The Future of Antiretroviral Therapy

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The Future of ART

• Where we are now – why current treatment is so great
• Current knowledge gaps and problems (yes there are still problems), illustrated by cases
• Possible changes coming in the future
• Several interactive questions to generate discussion
Question

• If you had a time machine and were transported back to the early 1990s – before effective combination ART – which fact about HIV treatment today would you find most exciting and/or surprising?

A. That most treatments are 1-2 pills a day.

B. That almost everyone who takes HIV therapy is virally suppressed, and these treatments will never fail if patients remain adherent.

C. That opportunistic infections are vanishingly rare among people on ART.

D. That survival for some people with HIV is projected to be comparable to people without HIV.

E. That suppressive HIV therapy eliminates the risk of sexual transmission.
8 year gap with ART initiation at CD4 ≥ 500. Life expectancy □ Blacks & IDU. Gap narrowed further if no hepatitis, drugs/alcohol, or smoking.

HIV Treatment Options Are Getting Simpler

### DHHS (7/2019)
Recommended for Most People With HIV

<table>
<thead>
<tr>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir/FTC/TAF</td>
</tr>
<tr>
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<tr>
<td>Dolutegravir + FTC/TDF or FTC/TAF</td>
</tr>
<tr>
<td>Raltegravir + FTC/TAF or FTC/TDF</td>
</tr>
</tbody>
</table>

### IAS-USA (7/2018)
Recommended Initial Regimens

<table>
<thead>
<tr>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir/FTC/TAF</td>
</tr>
<tr>
<td>Dolutegravir/ABC/3TC*†</td>
</tr>
<tr>
<td>Dolutegravir + FTC/TAF*‡</td>
</tr>
</tbody>
</table>

... And The Boosters Are Gone!

<table>
<thead>
<tr>
<th>DHHS (7/2019)</th>
<th>IAS-USA (7/2018)</th>
</tr>
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<tr>
<td><strong>Recommended for Most People With HIV</strong></td>
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<td>Dolutegravir/ABC/3TC*†</td>
</tr>
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<td>Dolutegravir + FTC/TDF or FTC/TAF</td>
<td>Dolutegravir + FTC/TAF*‡</td>
</tr>
<tr>
<td>Raltegravir + FTC/TAF or FTC/TDF</td>
<td></td>
</tr>
</tbody>
</table>

BIC and DTG-based Regimens Are Extraordinarily Effective

HIV RNA <50 Copies/mL at Week 48

Pre-specified per protocol analysis.

April 8th, 2018

Latest DHHS Guidelines for Initial HIV Therapy Now Include 5 Choices — But Really 2 Are Best

As of April 8, 2018 (the day I'm writing this post), the choice between the two remaining options reflects how we and our patients feel about two issues.

If giving one pill rather than two is most important, then go with bictegravir/TAF/FTC.

If accumulated safety and “real world” experience is most important, then go with dolutegravir plus TAF/FTC.

Hey, isn’t HIV treatment simple these days?

Best Regimens for Starting Therapy in 2019: One Opinion

• Reasons
  • Once daily
  • Clinically significant transmitted drug resistance extremely rare
  • Well-tolerated
  • No treatment-emergent resistance in clinical trials
  • Reduced renal and bone toxicity c/w TDF
  • No known excess cardiovascular risk c/w ABC
  • Small tablet sizes
  • Taken with or without food
  • Active vs hepatitis B
  • Ideal for same-day ART

OR

tenofovir AF/emtricitabine

+ dolutegravir

bicinegavitir/tenofovir AF/emtricitabine
Summary: HIV Today Treatment is Awesome

• Effective
• Well-tolerated
• Safe
• Simple
• Prevents HIV transmission
• So are we done here?

• Not yet!
• These cases will illustrate ongoing challenges and areas of uncertainty
Case #1

• A 31 year old woman with stable HIV infection returns for routine follow-up.

• She was diagnosed at age 28 during pregnancy; started TDF/FTC, RAL, which was changed to ABC/3TC/DTG after delivery.

• Reports no side effects, excellent adherence.

• Says she and her boyfriend are considering having another baby – irregular use of birth control.

• Lab tests fine. Pregnancy test negative.
Question

• What should we do with the HIV treatment?

A. No change in ART.
B. Switch back to TDF/FTC, RAL.
C. Switch to TDF/FTC, ATV/r
D. Switch to TDF/FTC, DRV/r
E. Something else
What to Start in Pregnancy: 
DHHS Guidelines Dec 7, 2018

**Two NRTIs**
Abacavir/3TC  
or  
TDF/FTC or TDF/3TC

**Integrase inhibitor:**
Raltegravir (twice daily) or  
Dolutegravir (only after 1st trimester; not in someone trying to conceive)

**Protease inhibitor:**
Darunavir/ritonavir (twice daily) or  
Atazanavir/ritonavir

**DO NOT USE:**
TAF (insufficient data)  
Bictegravir (insufficient data)  
Elvitegravir/cobi (PK concerns)  
DRV/cobi (PK concerns)  
ATV/cobi (PK concerns)  
DOR (insufficient data)
Tsepamo: Birth Outcomes Surveillance Study in Botswana

