Antiretroviral Therapy for the Treatment of HIV

Infectious Disease Conference
The Miriam Hospital
Wednesday, August 5, 2020
Speakers

Amy Brotherton, PharmD, AAHIVP, BCIDP  
Clinical Pharmacist Specialist, Infectious Disease  
The Miriam Hospital Infectious Disease & Immunology Clinic  
Contact: amy.brotherton@lifespan.org

Rajeev Shah, PharmD, AAHIVP, BCIDP  
Clinical Pharmacist Specialist, Infectious Disease  
The Miriam Hospital Infectious Disease & Immunology Clinic  
Contact: rshah4@lifespan.org
Disclosures

• None
Objectives

• Identify the recommended combination regimens for use in antiretroviral therapy (ART)-naïve patients, including disadvantages and advantages for each regimen
• Recognize class-specific and drug-specific pharmacokinetic factors that affect the efficacy and safety of ART
• Review recent updates to the DHHS Adult and Adolescent, Perinatal, and Opportunistic Infection Guidelines
• Summarize future treatment options that are currently in development
Outline

• Brief History
• When to Treat
• ARV Classes
• First-Line and Second-Line ART Regimens (DHHS & IAS-USA)
• Patient-Specific ART and Clinical Scenarios
• Additional Guideline Updates
• Novel Agents
Many Things Have Changed…

**Virologic Response**
(HIV-1 RNA <50 copies)

DTG/3TC vs. DTG + TDF/FTC

<table>
<thead>
<tr>
<th>Treatment-Naïve Adults, %</th>
<th>DTG/3TC</th>
<th>DTG + TDF/FTC</th>
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<tbody>
<tr>
<td></td>
<td>91%</td>
<td>93%</td>
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</table>

**BW 002: 24-Week Study of AZT vs. Placebo in Patients with AIDS or ARC**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>AZT</th>
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<tr>
<td>Deaths</td>
<td>19</td>
<td>45</td>
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<tr>
<td>Opportunistic Infections</td>
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<td>24</td>
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</table>
Tales of ART Past, Present, and Future

HIV-1 Discovered

AZT/3TC Saquinavir

Single Tablet Regimens

Dual Regimens
DTG/RPV
DTG/3TC

1983
AZT Monotherapy

1987

1995
Combination ART (Triple Drug Therapy)

1996

2006
Integrase Era

2010-now
RAL
EVG
DTG
BIC
CAB..

2019
Long-Acting Injectables

2021
???
WHEN TO START ART
When to Initiate ART
The Swinging Pendulum

<table>
<thead>
<tr>
<th>CD4 Count (cells/mm³)</th>
<th>1998</th>
<th>2001</th>
<th>2006</th>
<th>2009</th>
<th>2012</th>
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<tr>
<td>&gt; 500</td>
<td>Treat if VL &gt;20,000</td>
<td>Treat if VL &gt;55,000</td>
<td>Consider if VL &gt;100,000</td>
<td>Consider in certain patients</td>
<td>Consider in certain patients</td>
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<tr>
<td>350-500</td>
<td>Treat if VL &gt;20,000</td>
<td>Consider if VL &gt;55,000</td>
<td>Consider if VL &gt;100,000</td>
<td>Consider in certain patients</td>
<td>Treat</td>
</tr>
<tr>
<td>200-350</td>
<td>Treat if VL &gt;20,000</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>&lt;200 or symptomatic</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
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</tr>
</tbody>
</table>

Thanks to Dr. Jason Schaefer for use of this slide.
Early ART Reduces AIDS and Non-AIDS Events

START

- ART-naïve adults (n=4685)
  - CD4 cell counts >500
  - Randomized to initiate ART immediately or after CD4 count decline to <350
  - Primary endpoint: composite of serious AIDS and non-AIDS events

- Immediate ART reduced risk of serious events or death by 57%
- Most events (59%) occurred in the deferred arm

ART Reduces HIV Transmission
Treatment as Prevention (TasP)

- Supported by data from numerous studies from 2008-2016 demonstrating zero linked transmissions after >100,000 condomless sex acts among serodifferent couples when the partner living with HIV had a viral load <200 copies/mL.

Advocacy
Undetectable = Untransmittable (U = U)

People who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner.

September, 2017
When to Start ART
ASAP

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all persons with HIV to reduce morbidity and mortality (A) and to prevent the transmission of HIV to others (A1).
- The Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating ART immediately (or as soon as possible) after HIV diagnosis in order to increase the uptake of ART and linkage to care, decrease the time to viral suppression for individual patients, and improve the rate of virologic suppression among persons with HIV (AII).
- When initiating ART, it is important to educate patients regarding the benefits of ART and to deploy strategies to optimize care engagement and treatment adherence (AIII).

Most urgent patients: Acute HIV infection, pregnancy, AIDS-defining conditions, HBV or HCV co-infection, HIV-associated nephropathy
RAPID Initiation of ART – Systematic Review of RCTs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RR (95% CI)</th>
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<tr>
<td>ART start within 90 days</td>
<td>1.35 (1.13-1.62)</td>
</tr>
<tr>
<td>Retained in care at 12 mos</td>
<td>1.11 (0.99-1.26)</td>
</tr>
<tr>
<td>Viral suppression at 12 mos</td>
<td>1.17 (1.07-1.27)</td>
</tr>
<tr>
<td>LTFU at 12 mos</td>
<td>0.66 (0.42-1.04)</td>
</tr>
<tr>
<td>Mortality at 12 mos</td>
<td>0.53 (0.28-1.00)</td>
</tr>
</tbody>
</table>

RAPID ART associated with:

- **Increased** likelihood of ART initiation, retention in care, viral suppression
- **Decreased** likelihood of loss to follow-up and death

Adapted from clinicaloptions.com

RAPID Initiation of ART

• Observational, real-world data in the U.S. is emerging
  • Ward 86 RAPID Start Program in San Francisco
  • CrescentCare Start Initiative in New Orleans
  • Rapid Entry and ART in Clinic for HIV (REACH) program in Atlanta
  • PHARM-D RAPID Program in Providence
PHARMACIST-DRIVEN RAPID ART REDUCES TIME TO VIROLOGIC SUPPRESSION IN RHODE ISLAND

Amy L. Brotherton1, Rajeev R. Shah1, Joseph M. Garland1, Meghan McCarthy1, Fizza S. Gillani1, Martha C. Sanchez1

1The Miriam Hospital, Division of Infectious Diseases, Providence, Rhode Island, USA
2Alpert Medical School of Brown University, Providence, Rhode Island, USA

BACKGROUND
- Rapid start antiretroviral therapy (ART) protocols have emerged as an innovative care model for persons newly diagnosed with HIV (PNDWH). RCT data from Haiti and South Africa and observational data from the US have demonstrated positive clinical outcomes with rapid ART. However, logistical challenges limit widespread implementation and sustainability. Shifting to a model where clinical pharmacists are at the forefront of rapid ART may provide a sustainable solution for the challenges that limit implementation in the US. We began piloting our Pharmacist-Driven RAPID (PHARM-D) ART Protocol in January 2019.
- Study Aim: To evaluate a novel model for rapid ART implementation driven by Infectious Disease Clinical Pharmacists and its effect on clinical outcomes, including time to HIV viral suppression.

