2018 DHHS Guideline Update:
Switching Regimens

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Disclosures

- **Speaker’s Bureau**: Gilead, Merck, AbbVie, Viiv
- **Scientific Advisory Board**: Gilead, AbbVie
- **Grant/Research/Contracted Support**: CDC/HRSA, NWAETC, Pacific AETC, HealthHIV, Project ECHO, National Cancer Institute, Gilead Sciences, AbbVie
Learning Objectives

1) Identify changes to DHHS Guidelines
2) Review literature supporting *early initiation of ART for nearly everyone* living with HIV
3) Discuss changes to ’Recommended’ ART
4) Debate merits of Two Drug Regimens
BACKGROUND
US Department of Health and Human Services (DHHS)
October 25, 2018 - Antiretroviral Therapy Guidelines

- When to start ART?
- What to start?
- Baseline Evaluation, labs
- Treatment Goals
- Mgmt of Rx-experienced
- Special pops: acute HIV, adolescents, PWID, Women, HIV-2, Older patients, Co-infections (HBV, HCV, TB)
- Cost of ART
- Adverse Effects
- Drug-Drug Interactions

https://aidsinfo.nih.gov/
HIV-Related Guidelines

- DHHS Guidelines
- US Government-convened panel
- Released ~ Q6-12 months on aidsinfo.nih.gov
- Comprehensive resource
- More conservative

- IAS-USA Guidelines
- Panel of experts convened by IAS-USA
- Released ~Q2 yrs as a JAMA publication
- Moderate length review article
- More forward thinking
What’s New in the Guidelines?

Last Updated: October 25, 2018; Last Reviewed: October 25, 2018

**Resistance Testing**

New information has been added regarding the use of HIV-1 proviral DNA genotypic resistance tests to identify drug resistance mutations, especially in the setting of low-level viremia or when plasma HIV RNA is below the limit of detection. The section now includes a discussion on the benefits and limitations of these tests.

**Co-Receptor Tropism Testing**

For patients who have undetectable HIV RNA, the Panel now recommends using a proviral DNA tropism assay to assess co-receptor usage before maraviroc is initiated as part of a new regimen.

**Dolutegravir and Association with Neural Tube Defects**

Preliminary data from Botswana suggest that there is an increased risk of neural tube defects in infants born to women who were receiving dolutegravir (DTG) at the time of conception. In response to these preliminary data, several sections in the Adult and Adolescent Guidelines have been updated to provide guidance for clinicians who are considering the use of DTG or other integrase strand transfer inhibitors (INSTIs) in individuals who are pregnant, or in those of childbearing potential who plan to get pregnant or who are sexually active and not using effective contraception. The sections that have been updated with this new information include:
What’s New?

• ‘People-first’ language - A way of reducing stigma and showing respect for individuals who are living with HIV by focusing on the person instead of the disease
What’s New?

• Dolutegravir association w/ Neural Tube Defects
• What to Start - a few major changes:
  – B/F/TAF in; E/C/F/TAF out
• Virologic Failure: DTG, Ibalizumab (IBA)
• Optimizing ART in setting of Virologic Suppression (the ‘switch’ section)
WHEN TO START?
Case #1:

A 23-year-old man presents to your clinic after testing HIV+ at a bar with a rapid Oral swab. Previously healthy, 5-6 sexual partners, MSM, occasional condoms and not on PrEP.

Initial CD4 = 685 cell/mL, HIV Ag/Ab Positive, HIV VL PENDING; HIV Genotype PENDING
Case #1:

He feels fine and would rather not take ART if he ‘doesn’t have to’. What do DHHS guidelines recommend?

A. Start ART immediately, on the SAME DAY
B. Start ART as soon as possible, when patient ready
C. Start ART after HIV RNA to ensure not elite controller
D. Start ART after genotype to customize regimen
E. Defer ART until CD4 < 500, higher evidence level
Goals of Anti-Retroviral Therapy

- Suppress plasma HIV viral load
- Reduce HIV-associated morbidity
- Prolong survival
- Improve quality of life
- Restore and preserve immune function
- Prevent transmission
Initiating ART in Treatment-Naïve Patients
Change in CD4 Threshold in DHHS Guidelines

https://aidsinfo.nih.gov/
When to Start?

Panel’s Recommendations

- Antiretroviral therapy (ART) is recommended for all individuals with HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection (AI).
- ART is also recommended for individuals with HIV to prevent HIV transmission (AI).
- When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.