- May 2018: unplanned analysis found higher incidence of neural tube defects among infants born to women who conceived while on DTG
  - 4/426 (0.94%) on DTG- vs. 0.12% on non-DTG ART
- WHO, US DHHS, others recommended against use of DTG in women who want to become pregnant or are sexually active and not using contraception
- Current analysis: updated as of March 2019
  - From July to September 2018, surveillance area expanded to capture 72% of all births in Botswana
  - Study population: 1,683 DTG from conception; 14,792 non-DTG from conception

Neural Tube Defects by Exposure Category

NTDs/Exposures | 5/1683 | 15/14792 | 3/7959 | 1/3840 | 70/89372
--- | --- | --- | --- | --- | ---
% with NTD (95% CI) | 0.30% (0.13, 0.69) | 0.10% (0.06, 0.17) | 0.04% (0.01, 0.11) | 0.03% (0.0, 0.15) | 0.08% (0.06, 0.10)
Prevalence Difference (95% CI) | ref | 0.20% (0.01, 0.59) | 0.26% (0.07, 0.66) | 0.27% (0.06, 0.67) | 0.22% (0.05, 0.62)

MOAX0105LB;
“A woman-centered and rights-based approach should be applied to antiretroviral delivery. Women should be provided with information about benefits and risks to make an informed choice regarding the use of DTG or other ART”
ART and Pregnancy – So Many Questions

• A small relative risk (and even smaller absolute risk) for DTG at conception and NTD remains – is it real?
• Does it apply to all settings?
• If so, is this a class effect of all INSTIs?
• Right now – today – what what is the optimal regimen for women who desire pregnancy?
• What is the best regimen for women of childbearing potential independent of whether they say they want to become pregnant?
• What is the right way to counsel about this information?
• What is the safest treatment during pregnancy?
Case #2

• A 38-year-old man is admitted to the hospital with fever, weight loss, and cough.

• *Pneumocystis* pneumonia is suspected; started on TMP/SMX and prednisone.

• PMHx: Outside records – known HIV+ for 10 years, no sustained HIV treatment or regular follow-up.

• Also – substance use disorder (multiple); bipolar disease. Inconsistent housing.

• Labs: WBC 2.1; **CD4 10; HIV RNA 740,000 copies/mL;** genotype sent.
Question

• What regimen should we start?

A. TAF/FTC, DTG
B. TAF/FTC/BIC
C. TAF/FTC/DRV/c
D. ABC/3TC/DTG
E. Something else
Recent Clinical Trials in USA/Europe Do Not Include Many Patients with Advanced HIV Disease

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Regimens</th>
<th>CD4 &lt; 200 (%)</th>
<th>HIV RNA &gt;100K (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-102 (2012)</td>
<td>ECF-TDF vs TDF/FTC/EFV</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>GS-103 (2012)</td>
<td>ECF-TDF vs ATV/r, TDF/FTC</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>SINGLE (2013)</td>
<td>ABC/3TC, DTG vs TDF/FTC/EFV</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>SPRING-2 (2013)</td>
<td>DTG vs RAL</td>
<td>12</td>
<td>28</td>
</tr>
<tr>
<td>ACTG 5257 (2014)</td>
<td>RAL vs ATV/r vs DRV/r</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>GARDEL (2014)</td>
<td>LPV/r + NRTIs vs 3TC</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>GS-104/111 (2015)</td>
<td>ECF-TDF vs ECF-TAF</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>DRIVE AHEAD (2017)</td>
<td>TDF/3TC/DOR vs TDF/FTC/EFV</td>
<td>12</td>
<td>21</td>
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<tr>
<td>GS-1489 (2017)</td>
<td>TAF/FTC/BIC vs ABC/3TC/DTG</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>GS-1490 (2017)</td>
<td>TAF/FTC/BIC vs DTG, TAF/FTC</td>
<td>12</td>
<td>19</td>
</tr>
</tbody>
</table>
... And They Don’t Include Many Women, Either!

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Regimens</th>
<th>Women (%)</th>
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<tbody>
<tr>
<td>GS-102 (2012)</td>
<td>ECF-TDF vs TDF/FTC/EFV</td>
<td>11</td>
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<tr>
<td>GS-103 (2012)</td>
<td>ECF-TDF vs ATV/r, TDF/FTC</td>
<td>9</td>
</tr>
<tr>
<td>SINGLE (2013)</td>
<td>ABC/3TC, DTG vs TDF/FTC/EFV</td>
<td>15</td>
</tr>
<tr>
<td>SPRING-2 (2013)</td>
<td>DTG vs RAL</td>
<td>15</td>
</tr>
<tr>
<td>ACTG 5257 (2014)</td>
<td>RAL vs ATV/r vs DRV/r</td>
<td>24</td>
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<tr>
<td>GARDEL (2014)</td>
<td>LPV/r + NRTIs vs 3TC</td>
<td>16</td>
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<td>GS-1490 (2017)</td>
<td>TAF/FTC/BIC vs DTG, TAF/FTC</td>
<td>11</td>
</tr>
<tr>
<td>Characteristic</td>
<td>TDF/3TC + DTG (N=310)</td>
<td>TDF/3TC + EFV400 (N=303)</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>38 (31-46)</td>
<td>36 (29-43)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>197 (64%)</td>
<td>207 (68%)</td>
</tr>
<tr>
<td>Hepatitis B virus surface antigen positive</td>
<td>25 (8%)</td>
<td>34 (11%)</td>
</tr>
<tr>
<td>HIV RNA, median (IQR), log₁₀ c/mL</td>
<td>5.3 (4.8-5.8)</td>
<td>5.3 (4.7-5.8)</td>
</tr>
<tr>
<td>≥100,000</td>
<td>207 (67%)</td>
<td>200 (66%)</td>
</tr>
<tr>
<td>≥500,000</td>
<td>93 (30%)</td>
<td>95 (31.3%)</td>
</tr>
<tr>
<td>CD4+ cell count, median (IQR), cells/mm³</td>
<td>289 (157-452)</td>
<td>271 (147-427)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>97 (31%)</td>
<td>107 (35%)</td>
</tr>
<tr>
<td>200-350</td>
<td>89 (29%)</td>
<td>88 (29%)</td>
</tr>
<tr>
<td>350-500</td>
<td>63 (20%)</td>
<td>56 (18%)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>31 (20%)</td>
<td>52 (17%)</td>
</tr>
</tbody>
</table>