METHODS
- Study Design: We conducted a preliminary retrospective analysis comparing clinical outcomes of PNDWH prior to (2/2017 to 12/2017) and post-implementation (1/2019 to 12/2019) of our PHARM-D RAPID ART Protocol.
- Study Site: The Miriam Hospital Infectious Diseases & Immunology Center is a large, urban Ryan White funded clinic providing care for >90% of persons with HIV in Rhode Island (over 1,800 patients).
- Statistical Analysis: Biases were analyzed using a Student t-test, Wilcoxon rank sum, Chi-square, or Fisher exact test, as appropriate.

RESULTS
- Our PHARM-D RAPID ART Protocol significantly reduced time to HIV viral suppression by 48 days and reduced out-of-pocket costs to patients by $488,398 annually.
- Table 1: Baseline Demographics
- Table 2: Clinical Outcomes

CONCLUSIONS
- Pharmacist-driven rapid initiation of ART significantly decreased time to viral suppression by 48 days (>50%) and time to initiation of ART by 17 days. Our protocol helped patients avoid $488,398 annually on out-of-pocket ART costs and was not associated with any adverse outcomes.
- Clinical pharmacists play an integral role in the care of persons with HIV by providing patient counseling and education, recommendations for screening, vaccinations, and laboratory monitoring, and resolution of drug-drug interactions and medication access issues.
- This model may help overcome some of the barriers to implementation cited by previous studies and prevent potential provider burnout issues.
- Data collection is ongoing to evaluate retention in care measures, factors associated with HIV viral suppression, and sustainability beyond 1 year.
- Our PHARM-D RAPID protocol demonstrates a novel way to reduce time to HIV viral suppression for PNDWH thereby reducing risk of HIV transmission, an important component of our statewide efforts to achieve 90-90-90 goals.
RAPID Initiation of ART

_Reduce fear and stigma_

_Accessible treatment for all_

_PLWH are empowered_

_Improve confidence in healthcare team_

_Decrease barriers to care_
INTRO TO ARVs
Clinical Resources

• DHHS HIV Guidelines
  • Available at: http://aidsinfo.nih.gov/guidelines
    • Adult, adolescent, pediatric, and pregnancy guidelines for treatment, guidelines for prophylaxis for HIV and OI, drug-drug information resource

• IAS-USA HIV Treatment and HIV Resistance
  • Available at: https://www.iasusa.org/guidelines

• Stanford Database for HIV Resistance
  • Available at: https://hivdb.stanford.edu/

• University of Liverpool HIV drug-interaction database
  • Available at: www.hiv-druginteractions.org
ARV Classes

• Entry inhibitors*
  • CCR5 inhibitors, fusion inhibitors, post-attachment inhibitors
• Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
• Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**
• Integrase strand transfer inhibitors (INSTIs)
  • PK-boosted INSTIs**
  • Non-boosted INSTIs
• Protease inhibitors (PIs)**

*Not recommended in initial therapy
**Recommended in certain clinical situations
Mechanism of Action of ARVs

- Entry inhibitors
  - CCR5 inhibitors, fusion inhibitors, post-attachment inhibitors
- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Integrase strand transfer inhibitors (INSTIs)
- Protease inhibitors (PIs)

Mechanism of Action of ARVs

- **Entry inhibitors**
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- **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)**
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**
- **Integrase strand transfer inhibitors (INSTIs)**
- **Protease inhibitors (PIs)**

## Entry Inhibitors

<table>
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<tr>
<th>Generic</th>
<th>Administration</th>
<th>Brand</th>
<th>Abbreviation</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>Oral</td>
<td>Selzentry</td>
<td>MVC</td>
<td>CCR5 Inhibitor</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Intramuscular injection</td>
<td>Fuzeon</td>
<td>ENF, T20</td>
<td>Fusion inhibitor</td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>Intravenous</td>
<td>Trogarzo</td>
<td>IBA</td>
<td>Post-attachment inhibitor, monoclonal antibody</td>
</tr>
<tr>
<td>Fostemsavir</td>
<td>Oral</td>
<td>Rukobia</td>
<td>FTR</td>
<td>Attachment inhibitor</td>
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</tbody>
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Mechanism of Action of ARVs

- Entry inhibitors
  - CCR5 inhibitors, fusion inhibitors, post-attachment inhibitors
- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
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# NRTIs

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</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir</td>
<td>3TC</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>FTC</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>Viread</td>
<td>TDF</td>
</tr>
<tr>
<td>Tenofovir alafenamide</td>
<td>Vemlidy</td>
<td>TAF</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Videx</td>
<td>ddI</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zerit</td>
<td>D4T</td>
</tr>
<tr>
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**Nucleoside Reverse Transcriptase Inhibitors**
First-Line NRTIs

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# NRTI Combination Products: Make up part of a regimen

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
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<th>Combination Product (Brand)</th>
</tr>
</thead>
<tbody>
<tr>
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## Nucleoside Reverse Transcriptase Inhibitors
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NRTI Combination Products: Make up part of a regimen
Mechanism of Action of ARVs

- Entry inhibitors
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NNRTIs

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<tr>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva, component of Atripla(^{1**}), Symfi(^{1**}), Symfi Lo(^{1**})</td>
<td>EFV</td>
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<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>NVP</td>
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<tr>
<td><strong>Second Generation NNRTIs</strong></td>
<td></td>
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<tr>
<td>Doravirine</td>
<td>Pifeltro, component of Delstrigo(^{1**})</td>
<td>DOR</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Edurant, component of Odefsey(^{1}), Complera(^{1**}), Juluca(^{1})</td>
<td>RPV</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Intelence</td>
<td>ETR</td>
</tr>
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\(^1\)Single Tablet Regimen (STR)  
\(^{*}\)Contains TAF  
\(^{**}\)Contains TDF

Non-Nucleoside Reverse Transcriptase Inhibitors
**NNRTIs**: Consider Using First-Line in Certain Situations

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Non-Nucleoside Reverse Transcriptase Inhibitors
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# INSTIs

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<th>Abbreviation</th>
</tr>
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<tbody>
<tr>
<td><strong>First Generation INSTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir(^1)</td>
<td>Isentress, Isentress HD</td>
<td>RAL</td>
</tr>
<tr>
<td>Elvitegravir(^2)</td>
<td>Component of Stribild(^\ast), Genvoya(^*)</td>
<td>EVG</td>
</tr>
<tr>
<td><strong>Second Generation INSTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Tivicay, component of Triumeq, Dovato, Juluca (not for first line use)</td>
<td>DTG</td>
</tr>
<tr>
<td>Bictegravir(^2)</td>
<td>Component of Biktarvy(^*)</td>
<td>BIC</td>
</tr>
</tbody>
</table>

\(^1\)Not available as fixed-dose combination product  
\(^2\)Only available as fixed-dose combination product  
\(^\ast\)Contains TAF  
\(^\ast\)Contains TDF  

**Integrase Strand Transfer Inhibitors**  
(“Integrase Inhibitors”)
# First-Line INSTIs

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand(s)</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation INSTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir¹</td>
<td>Isentress, Isentress HD</td>
<td>RAL</td>
</tr>
<tr>
<td>Elvitegravir²</td>
<td>Component of Stribild**, Genvoya*</td>
<td>EVG</td>
</tr>
<tr>
<td><strong>Second Generation INSTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Tivicay, component of Triumeq, Dovato</td>
<td>DTG</td>
</tr>
<tr>
<td></td>
<td>Juluca (not for first line use)</td>
<td></td>
</tr>
<tr>
<td>Bictegravir²</td>
<td>Component of Biktarvy*</td>
<td>BIC</td>
</tr>
</tbody>
</table>