“Studies suggest that same-day initiation of ART may be feasible and could potentially improve clinical outcomes... resources may not be available in all settings and the long-term clinical benefits have yet to be proven in the United States, this approach remains investigational”
Evidence for Early Start

• **START Trial** – (n = 4685, CD4 >500 ART vs. not)
  – 57% reduction in risk of death or serious event
  – 72% reduction in serious AIDS events
  – 39% reduction in serious non-AIDS events
  – 68% of events occurred at CD4 >500

• **TEMPRANO trial** – (n = 2000, early ART +/- IPT)
  – early ART/IPT lowest event rate (5.7% vs. 14.1%)

• **HPTN 052** – (n = 1763 couples, early vs. later ART)
  – 96% reduction in HIV transmission
Case #2:

A 34 yo female Somali immigrant presents to establish care. She was diagnosed with HIV 5 yrs ago in refugee camp in Kenya during second pregnancy, and only took ART briefly ‘to protect the baby’.

Initial labs:

CD4 = 255 cells/mL, VL 120,000 copies/mL
HBsAg positive, Genotype = No resistance mutations, HLA-B*5701 negative
Case #2:

She has no further plans for pregnancy and has had a tubal ligation. Which of the following regimens is NOT recommended according to 10/18 DHHS guidelines?

A. FTC/TDF + DTG
B. ELV/c/FTC/TAF
C. ABC/3TC/DTG
D. BIC/FTC/TAF
E. FTC/TAF + RAL
F. B and C
DTG Association with NTD’s

**DTG avoided in:**
- 1\textsuperscript{st} trimester pregnancy
- Plans for pregnancy
- Potential pregnancy

**Not clear if INSTI class effect but:**
- BIC structurally similar
- E/C/F/TAF yields inadequate levels in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester
- RAL may be OK but limited data

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**Table 6b. Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors as Initial Therapy**

Pregnancy testing should be performed in those of childbearing potential prior to initiation of ART (AIII). Preliminary data suggest that there is an increased risk of NTDs in infants born to women who were receiving DTG at the time of conception.\textsuperscript{6,7}

**Before Initiating DTG:**
- Providers and people of childbearing potential should discuss the benefits and risks of using DTG, including the possible risk of NTDs; appropriate counseling should be provided so that the individual can make an informed decision about the use of this drug (AIII).
- DTG should not be prescribed for individuals:
  - Who are pregnant and within 12 weeks post-conception (AII); or
  - Who are of childbearing potential and planning to become pregnant (AII); or
  - Who are of childbearing potential, sexually active, and not using effective contraception (AIII).
- For those who are using effective contraception, a DTG-based regimen can be considered after weighing the risks and benefits of DTG use with the individual (BIII).
- It is not yet known whether other INSTIs pose a similar risk of NTDs (i.e., a class effect).
- The chemical structure of BIC is similar to DTG. There are no safety data on the use of BIC around the time of conception. For those who are of childbearing potential, but who are not pregnant, an approach similar to that outlined for DTG should be discussed before considering the use of BIC-containing ART (AIII).
- In a person who is pregnant, BIC is not recommended because of insufficient safety data (AIII).
- In a person who is pregnant, EVG/c is also not recommended because low EVG concentrations have been reported when this drug is given during the second and third trimesters (AII).\textsuperscript{13}
- Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States; however, data on RAL use during the first trimester is limited to fewer than 300 deliveries. As it is currently not known whether the association between DTG and NTDs represents a class effect, this potential risk should be discussed with people of childbearing potential who prefer an INSTI-containing regimen.

[https://aidsinfo.nih.gov/](https://aidsinfo.nih.gov/)
WHAT TO START?
Anti-retroviral drug targets

Source: David Spach, MD
(2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs) + Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
or
Protease Inhibitor (PI) (ritonavir-boosted)
or
Integrase Strand Transfer Inhibitor (INSTI)
## DHHS Antiretroviral Therapy Guidelines: Feb 2013

### Preferred Regimens for ARV-Naïve Patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Components</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-Based</td>
<td>Efavirenz/Tenofovir/Emtricitabine</td>
<td><img src="image" alt="Pill Burden" /></td>
</tr>
<tr>
<td>PI-Based</td>
<td>Atazanavir + Ritonavir + Tenofovir/Emtricitabine</td>
<td><img src="image" alt="Pill Burden" /></td>
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<tr>
<td></td>
<td>Darunavir + Ritonavir + Tenofovir/Emtricitabine</td>
<td><img src="image" alt="Pill Burden" /></td>
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<tr>
<td>INSTI-Based</td>
<td>Raltegravir + Tenofovir/Emtricitabine</td>
<td><img src="image" alt="Pill Burden" /></td>
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### DHHS Antiretroviral Therapy Guidelines: November 2014