Delaporte E, et al. NEJM 2019
## NAMSAL: Results in Advanced Disease Suboptimal

<table>
<thead>
<tr>
<th>HIV RNA</th>
<th>DTG N=310</th>
<th>EFV 400 N=303</th>
<th>Difference A-B IC 95%</th>
<th>Superiority Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA&lt; 50 copies/ml</td>
<td>231 (74.5%)</td>
<td>209 (69%)</td>
<td>5.5% (-1.6;+12.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>HIV RNA&gt; 50</td>
<td>Stop for death 62 6 (69%)</td>
<td>70 7 (70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA&gt; 50</td>
<td>Stop for other reasons (LTE, withdrawn) 9</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA&lt; 100 000</td>
<td>94/103 (91.3%)</td>
<td>86/103 (83.5%)</td>
<td>7.8% (-1.2;+16.8)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA&gt; 100 000</td>
<td>137/207 (66.2%)</td>
<td>123/200 (61.5%)</td>
<td>4.7% (-4.6;+14.0)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA&gt; 500 000</td>
<td>51/93 (54.8%)</td>
<td>55/95 (57.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Delaporte E, et al. NEJM 2019
Virologic Failure and DTG Resistance in a Treatment-naïve Patient with Advanced HIV Disease

“For those individuals in whom ART needs to begin urgently before resistance test results are available, boosted DRV may be an appropriate choice, as there is a low rate of transmitted PI resistance, it has a high barrier to resistance, and there is a low rate of treatment-emergent resistance. DRV/c/TAF/FTC is now available as an STR.”
CHORUS cohort: Evaluation of ART efficacy with baseline high HIV RNA

- DTG, n=736, 36%
- EVG, n=928, 46%
- RAL, n=48, 2%
- DRV, n=326, 16%

\( \geq 100,000 \text{ copies/mL With Virologic Suppression by 36 Weeks, Unadjusted} \)

Will “LAPTOP” tell us something different?

- Eligible: Active OI or other serious infection, or asymptomatic with CD4 < 100 (n=440)
- BIC/FTC/TAF vs DRV/c/FTC/TAF

https://clinicaltrials.gov/ct2/show/NCT03696160
Case #3

- 55 year old woman, diagnosed 2008
- Initial CD4 350, HIV RNA 33,000, weight 210 pounds, BMI 31
- Began TDF/FTC/EFV – no side effects, no treatment failure
- Gained 5 pounds between 2008 and 2016
- Diagnosed with osteopenia by DEXA scan – switched to TAF/FTC, DTG in July 2016
- One year later – now very upset about rapid weight gain – denies change in diet or activity level
- He’s sure it’s the new meds, asks to go back on TDF/FTC/EFV
Question

• Work-up for medical causes of weight gain are negative. What would you do now?

A. Continue current therapy (TAF/FTC, DTG)
B. Switch back to TDF/FTC/EFV
C. Switch to TDF/FTC/DOR
D. Something else
HIV Therapy and Abnormal Weight Gain – Emerging Clinical Evidence Implicating ART
Obesity among patients with HIV: the latest epidemic

HIV infection and obesity: where did all the wasting go?

Short communication: from wasting to obesity: initial antiretroviral therapy and weight gain in HIV-infected persons

The Fat of the Matter: Obesity and Visceral Adiposity in Treated HIV Infection

Practical Review of Recognition and Management of Obesity and Lipohypertrophy in Human Immunodeficiency Virus Infection
Factors Driving Increased Obesity Among People with HIV

- Geographic region
- Race
- Poverty
- Food insecurity

- But what about the HIV meds?

Self-Reported Obesity Among Blacks, 2015-2017
NA-ACCORD: Weight Gain After ART Initiation (n=21,867)

NEAT 022: Change in Weight After Switching PI to DTG in Patients at High CV Risk

- Factors associated with BMI gain on DTG in multivariable analysis:
  - Framingham >15% (P=0.042)
  - Hypertension (P=0.035).
- Protective factors:
  - Switching from PIs other than DRV or ATV (P=0.032)
  - Current smoking (P=0.006)
  - Daily exercise (P=0.036)
  - HDL-chol (P<0.001)

