Update From the 2019 Conference on Retroviruses and Opportunistic Infections

Constance A. Benson, MD
Professor of Medicine and Global Public Health
University of California San Diego
La Jolla, California

IAS–USA

Learning Objectives

After attending this presentation, learners will be able to:

- Describe new research data related to HIV cure
- Describe the implications of new research related to non-communicable end-organ diseases in people with HIV
- Describe new findings related to the effects of antiretroviral drugs used during pregnancy
- Interpret new research data on HIV-associated opportunistic infections and tuberculosis

Slide 3 of 45

Slide #4

HIV Cure and the Plan to End the HIV Epidemic

Slide 4 of 45

Slide #5

The London Patient

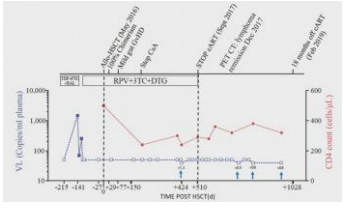
- HIV-1 diagnosed in 2003; preserved CD4+ cell count and low viral load so no ART initiated
- Diagnosed with Stage IVb Hodgkin lymphoma in 2013; started initially on efavirenz/TDF/FTC with viral suppression but switched to raltegravir/TDF/FTC when chemotherapy with ABVD was started
- Failed multiple cycles of chemotherapy and mobilization of stem cells for auto SCT so was referred for allogeneic HSCT with a donor who was homozygous for CCR5-Δ32 mutation
- Underwent LACE conditioning (lomustine, cyclophosphamide, cytarabine, etoposide) and then stem cell infusion in May, 2016
  - Complicated by sepsis, dental abscess, GVHD colitis, CMV and EBV reactivation

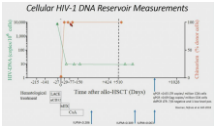
Gupta R, et al. CROI 2019; Abstr. 29LB

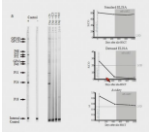
Slide #6

The London Patient

Events and Time Course Pre- and Post-Transplant







Gupta R, et al. CROI 2019; Abstr. 29LB

Slide #7

Comparison of Two HIV Cures

The London Patient	Timothy Brown
• Homozygous for wild type CCR5	• Heterozygous for CCR5-Δ32 mutation
• **Infection with CCR5 using virus**	• **Infection with CCR5 using virus**
• Hodgkin Lymphoma	• Acute Myelogenous Leukemia
• Single **HSCT**	• Two **HSCTs**
• No irradiation	• Total body irradiation
• Reduced intensity conditioning	• Full intensity conditioning
• **T cell depletion with** aCD52	• **T cell depletion with** ATG
• **Mild GVHD**	• **Mild GVHD**
• **100% T cell donor chimerism**	• **100% T cell donor chimerism**

Gupta R, et al. CROI 2019; Abstr. 29LB

Slide #8

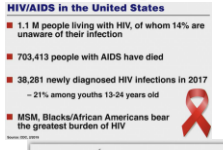
Other "Cure" Studies

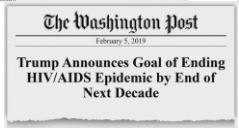
- Gene editing
  - Adenovirus vector-CRISPR/Cas9 system used to excise SIV DNA in gene editing treatment in non-human primates → No viral outgrowth from PBMCs after confirmed viral excision in tissues (Burdo T, et al. CROI 2019; Abstr. 24)
  - Adenovirus vector-CCR5 zinc finger nuclease gene editing following single dose cytoxan pre-Rx → significant delay in viral rebound during ATI and maintenance of low level viremia (Tebas P, et al. CROI 2019; Abstr. 25)
- Latency reversal
  - No increase in viremia by any measure after romidepsin (iHDAC inhibitor) infusion despite evidence of reservoir activation (McMahon D, et al. CROI 2019; Abstr. 26)
  - Pembrolizumab (anti-PD-1 Ab checkpoint inhibitor) → transient increase in HIV transcription in CD4+ T cells; early decrease in HIV DNA (Uldrick T, et al. CROI 2019; Abstr. 27)
- Trispecific BnAb displayed potent antiviral activity in SHIV-infected animals (Pegu A, et al. CROI 2019; Abstr. 28)

