTG Exposure (Tsepamo Study)

- Unplanned analysis of ongoing birth outcomes surveillance study among Botswanan women ± HIV infection[1,2]
- Avoid DTG in PLWH with childbearing potential not on effective contraception.
- HIV-infected women with virologic suppression on well-tolerated ART should continue that regimen in pregnancy

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<tr>
<th>Neural Tube Defects* (%, 95% CI)</th>
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<tr>
<td>0.12</td>
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<td>DTG</td>
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Conception | Pregnancy

*In 89,064 births as of May 1, 2018.

Cost: Less is More...

- Potential Impact of Two-drug regimens, generics, etc…

Clinical Infectious Diseases

MAJOR ARTICLE

HIV/AIDS

The Cost-effectiveness and Budget Impact of 2-Drug Dolutegravir-Lamivudine Regimens for the Treatment of HIV Infection in the United States

– Potential savings: >$500 million in ART costs in the US over 5 y
Strategies NOT RECOMMENDED (they’ve been tried and failed…)

- **Boosted Protease Inhibitor Monotherapy:**
  - Lower rates of virologic suppression
- **Dolutegravir Monotherapy**
  - Risk of virologic failure and subsequent development of INSTI resistance;
- **Boosted Atazanavir + Raltegravir**
  - High rate of virologic failure
- **Maraviroc + Boosted Protease Inhibitor/ or Maraviroc + Raltegravir**
  - High rate of virologic failure

Recap

- **Virologic Failure (When the going gets tough…)**
  - Define the Problem → Establish Goals → Analyze its Cause(s) → Determine Strategy (Ask for Help…)
  - Base strategy on likely patient, viral and ARV factors in failure.
- **Poor CD4 Count Recovery:** No targeted Interventions recommended
- **Optimizing ART in Setting of Virologic Suppression**
  - Why?: Simplification, Tolerability, Interactions, Food, Fertility (STIFF)
  - Analyze previous ART exposures/failures; Watch for DDI with new regimens
- **Discontinuation or Interruption of ART:** Just Don’t Do It…Please
ACTHIV 2019: A State-of-the-Science Conference for Frontline Health Professionals