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### NAMSAL and ADVANCE: Progressive Weight Gain and Clinical Obesity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NAMSAL</th>
<th>ADVANCE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Δ in weight, kg</td>
<td>DTG + 3TC/TDF (n = 293)</td>
<td>DTG + FTC/TAF</td>
<td></td>
</tr>
<tr>
<td>▪ Wk 48</td>
<td>+5</td>
<td>+6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>▪ Wk 96</td>
<td>NA</td>
<td>+8</td>
<td></td>
</tr>
<tr>
<td>Mean Δ in BMI at Wk 48</td>
<td>+1.7</td>
<td>NR</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Treatment-emergent overweight (BMI 25-29.9), %</td>
<td>DTG + 3TC/TDF (n = 278)</td>
<td>DTG + FTC/TDF</td>
<td></td>
</tr>
<tr>
<td>▪ Wk 48</td>
<td>16</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>▪ Wk 96</td>
<td>NA</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Treatment-emergent obesity (BMI ≥ 30), %</td>
<td>DTG + 3TC/TDF (n = 293)</td>
<td>DTG + FTC/TDF</td>
<td></td>
</tr>
<tr>
<td>▪ Wk 48</td>
<td>12</td>
<td>14</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>▪ Wk 96</td>
<td>NA</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Hill. IAS 2019. Abstr MOAX0102LB.
Significantly greater weight increase* with DTG vs EFV, with TAF vs TDF; plateauing in weight gain after Wk 48 observed in men but not in women.

**ADVANCE: Mean Change in Weight to Wk 96**

*Wilcoxon rank-sum comparison at Wk 96.*

Hill. IAS 2019. Abstr MOAX0102LB.
ADVANCE: Percentage change in weight over time: women

![Graph showing percentage change in weight over time for women, differentiated by medication regimens: TAF/FTC+DTG, TDF/FTC+DTG, TDF/FTC/EFV. The graph illustrates the distribution of weight changes among participants over time, with different colors representing various percentage loss categories.](image-url)
ADVANCE: BMI category over time: women (obese at baseline excluded)
ART and Weight Gain: Questions

• Patients have been *convinced* the HIV medications are to blame – it appears they are correct!

• INSTI-based treatment lead to more weight gain than other strategies. Is there a difference between INSTIs?

• What is going on with TAF vs TDF?

• Is excess weight gain reversible by stopping the offending drug(s)?

• How does ART, or a specific drug class, cause weight gain? Is it just better tolerated ART? Or an off-target effect altering appetite or metabolism?

• Are there adverse metabolic or other consequences of ART-induced weight gain?

• Should these emerging data change clinical practice?
Question

• Should the data on weight gain from INSTIs and TAF change clinical practice?

A. Yes.
B. No.
C. Depends.
Case #4

• 36 year old man, diagnosed with HIV earlier this year
• Started on TAF/FTC/BIC – rapid virologic suppression
• No side effects, 100% reported adherence
• Says he’s terrified of diagnosis being discovered by his family
• Wants the “new injectable” treatment he’s read about so he doesn’t need to keep pills at home
Injectable cabotegravir and rilpivirine will likely be FDA-approved in 2020. It will be two 3 ml injections given every 4 weeks, not self-administered. What percentage of patients will want this treatment?

A. <5%
B. 5-10%
C. 11-25%
D. >25%
Phase 3 Clinical Trials: ATLAS/FLAIR Week 48

- **ATLAS**: virologically suppressed; switch to monthly IM LA CAB/RPV vs. continue oral ART

- **FLAIR**: Treatment naïve; suppress with oral ART; switch to monthly IM LA CAB/RPV vs. continue oral ART
ATLAS/FLAIR Week 48 Pooled Results

Virologic outcomes

<table>
<thead>
<tr>
<th>Virologic Nonresponse (≥50 c/mL)</th>
<th>1.9</th>
<th>1.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic Success (&lt;50 c/mL)</td>
<td>93.1</td>
<td>94.4</td>
</tr>
<tr>
<td>No Virologic Data</td>
<td>5.1</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Adjusted treatment difference (95% CI)*

Primary Endpoint:
LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

Difference (%)

CAR

CAB + RPV LA

0.2

-1.7

4% NI margin

Key Secondary Endpoint:
LA noninferior to CAR (HIV-1 RNA <50 c/mL) at Week 48

Difference (%)

CAB + RPV LA

CAR

-1.4

-4.1

-10% NI margin

*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
86% to 90% of LA CAB + RPV recipients scored ISRs and pain at Wk 48 as totally or very acceptable in PIN questionnaire.

Greater improvement in treatment satisfaction by HIVTSQ at Wks 24, 44 with LA CAB + RPV vs daily oral ART.

### Acceptability, %

<table>
<thead>
<tr>
<th>Acceptability, %</th>
<th>LA CAB + RPV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 5 (n = 296)</td>
<td>Wk 48 (n = 303)</td>
</tr>
<tr>
<td>ISRs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totally</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>Very</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Moderately</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>A little</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Not at all</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totally</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>Very</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Moderately</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>A little</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Not at all</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

*Adjusted for BL score, sex, age, race, and BL third agent class.
†P < .001 for all listed differences.

