Lesson of the Day: ‘We Live in Zoom Now’

In a time of social distancing, a videoconferencing platform is where we work, learn and party.
Outline

• Novel ART
• ART during pregnancy
• Weight gain and ART
• COVID-19 and HIV
New Drugs in Development

Entry inhibitors:
- Attachment inhibitor: Fostemsavir
- UB-421
- CCR5 Antagonist: Leronlimab
- Fusion Inh.: Albuvirtide
- Multisite: Combinectin
- Broadly neutralizing Abs

Reverse Transcriptase Inh. (RTI)
- Nucleoside RTI (NRTIs)
  - Nonnucleoside RTI (NNRTIs)
    - Long-acting rilpivirine (RPV)
    - Elsulfavirine
- Nucleoside RT translocation inhibitor: Ilatrivir

Integrase strand transfer inhibitors (INSTI)
- Long-acting cabotegravir (CAB)

Maturation inhibitor
- GSK3640254 (non-boosted)
Monthly LA Cabotegravir/Rilpivirine in PWH with Suppressed HIV RNA: ATLAS/FLAIR

Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, available in long-acting nanosuspension formulations that can be given by injection.

Virologic outcomes

<table>
<thead>
<tr>
<th>Proportion of Participants (%)</th>
<th>CAB + RPV LA (n=591)</th>
<th>CAR (n=591)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic Nonresponse (≥50 c/mL)</td>
<td>1.9</td>
<td>1.7</td>
</tr>
<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

Week 96 FLAIR: monthly LA CAB/RPV non-inferior to oral DTG/ABC/3TC. No confirmed virologic failures in LA arm from Wk 48 to 96

Orkin C et al, CROI 2020, #482

*Adjusted for sex and baseline third agent class. CAR, current antiretroviral; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; Overton E, IAS 2019 MOPEB257; Swindells S et al, NEJM 2020; Orkin C et al, NEJM, 2020
ATLAS-2M

- Phase 3 open-label trial in people with HIV suppressed on CAB/RPV LA every 4 weeks (n=391) or oral ART (n=654)
  - Candidates excluded if history of virologic failure or INSTI or NNRTI resistance (except K103N)
- Randomized 1:1 to CAB/RPV LA every 4 weeks or every 8 weeks
- CAB/RPV Q8W non-inferior to Q4W: 1.7% vs. 1.0% VL >50 c/mL at wk 48
- >90% of participants preferred every 8 wk dosing over their previous dosing interval

Why we need new ART

New drugs

How will we use new drugs?

Overton E et al, CROI 2020, #34
CAB and RPV Pharmacokinetics after Discontinuation

- Participants (n=38) receiving LA CAB/RPV every 4 wk or every 8 wk who withdrew for any reason
- Switched to alternative ART and underwent PK sampling
- CAB and RPV concentrations shown in relation to lower limit of quantification and in vitro protein adjusted IC90
- CAB half life: 6.4 wk; RPV half-life: 29.6 wks

LA CAB/RPV: Practical Considerations and Questions

- Injections given into gluteus medius (upper outer quadrant of buttock)
  - Need private space: how will we set up clinics to deliver the drugs?
  - Alternative spaces: Pharmacies? Home healthcare?
- RPV LA requires cold chain (consideration in resource limited settings)
- Is 4-week oral lead-in needed? What about direct to inject?
- Can CAB/RPV be used in someone who is viremic?
  - Case: person with bowel resection; not able to absorb oral ART; suppressed on IM CAB/RPV
- Long PK tail (48 wk or longer) after stopping drugs. Will missed doses → resistance?
- How will we remind people to come in for visits? Might pharmacies play a role?
- Will CAB/RPV be useful in people who have difficulty with adherence? ACTG A5359
- What will the cost of the drugs be? Will the cost of administration be reimbursed?
New Drugs

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Maturation inhibitors
- Protease inhibitors (PI)

Capsid inhibitor
- GS-6207

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of temsavir: binds to gp120, inhibits HIV attachment to CD4
- Phase 3 trial in heavily treatment experienced participants (BRIGHTE)

Randomized Cohort (n = 272)
≥1 fully active drug in 1 or 2 classes.
FTR + optimized background therapy (OBT)

Nonrandomized Cohort (n = 99)
No fully active approved drug. FTR + OBT. 15 participants also took ibalizumab