**Integrase Strand Transfer Inhibitors**

("Integrase Inhibitors")

¹Not available as fixed-dose combination product
²Only available as fixed-dose combination product
*Contains TAF
**Contains TDF
Mechanism of Action of ARVs

• Entry inhibitors
  • CCR5 inhibitors, fusion inhibitors, post-attachment inhibitors
• Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
• Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
• Integrase strand transfer inhibitors (INSTIs)
• Protease inhibitors (PIs)

Pharmacokinetic Enhancers
“Boosters”

- **Ritonavir** and **cobicistat** are strong **CYP3A4 inhibitors** that are given in combination with **PIs** and the **INSTI**, **elvitegravir**

- Boosters inhibit the metabolism of PIs and elvitegravir to improve the pharmacokinetic/pharmacodynamic profile of these medications

- **This results in:**
  - Higher concentrations of PI or EVG
  - Less frequent dosing
  - Improved adherence
  - Decreased resistance
  - High potential for drug-drug interactions

---

**The following products contain boosters:**

- Norvir (RTV)
- Prezincobix (DRV/c)
- Evotaz (ATV/c)
- Symtuza (DRV/c/TAF/FTC)
- Stribild (EVG/c/TDF/FTC)
- Genvoya (EVG/c/TAF/FTC)
### Protease Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir plus ritonavir</td>
<td>Reyataz + Norvir</td>
<td>ATV/r</td>
</tr>
<tr>
<td>Atazanavir/cobicistat</td>
<td>Evotaz</td>
<td>ATV/c</td>
</tr>
<tr>
<td>Darunavir plus ritonavir</td>
<td>Prezista + Norvir</td>
<td>DRV/r</td>
</tr>
<tr>
<td>Darunavir/cobicistat</td>
<td>Prezcobix, component of Symtuza(^1)</td>
<td>DRV/c</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>FPV</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crixivan</td>
<td>IDV</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Kaletra</td>
<td>LPV/r</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept</td>
<td>NFV</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Forovase</td>
<td>SQV</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Kaletra</td>
<td>LPV/r</td>
</tr>
</tbody>
</table>

\(^1\)Single Tablet Regimen (STR)
**Protease Inhibitors**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
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<td>Fosamprenavir</td>
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<tr>
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<td>Kaletra</td>
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<td>Nelfinavir</td>
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</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Kaletra</td>
<td>LPV/r</td>
</tr>
</tbody>
</table>

\(^1\)Single Tablet Regimen (STR)
# PI Combination Products: Make up Part of a Regimen

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbreviation</th>
<th>Combination Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir plus ritonavir</td>
<td>Reyataz + Norvir</td>
<td>ATV/r</td>
<td></td>
</tr>
<tr>
<td>Atazanavir/cobicistat</td>
<td>Evotaz</td>
<td>ATV/c</td>
<td></td>
</tr>
<tr>
<td>Darunavir plus ritonavir</td>
<td>Prezista + Norvir</td>
<td>DRV/r</td>
<td></td>
</tr>
<tr>
<td>Darunavir/cobicistat</td>
<td>Prezcobix component of</td>
<td>DRV/c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symtuza¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>FPV</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crixivan</td>
<td>IDV</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Kaletra</td>
<td>LPV/r</td>
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</tr>
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<td>Nelfinavir</td>
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</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Kaletra</td>
<td>LPV/r</td>
<td></td>
</tr>
</tbody>
</table>

¹ Single Tablet Regimen (STR)

**Protease Inhibitors**
BUILDING AN ARV REGIMEN
First-line HIV treatment regimens typically contain at least 3* active drugs

*One first-line regimen only contains 2 active drugs
Building an ARV Regimen

First-line HIV treatment regimens typically contain at least 3* active drugs.

2 NRTIs + one of the following

- INSTI (non-boosted)
- PK-boosted PI
- PK-boosted INSTI
- NNRTI

*One first-line regimen only contains 2 active drugs.

Two Sides

One Protein

Veggie or Fish

Beef

Fried Chicken
Building an ARV Regimen

DHHS Recommended Initial Regimens for Most Patients

First-line regimens are all **INSTI based**!

*One regimen only contains 1 NRTI

Fish/veggie = “healthy option”
Building an ARV Regimen

DHHS Regimens to Consider in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with first-line regimens, or have less supporting data from randomized clinical trials.

- **PK-boosted INSTI**
- **PK-boosted PI**
- **NNRTI**

Not as “healthy” long-term, drug-drug interactions, or not as effective.

2 NRTIs + one of the following

Beef or fried chicken
The Shift to INSTI-Based Regimens

- INSTIs have high rates of virologic suppression and often greater tolerability than PIs and NNRTIs

<table>
<thead>
<tr>
<th>Study</th>
<th>INSTI</th>
<th>Comparator(s)</th>
<th>Follow-up</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARTMRK</td>
<td>RAL</td>
<td>Efavirenz</td>
<td>192 weeks</td>
<td>Raltegravir superior to efavirenz</td>
</tr>
<tr>
<td>ACTG A5257</td>
<td>RAL</td>
<td>Darunavir/ritonavir</td>
<td>96 weeks</td>
<td>Raltegravir superior to darunavir/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atazanavir/ritonavir</td>
<td></td>
<td>Raltegravir superior to atazanavir/r</td>
</tr>
<tr>
<td>GS-102</td>
<td>EVG</td>
<td>Efavirenz</td>
<td>144 Weeks</td>
<td>Elvitegravir non-inferior to efavirenz</td>
</tr>
<tr>
<td>GS-103</td>
<td>EVG</td>
<td>Atazanavir/ritonavir</td>
<td>144 Weeks</td>
<td>Elvitegravir non-inferior to atazanavir/ritonavir</td>
</tr>
<tr>
<td>WAVES</td>
<td>EVG</td>
<td>Atazanavir/ritonavir</td>
<td>48 Weeks</td>
<td>Elvitegravir superior to atazanavir/ritonavir in women</td>
</tr>
<tr>
<td>SINGLE</td>
<td>DTG</td>
<td>Efavirenz</td>
<td>48 Weeks</td>
<td>Dolutegravir superior to efavirenz</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>DTG</td>
<td>Darunavir/ritonavir</td>
<td>48 Weeks</td>
<td>Dolutegravir superior to darunavir/ritonavir</td>
</tr>
<tr>
<td>ARIA</td>
<td>DTG</td>
<td>Atazanavir/ritonavir</td>
<td>48 Weeks</td>
<td>Dolutegravir superior to atazanavir/ritonavir in women</td>
</tr>
<tr>
<td>GS-US-380-1489</td>
<td>BIC</td>
<td>Dolutegravir</td>
<td>48 Weeks</td>
<td>Bictegravir non-inferior to dolutegravir</td>
</tr>
<tr>
<td>GS-US-380-1480</td>
<td>BIC</td>
<td>Dolutegravir</td>
<td>48 Weeks</td>
<td>Bictegravir non-inferior to dolutegravir</td>
</tr>
</tbody>
</table>
DHHS RECOMMENDED INITIAL REGIMENS FOR MOST PEOPLE WITH HIV
## DHHS Panel’s Recommended Initial Regimens for Most People with HIV

