Update From the 2019 Conference on Retroviruses and Opportunistic Infections

Rajesh T. Gandhi, MD
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Acknowledgements: Doug Krakower, Susan Swindells, Jordan Lake, Betsey John, John Mellors, Kelly Dooley for sharing slides; Delaney Taylor for help with preparing slides

IAS–USA

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

Slide 3 of 41

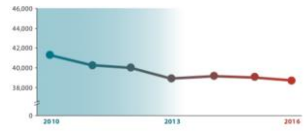
HIV Epidemiology: Can We End the Epidemic?

Slide 4 of 41

CDC FACT SHEET

HIV Incidence: Estimated Annual Infections in the U.S., 2010-2016

HIV Infections Started to Stabilize in 2013



New HIV Infections by Age Group, U.S. 2010 vs. 2016

From 2010-2016 Annual HIV Infections Increased Among Latino and African American Gay and Bisexual Men Ages 25-34

Issued Feb 2019

Slide 5 of 41

GOAL:

Our goal is ambitious and the pathway is clear – employ strategic practices in the *places* focused on the right *people* to:

75% reduction in new HIV infections in 5 years and at least **90%** reduction in 10 years.

- **Diagnose** all people with HIV as early as possible after infection.
- **Treat** the infection rapidly and effectively to achieve sustained viral suppression.
- **Protect** people at risk for HIV using potent and proven prevention interventions, including PrEP, a medication that can prevent HIV infections.
- **Respond** rapidly to detect and respond to growing HIV clusters and prevent new HIV infections.
- **HIV HealthForce** will establish local teams committed to the success of the Initiative in each jurisdiction.

Resources targeted to 48 highest burden counties; Washington, D.C.; San Juan, Puerto Rico; 7 states with substantial rural HIV burden.

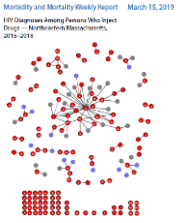
Counties targeted in NYC metro area include: Essex and Hudson counties in NJ; Bronx, Kings, New York, and Queens counties in NY

Ending the HIV Epidemic www.hiv.gov

Slide 6 of 41

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



John B et al, CROI 2019, #857
See also excellent plenary by Alexandra Oster, CROI 2019, #68

Slide 7 of 41

Cure Research

Slide 8 of 41

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

Slide 9 of 41

nature Accelerated Article Preview

LETTER

doi:10.1038/s41586-019-1027-4

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K Gupta, Sultan Abdul-jawad, Laura E McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M.J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew Innes, Luke Muir, Laura Waters, John Frater, Andrew ML Lever, SG Edwards, Ian H Gabriel & Eduardo Olavarria

Photo courtesy of Pablo Tebas, MD

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

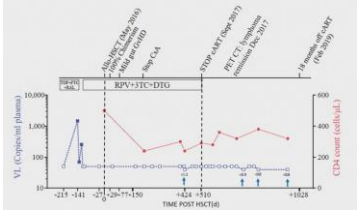
Slide 10 of 41

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)

Jensen BE et al, CROI, 2019, # 394

Opinion

This is Not A Cure for My H.I.V.

The news about a second person who may be free of the infection is a distraction from the work we need to keep focusing on.

By Gregg Gonsalves

NY Times, March 9, 2019

Why do some patients have low-level, non-suppressible viremia on ART?

Slide 14 of 41

Halvas E et al, CROI 2019, #23

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

Slide 15 of 41

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

Slide 16 of 41

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

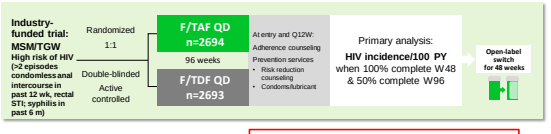
Halvas E et al, CROI 2019, #23; Also Zhang X et al, CROI 2019, #348

Slide 17 of 41

Pre-exposure prophylaxis (PrEP)

Slide 18 of 41

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



Primary efficacy endpoint:
HIV incidence

- Evaluated by rate ratio with noninferiority margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

Who was in DISCOVER?