New drug application filed with FDA in Dec 2019 and EMA in Jan 2020. Compassionate access program.
Islatravir (MK-8591)

• Nucleoside RT translocation inhibitor (NRTTI)

• Potent at low doses: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days

• High barrier to resistance

• Long intracellular half-life (78-120 h)
  • Potential for once daily, once weekly or less frequent dosing

Phase 1b, single-dose, monotherapy study
Study population: ART naïve (N=30)

Change From Baseline HIV-1 RNA
(log₁₀ copies/mL)

Time (days)

Grobler et al CROI 2017 #435; Matthews et al IAS 2017 #TUPDB0202LB; Schurmann et al, Lancet HIV, 2020
Phase 2b study for treatment: DRIVE2Simplify: ISL + DOR vs. DOR/3TC/TDF

Participants initially received ISL+DOR+3TC; then switched to ISL+DOR during week 24-48 after achieving virologic suppression. Week 48 virologic outcomes (FDA Snapshot)
Islatravir (ISL)

- **Phase 3 trials of ISL/DOR (0.75 mg/100 mg):**
  - Switch studies: from BIC/FTC/TAF (n=578)\(^1\) or other 2- or 3-drug regimen (n=578)\(^2\)
  - Highly treatment-experienced participants (at least 3 class resistance) (n=100)\(^3\)
  - Treatment naïve participants: DOR/ISL vs. BIC/FTC/TAF (n=680)\(^4\)

**Future possibilities:**
- In SIV model, weekly oral ISL provided effective post-exposure prophylaxis\(^5\)
- May have applications for PrEP
  - Phase 2 trial in people at low risk of HIV: once monthly oral (60, 120 mg)\(^6\)
  - Promising PK results with ISL implant\(^7\)

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1\(^{\text{NCT04223791; NCT04223778; NCT04233216; NCT04233879; Markowitz M, CROI 2020, #89LB; NCT04003103; Matthews R, IAS 2019, TUAC0401LB}}\)
GS-6207 (Capsid Inhibitor)

- Picomolar activity against HIV in vitro
- Retains activity against HIV mutants resistant to other HIV classes
- Subcutaneous (SC) injection: sustained levels for >24 wk
- Oral formulation: median half-life 11-13 days
GS-6207 (Capsid Inhibitor): Antiviral activity after single subcutaneous dose in people with HIV

- **Phase 2/3 study in heavily treatment experienced PWH (CAPELLA)**
  - GS-6207 oral lead-in followed by SC injections (900 mg, 2 x 1.5 mL) every 6 mo + OBR

- **Phase 2 trial in treatment naïve PWH (CALIBRATE)**
- GS-6207 is also being developed for PrEP

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![Graph showing mean change in HIV RNA: -1.3 to 2.3 log_{10} c/mL over 10 days](#)

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1. Daar E CROI 2020 # 469; Daar E IAS 2019 LBPEB13; Daar E EACS 2019 PE3/17
2. clinicaltrials.gov: NCT04150068; NCT04143594

OBR: optimized background regimen
## Long-acting Therapies: Lessons from Other Fields

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Route/Dosing Interval</th>
<th>Findings</th>
<th>Lessons/Questions for ART</th>
</tr>
</thead>
</table>
| Long-acting reversible contraceptives (LARC) | • IUDs/implants: yrs (“get it & forget it”)  
                     • Medroxyprogesterone acetate inj: q 3 mo. | • IUDs/implants: lower failure rate than shorter acting contraceptives  | • Choice matters!  
                      • Could inj. contraceptive & LA ART be combined/delivered together?                                                                                     |
| Bisphosphonates for osteoporosis            | • Yearly injectable; monthly, weekly or daily oral medication | • Adherence and persistence: yearly injectable > weekly oral > daily oral. | • When it comes to dosing interval: the longer, the better                                                                                              |
| Long-acting injectable psychiatric medications | • Every 3 months                       | • Decreased discontinuation rate, lower hospitalization                 | • Pay attention to facilitating delivery!                                                                                                                 |
| PCSK-9 inhibitors for cardiovascular disease prevention | • Every 2 or 4 weeks  
                     • Self administered | • Limited uptake, in part because of cost                               | • Self-administration desirable  
                      • Price competitively so cost not a barrier!                                                                                                       |

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**Why we need new ART**  
**New drugs**  
**How will we use new drugs?**
Who Will We Treat with Long-Acting ART?