#### Recommended Regimens for ARV-Naïve Patients

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<td><img src="image" alt="Pill Burden" /></td>
</tr>
<tr>
<td></td>
<td>Elvitegravir/Cobicistat/Tenofovir/Emtricitabine*</td>
<td><img src="image" alt="Pill Burden" /></td>
</tr>
<tr>
<td></td>
<td>Dolutegravir + Tenofovir/Emtricitabine; Dolutegravir/Abacavir/Lamivudine+</td>
<td><img src="image" alt="Pill Burden" /></td>
</tr>
</tbody>
</table>

* only of eGFR > 70 mL/min; + only if HLA-B*5701 negative
### DHHS Antiretroviral Therapy Guidelines: July 2016

#### Recommended Regimens for ARV-Naïve Patients

<table>
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<tr>
<th>Class</th>
<th>Therapy</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-Based</td>
<td>Darunavir + Ritonavir + Tenofovir (DF/AF)/Emtricitabine</td>
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</tr>
<tr>
<td></td>
<td>Raltegravir + Tenofovir (DF/AF)/Emtricitabine</td>
<td></td>
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DHHS Antiretroviral Therapy Guidelines: Oct 2017
Recommended Regimens for Most People with HIV

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<td>Raltegravir + Tenofovir (DF/AF)/Emtricitabine</td>
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<tr>
<td>INSTI-Based</td>
<td>Elvitegravir/Cobicistat/Tenofovir(DF/AF)/Emtricitabine*</td>
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<tr>
<td>INSTI-Based</td>
<td>Dolutegravir/Abacavir/Lamivudine</td>
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<tr>
<td>INSTI-Based</td>
<td>Dolutegravir + Tenofovir-Emtricitabine OR Abacavir-Lamivudine</td>
<td><img src="image4" alt="Pill Burden" /></td>
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* only of eGFR > 70 mL/min
DHHS Antiretroviral Therapy Guidelines: Oct 2018

Recommended Regimens for Most People with HIV

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# DHHS Antiretroviral Therapy Guidelines: Oct 2018

## Recommended Regimens for Certain Clinical Situations

### Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

#### INSTI plus 2 NRTIs:

**Note:** For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/tenofovir\(^b\)/FTC (BI for both TAF/FTC and TDF/FTC)
- RAL\(^c\) plus ABC/3TC\(^a\) (CII)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL

#### Boosted PI plus 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) plus tenofovir\(^b\)/FTC\(^a\) (AI)
- (ATV/c or ATV/r) plus tenofovir\(^b\)/FTC\(^a\) (BI)
- (DRV/c or DRV/r) plus ABC/3TC\(^a\) —if HLA-B*5701 negative (BII)

#### NNRTI plus 2 NRTIs:

- DOR/TDF\(^b\)/3TC (BI) or DOR plus TAF\(^b\)/FTC (BII)
- EFV plus TDF\(^b\)/FTC\(^a\) (BI for EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC, BII for EFV 600 mg plus TAF/FTC)
- RPV/tenofovir\(^b\)/FTC\(^a\) (BI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm\(^3\)

### Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG plus 3TC (BI)
- DRV/r plus RAL BID (Cl)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm\(^3\)
- DRV/r once daily plus 3TC\(^a\) (Cl)

### Changes:

- Doravirine (DOR)
- E/C/F/TAF
- Boosted PI’s
- Two-drug Regimens:
  - DTC/3TC
  - DRV/r+RAL
  - DRV/r+3TC

[https://aidsinfo.nih.gov/](https://aidsinfo.nih.gov/)
### Table 7 - ART based on Certain Clinical Scenarios