<table>
<thead>
<tr>
<th>Generic (Abbreviation)</th>
<th>Brand</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)</td>
<td>Biktarvy</td>
<td><img src="5G5T" alt="G5T" /></td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)</td>
<td>Trumeq</td>
<td>![572 Tm](572 Tm)</td>
</tr>
<tr>
<td>Dolutegravir/lamivudine (AI) (DTG/3TC)</td>
<td>Dovato</td>
<td><img src="TRV" alt="TRV" /></td>
</tr>
<tr>
<td>Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)</td>
<td>Tivicay + Descovy</td>
<td><img src="225" alt="225" /></td>
</tr>
<tr>
<td>Dolutegravir + tenofovir disoproxil fumarate/emtricitabine (AI) (DTG + TDF/FTC*)</td>
<td>Tivicay + Truvada</td>
<td><img src="701" alt="701" /></td>
</tr>
<tr>
<td>Raltegravir + tenofovir alafenamide/emtricitabine (BI) (RAL + TAF/FTC*)</td>
<td>Isentress + Descovy</td>
<td>![227 227 225](227 227 225)</td>
</tr>
<tr>
<td>Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)</td>
<td>Isentress + Truvada</td>
<td>![227 227 701](227 227 701)</td>
</tr>
</tbody>
</table>

*May substitute 3TC for FTC

---

**First-Line Regimens**

**DHHS Guidelines 2019**
Initiation of Antiretroviral Therapy
DHHS Recommendations (Adults & Adolescents)

**“TEGRAVIR” = integrase inhibitor**

<table>
<thead>
<tr>
<th>Generic (Abbreviation)</th>
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</tr>
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<tbody>
<tr>
<td>Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)</td>
<td>Biktarvy</td>
<td>![image]</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)</td>
<td>Triumeq</td>
<td>![image]</td>
</tr>
<tr>
<td>Dolutegravir/lamivudine (AI) (DTG/3TC)</td>
<td>Dovato</td>
<td>![image]</td>
</tr>
<tr>
<td>Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)</td>
<td>Tivicay + Descovy</td>
<td>![image]</td>
</tr>
<tr>
<td>Dolutegravir + tenofovir disoproxil fumarate/emtricitabine (AI) (DTG + TDF/FTC*)</td>
<td>Tivicay + Truvada</td>
<td>![image]</td>
</tr>
<tr>
<td>Raltegravir + tenofovir alafenamide/emtricitabine (BI) (RAL + TAF/FTC*)</td>
<td>Isentress + Descovy</td>
<td>![image]</td>
</tr>
<tr>
<td>Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)</td>
<td>Isentress + Truvada</td>
<td>![image]</td>
</tr>
</tbody>
</table>

*May substitute 3TC for FTC*
### DHHS Panel’s Recommended Initial Regimens for Most People with HIV

<table>
<thead>
<tr>
<th>Generic (Abbreviation)</th>
<th>Brand</th>
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</tr>
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<tbody>
<tr>
<td>Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)</td>
<td>Biktarvy</td>
<td>![Pill Image]</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)</td>
<td>Trumeq</td>
<td>![Pill Image]</td>
</tr>
<tr>
<td>Dolutegravir/lamivudine (AI) (DTG/3TC)</td>
<td>Dovato</td>
<td>![Pill Image]</td>
</tr>
<tr>
<td>Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)</td>
<td>Tivicay + Descovy</td>
<td>![Pill Image]</td>
</tr>
<tr>
<td>Dolutegravir + tenofovir disoproxil fumarate/emtricitabine (AI) (DTG + TDF/FTC*)</td>
<td>Tivicay + Truvada</td>
<td>![Pill Image]</td>
</tr>
<tr>
<td>Raltegravir + tenofovir alafenamide/emtricitabine (BI) (RAL + TAF/FTC*)</td>
<td>Isentress + Descovy</td>
<td>![Pill Image]</td>
</tr>
<tr>
<td>Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)</td>
<td>Isentress + Truvada</td>
<td>![Pill Image]</td>
</tr>
</tbody>
</table>

*May substitute 3TC for FTC*
# Initiation of Antiretroviral Therapy

## DHHS Recommendations (Adults & Adolescents)

DHHS Panel’s Recommended Initial Regimens for **Most** People with HIV

<table>
<thead>
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<th>Generic (Abbreviation)</th>
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</tr>
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<tbody>
<tr>
<td>Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)</td>
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<td><img src="pill.png" alt="pill" /></td>
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<tr>
<td>Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)</td>
<td>Triumeq</td>
<td><img src="pill.png" alt="pill" /></td>
</tr>
<tr>
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<td>Dovato</td>
<td><img src="pill.png" alt="pill" /></td>
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<td>Dolutegravir + tenofovir alafenamide/emtricitabine (AI) (DTG + TAF/FTC*)</td>
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<tr>
<td>Raltegravir + tenofovir disoproxil fumarate/emtricitabine (BII) (RAL + TDF/FTC*)</td>
<td>Isentress + Truvada</td>
<td><img src="pill.png" alt="pill" /></td>
</tr>
</tbody>
</table>

*May substitute 3TC for FTC*
Single Tablet Regimens (STR)

“We combined all your medications into ONE convenient dose!”
## DHHS Panel’s Recommended Initial Regimens for Most People with HIV
### (Single Tablet Regimens)

<table>
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<th>Generic (Abbreviation)</th>
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<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir/tenofovir alafenamide/emtricitabine (AI) (BIC/TAF/FTC)</td>
<td>Biktarvy</td>
<td>![Image of Biktarvy pill]</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine (AI) (DTG/ABC/3TC)</td>
<td>Triumeq</td>
<td>![Image of Triumeq pill]</td>
</tr>
<tr>
<td>Dolutegravir/lamivudine (AI) (DTG/3TC)</td>
<td>Dovato</td>
<td>![Image of Dovato pill]</td>
</tr>
</tbody>
</table>

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### First-Line STRs

---

### Initiation of Antiretroviral Therapy

**DHHS Recommendations (Adults & Adolescents)**
DHHS RECOMMENDED INITIAL REGIMENS IN CERTAIN CLINICAL SITUATIONS
## DHHS Panel’s Recommended Initial Regimens in Certain Clinical Situations

### Boosted INSTI + 2 NRTIs

<table>
<thead>
<tr>
<th>Regimen Description</th>
<th>Brand</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir/cobicistat/tenofovir AF/emtricitabine (EVG/c/TAF/FTC)</td>
<td>Genvoya</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/tenofovir DF/emtricitabine (EVG/c/TDF/FTC)</td>
<td>Stribild</td>
<td></td>
</tr>
</tbody>
</table>