**Patient Preference for ART Delivery Method by Population, % (n/N)**

<table>
<thead>
<tr>
<th></th>
<th>Long-acting IM</th>
<th>Daily PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT-E</td>
<td>86 (266/308)</td>
<td>2 (7/308)</td>
</tr>
<tr>
<td>Responding patients</td>
<td>97 (266/273)</td>
<td>3 (7/273)</td>
</tr>
</tbody>
</table>

P < .001 for Δ over time in “acceptability of ISRs” domain of PIN.
## Treatment Emergent Resistance (CAB/RPV Groups)

<table>
<thead>
<tr>
<th>Site/HIV subtype</th>
<th>Baseline Resistance (HIV DNA)</th>
<th>Resistance at Virologic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATLAS</td>
<td></td>
</tr>
<tr>
<td>Russia/A1</td>
<td>E138E/A</td>
<td>E138A, L74I</td>
</tr>
<tr>
<td>Russia/A1</td>
<td>None</td>
<td>E138E/K, N155H, L74I</td>
</tr>
<tr>
<td></td>
<td>FLAIR</td>
<td></td>
</tr>
<tr>
<td>Russia/A1</td>
<td>None</td>
<td>E138E/A/K/T, L74I, Q148R</td>
</tr>
<tr>
<td>Russia/A1</td>
<td>None</td>
<td>K101E, L74I, G140R</td>
</tr>
<tr>
<td>Russia/A1</td>
<td>None</td>
<td>E138K, L74I, Q148R</td>
</tr>
</tbody>
</table>

CAB and RPV concentrations at time of failure below population means but within range for majority of individuals who maintained suppression.

Case #5

• A 48-year-old woman with a long history of HIV infection is referred for evaluation of novel ART strategies.

• History is notable for several complications of advanced HIV disease, including PCP, disseminated zoster, wasting syndrome – all occurring during poor (i.e., zero!) medication adherence.

• Current HIV RNA < 20 copies/mL, CD4 250 on TAF/FTC/RPV + DTG – administered via G-tube, which is to be removed shortly.

• Over a dozen HIV genotypes – either wild-type or M184V only.

• Requests an injectable ART option, as she cannot take pills.
The label for injectable CAB/RPV will likely be for people similar to ATLAS/FLAIR population – adherent with no history of treatment failure.

Will you be using it in people who struggle with adherence, such as in this case?

A. Yes
B. No
ACTG 5359: Long-acting Cabotegravir + Rilpivirine in Non-adherent Persons with HIV

**Step 1: 24 wks**

- **SOC** (3 ARVs at least 2 active)

**Step 2: 52 wks**

- **IM CAB LA** (600 mg LD ☑️ 400 mg maint) + IM RPV LA (900 mg LD ☑️ 600 mg maint) (Q4wk)
- **RPV 25mg + CAB 30mg (QD)**

**Step 3: 52 wks**

- 48 wks of IM CAB-LA + RPV-LA (cross over)
- **NOT randomized**

**Step 4: up to 52 weeks SOC “tail” for anyone receiving at least one dose of LA ARV**

**Study entry week**

**Conditional Economic Incentives**

<table>
<thead>
<tr>
<th>Step 1, Week</th>
<th>Milestone</th>
<th>Incentive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Completed visit</td>
<td>$75.00</td>
</tr>
<tr>
<td>4</td>
<td>HIV-1 RNA &gt;1 log_{10} drop</td>
<td>$75.00</td>
</tr>
<tr>
<td>8</td>
<td>HIV-1 RNA &gt;2 log_{10} drop</td>
<td>$75.00</td>
</tr>
<tr>
<td>12</td>
<td>HIV-1 RNA &lt;200 copies/mL</td>
<td>$150.00</td>
</tr>
<tr>
<td>16</td>
<td>HIV-1 RNA &lt;200 copies/mL</td>
<td>$150.00</td>
</tr>
<tr>
<td>20</td>
<td>HIV-1 RNA &lt;50 copies/mL</td>
<td>$150.00</td>
</tr>
</tbody>
</table>
Questions Regarding LA-CAB+RPV

• How will the strategy work outside of a clinical trials population?
• Oral lead-in – is it required?
• How will drug toxicity be managed?
• Who will administer the injections, and where?
• The every 8 week regimen appears preferred – will it comparably effective, with an acceptable risk of resistance? (ATLAS-2M study)
• How does a patient stop this regimen?
Long-Acting ART Options in Development

- Islatravir
- GS-6207
- Monoclonal antibodies
  - PRO140
  - UB-421
  - *Many* broadly neutralizing antibodies (bNAbs) with “extendification”
- Subcutaneous implants
- Gastric drug reservoir

Islatravir (MK-8591)

- ISL: nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Potent at low doses
- High barrier to resistance
- Long intracellular half life (about 120 h in healthy adults)
- Potential for once daily, once weekly or less frequent dosing
DRIVE2Simplify: Phase 2b Dose Ranging Trial of ISL + DOR vs. DOR/3TC/TDF

Efficacy and safety at Wk 48 of different doses of ISL + DOR following ISL + DOR + 3TC induction for 24 wks vs DOR/3TC/TDF (n=121)

**Part 1: 3-Drug Dose Ranging**
- ISL 0.25mg QD + DOR QD + 3TC QD (+ DOR/3TC/TDF PBO)
- ISL 0.75mg QD + DOR QD + 3TC QD (+ DOR/3TC/TDF PBO)
- ISL 2.25mg QD + DOR QD + 3TC QD (+ DOR/3TC/TDF PBO)

