ACTHIV
The American Conference for the Treatment of HIV

ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals
Is HIV Therapy Good Enough or Do We Still Need New Drugs?

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Learning Objectives

- Discuss the rationale for continued drug development in the era of well tolerated, single-tablet regimens
- Give examples of new agents in development and list their advantages over existing therapies
- List current regimens that could be initiated immediately, before baseline laboratory results are available
- Discuss the data supporting specific two-drug regimens
Do we need new drugs?

1. No, treatment is good enough. Drug development should focus on vaccines, prevention, and cure.

2. No, what’s the point? We’re all going to be prescribing generics soon anyway.

3. I hope they develop new drugs so I won’t get bored, but we don’t need them.

4. Yes, we need new drugs. There is still room for improvement.
DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents, July 2016.

**DHHS Guidelines, July 2016: What to Start**

<table>
<thead>
<tr>
<th>Recommended regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI based</strong></td>
</tr>
<tr>
<td>DRV/r + (TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td><strong>INSTI based</strong></td>
</tr>
<tr>
<td>RAL + (TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>EVG/c/TDF/FTC or EVG/c/TAF/FTC</td>
</tr>
<tr>
<td>DTG + (TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI based</strong></td>
</tr>
<tr>
<td>EFV/TDF/FTC or EFV + TAF/FTC</td>
</tr>
<tr>
<td>RPV/TDF/FTC or RPV/TAF/FTC (VL &lt;100,000; CD4 &gt;200)</td>
</tr>
<tr>
<td><strong>PI based</strong></td>
</tr>
<tr>
<td>(ATV/c or ATV/r) + (TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>(DRV/c or DRV/r) + ABC/3TC</td>
</tr>
<tr>
<td>DRV/c + (TDF/FTC or TAF/FTC)</td>
</tr>
</tbody>
</table>
## IAS–USA Guidelines, July 2016: What to Start

### Recommended Regimens

- DTG/ABC/3TC
- DTG + FTC/TAF
- EVG/c/FTC/TAF
- RAL + FTC/TAF

### Regimens When INSTIs are Not an Option

- DRV/c or DRV/r + (FTC/TAF, FTC/TDF or ABC/3TC)
- EFV/FTC/TDF
- RPV/FTC/(TAF or TDF)

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Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
Characteristics of ARV regimens

- Efficacy and durability
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SINGLE: Dolutegravir + ABC/3TC vs. EFV/TDF/FTC

Week

DTG 50 mg + ABC/3TC QD

EffV/TDF/FTC QD

BL 2 4 8 12 16 24 32 40 48

Proportion (%) with <50 c/mL

0 10 20 30 40 50 60 70 80 90 100

WK 48 difference in response (95% CI):
+7.4% (+2.5% to +12.3%); p=0.003

DTG + ABC/3TC QD superior to EFV/TDF/FTC at Wk 48 (1° endpoint)

## SINGLE: DTG + ABC/3TC vs. EFV/TDF/FTC: Disposition

### Outcome (snapshot) at Week 48

<table>
<thead>
<tr>
<th></th>
<th>DTG 50 mg +ABC/3TC</th>
<th>EFV/TDF/FTC (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virologic success</strong></td>
<td>364 (88)</td>
<td>338 (81)</td>
</tr>
<tr>
<td><strong>Virologic nonresponse</strong></td>
<td>21 (5)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Data in window not &lt;50 c/mL</td>
<td>6 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>7 (2)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Discontinued for other reason while not &lt;50 c/mL</td>
<td>8 (2)</td>
<td>12 (3)</td>
</tr>
<tr>
<td><strong>No virologic data at Week 48</strong></td>
<td>29 (7)</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Discontinued because of AE or death*</td>
<td>9 (2)</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>20 (5)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*Deaths: n=2, both on EFV/TDF/FTC: n=1 primary cause of death (sepsis) judged unrelated to study drug but complicated by renal failure judged possibly related to EFV/TDF/FTC; n=1 not related to EFV/TDF/FTC (pneumonia).*  