• For most people, oral daily ART will remain effective and convenient option
• LA ART may be good option for people who struggle with daily oral regimen (e.g., swallowing difficulties; not taking oral medications after surgery; stigma – external or internal) or who don’t want to take medicine every day
• Combining visits for injections with other appointments may be helpful, e.g. picking up methadone refills, psychiatrist/psychologist/support groups, health centers
• Considerations: long PK tail, need for oral bridging if missed injection, reminders, logistics of administration, managing toxicities if they develop; what to do if recipient becomes pregnant
HIV broadly neutralizing antibodies (bNAbs) in Clinical Trials

**gp41 MPER:**
- **10E8VLS:** no ongoing trial

**SAR441236 - trispecific**
- VRC01LS/PGDM1400/10E8: Phase 1-2

**TMB-Bispecific**
- ibalizumab/10E8.4: Phase 1

**V1V2 Glycan:**
- CAP256V2LS: Phase 1 soon
- PGDM1400 and LS: Phase 1-2

**N332 Glycan Supersite:**
- PGT121: Phase 1-2
- PGT121.B1J414LS: Phase 1 soon
- 10-1074: Phase 1-2

**CD4 Binding Site:**
- VRC01: Phase 1-2b
- VRC01-LS: Phase 1
- VRC07-523LS: Phase 1-2
- N6LS: Phase 1
- 3BNC117 and LS: Phase 1-2

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups.

Promise: may be engineered to be very long-lasting; may be amenable to vectored delivery; may be combined with long-acting small molecules, eg study of LA cabotegravir + VRC07-523 LS (ACTG)
New Data on bNAbs in Humans at CROI 2020

- Durable HIV antibody production in humans after AAV-mediated gene transfer
  - > 1 year after single administration of vector
  - Prospect of vectored delivery of bNAbs

Longitudinal Serum VRC07 Concentrations

![Graph showing VRC07 Concentration vs. Week Post-Product Administration]

Casazza JP et al, CROI 2020, #41LB
ART and Pregnancy

32 yo F with HIV. She and her boyfriend (who is not infected with HIV) are hoping to have children soon. Which regimen do you start?

1) Dolutegravir + FTC/TDF
2) Dolutegravir + FTC/TAF
3) Bictegravir/FTC/TAF
4) Raltegravir + FTC/TDF
5) EFV/FTC/TDF
### What to Start in Pregnancy: DHHS Guidelines Dec 24, 2019

<table>
<thead>
<tr>
<th>Two NRTIs</th>
<th>Integrate inhibitor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir/3TC</td>
<td>Raltegravir (twice daily) or</td>
</tr>
<tr>
<td>or</td>
<td>Dolutegravir (<em>Preferred ARV drug throughout pregnancy and an Alternative ARV for those trying to conceive</em>)</td>
</tr>
<tr>
<td>TDF/FTC or TDF/3TC</td>
<td>or</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DO NOT USE:</strong></th>
<th><strong>Protease inhibitor:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF (insufficient data)</td>
<td>Darunavir/ritonavir (twice daily) or</td>
</tr>
<tr>
<td>Bictegravir (insufficient data)</td>
<td>Atazanavir/ritonavir</td>
</tr>
<tr>
<td>Elvitegravir/cobi (PK concerns)</td>
<td></td>
</tr>
<tr>
<td>DRV/cobi (PK concerns)</td>
<td></td>
</tr>
<tr>
<td>ATV/cobi (PK concerns)</td>
<td></td>
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<tr>
<td>DOR (insufficient data)</td>
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</table>
IMPAACT 2010 (VESTED)

- Phase III trial compared safety and efficacy of DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF in ART-naive women initiating ART during pregnancy.

Who was in VESTED?

- Age: 26-27 yo
- Enrolled in Africa: 86-89%
- Median gestational age: 21-22 wk

ART-naïve, * HIV-infected pregnant women at 14-28 wks of gestation (N = 643)

*< 14 days ART in pregnancy permitted.