**Part 2: 2-Drug Dose Ranging**
- ISL 0.25mg QD + DOR QD
- ISL 0.75mg QD + DOR QD
- ISL 2.25mg QD + DOR QD

**Part 3: Maintenance**
- ISL Selected Dose + DOR QD
- DOR/3TC/TDF (+ ISL + DOR + 3TC QD PBO)

Key Inclusion Criteria:
- Treatment-naive
- HIV-1 RNA ≥1000 c/mL
- CD4+ T-cell count ≥200 cells/mL
- No ARV drug resistance
- No active hepatitis C virus (HCV) co-infection or active HBV co-infection

Stratification by screening HIV-1 RNA level (≤100,000 or >100,000 copies/mL)

N = ~30 per arm

ClinicalTrials.gov
NCT03272347

After 24 weeks of dosing in Part 1, participants who are virologically suppressed (HIV-1 RNA <50 copies/mL) at the Week 20 visit and have not met any viral failure criteria are eligible to switch to Part 2 of the trial at Week 24. Participants with HIV-1 RNA levels ≥50 copies/mL at Week 20 will remain in Part 1 until the HIV-1 RNA is <50 copies/mL and they have not met any of the viral failure criteria, at which point they transition to Part 2 at their next visit.
Virologic Outcomes Through Week 48 (FDA Snapshot)

- ISL (0.25 mg) + DOR* QD: 89.7%, 77.4%, 83.9%
- ISL (0.75 mg) + DOR* QD: 90%, 77.4%, 83.9%
- ISL (2.25 mg) + DOR* QD: 6.9%, 6.7%, 12.9%
- DOR/3TC/TDF QD: 6.5%, 12.9%, 6.5%

- HIV-1 RNA <50 copies/mL: 26/29, 27/30, 24/31, 26/31
- HIV-1 RNA ≥50 copies/mL: 2/29, 2/30, 4/31, 2/31
- No Virologic Data in Window: 1/29, 1/30, 3/31, 3/31

*Participants initially received ISL+DOR+3TC and switched to ISL+ DOR during the week 24-48 period of the study.
ISL + DOR: Other Results

• All participants with protocol defined virologic failure had confirmed VL <80
• No participants met criteria for resistance testing
• Plan: phase 3 trial of this two-drug regimen

Future possibilities:
• Based on PK considerations, ISL has potential for once weekly dosing for treatment – partner TBD
• Also being considered for PrEP – ISL implant could potentially maintain protective concentrations for 12 months
GS-6207: HIV Capsid Inhibitor

In people without HIV, single subcutaneous injection maintained exposures for >24 wks.
<table>
<thead>
<tr>
<th>Time, Day</th>
<th>Single SC GS-6207 dose</th>
<th>Start of B/F/TAF</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=6)</th>
<th>GS-6207 50 mg (n=6)</th>
<th>GS-6207 150 mg (n=6)</th>
<th>GS-6207 450 mg (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change in HIV-1 RNA, Log_{10} copies/mL (95% CI)</td>
<td>-3.0 ± 0.3</td>
<td>-2.5 ± 0.2</td>
<td>-2.0 ± 0.1</td>
<td>-1.5 ± 0.1</td>
</tr>
</tbody>
</table>

Maximum reduction of HIV RNA: -1.8 to 2.0 log_{10} c/mL
Case #6

• 67-year-old man, diagnosed with HIV infection in 1989.
• Treated initially with single and dual NRTIs; subsequently received agents in all available drug classes.
• Although clinically stable with a relatively preserved CD4 cell count, he has had viral suppression only transiently when receiving LPV/r, ZDV/3TC, TDF in early 2000s; that regimen was stopped for injection site reactions.
• Most recent regimen: DTG, ETR, twice-daily DRV/r.
• Resistance testing sent for viral load of 2100.
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Genotypic Name</th>
<th>Brand Name</th>
<th>Net Assessment</th>
<th>Cutoffs (Lower-Upper)</th>
<th>Fold Change</th>
<th>Drug Susceptibility</th>
<th>Pheno Type</th>
<th>Geno Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Abacavir</td>
<td>ZiaGen</td>
<td>Resistant</td>
<td>(4.5 - 6.5)</td>
<td>9.18</td>
<td>Increasing</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
<td>Videx</td>
<td>Resistant</td>
<td>(1.3 - 2.2)</td>
<td>1.43</td>
<td>Decreasing</td>
<td>P</td>
<td>N</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>Resistant</td>
<td>(3.5)</td>
<td>&gt;MAX</td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamivudine</td>
<td>Epivir</td>
<td>Resistant</td>
<td>(3.5)</td>
<td>&gt;MAX</td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stavudine</td>
<td>Zerit</td>
<td>Resistant</td>
<td>(1.7)</td>
<td>3.20</td>
<td></td>
<td>N</td>
<td>N</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Zidovudine</td>
<td>Retrovir</td>
<td>Resistant</td>
<td>(1.9)</td>
<td>&gt;MAX</td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Viread</td>
<td>Resistant</td>
<td>(1.4 - 4)</td>
<td>3.77</td>
<td></td>
<td>P</td>
<td>N</td>
<td>1.3</td>
</tr>
</tbody>
</table>

| NRTI       | Delavirdine    | Rescriptor | Resistant      | (6.2)                | >MAX        |                     | N          | N         |          |
|            | Efavirenz      | Sustiva    | Resistant      | (3)                  | >MAX        |                     | N          | N         |          |
|            | Etravirine     | Instenice  | Resistant      | (2.9 - 10)           | >MAX        |                     | N          | N         |          |
|            | Nevirapine     | Viramune   | Resistant      | (4.5)                | >MAX        |                     | N          | N         |          |
|            | Rilpirvirine   | Edurant    | Resistant      | (2)                  | >MAX        |                     | N          | N         |          |
| NRTI       |               |            | NRTI Mutations | K103N, E138Q, H221Y, M230L, L234I, N348I |