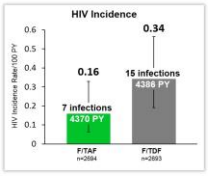
- MSM/TGW (no cis-gender women)
- Median age: 34
- 84% W, 9% B
- 24% Hispanic/Latinx
- 1-2% Transgender women
- 16-17% taking PrEP at baseline

Hare B et al. CROI 2019, #104

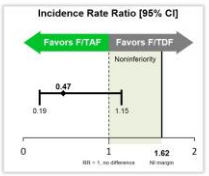
Slide 19 of 41

TAF/FTC non-inferior to TDF/FTC as Daily PrEP for MSM/TGW

22 HIV infections in 8756 PY of follow-up



F/TAF is noninferior to F/TDF



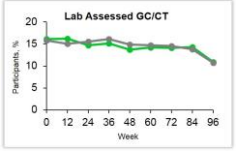
NB: 5 participants with probable acute HIV at study entry. Resistance to FTC developed in 4 participants, all with suspected acute HIV. 15 of the 22 seroconversions occurred in people with low tenofovir levels on dried blood spot

Slide 20 of 41

Hare B et al. CROI 2019, #104

DISCOVER: Other Notable Findings

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



Lab Assessed GC/CT Incidence

	n (Rate: n/100 PY)	
	F/TAF	F/TDF
Gonorrhea (any site)	1053 (47.1)	1059 (45.3)
Rectal	651 (21.6)	662 (20.5)
Chlamydia (any site)	1049 (41.9)	1071 (41.6)
Rectal	810 (27.5)	835 (28.2)
Syphilis	365 (10.3)	370 (9.5)

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

Slide 21 of 41

Hare B et al. CROI 2019, #104

ART Updates

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

Slide 22 of 41

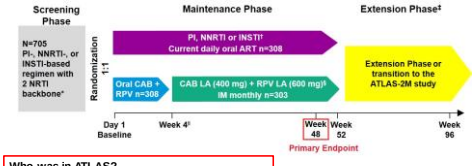
Long-acting Cabotegravir and Rilpivirine

- 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

Swindells S, et al. CROI 2019; #139
Orkin C, et al. CROI 2019; #140.

Slide 23 of 41

ATLAS: Randomized Open Label Trial in Adults with Virologic Suppression

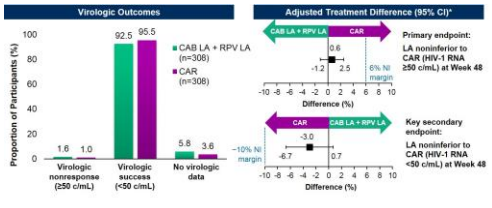


Who was in ATLAS?
- Median age: 42 (18-82)
- 33% female
- Median (range) duration of ART: 4 (1-21)
- Baseline ART: NNRTI 50%; INSTI 33%; PI: 17%

Swindells S, et al. CROI 2019; #139

Slide 24 of 41

ATLAS: Virologic Outcomes

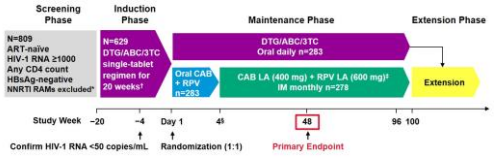


CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
*Adjusted for sex and baseline third agent class.

Swindells S, et al. CROI 2019; #139

Slide 25 of 41

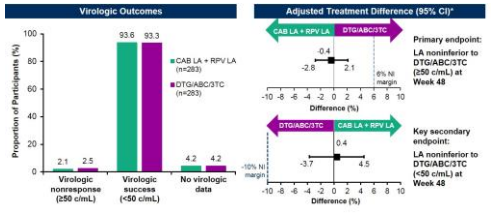
FLAIR: Randomized Open Label Trial in ART-naïve Adults



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

Orkin C, et al. CROI 2019; #140.

FLAIR: Virologic Outcomes



3TC, lamivudine; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; DTG, dolutegravir; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
*Adjusted for sex and baseline HIV-1 RNA (< vs ≥100,000 c/mL).

Orkin C, et al. CROI 2019; #140.