Initial ART with E/C/F/TAF vs. E/C/F/TDF: 144 Week Efficacy

- **Efficacy similar across subgroups, trending toward or significantly better with TAF in each group**
  - By baseline VL, baseline CD4, adherence, age, sex, race, region
- **Virologic failure with resistance by Wk 144: 1.4% in each arm**

Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
IAS–USA Guidelines, July 2016:
Pill burden and dosing frequency of recommended regimens

<table>
<thead>
<tr>
<th>Recommended Regimens</th>
<th>Pills</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG/ABC/3TC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>DTG + FTC/TAF</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>EVG/c/FTC/TAF</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RAL + FTC/TAF</td>
<td>3</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
GS 119: E/C/F/TAF + DRV for treatment-experienced patients

Randomized (2:1), open-label (N=135)

Eligibility:
- ≥4 mos <50 on ART containing DRV
- 2 prior failures ≥ 2-class resistance by historical genotype (inc. ≤3 TAMs and K65R)
- Historical genotype with no INSTI-R or currently on RAL
- No Q151M, T69ins, or DRV RAMS
- eGFR >50 mL/min

Objectives
- Primary
  - Efficacy of E/C/F/TAF + DRV vs. BR at Week 24: FDA snapshot (<50)
- Secondary
  - Safety and tolerability in both treatment arms over 24 and 48 weeks
  - Efficacy at Week 48: VL <50
  - Efficacy at Week 48: VL <20

## GS 119: Baseline Characteristics

### %, unless otherwise indicated

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>E/C/F/TAF + DRV n=89</th>
<th>Baseline Regimen n=46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>Male</td>
<td>82</td>
<td>61</td>
</tr>
<tr>
<td>Black (or African descent)</td>
<td>39</td>
<td>57</td>
</tr>
<tr>
<td>Median CD4 count, cells/μL</td>
<td>519</td>
<td>518</td>
</tr>
<tr>
<td>Median eGFR&lt;sub&gt;CG&lt;/sub&gt;, mL/min</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>DM / HTN / CVD / Hyperlipidemia</td>
<td>8 / 34 / 7 / 46</td>
<td>11 / 37 / 4 / 28</td>
</tr>
</tbody>
</table>

### Baseline Regimen

<table>
<thead>
<tr>
<th>Baseline Regimen</th>
<th>E/C/F/TAF + DRV n=89</th>
<th>Baseline Regimen n=46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median No. pills per day</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>≥6 pills per day</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>At least BID dosing</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>TDF / ABC / other NRTIs</td>
<td>61 / 11 / 12</td>
<td>54 / 11 / 13</td>
</tr>
<tr>
<td>RAL</td>
<td>56</td>
<td>50</td>
</tr>
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</table>

### Resistance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>E/C/F/TAF + DRV n=89</th>
<th>Baseline Regimen n=46</th>
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</thead>
<tbody>
<tr>
<td>2-class / 3-class resistance</td>
<td>70 / 26</td>
<td>74 / 20</td>
</tr>
<tr>
<td>M184V/I</td>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>K65R</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>NNRTI-R / PI-R</td>
<td>89 / 38</td>
<td>87 / 28</td>
</tr>
</tbody>
</table>

At Week 48, higher virologic success (VL <20) with E/c/F/TAF + DRV vs. BR (90% vs 72%, p=0.012)

- No emergent resistance in E/c/F/TAF + DRV arm; 1 pt with viral rebound (Week 36) developed resistance (M184V+K65R) in BR arm