- DTG 50 mg QD + FTC/TAF 200/25 mg QD (n = 217)
- DTG 50 mg QD + FTC/TDF 200/300 mg QD (n = 215)
- EFV/FTC/TDF 600/200/300 mg QD (n = 211)

Mothers and infants followed for 50 wks postpartum.
IMPAACT 2010: Virologic Suppression at Delivery

- Virologic efficacy of DTG-based ART at delivery superior to that of EFV/FTC/TDF
- Time to viral suppression shorter with DTG-based ART ($P < .001$)

<table>
<thead>
<tr>
<th>Women With HIV RNA &lt; 200 at Delivery, %</th>
<th>Combined DTG-Based ART</th>
<th>EFV/FTC/TDF</th>
<th>$P$ Value</th>
<th>Risk Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>97.5</td>
<td>91</td>
<td>.005</td>
<td>6.5 (2.0-10.7)</td>
</tr>
</tbody>
</table>

Chinua. CROI 2020. Abstr 130LB.
**IMPAACT 2010: Adverse Pregnancy Outcomes**

<table>
<thead>
<tr>
<th>Adverse Pregnancy Outcomes, %</th>
<th>DTG + FTC/TAF</th>
<th>DTG + FTC/TDF</th>
<th>EFV/FTC/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse pregnancy outcome</td>
<td>24.1*</td>
<td>32.9</td>
<td>32.7</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>5.8†</td>
<td>9.4</td>
<td>12.1</td>
</tr>
<tr>
<td>Stillbirth‡</td>
<td>3.7</td>
<td>5.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>1.0</td>
<td>1.5</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*P = .043 vs DTG + FTC/TDF and P = .047 vs EFV/FTC/TDF. †P = .023 vs EFV/FTC/TDF. ‡Post hoc analysis.

- Adverse pregnancy composite outcome: preterm delivery (< 37 wks), small for gestational age (< 10th percentile), stillbirth (≥ 20 wks), spontaneous abortion (< 20 wks)
  - Adverse pregnancy outcomes significantly less frequent with DTG + FTC/TAF vs DTG/FTC/TDF and EFV/FTC/TDF (P < .05)
In treatment-naive women with HIV initiating ART during pregnancy, virologic suppression rates at delivery significantly higher with DTG-based ART vs EFV/FTC/TDF
- HIV RNA < 200 c/mL: 97.5% vs 91.0% ($P = .005$; difference: 6.5; 95% CI: 2.0-10.7)

Adverse pregnancy outcomes significantly less frequent with DTG + FTC/TAF vs DTG + FTC/TDF and EFV/FTC/TDF ($P < .05$)
- Neonatal death significantly less frequent with DTG + FTC/TAF vs EFV/FTC/TDF ($P = .019$)
Do particular antiretroviral medications cause weight gain?
Case

• 43 yo African American woman diagnosed with HIV in the 1990s
• Previous regimens: TDF/FTC/EFV; DRV/r + ETR + TAF/FTC (because of drug resistant virus)
• Switched to DTG + DRV/r + TAF/FTC
• Gained 40 lb over ensuing 2 years (from 210 lb to 250 lb)
• She asks you if her weight gain is related to her medicines

Weight gain is associated with:

1) All antiretroviral regimens
2) Integrase inhibitor-based regimens
3) Protease inhibitor-based regimens
4) Non-nucleoside reverse transcriptase inhibitor-based regimens
5) The jury is still out
ADVANCE: Mean Change in Weight to Wk 96 by Sex

- Significantly greater weight increase with DTG vs EFV, with TAF vs TDF
- Plateau in weight gain after Wk 48 observed in men but not in women
ADVANCE: Projected Risks of Metabolic Syndrome, Diabetes, and CVD

- DTG + F/TAF associated with higher risk of:
  - Clinical obesity
  - Metabolic syndrome: 8% vs. 6% in DTG +F/TDF and 3% in EFV/F/TDF
  - Rises in VAT and SAT
  - Predicted risk of diabetes

- Limitations
  - Young population (relatively low risk of MI and DM); models do not account for additional weight gain after week 96

<table>
<thead>
<tr>
<th>Risk Scores</th>
<th>Dolutegravir +F/TAF (n=351)</th>
<th>Dolutegravir + F/TDF (n=351)</th>
<th>Efavirenz/ F/TDF (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham (%) – median change (10-year risk of MI or coronary death)</td>
<td>0.43</td>
<td>0.22</td>
<td>0.28</td>
</tr>
<tr>
<td>QRisk (%) (10-year risk of heart attack or stroke)</td>
<td>0.2*</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>QDiabetes (%) (10-year risk)</td>
<td>0.9†</td>
<td>0.5</td>
<td>0.7‡</td>
</tr>
</tbody>
</table>

*P=0.03 versus efavirenz/F/TDF.
†P=0.004 versus dolutegravir + F/TDF.
‡P=0.005 versus dolutegravir + F/TDF.