### Boosted PI + 2 NRTIs

<table>
<thead>
<tr>
<th>Regimen Description</th>
<th>Brand</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir/cobicistat/tenofovir AF/emtricitabine (DRV/c/TAF/FTC)</td>
<td>Symtuza</td>
<td></td>
</tr>
<tr>
<td>Darunavir/cobicistat + tenofovir/emtricitabine (DRV/c + TDF (or TAF)/FTC*)</td>
<td>Prezcobix + Truvada (or Descovy)</td>
<td>800 225</td>
</tr>
<tr>
<td>Darunavir + ritonavir + tenofovir/emtricitabine (DRV/r + TDF (or TAF)/FTC*)</td>
<td>Prezista + Norvir + Truvada (or Descovy)</td>
<td>800 225</td>
</tr>
<tr>
<td>Atazanavir/cobicistat + tenofovir/emtricitabine (ATV/c + TDF (or TAF)/FTC*)</td>
<td>Evotaz + Truvada (or Descovy)</td>
<td>364 225</td>
</tr>
<tr>
<td>Atazanavir + ritonavir + tenofovir/emtricitabine (ATV/r + TDF (or TAF)/FTC*)</td>
<td>Reyataz + Norvir + Truvada (or Descovy)</td>
<td></td>
</tr>
</tbody>
</table>

### NNRTI + 2 NRTIs

<table>
<thead>
<tr>
<th>Regimen Description</th>
<th>Brand</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz/tenofovir/emtricitabine (EVF/TDF/FTC*)</td>
<td>Atripla**</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine/tenofovir AF/emtricitabine (RPV/TAF/FTC)</td>
<td>Odefsey</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine/tenofovir DF/emtricitabine (RPV/TDF/FTC)</td>
<td>Complera</td>
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</tr>
<tr>
<td>Doravirine/tenofovir DF/lamivudine (DOR/TDF/3TC)</td>
<td>Delstrigo</td>
<td></td>
</tr>
<tr>
<td>Doravirine + tenofovir AF/emtricitabine (DOR + TAF/FTC*)</td>
<td>Pifeltro + Descovy</td>
<td></td>
</tr>
</tbody>
</table>

*May substitute 3TC for FTC  
**Additionally, Symfi, Symfi Lo, Sustiva plus Descovy, Sustiva plus Cimduo
## Initiation of Antiretroviral Therapy  
### DHHS Recommendations (Adults & Adolescents)

<table>
<thead>
<tr>
<th>DHHS Panel’s Recommended Initial Regimens in Certain Clinical Situations (Single Tablet Regimens)</th>
<th>Brand</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boosted INSTI + 2 NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/tenofovir AF/emtricitabine (EVG/c/TAF/FTC)</td>
<td>Genvoya</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/tenofovir DF/emtricitabine (EVG/c/TDF/FTC)</td>
<td>Stribild</td>
<td></td>
</tr>
<tr>
<td><strong>Boosted PI + 2 NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir/cobicistat/tenofovir AF/emtricitabine (DRV/c/TAF/FTC)</td>
<td>Symtuza</td>
<td></td>
</tr>
<tr>
<td><strong>NNRTI + 2 NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC)</td>
<td>Atripla*</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine/tenofovir AF/emtricitabine (RPV/TAF/FTC)</td>
<td>Odefsey</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine/tenofovir DF/emtricitabine (RPV/TDF/FTC)</td>
<td>Complera</td>
<td></td>
</tr>
<tr>
<td>Doravirine/tenofovir DF/lamivudine (DOR/TDF/3TC)</td>
<td>Delstrigo</td>
<td></td>
</tr>
</tbody>
</table>

*Additionally, Symfi, Symfi Lo

DHHS Guidelines 2019
Initiation of Antiretroviral Therapy
Recommendations - International Antiviral Society, USA Panel

<table>
<thead>
<tr>
<th>Recommended Initial Regimens</th>
<th>When Initial Regimens Are Not an Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bictegravir/TAF/emtricitabine (Ala)</td>
<td>• Darunavir* plus tenofovir/emtricitabine (Ala)</td>
</tr>
<tr>
<td>• Dolutegravir/abacavir/lamivudine (Ala)</td>
<td>• Efavirenz/TDF/emtricitabine (Ala)</td>
</tr>
<tr>
<td>• Dolutegravir plus TAF/emtricitabine (Ala)</td>
<td>• Elvitegravir/cobi/tenofovir/emtricitabine (Ala)</td>
</tr>
</tbody>
</table>

• BIC and DTG do not require boosting, have a high barrier to resistance, and are part of regimens with a low pill burden and toxicity

• TAF results in fewer tenofovir-associated renal and bone toxic effects

• RAL is well tolerated with few drug interactions, but has a low barrier to resistance and a high pill burden

• EVG has a lower barrier to resistance and requires boosting, resulting in more drug interactions

*Boosted with ritonavir or cobicistat
PROCESS FOR SELECTING INITIAL ART
Process for Selecting Initial ART

- **Regimen efficacy**
  - Guidelines recommendations, superiority data?

- **Drug resistance**
  - Transmitted resistance 10-17%
  - Prevalence: NNRTIs > NRTIs > PIs > INSTI
  - If genotype pending, use DTG-, BIC-, or PI-based regimens (strongest barrier to resistance)

- **Pretreatment labs and considerations**
  - i.e. RPV: only if CD4 >200, HIV RNA <100,000
    - DTG/3TC only if HIV RNA <500,000
  - HBV status
  - HLA-B*5701 status
  - Childbearing potential, pregnancy status

- **Comorbidities, comedications**
  - Potential for adverse effects or drug-drug interactions (most common with boosters and PIs), renal dosing or hepatic dosing

- **Adherence potential**
  - Pill burden, dosing frequency, food restrictions (RPV, EVG/c, PIs must be administered with food), side-effect profile
SELECTING A FIRST-LINE REGIMEN
Selecting a First-Line Regimen

DTG/ABC/3TC

DTG/3TC

BIC/TAF/FTC

DTG + TFV/XTC

RAL + TFV/XTC

TFV = TAF or TDF
XTC = FTC or 3TC
Selecting a First-Line Regimen

- DTG/ABC/3TC (Triumeq)
- DTG/3TC
- BIC/TAF/FTC
- DTG + TFV/XTC
- RAL + TFV/XTC

TFV = TAF or TDF
XTC = FTC or 3TC
Triumeq
(Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg)

- Fallen out of favor for persons who are newly diagnosed with HIV outside of being a preferred STR in women who are pregnant and living with HIV

- Can be given without dose adjustment with rifabutin

- Cannot be rapidly initiated due to several limitations
  - Requires testing for HLA-B*5701 allele prior to initiation (abacavir hypersensitivity)
  - Does not adequately cover HBV co-infection (regimen lacks tenofovir)

- Largest pill size as a STR

- Controversial association between abacavir and cardiovascular risk
Abacavir and CV Risk

• Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D):
  • 33,000 patients, observational study, **RR 1.91** (95% CI, 1.5-2.42) with ABC
  • Increased risk with PIs (darunavir and lopinavir/ritonavir) also
• Several additional studies show conflicting results
• No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association

• **Guidelines state to use caution or avoid** in patients with known high CV risk
Selecting a First-Line Regimen

DTG/ABC/3TC

DTG/3TC

BIC/TAF/FTC

DTG + TFV/XTC

RAL + TFV/XTC

Dovato

TFV = TAF or TDF
XTC = FTC or 3TC
Results from GEMINI-1 and GEMINI-2

Virologic Success at 48 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GEMINI-1</th>
<th>GEMINI-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG/3TC</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>DTG/3TC/TDF</td>
<td>93%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Dovato (Dolutegravir 50 mg/lamivudine 300 mg)