What’s coming?
New single-tablet regimens and longer-acting formulations

- **DRV/c/FTC/TAF** – 1st PI-based single tablet regimen (STR)
- **BIC/FTC/TAF** – 1st STR with an unboosted INSTI (bictegravir) and TAF/FTC
- Once-daily **RAL** – two 600 mg tablets once daily (no STR)
- **DOR/TDF/3TC** – STR with doravirine (NNRTI) and generic NRTI backbone
- **CAB/RPV** – Long-acting 2-drug injectable regimen (INSTI + NNRTI)
- **MK 8591** – Long acting oral or injectable NRTI
Bictegravir + FTC/TAF vs DTG + FTC/TAF: Wk 24 and Wk 48 Efficacy (FDA Snapshot)

No drug resistance detected in either arm through Wk 48

LATTE-2: IM cabotegravir + rilpivirine
Week 48 Results: VL <50 Snapshot (ITT-ME)

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
LATTE-2 VL <50 at Week 48
ITT-ME (Snapshot)

**Virologic outcomes**

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt;50 c/mL, %</th>
<th>Q8W (n=115)</th>
<th>Q4W (n=115)</th>
<th>CAB 744 (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success</td>
<td>92</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>7</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>No virologic data</td>
<td>&lt;1</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

**Treatment differences (95% CI)**

- Oral Q8W IM: -6.6 to 2.9
- Oral Q4W IM: -7.6 to 2.0
- IM Q8W IM: 2.9 to 12.4
- IM Q4W IM: 2.0 to 11.6

Both Q8W and Q4W comparable to Oral CAB at Week 48

2 subjects with resistance in 8 wk arm: 1 with INSTI mutations, 1 with NNRTI mutations

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
MK-8591: Long-acting NRTI

- Active phosphorylated metabolite has prolonged intracellular half-life in PMBCs: 150-160 hrs
- Exploratory study of single 10 mg oral dose in HIV infected volunteers
- Potential for novel dosing or administration strategies

Grobler J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 98;
Friedman E, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 437LB.
Possible Long Acting Subdermal Implantable Devices for TAF Delivery

- Silicone scaffold diffusion system\(^1\)
- Long-acting biodegradable polycaprolactone thin-film membrane\(^2\)

Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
ACTG 5257: Cumulative Incidence of Virologic Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- ATV/r vs RAL: 3.4% (-0.7%, 7.4%)
- DRV/r vs RAL: 5.6% (1.3%, 9.9%)
- ATV/r vs DRV/r: -2.2% (-6.7%, 2.3%)

ACTG 5257: Cumulative Incidence of Tolerability Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- ATV/r vs RAL: 13% (9.4%, 16%)
- DRV/r vs RAL: 3.6% (1.4%, 5.8%)
- ATV/r vs DRV/r: 9.2% (5.5%, 13%)

ACTG 5257: Cumulative Incidence of Virologic or Tolerability Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- **ATV/r vs RAL**: 15% (10%, 20%)
- **DRV/r vs RAL**: 7.5% (3.2%, 12%)
- **ATV/r vs DRV/r**: 7.5% (2.3%, 13%)

GS-109: Switching to E/C/F/TAF from TDF-based regimens

Primary Endpoint

- All Prior Regimens
- Prior EFV/TDF/FTC
- Prior Boosted ATV + TDF/FTC
- Prior EVG/COBI/FTC/TDF

Wk 48 VL < 50, %

- EVG/COBI/FTC/TAF
- TDF-Based Regimen

N/All

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>EVG/COBI/FTC/TAF</th>
<th>TDF-Based Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Prior Regimens</td>
<td>932/959</td>
<td>444/477</td>
</tr>
<tr>
<td>Prior EFV/TDF/FTC</td>
<td>241/251</td>
<td>112/125</td>
</tr>
<tr>
<td>Prior Boosted ATV + TDF/FTC</td>
<td>390/402</td>
<td>183/199</td>
</tr>
<tr>
<td>Prior EVG/COBI/FTC/TDF</td>
<td>301/306</td>
<td>149/153</td>
</tr>
</tbody>
</table>