<table>
<thead>
<tr>
<th>Patient or Regimen Characteristics</th>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-ART Characteristics</strong></td>
<td>CD4 count &lt; 200 cells/mm²</td>
<td>Do Not Use the Following Regimens:</td>
<td>A higher rate of virologic failure has been observed in those with low pretreatment CD4 count.</td>
</tr>
<tr>
<td></td>
<td>HIV RNA &gt; 100,000 copies/mL</td>
<td>Do Not Use the Following Regimens:</td>
<td>Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA.</td>
</tr>
<tr>
<td></td>
<td>HLA B*5701-positive</td>
<td>Do not use ABC-containing regimens.</td>
<td>Abacavir hypersensitivity, a potentially fatal reaction, is highly associated with positivity for the HLA B*5701 allele.</td>
</tr>
<tr>
<td><strong>ART must be started before HIV drug resistance results are available (e.g., in a person with acute HIV or when a rapid initiation of ART is warranted). See Initiation of Antiretroviral Therapy.</strong></td>
<td></td>
<td>Avoid NNRTI-based regimens.</td>
<td>Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommended ART Regimens:</td>
<td>Resistance to DRV and DTG emerges slowly; transmitted resistance to DRV is rare and transmitted resistance to DTG has not been reported to date.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(DRV/r or DRV/c) + tenofovir²/FTC; or; or; DTG + tenofovir²/FTC</td>
<td></td>
</tr>
<tr>
<td><strong>ART-Specific Characteristics</strong></td>
<td>A once-pill, once-daily regimen is desired.</td>
<td><strong>STI Options Include:</strong></td>
<td>Do not use RPV-based regimens if HIV RNA &gt; 100,000 copies/mL and CD4 count &lt; 200/mm³.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- DTG/ABC/3TC</td>
<td>Since RPV-containing STRs are smaller in size than other STRs, they may be considered when a person has difficulty swallowing a larger pill.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- EFV/TFD/TDC</td>
<td>Do not use DTG/ABC/3TC if patient is HLA B*5701 - positive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- EVG/TAF/FTC</td>
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- CD4/VL levels
- Co-morbidity (CKD, TB, Lipids, CAD, HBV/HCV)
- Patient preference
- No Resistance data
- Poor Adherence
- Opioid Substitution
10/18 DHHS ‘Recommended for Most’

Backbone

(2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Third Agent

Integrase Strand Transfer Inhibitor (INSTI)
Case #3:

A 64 yo Caucasian male transferring care. HCV+, never treated. Dx’d 2004. Struggles with depression.

ART History:

Initial labs:
CD4 = 145 cells/mL, VL 120,000 copies/mL
HBsAg negative, HCV Ab +, Genotype = WT, HLA-B*5701 neg

Recent labs:
CD4 = 750 cells/mL, VL <20 copies/mL
Tchol 254, TG340, HDL 25, LDL 165; Cr 2.2, eGFR 38
AST/ALT 72/54, HCV GT-3, HCV RNA 650,000
Case #3:

How would you approach his current ART Regimen?

A. No change unless he initiates conversation
B. Offer a few options but only switch if he seems motivated
C. Suggest a switch because of GFR
D. Suggest a switch because of lipids
E. Suggest a switch because of h/o depression
F. Suggest a switch because of HCV co-infection
Key Factors Influencing First-line Regimen

- Baseline Viral Load
- Tropism (CCR5, CXCR4)
- Transmitted Resistance

- Efficacy, Tolerability
- Long-term safety
- Drug-Drug interactions
- Pharmacokinetics
- Pill burden, cost

- Age, Sex, Family Plans
- Meds/Co-morbidities
- Occupation/Lifestyle
- Predicted Adherence
- HLA-B*5701
- Patient Preference
Reasons to Consider Switch in the Setting of Viral Suppression

- To simplify a regimen by reducing pill burden and/or dosing frequency
- To enhance tolerability and/or decrease short/long-term toxicity
- To prevent or mitigate drug-drug interactions
- To eliminate food requirements
- To allow for optimal use of ART during pregnancy or in cases where pregnancy may occur
- To reduce costs

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If there is uncertainty about prior resistance, it is generally not advisable to switch a suppressive regimen unless the new regimen is likely to be at least as active against potential resistant virus as the suppressive regimen
The Switch Process

Rationale:
- Toxicity
- Side Effects
- Pill Burden
- Simplification
- DDI
- Cost
- Food Requirement

Ensure Safety:
- ART history
- Resistance testing
- HBV status
- Check for DDI’s
- Pregnancy?

Monitor:
- Maintain Viral Suppression
- Ensure Tolerability

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Switch strategies with Evidence

- TDF → TAF
- RAL → ELV/c or DTG
- DTG, ELV/c or RAL → BIC
- EFV → RPV
- PI/r → PI/c
- PI/r → INSTI
- PI/R → RPV
- NNRTI → INSTI

- **No h/o virologic failure** → DTG+RPV, DTG+ 3TC; ATZ/r+3TC, DRV/r+3TC or LPV/r+3TC
- **H/o virologic failure** → ELV/c/FTC/TAF+DRV

https://aidsinfo.nih.gov/
Summary

• DHHS Guidelines continue to evolve
  – ART for everyone (with good evidence)
  – INSTI-based regimens for most
  – Still a role for other regimens (PI’s, NNRTI’s, two-drug regimens) in certain settings
  – More advice on switching, what to do in various clinical scenarios.
  – Data emerging on two-drug regimens
References

- https://aidsinfo.nih.gov/