Weight Gain after Initiation of ART: Randomized Trials

- Pooled analysis of 8 industry-sponsored randomized trials of people initiating ART between 2003-2015
- N=5680 participants
- 96-week median weight gain: 2.0 kg
- Risk factors for weight gain >10% from baseline over 48 weeks (12.8% of participants)
  - Lower CD4 cell count, higher HIV RNA
  - Female sex, black race
  - BIC = DTG >EVG/c
  - TAF > ABC, TDF > AZT

Sax P et al, CID, 2019
NA-ACCORD: Impact on Weight After Switch to INSTI-Based Regimen From NNRTI- and PI-Based Regimens

- Adults with HIV who switched from NNRTI- or PI-to INSTI-based ART (n=870; 2007-2014)
  - HIV RNA <1000 copies/mL for 2 years
- People on NNRTI-based ART had higher annualized weight gain after switch to INSTI regimens than people switched from PI-based ART
- Among those who switched from NNRTI-to INSTI-based ART, annualized weight gain was greatest for females, non-whites, and older adults

COVID-19 and HIV

Interim Guidance for COVID-19 and Persons with HIV

Last Updated: March 20, 2020; Last Reviewed: March 20, 2020
COVID-19 and HIV

- Risk factors for severe COVID-19: age > 60 yo, DM, HTN, CVD or pulmonary disease
- Not known if people with HIV have a different disease COVID-19 course
- Advanced HIV (CD4 <200) is risk factor for complications of other respiratory viruses. Not known if this is true for COVID-19
- Some people with HIV have other comorbidities (CVD, lung disease) that increase risk for more severe COVID-19. Smokers also at increased risk for severe disease
- Thus, until more is known, additional caution for all people with HIV, especially those with advanced HIV or poorly controlled infection, is warranted
- Maintain adequate supply of medications (at least 30 d, ideally 90 d)
- Influenza and pneumococcal vaccinations should be kept up to date
- For persons with suppressed VL and stable health, routine medical and lab visits should be postponed to the extent possible
COVID-19 and HIV: The Question of LPV/r

- LPV/r has been used as an off-label treatment for people with COVID-19 and clinical trials, including one launched by WHO, are underway.

- If PI is not part of a person’s regimen, the regimen should NOT be changed to include a PI.

- In a small open-label trial, 199 hospitalized patients with COVID-19 were randomized to either 14 days of LPV/r or standard of care alone. No statistically significant difference was seen between the 2 groups in time to clinical improvement or mortality.
Acknowledgements

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• Delaney Taylor
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• Chloe Orkin

• Melanie Thompson
• Ken Freedberg
• Diana Brainard
• Martin Rhee
• Kim Smith
• Max Lataillade
• Michael Aboud
• Mei-June Liao
• Jonah Sacha
• Nader Pourhassan
• Malini and Kavish Gandhi
ATLAS-2M: Confirmed Virologic Failures (CVF)

- CVF in CAB LA + RPV LA Q8W arm: n=8
  - 5 had preexisting major RPV RAMs (E138A, Y188L, Y181Y/C, H221H/Y, E138E/A, Y188Y/F/H/L)
  - 1 had preexisting major INSTI RAM (G140G/R)
- Fully active oral ART resulted in viral resuppression in 9/10 patients with CVF
  - 1 patient noncompliant on PI-based ART
- In all patients with CVF (n=10), virus had phenotypic sensitivity to DTG

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAB LA + RPV LA Q8W (n = 522)</th>
<th>CAB LA + RPV LA Q4W (n = 523)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVF, n (%)</td>
<td>8 (1.5)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>CVF with RPV RAMs,* n/N</td>
<td>6/8</td>
<td>1/2</td>
</tr>
<tr>
<td>CVF with INSTI RAMs,* n/N</td>
<td>5/8</td>
<td>2/2</td>
</tr>
<tr>
<td>Treatment-emergent INSTI RAMs</td>
<td>Q148R, N155H†</td>
<td>E138E/K, Q148R, N155N/H</td>
</tr>
</tbody>
</table>

*Post hoc BL PBMC HIV-1 DNA testing. †Or a mixture.