P < .001
P = .02
P = .02
P = NS

Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
Drug toxicities we’re no longer forced to deal with

- Metabolic toxicity (early PIs)
- Neuropathy (early NRTIs)
- Lipoatrophy (early NRTIs)
- Hepatic steatosis and lactic acidosis (early NRTIs)
- CNS toxicity (EFV)
- Nephrotoxicity (IDV, TDF)
- Bone toxicity (TDF and other NRTIs)
TAF vs. TDF: Mechanism of Action

Summary of TAF Switch Studies in Virologically Suppressed Patients

**Trials:**
- **GS-109**: TDF-containing regimens to EVG/COBI/FTC/TAF
- **GS-112**: Switch to EVG/COBI/FTC/TAF in patients with impaired renal function
- **GS-119**: ART + DRV/r to EVG/COBI/FTC/TAF + DRV in ART-experienced patients
- **GS-1089**: FTC/TDF to FTC/TAF
- **GS-1160**: EFV/FTC/TDF to RPV/FTC/TAF
- **GS-1216**: RPV/FTC/TDF to RPV/FTC/TAF

**Results:**
- Noninferiority, with superiority in GS-109 (switch from EFV/FTC/TDF or ATV/r + FTC/TDF) and superiority in GS-119
- Increase in bone density
- Stability of eGFR (increase in GS-1089 and GS-112) with no tubular toxicity and decrease in overall and tubular proteinuria
GS 1089: Switch from F/TDF to F/TAF
Change in Renal Biomarkers at Weeks 48 and 96

All differences between treatments statistically significant (p <0.001)

Raffi F, et al. HIV Glasgow, October 2016, Glasgow, UK, Presentation O125
GS 1089: Switch from F/TDF to F/TAF: Bone density changes through Week 96

**Spine**

<table>
<thead>
<tr>
<th>Week</th>
<th>FTC/TAF</th>
<th>FTC/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>321</td>
<td>320</td>
</tr>
<tr>
<td>24</td>
<td>310</td>
<td>310</td>
</tr>
<tr>
<td>48</td>
<td>300</td>
<td>306</td>
</tr>
<tr>
<td>72</td>
<td>294</td>
<td>297</td>
</tr>
<tr>
<td>96</td>
<td>287</td>
<td>292</td>
</tr>
</tbody>
</table>

Mean % Change (95% CI)

-1 to 0.2

FTC/TAF: 1.7
FTC/TDF: -0.1

*p < 0.001*

**Hip**

<table>
<thead>
<tr>
<th>Week</th>
<th>FTC/TAF</th>
<th>FTC/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>321</td>
<td>317</td>
</tr>
<tr>
<td>24</td>
<td>309</td>
<td>305</td>
</tr>
<tr>
<td>48</td>
<td>300</td>
<td>303</td>
</tr>
<tr>
<td>72</td>
<td>293</td>
<td>296</td>
</tr>
<tr>
<td>96</td>
<td>288</td>
<td>289</td>
</tr>
</tbody>
</table>

Mean % Change (95% CI)

-1 to 0.3

FTC/TAF: 1.9
FTC/TDF: -0.3

*p < 0.001*

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>FTC/TAF</th>
<th>FTC/TDF</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>≥ 3% increase</td>
<td>40%</td>
<td>18%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 3% decrease</td>
<td>8%</td>
<td>19%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td>11%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>15%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Raffi F, et al. HIV Glasgow, October 2016, Glasgow, UK, Presentation O125
TDF to TAF switch

**Advantages:**
- Increased eGFR
- Decreased proteinuria
- Improved bone density
- Smaller pill size

**Disadvantages:**
- Loss of TDF lipid effect
- TAF will be more expensive than *generic* TDF

**IAS-USA recommendations:** “If there is no increase in the price of TAF vs. that of TDF, switching from TDF to TAF is reasonable even if patients are not experiencing TDF-related toxic effects.”