Slide 8 of 45

Slide #9

Ending the HIV Epidemic by 2030




The Washington Post
February 5, 2019
Trump Announces Goal of Ending HIV/AIDS Epidemic by End of Next Decade

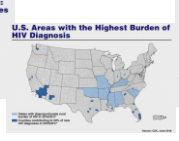

The Washington Post
January 10, 2016
OPINIONS
No More Excuses. We Have the Tools to End the HIV/AIDS Pandemic.
Anthony S. Fauci

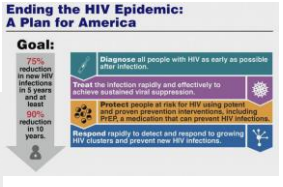
Fauci A, CROI 2019

Slide 9 of 45

Slide #10

Plan for Ending the HIV Epidemic in the US by 2030





Fauci A, CROI 2019

Slide 10 of 45

Slide #11

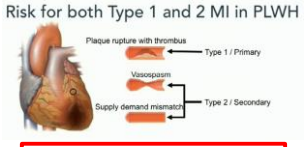
HIV-Associated End Organ Disease and Metabolic Complications

Slide 11 of 45

Slide #12

COPD and Risk for Myocardial Infarction in PLWH

- Previous studies in HIV-uninfected pts:
  - Association between COPD and increases in subclinical markers of CVD and incident MI
- In PLWH, more severe emphysema by chest CT was associated with higher coronary artery calcification scores (after adjusting for Framingham risk and other factors)



Type 2 MI is associated with:
- Sepsis, bacteremia, recent cocaine use
- More likely in younger ages in PLWH
- Lower CD4 cell counts, lipid levels, Framingham risk scores associated with Type 2

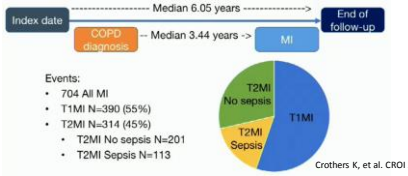
Crothers K, et al. CROI 2019; Abstr. 31; Crane et al. JAMA Cardiology 2017

Slide 12 of 45

Slide #13

COPD and Risk for Myocardial Infarction in PLWH

- 22,596 PLWH from 5 CNICS sites (UW, UAB, UNC, JH, UCSD)
  - COPD defined by EHR algorithms
  - Validated by spirometry in a subset
  - Also required the presence of + ≥ 90d continuous short and/or long-acting COPD meds and ICD codes related to COPD



Events:
- 704 All MI
- T1MI N=390 (55%)
- T2MI N=314 (45%)
  - T2MI No sepsis N=201
  - T2MI Sepsis N=113

Crothers K, et al. CROI 2019; Abstr. 31

Slide 13 of 45

Slide #14

COPD and Risk for Myocardial Infarction in PLWH

- COPD was associated with a ~2-2.5 fold increased risk for both Type 1, Type 2 MI independent of smoking in PLWH
  - Multiple mechanisms proposed – COPD severity, inadequate disease control, recurrent pneumonia; different factors for Type 1, Type 2

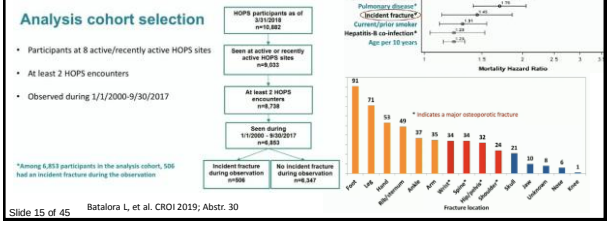
	Hazard ratio (95%CI)			
	Unadjusted	Adjusted[a]	Adjusted with smoking[b]	Adjusted with pack-years[c]
All MI	3.03 (2.45-3.76)	2.40 (1.93-2.98)	2.23 (1.78-2.78)	2.08 (1.61-2.70)
Type 1 MI	2.46 (1.80-3.36)	1.91 (1.40-2.62)	1.76 (1.28-2.42)	1.73 (1.21-2.48)
Type 2 MI	3.80 (2.82-5.11)	3.15 (2.32-4.27)	2.96 (2.17-4.04)	2.65 (1.82-3.86)
Type 2 MI due to sepsis/bacteremia	3.64 (2.20-6.04)	2.87 (1.71-4.83)	2.75 (1.62-4.66)	2.43 (1.25-4.73)
Type 2 MI due to other causes	3.34 (2.27-4.93)	2.82 (1.90-4.20)	2.61 (1.74-3.91)	2.77(1.75-4.38)

