Learning Objectives

After attending this presentation, learners will be able to:

▪ Assess challenges in eliminating HIV from the US
▪ Describe new medications for treatment and prevention of HIV
▪ Evaluate potential complications of antiretroviral therapy

HIV Epidemiology: Can We End the Epidemic?
Resources targeted to 48 highest burden counties; Washington, D.C.; San Juan, Puerto Rico; 7 states with substantial rural HIV burden.

HIV Outbreak in Massachusetts: Molecular Surveillance Expands Investigation

- Outbreak of HIV among people who inject drugs in MA (n=129)
- Near real-time analysis of HIV sequences generated from drug resistance testing allowed identification of linked transmissions
- Epidemiologic linkage (e.g. partner services) coupled with molecular surveillance
  - Molecular data expanded number linked to investigation by 44%
- Multi-pronged approach needed
ARS Question 1: HIV cure has been achieved with:

1. Early antiretroviral therapy
2. Stem cell transplantation
3. Gene Therapy
4. All of the above
5. None of the above
**London Patient**

- 2003: Diagnosed with HIV
- 2012: Initiated ART. Diagnosed with stage IV Hodgkin lymphoma; multiple rounds of salvage chemotherapy to achieve remission
- 2016: Stem cell transplant from CCR5 Δ32/Δ32 donor.
  - Reduced intensity conditioning; no total body irradiation
  - Course complicated by EBV reactivation (received rituximab), CMV reactivation, mild GVHD
  - 100% donor chimerism (all of his CD4 cells lacking CCR5)
  - 16 months after transplant, ART stopped

Gupta RK et al. Nature 2019 Mar 5; [e-pub].

**London Patient**

- No viral rebound in plasma for 18 months
- HIV undetectable on multiple tests, including virus outgrowth assay
- Declining HIV-specific immune responses

Gupta RK et al. Nature 2019 Mar 5; [e-pub].

**Cautionary Notes . . . and a Way Forward**

- In the London patient (and a second similar case, the "Dusseldorf patient"): HIV relapse still possible; longer follow-up needed
- Stem cell transplant only appropriate in people with malignancy
- London patient’s virus used CCR5; some people have HIV that enters cells through other co-receptors
- Nevertheless, suggests promising way forward for HIV cure research:
  - CCR5 and coreceptor modulation
  - Example: gene therapy to modify host cells (Tebas P et al, CROI 2019; #25)

Jenner R et al, CROI 2019, # 304

NY Times, March 9, 2019

Jensen BE et al, CROI, 2019, # 394
Why do some patients have low-level, non-suppressible viremia on ART?

ARS Question 2: Do you care for any people with HIV with non-suppressible viremia*?

*Persistently detectable VL despite being on ART and with no suspicion for nonadherence

1. Yes
2. No

ARS Question 3: What do you do with such patients?

1. Change their ART regimen
2. Intensify their ART regimen
3. Leave them alone
4. Something else
Non-suppressible viremia due to large clones producing HIV particles

- 10 participants; no suspected non-adherence
- Median VL: 98 (range: 43, 378); median duration viremia on ART: 3.2 yr
- Sequencing and integration site analyses:
  - Plasma viremia due to clonal proliferation of CD4 cells carrying replication-competent proviruses ("repliclones")
  - No evidence for drug resistance, inadequate drug levels
- Implications:
  - Intensification or ART changes would not be effective
  - Repliclones may need to be eliminated to cure HIV

Halvorsen E et al, CROI 2019, #23; Also Zhang X et al, CROI 2019, #348

Pre-exposure prophylaxis (PrEP)

DISCOVER: TDF/FTC vs. TAF/FTC for PrEP

Primary efficacy endpoint:
- HIV incidence
  - Evaluated by rate ratio with noninferiority margin 1.52
  - Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

Primary analysis:
- HIV incidence/100 PY when 100% complete W48 & 50% complete W96

Industry-funded trial:
- MSM/TGW
- High risk of HIV (>2 episodes condomless anal intercourse in past 12 wk, rectal STI; syphilis in past 6 m)

96 weeks
- Open-label switch for 48 weeks
- At entry and Q12W:
  - Adherence counseling
  - Prevention services
  - Risk reduction counseling
  - Condoms/lubricant

F/TAF QD n=2694
F/TDF QD n=2693

Who was in DISCOVER?
- MSM/TGW (no cis-gender women)
- Median age: 34
- 84% W, 9% B
- 24% Hispanic/Latinx
- 1-2% Transgender women
- 18-17% taking PrEP at baseline

New York, New York, March 18, 2019
TAF/FTC non-inferior to TDF/FTC as Daily PrEP for MSM/TGW

NB: 5 participants with probable acute HIV at study entry. Resistance to FTC developed in 4 participants, all with suspected acute HIV. 15 of the 22 seroconversions occurred in people with low tenofovir levels on dried blood spot.