• Garnering more attention as an option for newly-diagnosed persons (or switch), especially in an aging population with HIV

• Cannot be rapidly initiated
  • Requires baseline viral load, genotype
  • Does not adequately cover HBV co-infection (regimen lacks tenofovir)

• Has potential benefits when compared to other two-drug regimen DTG/RPV (Juluca)

• Medium pill size as a STR

• Avoid if potential for poor adherence, and carefully review resistance history prior to switch

• Can be given without dose adjustment with rifabutin

• Consider for those with baseline kidney or bone dysfunction or for those with high cardiovascular risk
Selecting a First-Line Regimen

- DTG/ABC/3TC
- DTG/3TC
- BIC/TAF/FTC (Biktarvy)
- DTG + TFV/XTC
- RAL + TFV/XTC

TFV = TAF or TDF
XTC = FTC or 3TC
Biktarvy
(Bictegravir 50 mg/tenofovir AF 25 mg/emtricitabine 200 mg)

- Most commonly prescribed regimen for persons who are newly diagnosed with HIV (or switch)

- Only first-line STR that is appropriate for rapid initiation
  - No viral load restrictions
  - High barrier to resistance
  - Adequately treats HBV coinfection

- Smallest pill size as a first-line STR

- Insufficient data for use during pregnancy or in patients with INSTI resistance

- Consider avoiding in those with baseline renal or bone dysfunction
  - (No TFV>TAF>TDF)
Tenofovir alafenamide vs. Tenofovir disoproxil fumarate

- TFV (tenofovir) Parent nucleotide
- TDF (tenofovir disoproxil fumarate) 300 mg
- TAF (tenofovir alafenamide fumarate) 25 mg

- GI TRACT
- TUBULE
- HIV TARGET CELL (lymphoid cell)
- TVF
- TFV-MP
- TFV-DP

- PLASMA
- HIV

90% lower plasma TFV levels with TAF
TAF vs. TDF
Clinical Trials Data

• Studies 104/111: TAF-Based Regimen **Superior** to TDF Through 144 Weeks in Treatment-Naïve Patients

• Key Conclusions at 144 Weeks
  • TAF regimen statistically **superior virologic efficacy**
    • HIV-1 RNA <50 copies/mL difference: 4.2% (95% CI: 0.6-7.8%; P=.02), largely driven by discontinuations
  • Significantly fewer discontinuations due to AEs with TAF vs TDF
  • Significantly fewer discontinuations due to renal and bone AEs with TAF vs TDF (none in TAF arm)
  • Significantly smaller losses in spine and hip bone mineral density with TAF vs TDF
  • Significantly smaller decreases from baseline for renal parameters with TAF vs TDF
TAF vs. TDF
Not always interchangeable!

- **Use TAF or TFV-sparing**
  - Concern for renal/bone toxicity?

- **TAF or TDF**
  - ESRD?

- **TAF* or TDF**
  - PrEP?

- **TDF**
  - Pregnancy?

- **TDF**
  - DDIs (rifamycins, anti-seizure meds)

- **TAF or TDF**
  - Hepatitis B co-infection?

*Only approved for MSM and TGW*
### Selecting a First-Line STR: Summary

<table>
<thead>
<tr>
<th></th>
<th>Triumeq (DTG/ABC/3TC)</th>
<th>Dovato (DTG/3TC)</th>
<th>Biktarvy (BIC/TAF/FTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid start</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Requires HLA-B*5701</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Viral load restrictions</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Covers HBV co-infection</strong></td>
<td>No</td>
<td>No</td>
<td>Yes (tenofovir component)</td>
</tr>
<tr>
<td><strong>Tablet size</strong></td>
<td>Large</td>
<td>Medium</td>
<td>Small</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Without regard to meals</td>
<td>Without regard to meals</td>
<td>Without regard to meals</td>
</tr>
<tr>
<td><strong>Considerations for renal dose adjustment</strong></td>
<td>No renal dose adjustment required</td>
<td>No renal dose adjustment required</td>
<td>No renal dose adjustment required in ESRD; consider alternative in CKD</td>
</tr>
<tr>
<td><strong>Bottom line</strong></td>
<td>Not initiated frequently anymore outside of pregnancy</td>
<td>Consider in those with kidney or bone disorders or cardiovascular risk</td>
<td>Most frequently initiated regimen in persons newly diagnosed with HIV</td>
</tr>
</tbody>
</table>
Renal dose adjustment of 3TC/FTC in hemodialysis

**Dose:** elviteg-cobicist-emtricit-tenofovir, 1 Tab, Oral, Once Daily
- Specific dosing guidelines are not available for this patient's level of renal impairment. The ordered dose is within the limits that do not consider renal impairment but otherwise match the patient's conditions.
- Renal adjustment note: Not recommended in patients with ESRD (CrCl < 15 mL/min) who are NOT receiving hemodialysis. No adjustment required in patients with ESRD (CrCl < 15 mL/min) who ARE receiving hemodialysis.

**Dose:** abacavir-dolutegravir-lamivudine, 1 Tab, Oral, Once Daily
- This drug is not recommended for use in patients with this level of renal impairment (CrCl 0 - 49 mL/min).
- Warnings are based on assumed values for the following undetermined data:
- Creatinine Clearance

**Prescription:**
- **elviteg-cobicist-emtricit-tenofovir (GENVOYA)** 150-150-200 mg Tab tablet
- **abacavir-dolutegravir-lamivudine (TRIUMEQ)** 600-50-300 mg Tab tablet
Renal dose adjustment of 3TC/FTC in hemodialysis

- **EVG/c/TAF/FTC**
  - Phase 3b, open labeled, single armed study in 55 patients with ESRD on chronic HD
  - Overall no major side effects, 82% maintained viral suppression at 48 weeks, and 78% were more satisfied with single tablet regimen

- **DTG/ABC/3TC**
  - Case series of 6 PLWH simplified to STR of DTG/ABC/3TC 50-600-300 mg daily
  - All 6 maintained HIV RNA < 200 copies/mL
  - No serious adverse effects reported
Selecting a First-Line Regimen: Non-STRs

- DTG/ABC/3TC
- DTG/3TC
- BIC/TAF/FTC
- DTG + TFV/XTC
- RAL + TFV/XTC

Tivicay + Descovy (or Truvada, Cimduo)
Isentress + Descovy (or Truvada, Cimduo)

TFV = TAF or TDF
XTC = FTC or 3TC
## Initiation of First-Line Non-STRs

<table>
<thead>
<tr>
<th>Tivicay plus Descovy (or Truvada, Cimduo)</th>
<th>Isentress plus Descovy (or Truvada, Cimduo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May be selected if persons develop <strong>intolerance to bicitegravir</strong></td>
<td></td>
</tr>
<tr>
<td>• May be selected if certain <strong>drug-drug interactions</strong> preclude the use of BIC/TAF/FTC (most often DTG 50 mg BID or RAL 800 mg BID plus TDF/XTC)</td>
<td></td>
</tr>
<tr>
<td>• DTG 50 mg daily or RAL 400 mg BID plus TDF 300 mg/FTC 200 mg (or TDF 300 mg/3TC 300 mg) is a preferred regimen in <strong>pregnant women</strong> living with HIV</td>
<td></td>
</tr>
<tr>
<td>• May be selected if persons have <strong>INSTI resistance</strong> (requires DTG 50 mg BID)</td>
<td></td>
</tr>
<tr>
<td>• Lower genetic barrier to resistance than BIC or DTG</td>
<td></td>
</tr>
</tbody>
</table>