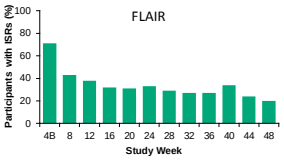
ATLAS/FLAIR: Treatment Emergent Resistance (CAB/RPV Groups)

Site/HIV subtype	Baseline Resistance (HIV DNA)		Resistance at Virologic failure	
	RT	IN	RT	IN
ATLAS				
Russia/A1	E138E/A	L74I	E138A	L74I
France/AG	V108V/I, E138K	None	V108I, E138K	None
Russia/A1	None	I74I	E138E/K	N155H, L74I
FLAIR				
Russia/A1	None	L74I	E138E/A/K/T	L74I, Q148R
Russia/A1	None	L74I	K101E	L74I, G140R
Russia/A1	None	L74I	E138K	L74I, Q148R

Swindells S, et al. CROI 2019; #139 Orkin C, et al. CROI 2019; #140.

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



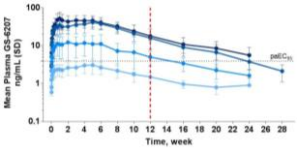
- The majority (99%, 2189/2203) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days

Slide 29 of 41

Swindells S, et al. CROI 2019; #139 Orkin C, et al. CROI 2019; #140.

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

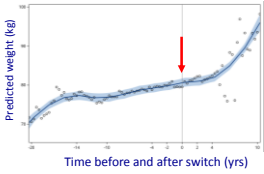


Slide 30 of 41

Sanger J et al, CROI 2019; #141

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)



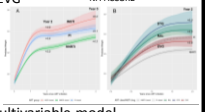
Slide 31 of 41

Lake J et al, CROI 2019, #669

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

NA-ACCORD



Slide 32 of 41

Bourgi K et al, CROI 2019, #670; Kerchberger A et al, CROI 2019, #672; Pallela F J et al, CROI 2019, #674; McComsey G et al, CROI 2019, #671; Landovitz R et al, CROI 2019, #34

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

Slide 33 of 41

Coinfections and Comorbidities

Slide 34 of 41

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

Slide 35 of 41

Treatment Options for Latent TB in people with HIV

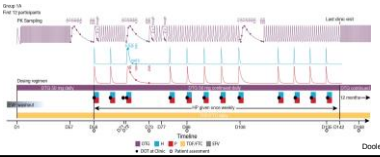
- INH for 9 months
- Rifampin for 4 months
- Weekly INH + rifapentine for 3 months (3HP)
- Daily INH + rifapentine for 1 month (1 HP)
- Drug interactions:
  - Efavirenz and raltegravir OK with 3HP
  - Bictegravir should not be given with rifamycins, including rifapentine
  - Healthy volunteer study of 3HP with dolutegravir: stopped when 2 of 4 participants experienced adverse events

Brooks KM *et al* CID 2018
Swindells S *et al* NEJM 2019

Slide 36 of 41

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



Dooley K et al, CROI 2019, # 80

Slide 37 of 41

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

Dooley K et al, CROI 2019, # 80

Slide 38 of 41

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 pangenotypic 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

Slide 39 of 41

Fierer D et al, CROI 2019, # 86; Chappell CA et al, CROI 2019, #87; Falade-Nwulia O et al, CROI 2019, #574

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

Slide 40 of 41

Question-and-Answer

Slide 41 of 41

IAS–USA

London and Berlin Patients: Comparison

London Patient	Berlin Patient
• Donor: CCR5 Δ32/Δ32	• Donor: CCR5 Δ32/Δ32
• Recipient: CCR5 WT/WT	• Recipient: CCR5 Δ32/WT
• R5 virus	• R5 virus
• Hodgkin lymphoma	• AML
• Single HSCT; no irradiation; reduced intensity conditioning; T cell depletion: anti-CD52	• 2 HSCT; total body irradiation; full intensity conditioning; T cell depletion: ATG
• Mild GVHD	• Mild GVHD
• 100% T cell donor chimerism	• 100% T cell donor chimerism
• Duration of remission: 18 m	• Duration of cure: 12 y

Slide 42 of 41

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)

Jensen BE et al, CROI, 2019, # 394

Slide 43 of 41