<p>| INSTI      | Delatrogravir  | Tivicay     | Partially Susceptible | (4 - 13)    | 4.75        |                     | P          | P         |          |
|            | Elatrogravir   | Elotegravir | Resistant      | (3.5)                | &gt;MAX        |                     | N          | N         |          |
|            | Raltegravir    | Isentress   | Resistant      | (2.2)                | &gt;MAX        |                     | N          | N         |          |
| INSTI      |               |            | INSTI Mutations | G140S, Q148H |</p>
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Net Assessment</th>
<th>Cutoffs (Lower-Upper)</th>
<th>Fold Change</th>
<th>Increasing</th>
<th>Decreasing</th>
<th>Photo Type</th>
<th>Geno Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Rayataz</td>
<td>Resistant</td>
<td>2.2</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Rayataz / r²</td>
<td>Resistant</td>
<td>5.2</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>Prezista / r²</td>
<td>Resistant</td>
<td>10 - 90</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva / r²</td>
<td>Resistant</td>
<td>4 - 11</td>
<td>&gt;MAX</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crixivan / r²</td>
<td>Resistant</td>
<td>10</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Kaletra</td>
<td>Resistant</td>
<td>9 - 55</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viread</td>
<td>Resistant</td>
<td>3.6</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>Resistant</td>
<td>2.5</td>
<td>&gt;MAX</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Invirase / r²</td>
<td>Resistant</td>
<td>2.3 - 12</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Aptivir / r²</td>
<td>Resistant</td>
<td>2 - 8</td>
<td>4.79</td>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

**PI Mutations**

**Phenotype / Genotype Comments (clinical significance may vary)**

1. **Mixture**: Mixtures detected at resistance-associated position(s); minor populations with decreased susceptibility may be present and may increase in the presence of drug pressure.

2. **IC50 reduced**: Phenotypic measurement reflects possible enhanced susceptibility due to M184I or V.
Hey HIV treaters out there--in the past 2 years, do you follow, or have you seen, any people with viral failure and resistance to ALL major HIV drug classes? (Enfuvirtide and ibalizumab excluded.) If yes, share how many in the replies. (I've seen 2.)

- Yes. 12%
- No. 53%
- Not an HIV treater. 35%
Unmet Need? Heavily Treatment–Experienced People With HIV

• ART with novel mechanisms of action play a critical role for a small proportion of people with HIV: those with resistance to multiple classes and no treatment options

• Two primary target populations
  1) Older people with HIV treated in early days of ART with less potent regimens that had low resistance barriers
  2) Younger people with congenital infection, now young adults

• Currently, ibalizumab and enfuvirtide are the only options
  • Both injectable and expensive
  • Some people already have resistance to enfuvirtide

Prevalence of Heavily Treatment Experienced (HTxE) with Multi-class Resistance

• CNICS cohort of > 32,000 ART-experienced people with HIV receiving care in USA
• HTxE defined as <= 2 available classes by resistance testing

Bajema K et al. IAS 2019 MOPEB246.
BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults With Multidrug Resistant HIV

- Wk 96 analysis of randomized, double-blind phase III trial in heavily treatment–experienced adults failing current ART with confirmed HIV-1 RNA ≥ 400 c/mL
  - At BL: median HIV-1 RNA, 4.6 \( \log_{10} \) c/mL; median CD4+ cell count, 80 cells/mm\(^3\); AIDS history, 86%

**Randomized Cohort**
- 1-2 remaining ARV classes (≥ 1 fully active\(^8\) approved agent/class), cannot construct viable regimen with remaining agents (n = 272)

**Nonrandomized Cohort**
- No remaining ARV classes and no fully active\(^8\) approved agents (n = 99)

**Primary Endpoint**
- Mean Δ in HIV-1 RNA,\(^†\) \( \log_{10} \) c/mL (95% CI)
- Day 9: -0.79 (-0.88 to -0.70)
- Day 8: -0.17 (-0.33 to -0.01)

**Day 1**
- FTR 600 mg BID + Failing Regimen\(^*\) (n = 203)
- Placebo + Failing Regimen\(^*\) (n = 69)

**Day 8**
- FTR 600 mg BID + OBT\(‡\)
- Treatment Δ: -0.63
- FTR 600 mg BID + OBT\(‡\)

**Day 9**
- FTR 600 mg BID + OBT\(‡\)

**Wk 96\(‖\)**
- FTR 600 mg BID + OBT\(‡\) (investigational agents allowed)

*Blinded. †Day 8 adjusted by Day 1. ‡Open-label. §No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV. ‖Measured from start of open-label tx. Study conducted until another option, rollover study, or approved ARV available.

**BRIGHTE: ITT-E Virologic Response Through Wk 96**

**Randomized Cohort (n = 272)**

- **HIV-1 RNA < 40 copies/mL (%):**
  - Baseline*: 0%
  - Wk 24: 53%
  - Wk 48: 54%
  - Wk 72: 53%
  - Wk 96: 60%

**Nonrandomized Cohort (n = 99)**

- **HIV-1 RNA < 40 copies/mL (%):**
  - Baseline*: 0%
  - Wk 24: 37%
  - Wk 48: 38%
  - Wk 72: 35%
  - Wk 96: 37%

*Snapshot analysis excluded baseline data. 1 patient had BL HIV-1 RNA < 40 copies/mL.