XTC = FTC or 3TC
**INSTIs and Weight Gain**

- Weight gain has been associated particularly DTG/BIC + TAF compared to EFV

- Trials have shows statistically significant weight gain; however overall absolute differences have not been clinically significant

- 10-40% of patients have experienced significant weight gain (> 10% of original weight)

- Phenomenon seems to be more prevalent in women and black/Hispanic race, lower CD4 count, and higher HIV RNA

- Overall significance of weight gain is controversial

**References**

Considerations for Clinical Practice

• Discuss association with patients

• Consider historical adherence patterns

• Review treatment history and prior genotypes for alternative agents

• Evaluate alternative agents for toxicities

• Assess current medications for drug-drug interactions
Drug-Drug Interaction Risk: Differences Among ARVs

- **Boosted ARV**
  - Raltegravir
  - Dolutegravir
  - Bictegravir

- **Efavirenz**
- **Etravirine**
- **Rilpivirine**
- **Doravirine**

Legend:
- Green: No interaction
- Yellow: Potential weak interaction
- Orange: Interaction of clinical relevance
- Red: Drugs should not be coadministered

Courtesy of Dr. David Back. Data from Mixpanel analytics of https://www.hiv-druginteractions.org.

Slide credit: clinicaloptions.com
First-Line INSTI Drug-Drug Interactions

• **Polyvalent and divalent cations** and all INSTIs
  • Some can be given simultaneously with food
  • Separate by 12 hours is simplest thing to tell patients on daily supplements (more difficult with iron, need to look up specifics)
  • If frequent use of antacids, evaluate for cause, educate patient, consider H2-antagonist if using acutely

• **Metformin** and dolutegravir, bictegravir (less so)

• **Rifampin, antiepileptics** and all INSTIs (and TAF)
SELECTING AN ALTERNATIVE REGIMEN
Selecting an Alternative Regimen

- INSTI-based
- NNRTI-based
- PI-based
Selecting an Alternative Regimen

- INSTI-based
- NNRTI-based
- PI-based
Genvoya or Stribild
(Elvitegravir 150 mg/cobicistat 150 mg/tenofovir/emtricitabine 200 mg)

- Removed from first-line regimens due to poorer tolerability (GI side-effects) and multiple drug-drug interactions
- Requires food for absorption
- Lower genetic barrier to resistance than BIC or DTG
- May be considered in persons with intolerance to other INSTIs
Drug-Drug Interaction Risk: Differences Among ARVs

- Boosted ARV
  - No interaction
  - Potential weak interaction
  - Interaction of clinical relevance
  - Drugs should not be coadministered

- Efavirenz
  - No interaction
  - Potential weak interaction
  - Interaction of clinical relevance
  - Drugs should not be coadministered

- Etravirine
  - No interaction
  - Potential weak interaction
  - Interaction of clinical relevance
  - Drugs should not be coadministered

- Rilpivirine
  - No interaction
  - Potential weak interaction
  - Interaction of clinical relevance
  - Drugs should not be coadministered

- Doravirine
  - No interaction
  - Potential weak interaction
  - Interaction of clinical relevance
  - Drugs should not be coadministered

Courtesy of Dr. David Back. Data from Mixpanel analytics of https://www.hiv-druginteractions.org.

Slide credit: clinicaloptions.com
INSTI Drug-Drug Interactions

EVG/c

To name a few....

• Inhaled/intranasal/injectable/systemic steroids

• Hormonal contraceptives and hormone replacement therapy

• Statins

• Anticoagulants and antiplatelets

• Antidepressants/anxiolytics/antipsychotics

• Cardiac Medications
**INSTI Drug-Drug Interactions**

**EVG/c**

- **Inhaled/intranasal/injectable/systemic steroidal agents**
  *Beclomethasone, prednisone, and prednisolone preferred*

- **Hormonal contraceptives and hormone replacement therapy**
  *Hormonal contraceptive should contain at least 30 mcg of ethinylestradiol*

- **Statins**
  *Contraindicated with lovastatin, simvastatin, no more than atorvastatin 20 mg daily*

- **Anticoagulants and antiplatelets**
  *Avoid DOACs, utilize warfarin or consider changing ARV regimen*

- **Antidepressants/anxiolytics/antipsychotics**
  *Initiate with lowest dose and titrate carefully*

- **Cardiac Medications**
  *Consider beta-blockers such as atenolol, labetalol, nadolol; monitor for AEs with amlodipine*
Selecting an Alternative Regimen

- INSTI-based
- NNRTI-based
- PI-based
Selecting an NNRTI-Based Regimen: EFV vs. RPV vs. DOR

<table>
<thead>
<tr>
<th>Efavirenz-based</th>
<th>Rilpivirine-based</th>
<th>Doravirine-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Preferred in setting of HIV RNA &gt;100,000 and CD4 count &lt;200 when combined with XTC/TFV</td>
<td>• Higher incidence of <em>failure</em> when HIV RNA &gt;100,000 and CD4 count &lt;200; avoid use</td>
<td>• Preferred in setting of HIV RNA &gt;100,000 and CD4 count &lt;200; least amount of data</td>
</tr>
<tr>
<td>• Higher incidence of <strong>neuropsychiatric</strong> side-effects, elevated cholesterol</td>
<td>• Lower incidence of neuropsychiatric side-effects, better tolerability</td>
<td>• Lower incidence of neuropsychiatric side-effects, better tolerability</td>
</tr>
<tr>
<td>• CYP3A4 substrate; CYP3A4, CYP2C19 and UGT1A1 <strong>inducer</strong>; many drug-drug interactions</td>
<td>• CYP3A4 substrate; drug-drug interactions with <strong>acid-reducing medications</strong></td>
<td>• CYP3A4 substrate; less potential for drug-drug interactions</td>
</tr>
<tr>
<td>• Only coformulated with TDF</td>
<td>• Coformulations with <strong>TAF</strong> and TDF</td>
<td>• Only coformulated with TDF</td>
</tr>
</tbody>
</table>

• Avoid if unknown HIV genotype or HIV genotype pending
Drug-Drug Interaction Risk: Differences Among ARVs

- **Boostered ARV**
- **Raltegravir**
- **Dolutegravir**
- **Bictegravir**

**Drug**
- Efavirenz
- Etravirine
- Rilpivirine
- Doravirine

**Interaction Risk**
- **No interaction**
- **Potential weak interaction**
- **Interaction of clinical relevance**
- **Drugs should not be coadministered**

Courtesy of Dr. David Back. Data from Mixpanel analytics of https://www.hiv-druginteractions.org.