Characteristics of ARV regimens

- Efficacy and durability
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- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
# Genetic Barrier to Resistance: Recommended INSTI-Based Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Barrier to Resistance</th>
<th>Comments</th>
<th>Mutations Highly Reducing Susceptibility*</th>
</tr>
</thead>
</table>
| DTG/3TC/ABC        | High                  | - Resistance to DTG emerges slowly; multiple mutations required for resistance  
                      |                       | - DTG + (FTC/TDF or FTC/TAF) recommended by DHHS if must treat before resistance results available | --                                       |
| DTG + (FTC/TDF or  |                       |                                                                          |                                          |
| FTC/TAF)           |                       |                                                                          |                                          |
| EVG/c/FTC/TDF      | Low/Moderate          | - Few EVG mutations required for resistance                              | T66I/A/K                                 |
| EVG/c/FTC/TAF      |                       |                                                                          | E92Q                                     |
|                    |                       |                                                                          | S147G                                    |
|                    |                       |                                                                          | Q148H/R/K                                |
| RAL + (FTC/TDF or  | Low/Moderate          | - Few RAL mutations required for resistance                              | Y143C/R/H                                |
| FTC/TAF)           |                       |                                                                          | Q148H/R/K                                |
|                    |                       |                                                                          | N155H                                    |

*NRTI backbone mutations not shown in column: FTC/TDF, M184V/I, K65R, T69ins; ABC/3TC, M184V/I, K65R, L74V/I, T69ins, Y115F, Q151M.
**Genetic Barrier to Resistance: PI- or NNRTI-Based Regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Barrier to Resistance</th>
<th>Comments</th>
<th>Mutations Highly Reducing Susceptibility*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(DRV/r or DRV/c) + (FTC/TDF or FTC/TAF)</td>
<td>High</td>
<td>- Resistance to DRV/r emerges slowly</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- DRV/r + (FTC/TDF or FTC/TAF) recommended by DHHS if must treat before resistance results available</td>
<td></td>
</tr>
<tr>
<td>(ATV/r or ATV/c) + (FTC/TDF or FTC/TAF)</td>
<td>High</td>
<td>- Fewer mutations required for ATV/r resistance vs DRV/r</td>
<td>I50L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I84V</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>N88S</td>
</tr>
<tr>
<td>RPV/FTC/TDF or RPV/FTC/TAF</td>
<td>Low</td>
<td>- Few RPV mutations required for resistance</td>
<td>L100I</td>
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<td></td>
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<td>K101P</td>
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<td>G190E/Q</td>
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*NRTI backbone mutations not shown in column: FTC/TDF, M184V/I, K65R, T69ins; ABC/3TC, M184V/I, K65R, L74V/I, T69ins, Y115F, Q151M.*
Emergence of INSTI Resistance in Acute Infection Treated With DTG + FTC/TDF

- 45-yo man with PCP and ARS
- Started DTG + FTC/TDF and discharged; readmitted to ICU several days later for hypoxia
- VL increased after readmission despite adherence (including DOT in hospital); no divalent cation use
  - DRV/r added, VL decreased
  - Pneumonia improved; pt discharged
- Rapid INSTI emergence by deep seq: eg, Q148K population increased from 0.0015% at Timepoint 1 to 20.9% at Timepoint 3

Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- **Activity against resistant virus**
- Drug interactions
- Testing requirements
- Cost
What’s coming?
Drugs with activity against resistant virus

- **Bictegravir** – INSTI with possible activity against RAL, EVG, and DTG-resistant virus

- **Ibalizumab** – Monoclonal antibody that binds CD4 receptor, blocking post-attachment entry, given by IV infusion

- **Fostemsavir** – Attachment inhibitor

- **BMS-955176** – Maturation inhibitor, withdrawn from further development
TMB-301: Long-Acting Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to conformational epitope on CD4 receptor that blocks postattachment HIV entry into CD4 cells without altering normal cell function
- Single-arm, open-label phase III trial
  - Primary endpoint: ≥ 0.5 log_{10} VL decrease at Day 14