Slide 14 of 45

Slide #15

"Breaking Bones is Bad"

- HOPS Observational Cohort Study from 2000-2017



Slide 15 of 45

Batalora L, et al. CROI 2019; Abstr. 30

Slide #16

"Breaking Bones is Bad"

- Incident fracture was independently associated with a 45% increased risk of all-cause mortality.
- Independent predictors of all-cause mortality were chronic renal disease, HCV co-infection, non-AIDS cancer, and underlying chronic pulmonary disease.

Characteristics at/after incident fracture (n=506)		
Age in years at fracture date, median (IQR)		48 (41-56)
CD4+ cell count (cells/mm³) closest to fracture date, median (IQR)		486 (291-686)
Viral load (cells/mL) closest to fracture date, median (IQR)*		25 (13-332)
Characteristics at/closest to death (n=75)		
Age in years, median (IQR)		53 (47-60)
CD4+ cell count (cells/mm³), median (IQR)		267 (111-440)
Viral load (cells/mL), median (IQR)*		25 (10-17,158)
Deaths and mortality rates	**Deaths**	**Mortality rate**
Major osteoporotic fractures†	22 (29.3)	1.65/100 PY
Fractures at other sites	53 (70.7)	1.24/100 PY

Slide 16 of 45

Batalora L, et al. CROI 2019; Abstr. 30

Slide #17

HPV Vaccine Plus LEEP for Recurrent Cervical HSIL in Women with HIV Infection

- Randomized, double-blind placebo controlled trial in 180 women with HIV and cervical HSIL
- HPV vaccine (VLP types 6, 11, 16, 18) or saline placebo at entry, week 4 and week 26
- All women had LEEP at week 4 followed by colposcopic biopsy, cervical cytology at week 16, 52
- 97% completed vaccine and had biopsy result at week 26 or 52
  - 53% had LEEP margins (+) for HSIL

Week 4 LEEP	No (%)
No evidence or SIL or malignancy	1 (0%)
CIN 1 (LSIL)	49 (27%)
CIN 2	53 (30%)
CIN 3	75 (42%)
inadequate	1 (0%)

Endpoint	qHPV (n=87)	Placebo (n=87)	RR, 95% CI
Primary endpoint Cytologic or histologic HSIL	46 (52.9%)	39 (44.8%)	1.2 (.87-1.6), P=.29
Histologic HSIL CIN 2 or CIN 3	28 (32%)	27 (31%)	1.04 (.67-1.6), P=.8
CIN 3	9 (10%)	11 (13%)	.82 (.36-1.9), P=.64

Firnhaber C, et al. CROi 2019; Abstr. 14

Slide #18

Integrase Inhibitors and Safety in Pregnancy

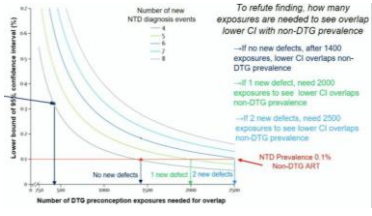
- Interim analysis of birth defect surveillance study in Botswana raised concerns about possible increased risk of neural tube defects (NTDs) with DTG at conception
- Prospective analyses of pregnancy outcomes since initial report of neural tube defect with DTG → no other NTD reports with INSTI use during pregnancy
  - Antiretroviral Pregnancy Registry (Europe and US) → no NTDs after INSTI use in pregnancy
  - NTD risk not zero (0.1%) regardless of ART use or HIV; linked to poor dietary folate

Pre-term delivery higher with pre-conception ART in HIV compared to non-HIV

Mofenson L, et al. CROI 2019

Slide #19

Integrase Inhibitors and Safety in Pregnancy



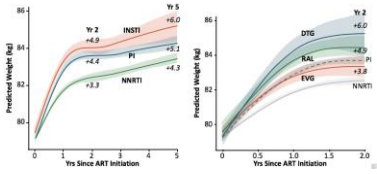
- Best data will likely come from the Botswana Tsepamo study in mid-2019 (following > 1400 pregnant women) combined with APR
- The risk of NTD, if confirmed, is still relatively small
  - 1 in 1000 in the general population
  - 7 in 1000 in DTG exposure pre-conception