DISCOVER: Other Notable Findings

- High rate of STIs (participants were at substantial risk for acquiring HIV)

<table>
<thead>
<tr>
<th></th>
<th>Lab Assessed GC/CT Incidence</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>F/TAF</td>
</tr>
<tr>
<td>Gonorrhea (any site)</td>
<td>1053 (47.1)</td>
</tr>
<tr>
<td>Rectal</td>
<td>651 (21.6)</td>
</tr>
<tr>
<td>Chlamydia (any site)</td>
<td>1049 (41.9)</td>
</tr>
<tr>
<td>Rectal</td>
<td>810 (27.5)</td>
</tr>
</tbody>
</table>

- Bone and renal effects similar to previous trials: TAF/FTC had smaller impact on bone mineral density and kidney markers than TDF/FTC

ART Updates

- Injectable ART: long-acting cabotegravir and rilpivirine
- On the horizon: long-acting capsid inhibitor
- Weight gain and integrase inhibitors
Long-acting Cabotegravir and Rilpivirine

- Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, available in long-acting nanosuspension formulations; half-lives of months
- Promising phase II results (LATTE-2)
- Phase 3 studies
  - ATLAS: Suppressed people with HIV; switch to monthly IM LA CAB/RPV or continue oral ART
  - FLAIR: Treatment naïve people with HIV; suppress with oral ART; then switch to monthly IM LA CAB/RPV or continue oral ART
  - ATLAS-2M (ongoing): Suppressed people with HIV; every 4 week vs. every 8 week IM LA CAB/RPV

ATLAS: Randomized Open Label Trial in Adults with Virologic Suppression

Who was in ATLAS?
- Median age: 42 (18-82)
- 33% female
- Median (range) duration of ART: 4 (1-21)
- Baseline ART: NNRTI 50%, INSTI 33%, PI: 17%

ATLAS: Virologic Outcomes

- Adjusted Treatment Difference (RPV, CI)

Key:
- CAB: CAB; RPV: RPV; AV: Avir; LY: Lyrica; D: Dorsal; P: Penile; V: Vaginal; F: Femoral; LA: Long-acting ART
- Primary endpoint: LA adherence in CAB group vs. RPV group at Week 48
- Secondary endpoints: LA adherence in CAB group vs. RPV group at Week 48; Switch to CAB vs. Switch to RPV at Week 48;堡垒}
FLAIR: Randomized Open Label Trial in ART-naïve Adults

Who was in FLAIR?
- Median age: 34
- 22% female
- Baseline VL >100,000: 20%; baseline CD4 count <200: 7%

FLAIR: Virologic Outcomes

ATLAS/FLAIR: Treatment Emergent Resistance (CAB/RPV Groups)

ATLAS

<table>
<thead>
<tr>
<th>Site/HIV subtype</th>
<th>Baseline Resistance (HIV DNA)</th>
<th>Resistance at Virologic failure</th>
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</thead>
<tbody>
<tr>
<td>Russia/A1</td>
<td>E138A, L74V, E138K</td>
<td>None</td>
</tr>
<tr>
<td>France/AG</td>
<td>V108I, E138K</td>
<td>None</td>
</tr>
<tr>
<td>Russia/A1</td>
<td>None</td>
<td>L74I, Q148R</td>
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FLAIR

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ATLAS/FLAIR: Safety and Tolerability

- Injection site reactions (ISR) common; mostly grade 1/2
  - Rarely led to treatment discontinuation (1%)
- Serious adverse events infrequent
- High participant satisfaction with preference for injectable therapy
  - The majority (99%, 2189/2203) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days

GS-6207: New Capsid Inhibitor

- Inhibits multiple steps in HIV replication
- Picomolar antiviral potency
- Phase 1 study in healthy volunteers
  - Sustained exposure following subcutaneous injection
  - Supports dosing interval of at least 12 weeks
- Phase 1 study in people with HIV ongoing

Weight Gain and Integrase Inhibitors

- ACTG study
  - 972 adults who switched to INSTI-based ART (observational study)
  - Women, blacks and those >60 years had greatest weight gain
  - DTG associated with greatest increase in annual weight (1.0 kg per year compared with 0.5 and -0.2 for EVG and RAL, respectively)
Weight Gain and Integrase Inhibitors

- Other studies at CROI showing association between INSTIs and weight gain
  - NA-ACCORD: 24,001 participants initiating ART (observational)
    - INSTIs, PIs associated with greater increase in weight than NNRTI
    - DTG and RAL associated with greater weight gain than EVG
  - HOPS: observational switch study
    - BMI trajectory slopes: DTG > RAL or EVG
  - WIHS: observational switch study in women
- Studies showing mixed result or no association
  - TRIO study: associated in bivariate analysis, not in multivariable model
  - HPTN 077: Cabotegravir in people without HIV: no association

My Take:
Are INSTI-Based Regimens associated with weight gain?