VL > 1000; on ART ≥ 6 mos, on stable ART ≥ 8 wks; resistant to ≥ 1 ARV from 3 classes, sensitive to ≥ 1 ARV for OBR (N = 40)

Control Period: Day 0-7
Primary Endpoint: Day 14

Ibalizumab 2000 mg IV Day 7 (loading dose)
Continue Failing ART Days 0-14

Ibalizumab 800 mg IV Day 21, Q2W (maintenance dose)
Switch to OBR Day 14

- 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance

Efficacy, Safety of Ibalizumab Through 24 Wks

- Primary endpoint: 83% with $\geq 0.5 \log_{10} VL$ decrease at Day 14 vs 3% at end of control period ($P < .0001$)
  - 60% with $\geq 1.0 \log_{10} VL$ decrease
  - Mean decrease by Day 14: 1.1 $\log_{10}$

- 9 pts reported 17 serious AEs
  - 1 drug-related serious AE (IRIS) resulted in discontinuation

- 9 other pts discontinued
  - Death ($n = 4$; liver failure, Kaposi sarcoma; end-stage AIDS, lymphoma)
  - Consent withdrawal ($n = 3$)
  - Lost to follow-up ($n = 2$)

- No cases of anti-ibalizumab antibodies

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<th>Wk 24 Virologic Outcome</th>
<th>Ibalizumab + OBR</th>
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<td>$\geq 2.0 \log_{10} VL$ decrease, %</td>
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<td>VL &lt; 50, %</td>
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<td>VL &lt; 200, %</td>
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<td>Mean VL decrease from baseline, $\log_{10}$</td>
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AI438011 Subgroup Analysis: Fostemsavir + RAL + TDF at Wk 96

- Fostemsavir (GSK3684934, formerly BMS-663068): prevents attachment by binding to gp120
- AI438011: randomized, active-controlled phase IIb study, blinded to dose
- Current post hoc subgroup analysis of efficacy, safety of pooled data at Wk 96

HIV+ pts with exposure to ≥ 1 ARV for ≥ 1 wk; VL ≥ 1000; CD4 ≥ 50; virus susceptible to RAL, TDF, ATV, and GSK-2616713 IC₅₀ < 100 nM (N = 251)

Fostemsavir + RAL + TDF: Virologic Efficacy Across Subgroups at Wk 96

- 90% of pts had VL <50 at Wk 96 in fostemsavir and ATV/r arms in observed analysis
- Rates of VL < 50 generally similar across fostemsavir IC\textsubscript{50} subgroups
  - < 0.1 vs ≥ 0.1 nM: 83% vs 90%
  - < 1.0 vs ≥ 1.0 nM: 89% vs 91%
  - < 10.0 vs ≥ 10.0 nM: 89% vs 94%

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<th>ATV/r (n = 51)</th>
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Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
# Key Interactions: INSTI-Containing ART Regimens