Slide credit: clinicaloptions.com
NNRTI Administration Concerns and DDIs

- **Efavirenz** (in Sustiva, Atripla, Symfi, Symfi Lo)
  - At bedtime on an **empty stomach** (food increases absorption, leading to higher side-effects)
  - CYP inducer, **decreases** levels of other medications

- **Rilpivirine** (in Edurant, Complera, Odefsey, Juluca)
  - **With high calorie meal**, requires acid for absorption
  - Avoid acid-reducing medications, **CONTRAINDICATED** with PPIs

- **Doravirine** (in Pifeltro, Delstrigo)
  - **No concerns**; can be taken with or without food and with acid-reducing medications
Selecting an Alternative Regimen

- INSTI-based
- NNRTI-based
- PI-based
Selecting a PI-Based Regimen
ATV vs. DRV

<table>
<thead>
<tr>
<th>Atazanavir-based</th>
<th>Darunavir-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Administer with food, GI upset, dyslipidemia, many DDIs</td>
<td>• No DDIs with acid-reducing agents (inhibitor of CYP3A4 and p-glycoprotein)</td>
</tr>
<tr>
<td>• <strong>Acidic environment required</strong> for absorption; DDIs with acid-reducing agents in addition to typical DDIs (CYP3A4 and p-glycoprotein)</td>
<td>• <strong>Higher genetic barrier</strong>, may be used in the setting of failure or if genotype pending</td>
</tr>
<tr>
<td>• High genetic barrier but lower genetic barrier than DRV</td>
<td>• Indirect hyperbilirubinemia, jaundice, cholelithiasis, nephrolithiasis</td>
</tr>
<tr>
<td>• Smaller combination tablet size</td>
<td>• Potentially higher cardiovascular risk, contains sulfonamide</td>
</tr>
</tbody>
</table>

• PIs mainly reserved for resistant HIV or poor adherence
• In general, boosted DRV is preferred over boosted ATV
Drug-Drug Interaction Risk: Differences Among ARVs

Boosted ARV  Raltegravir  Dolutegravir  Bictegravir

Efavirenz  Etravirine  Rilpivirine  Doravirine

- No interaction
- Potential weak interaction
- Interaction of clinical relevance
- Drugs should not be coadministered

Slide credit: clinicaloptions.com

Courtesy of Dr. David Back. Data from Mixpanel analytics of https://www.hiv-druginteractions.org.
Pis, Boosters, and Drug-Drug Interactions

To name a few....

• Inhaled/intranasal/injectable/systemic steroids

• Hormonal contraceptives and hormone replacement therapy

• Statins

• Anticoagulants and antiplatelets

• Antidepressants/anxiolytics/antipsychotics

• Cardiac Medications

Not all PIs and boosters are created equal. Always look up specific recommendation!
Summary of Clinical Considerations for Alternative Agents

- **NNRTIs are typically used when patient’s have intolerance to INSTIs**
  - Of the three, DOR is the most appealing from a side-effect and PK/PD standpoint
  - Lowest barrier to resistance and highest incidence of transmitted resistance

- **PIs are typically reserved for when there is concern for poor adherence (to protect the integrase class) or in patients with multi-drug resistant HIV (limited treatment options)**
  - High barrier to resistance but use is limited by DDIs, adverse effects, and administration requirements
  - DRV is preferred agent

- **EVG/c may be selected when patient’s have intolerance to other INSTIs**
  - Low barrier to resistance, use is limited by DDIs, adverse effects, and administration requirements
  - May also consider NNRTI if possible in this scenario
ADDITIONAL GUIDELINE UPDATES
Dolutegravir use in Women of Childbearing Potential and Pregnancy

• Botswana birth surveillance study first reported increase in Neural Tube Defects (NTD) in patients on dolutegravir compared to those on alternative ART
  • Incidence of NTD in patients on DTG vs. any other ART: 0.30% vs. 0.10%
  • No birth defects were seen in those who started DTG during pregnancy

• Other studies have not found NTDs in patients taking DTG

• RAL remains preferred INSTI in those who are trying to conceive

• Insufficient data regarding BIC in pregnancy

### Summary of DHHS Recommendations on Dolutegravir

<table>
<thead>
<tr>
<th>ART for treatment naïve pregnant patients</th>
<th>Continuing ART for patients suppressed and on well-tolerated regimen</th>
<th>ART for patients who have received ART in the past, but currently off treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Continue</td>
<td>Preferred</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New ART regimen for pregnant patients intolerant of/failing current ART</th>
<th>ART for non-pregnant patients trying to conceive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Alternative</td>
</tr>
</tbody>
</table>
Updates from AIDS 2020

NTD Prevalence (95% CI) with DTG at conception, Apr 1, 2019-April 30, 2020

Total: 7 NTDs/3591 exposures

0.30% (0.13, 0.69) vs 0.19% (0.09, 0.40)
Considerations for DTG use in Women of Childbearing Potential

• Assess the patient’s desire for pregnancy

• Discuss risks with patients

• Review treatment history and prior genotypes for alternative agents

• Consider adherence and ability to follow multiple tablet or BID regimen
Prophylaxis of Opportunistic Infections – Opportunities for Antibiotic Stewardship

- Primary Prophylaxis of Mycobacterium Avium Complex
  - MAC prophylaxis no longer recommended in those who immediately initiate ART

- Primary Prophylaxis of Pneumocystis Pneumonia and Toxoplasma gondii encephalitis
  - Okay to D/C if CD4 100-200 cells/mm³ with an undetectable viral load
NOVEL AGENTS
Fostemsavir (FTR)

• Attachment inhibitor that binds to gp120 to prevent viral attachment and CD$_4$ entry
  • No cross resistance to other classes of ART

• Ongoing phase 3 study of fostemsavir based salvage regimens in multi-drug resistant HIV (BRIGHTE)
  • 60% of patients in randomized cohort and 37% of patients in the non-randomized cohort had HIV RNA $<$ 40 copies/mL at week 96

• Most common adverse events: nausea (4%), diarrhea (2%), and headache (2%)

• Received FDA approval for MDR HIV 07/2020

Injectable ART: Cabotegravir/Rilpivirine (CAB/RPV)

• Studied in treatment naïve subjects after 20 weeks of oral therapy (FLAIR) or for stable switch in suppressed patients (ATLAS)

• 48 week virologic suppression was similar for injectable compared to conventional ART

• 3 subjects in each study experienced confirmed virologic failure
  • FLAIR – all subjects developed RPV and INSTI resistance mutations
  • ATLAS – one subject developed RPV/INSTI resistance; others had RPV resistance at baseline

Practical Considerations for use of CAB/RPV

- Initiation requires loading dose
- Agents are not co-formulated
- Screen for pre-existing resistance to RPV or INSTIs
- Rule out chronic HBV infection
- Ensure virologic suppressed before initiation
- Assess adherence to monthly clinic visits
- Oral lead-in period required
Thank you!

To all of the clinic staff and physicians, including

- Dr. Joseph Garland

- Pharmacy Liaisons
  - Melanie Ferreira
  - James Wisnaskas

- Clinic Nurses

- Clinic Social Workers

- Clinic Outreach Workers

- Research Team, including Dr. Karen Tashima
Questions?

Amy Brotherton, PharmD, AAHIVP, BCIDP
Clinical Pharmacist Specialist, Infectious Disease
The Miriam Hospital Infectious Disease & Immunology Clinic
Contact: amy.brotherton@lifespan.org

Rajeev Shah, PharmD, AAHIVP, BCIDP
Clinical Pharmacist Specialist, Infectious Disease
The Miriam Hospital Infectious Disease & Immunology Clinic
Contact: rshah4@lifespan.org