- Accumulating data indicate INSTI-based regimens may be associated with greater weight gain than some other regimens; however, additional randomized data from initial therapy trials still needed
- Whether there are differences between INSTIs is uncertain
- Mechanism of weight gain and distribution of fat after initiation of modern regimens, including INSTI-based therapies, should be evaluated
- In patients with significant weight gain, the impact of changing to a non-INSTI based regimen needs to be studied

Coinfections and Comorbidities
ARS Question 4: Which of the following cannot be given with weekly INH and rifapentine for latent TB infection treatment?

1. Efavirenz
2. Raltegravir
3. Dolutegravir
4. Bictegravir

Treatment Options for Latent TB in people with HIV

- INH for 9 months
- Rifampin for 4 months
- Weekly INH + rifapentine for 3 months (3HP)
- Daily INH + rifapentine for 1 month (1 HP)

Drug interactions:
- Efavirenz and raltegravir OK with 3HP
- Bictegravir should not be given with rifamycins, including rifapentine
- Healthy volunteer study of 3HP with dolutegravir: stopped when 2 of 4 participants experienced adverse events

3HP in Adults on DTG: DOLPHIN Trial

- Single arm study of DTG-based ART and 3HP in adults with HIV with suppressed VL and indication for LTBI treatment
- Participants (n=60) switched to DTG 50 mg daily + TDF/FTC for 8 weeks; then weekly INH/rifapentine (900/900) for 12 weeks
3HP in Adults on DTG: Results

- Co-administration of DTG-based ART and 3HP well-tolerated
  - No adverse events leading to withdrawal
  - No HP-related Grade 3 or higher clinical or lab adverse events
- Trough DTG concentrations reduced by ~50% with 3HP
  - Median DTG level > 300 ng/mL at all time points
- Virologic suppression maintained throughout 3HP treatment in all participants

HCV Headlines

- Among 305 MSM with HIV in NYC who had HCV clearance (treatment or spontaneous), 38 (12%) had HCV reinfection
  - Median 1.9 years after clearance
- In first prospective study of HCV treatment in pregnant women, 8 of 8 had HCV cure with ledipasvir/sofosbuvir
  - Larger studies, including of pan-genotypic agents, needed
- Progress towards HCV micro-elimination ... more to be done
  - Among 594 HIV/HCV coinfected individuals at Hopkins, 64% had been cured as of March 2018

Summary

- Drop in HIV incidence appears to be slowing; need to redouble efforts to diagnose, treat and prevent HIV
- Second HIV remission after stem cell transplantation with a CCR5 Δ32/Δ32 donor ⇒ need to develop less-toxic methods to modulate CCR5 and other coreceptors, perhaps through gene therapy
- For PrEP, daily TAF/FTC non-inferior to TDF/FTC in MSM/TGW
  - TAF/FTC has not been studied in cis-gender women or with on-demand dosing
- Long-acting cabotegravir/rilpivirine comparable to oral ART
- Accumulating evidence that INSTI associated with weight gain — what should be done about it is not clear
- Be alert for HCV re-infection in MSM with HIV
Question-and-Answer

London and Berlin Patients: Comparison

**London Patient**
- Donor: CCR5 Δ32/Δ32
- Recipient: CCR5 WT/WT
- R5 virus
- Hodgkin lymphoma
- Single HSCT; no irradiation; reduced intensity conditioning; T cell depletion: anti-CD52
- Mild GVHD
- 100% T cell donor chimerism
- Duration of remission: 18 m

**Berlin Patient**
- Donor: CCR5 Δ32/Δ32
- Recipient: CCR5 Δ32/WT
- R5 virus
- AML
- 2 HSCT; total body irradiation; full intensity conditioning; T cell depletion: ATG
- Mild GVHD
- 100% T cell donor chimerism
- Duration of cure: 12 y

Dusseldorf Patient

- 49 yo M with HIV and AML (2nd complete remission)
- Feb 2013: Received HSCT from CCR5 Δ32/Δ32 donor
- June 2013: 2nd relapse of AML. Received 8 courses of 5-aza C and 4 donor lymphocyte infusions → complete remission
- Remained on ART: undetectable plasma HIV RNA
- Blood and tissue assays: most (but not all) negative for HIV
- ART stopped Nov 2018: no HIV relapse to date (3 months off ART)