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<th>Regimen</th>
<th>Key Drug–Drug Interaction Considerations</th>
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<td>All</td>
<td>▪ Use caution with/avoid polyvalent cation-containing antacids</td>
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<tr>
<td>DTG/3TC/ABC</td>
<td>▪ Avoid dofetilide</td>
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<tr>
<td>DTG + (FTC/TDF or FTC/TAF)</td>
<td>▪ Dose adjust metformin</td>
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<tr>
<td>EVG/c/FTC/TDF</td>
<td>▪ Avoid lovastatin, simvastatin, salmeterol</td>
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<tr>
<td>EVG/c/FTC/TAF</td>
<td>▪ Dose adjust metformin</td>
</tr>
<tr>
<td></td>
<td>▪ Use caution with hormonal contraceptives</td>
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<tr>
<td>RAL + (FTC/TAF or FTC/TAF)</td>
<td>▪ No notable comediations to avoid for RAL aside from Al or Mg-containing antacids</td>
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</table>
### Key Interactions: Boosted PI- or NNRTI-Containing ART Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Key Drug–Drug Interactions</th>
</tr>
</thead>
</table>
| (ATV/r or ATV/c) + (FTC/TDF or FTC/TAF) | - Avoid lovastatin, simvastatin, atorvastatin*, simprevir, elbasvir/grazoprevir, salmeterol  
- Use caution with/avoid specific antiarrhythmics (eg, amiodarone)  
- Avoid PPIs (eg, omeprazole) with ATV  
- Use caution with/avoid specific glucocorticoids (eg, budesonide, fluticasone)  
- Use caution with hormonal contraceptives |
| (DRV/r or DRV/c) + (FTC/TDF or FTC/TAF) | |
| RPV/FTC/TDF | - Avoid PPIs (eg, omeprazole, pantoprazole), dexamethasone |
| RPV/FTC/TAF | |

*ATV/r only.
Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
Integrase resistance in the U.S.

- Transmitted INSTI resistance remains rare; rates of on-treatment INSTI resistance remains low[1-3]

- **CDC National HIV Surveillance System[1]:**
  - Prevalence of INSTI resistance through 2014: 65/14,468 (0.4%)
  - Pre-ART prevalence of INSTI resistance (ie, transmitted): 2/4631 (0.04%)

- **UNC CFAR HIV Clinical Cohort[2]:**
  - 2015 INSTI resistance prevalence in 685 pts who began ART in 2007 or later: 1%

- Modeling: assuming 0.1% rate of transmitted INSTI resistance and $250 cost per test: pre-ART INSTI resistance testing correlated with worse outcomes, higher costs vs no test[3]

RAPID Start of ART: UCSF experience

Referral | 1st Clinic Visit | 1st PCP Visit | ART Prescribed | Viral load suppressed

CD4-guided (2006-9)

Universal (2010-3)

RAPID

Rapid Start: Potential regimens

Regimens to consider
- DTG + FTC/TAF
- EVG/c/FTC/TAF
- DRV/c + FTC/TAF

Drugs to avoid
- ABC (need HLA B*5701)
- TDF (need eGFR)
- RPV (need VL, CD4)
- EFV, NVP (need genotype)
Characteristics of ARV regimens

- Efficacy and durability
- Convenience: pill burden, dosing frequency
- Tolerability
- Toxicity
- Resistance barrier
- Activity against resistant virus
- Drug interactions
- Testing requirements
- Cost
The rationale for 2-drug regimens

- (To avoid NRTI toxicity)
- Reduce cost (e.g. 3TC + X)
- Allow for long acting therapy (e.g. CAB + RPV)
SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV

- Open-label, multicenter phase III trials of pts with virologic suppression (N=1024) randomized to continue baseline ART vs switch to DTG + RPV
- 1 pt with confirmed criteria for virologic withdrawal at Wk 36 in DTG + RPV arm had K101K/E
  - Documented nonadherence at VF
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance

Llibre JM, et al. CROI 2017. Abstract 44LB.
SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV: Safety Outcomes

- AE rates generally similar between arms through Wk 52
  - Numerically higher rate of drug-related grade 1/2 AEs with switch: 17% vs 2%
  - Numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%

- No notable change in lipids through Wk 48 in either treatment arm

Llibre JM, et al. CROI 2017. Abstract 44LB.
# PADDLE: Dolutegravir + Lamivudine for Treatment-Naive Pts


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**HIV-1 RNA (copies/mL)**

**SAE**

**Virologic failure**
ANRS 167 LAMIDOL: Switch to DTG + 3TC in Suppressed Pts

Noncomparative, open-label, single-arm multicenter trial

1° endpoint: therapeutic success at Wk 56 (ie, after 48 wks of dual therapy)

Therapeutic failure: VL > 50 interruption, lost to f/u, death

VL ≤ 50 x ≥ 2 yrs on 1st-line ART; ≤ 2 ART modifications, except within 6 mos of study start; CD4 > 200 (N = 110)

*Pts with VL ≤ 50 proceeded to phase II.
†In phase I, third agent in regimen replaced with DTG; baseline NRTI backbone maintained.