Question

• How many patients do you follow who could be eligible for fostemsavir therapy?

A. Zero
B. 1-3
C. More than 3
Case #6 -- Outcome

• Placed on ibalizumab, enfuvirtide, DTG BID, and TAF/FTC.
• HIV RNA < 20!
• Uncertain whether fostemsavir (when approved) should replace ibalizumab, or enfuvirtide, or both!
Case #7

• 50 year-old man, diagnosed with HIV infection in 2013.
• Initial CD4 770, HIV RNA 1000, no resistance. Asymptomatic.
• Refuses to go on ART initially due to insurance concerns and confidentiality.
• Ultimately agrees in 2015 when he realizes he can purchase ART in South Africa during his business trips – buys TDF/3TC, RAL ($110/month), tolerates well.
• HIV since then < 20 copies/mL.
• Recently researched an even cheaper treatment, and switches to DTG + 3TC, which costs him $65/month.
Question

• Should we support this strategy?

A. Yes
B. No
C. Sort of, but it makes me nervous
TANGO: Switch to DTG/3TC vs Continuing TAF-Based 3-Drug Regimen

- International, randomized, open-label phase III noninferiority study

- Adults with HIV-1 RNA < 50 c/mL for > 6 mos on stable TAF-based ART*; no prior VF, NRTI or INSTI resistance, HBV infection or HCV requiring tx (N = 741)

- Switch to DTG/3TC (n = 369)
- Continue TAF-Based Regimen (n = 372)

- Wk 196
- Primary Analysis
  - Wk 48
  - Wk 148

- Continuation of DTG/3TC permitted

*Initial regimen of FTC/TAF + PI, NNRTI, or INSTI, or TDF switched to TAF ≥ 3 mos prior to screening with no other regimen changes.

- Primary endpoint: virologic failure at Wk 48 by FDA Snapshot analysis (ITT-E)
  - Noninferiority margin: 4%

- Secondary endpoint: safety

TANGO: Virologic Outcomes by FDA Snapshot at Wk 48 (ITT-E)

- No CVW in DTG/3TC arm, CVW in 1 (< 1%) patient in TAF-ART arm; no resistance detected at failure
- All 7 patients (4 in DTG/3TC group and 3 in TAF-based ART group) with proviral M184V/I mutation at BL maintained HIV-1 RNA < 50 copies/mL at Wk 48

*Adjusted for BL third agent class.

GEMINI-1 and -2: Virologic Response at Wk 96

- Rates of HIV-1 RNA ≥ 50 copies/mL unchanged from Wk 48; d/c for reasons other than AEs or death higher with DTG + 3TC at Wk 96 (8% vs 5% with 3-drug ART)

Endpoint, % (n)

<table>
<thead>
<tr>
<th>Endpoint, % (n)</th>
<th>DTG + 3TC (n = 716)</th>
<th>DTG + FTC/TDF (n = 717)</th>
<th>Difference,* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>86.0 (616)</td>
<td>89.5 (642)</td>
<td>-3.4 (-6.7 to 0)</td>
</tr>
</tbody>
</table>

*Adjusted for BL HIV-1 RNA, BL CD4+ cell count, and study.

Question

• Where do you think DTG/3TC will have the greatest impact?

A. As initial therapy
B. As switch therapy
Cost-effectiveness of 2-drug DTG-3TC

• Modeling study projecting cost effectiveness and budget impact of 2-drug DTG-3TC as an “induction-maintenance” strategy

• Results
  • DTG-3TC after virologic suppression highly cost-effective (ICER $22,500/QALY)
  • US cost savings could be $500-800 million/year for new diagnoses – even higher ($3 billion/year) if existing suppressed patients switch

• Limitation: Study done with price estimates

Perspective

Treating and Preventing HIV with Generic Drugs — Barriers in the United States

Erika G. Martin, Ph.D., M.P.H., and Bruce R. Schackman, Ph.D.

- Loss of coformulations due to different patent expiry dates
- Variable payment models for HIV care mean variable incentives to use generics
- Will there be sufficient generic manufacturers to decrease costs?
- Will cost savings be passed along to patients? What about co-pays?
- What about 340b pharmacy revenue?

Martin EG and Schackman BR. N Engl J Med 2018; 378:316-319
DTG/3TC: Questions Raised by GEMINI and TANGO Results

• Should DTG/3TC now be a recommended first-line regimen?
• Will there be a higher risk of resistance in clinical practice not seen in clinical trials?
• In GEMINI, how can the lower response rate in those with CD4 < 200 be explained?
• What specific drug toxicity are we avoiding when TAF/FTC is the NRTI pair?
• Right now 3TC separately is generic – is the premium for the coformulated tablet worthwhile?
Future ART – Conclusions

- Current treatments are extraordinarily safe and effective, but future ART will need to address
  - Pregnancy
  - Advanced HIV disease (low CD4, high HIV RNA)
  - Emerging toxicities (weight gain)
  - Non-adherent patients
  - People with limited treatment options
  - Cost
- Dual-therapy, long-acting ART, and novel drug classes will all play a role – as will additional clinical and translational research!
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