ANRS 167 LAMIDOL: Switch to DTG + 3TC in Suppressed Pts

- 97% (101/104) remained suppressed through 40 wks of dual therapy (study Wk 48)[1]
  - No INSTI resistance in 3 pts with virologic failure
  - 7 with SAEs, only 2 related to dual therapy

- Switch to DTG-based dual therapy vs continued triple ART currently under evaluation in several phase III trials[2,3]

<table>
<thead>
<tr>
<th>Therapeutic Success, n/N* (%)</th>
<th>DTG + 3TC</th>
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<tr>
<td>Wk 0 (entry; on BL triple therapy)</td>
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<tr>
<td>Wk 8 (end of phase I, start of phase II)</td>
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<td>Wk 12</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>Wk 16</td>
<td>103/104 (99)</td>
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<td>Wk 24</td>
<td>103/104 (99)</td>
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<td>Wk 32</td>
<td>103/104 (99)</td>
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<td>Wk 40</td>
<td>102/104 (98)</td>
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<tr>
<td>Wk 48</td>
<td>101/104 (97)</td>
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</table>

*Pts enrolled in phase I, N = 110; pts enrolled in phase II, N = 104.

2. ClinicalTrials.gov. NCT02263326.
DOMOMO: Switch to DTG Monotherapy in Virologically Suppressed Pts

- Randomized comparison: switch to DTG monotherapy vs continued baseline ART for 24 wks in suppressed pts without previous VF\(^2\)
- At Wk 24, DTG monotherapy noninferior to continued baseline ART (VL <200)
  - After 24 wks, all pts allowed to switch to monotherapy
- Study stopped early because of high VF rate after 48 wks of monotherapy
  - VF in 8/77 pts with DTG monotherapy vs 3/152 pts on combination ART in concurrent control group (\(P = .03\))
  - Among 6 VF cases with resistance data in DTG monotherapy group, 3 developed INSTI resistance

Emergent INSTI Resistance After Switch to DTG Monotherapy

- **International, multicenter retrospective study**
  - Evaluated virologically suppressed pts switched to DTG monotherapy
  - Pts with history of VF on INSTI and INSTI resistance excluded

- **11 of 122 pts (9%) switched to DTG monotherapy experienced VF**
  - 9 of 11 had genotypic INSTI resistance at VF

INSTI resistance pathways varied

<table>
<thead>
<tr>
<th>INSTI Resistance at VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>92Q/155H (n = 1)</td>
</tr>
<tr>
<td>97A/155H (n = 1)</td>
</tr>
<tr>
<td>155H/148R (n = 1)</td>
</tr>
<tr>
<td>118R (n = 2)</td>
</tr>
<tr>
<td>148K (n = 1)</td>
</tr>
<tr>
<td>148H (n = 2)</td>
</tr>
<tr>
<td>148R (n = 1)</td>
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</tbody>
</table>

1. No, treatment is good enough. Drug development should focus on vaccines, prevention, and cure.

2. No, what’s the point? We’re all going to be prescribing generics soon anyway.

3. I hope they develop new drugs so I won’t get bored, but we don’t need them.

4. Yes, we need new drugs. There is still room for improvement.
Conclusions

• ART continues to improve with respect to efficacy, safety, tolerability, convenience, and barrier to resistance
• Investigational drugs and strategies may allow for greater simplification, less frequent dosing, 2-drug regimens, and lower cost
• What’s left?
  • Treatments that decrease residual immune activation and inflammation
  • Vaccine
  • Cure