Mofenson L, et al. CROI 2019

Slide #20

NA-ACCORD: Weight Gain Among 24,001 ART-Naïve Patients Initiating ART

- Multivariate analysis of weight gain following ART initiation between January 2007 – December 2016 (Bourgi K, et al. CROI 2019; Abstr. 670)
  - INSTI-based: N=4740; PI-based: N=7436; NNRTI-based N=11,825
- Greater weight gain with DTG vs. RAL vs. EVG; did not vary by sex or race



Slide 20 of 45

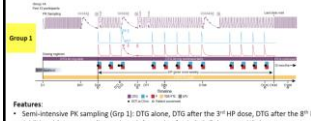
Slide #21

Opportunistic Infections

Slide 21 of 45

Slide #22

Safety and PK of Weekly Rifapentine/Isoniazid (3HP) in Adults with HIV Receiving Dolutegravir



Features:
- Semi-intensive PK sampling (Grp 1): DTG alone, DTG after the 3rd HP dose, DTG after the 8th HP dose
- Additional Sparse sampling, to have information for 1, 2, 6, 7 days post-HP dose
- Safety laboratories: Baseline, Weeks 9, 11, 13, 16, 20, 24
- C-reactive protein at Baseline and Weeks 9 and 11
- HIV-1 viral load at Baseline (DTG alone), Week 11 (DTG+HP), Week 24 (4 weeks post-HP)
- 3 interim analyses (for safety, PK and dosing)
- Group 2 (n=30) with sparse PK sampling (DTG+HP), safety labs, HIV testing

Group 1: Intensive PK on DTG alone; after HP dose 3, 8
Group 2: Sparse PK sampling after DTG + HP

N=61; 60 pts completed all 12 doses
- One pregnancy at week 24

CRP WNL at all time points

VL < 40 copies/ml at BL, wk 9 during DTG + 3HP in all pts
- 1 pt with VL 2,300 copies/ml wk 24 → resuppressed after adherence counseling

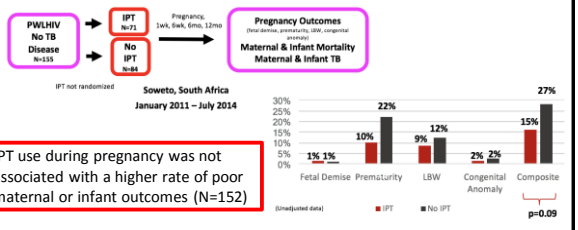
- 3 pts had grade 2 or 3 AE
  - 1 pt with flu-like illness

Dooley K, et al., CROI 2019; Abstr. 80LB

Slide 22 of 45

Slide #23

TSHEPISO Cohort: Women with HIV, No TB Disease, IPT Exposed and Unexposed During Pregnancy



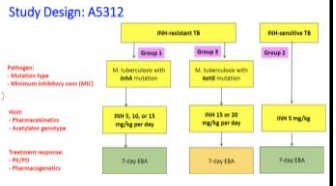
IPT use during pregnancy was not associated with a higher rate of poor maternal or infant outcomes (N=152)

TSHEPISO Cohort; CROI 2019; Abstr. 77

Slide #24

Early Bactericidal Activity (EBA) of High-Dose INH in MDR-TB

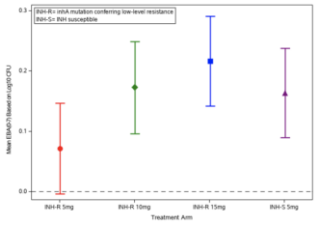
- High dose INH is a component of short course therapy of MDR-TB
- 2 key INH resistance mutations
  - *katG* → high-level resistance
  - *inhA* → low-level resistance
- A5312 evaluated EBA (as measured by serial sputum culture colony counts [cfu] and time to positivity [TTP] in liquid culture) of different doses of INH in pts with MDR-TB



Dooley KA, et al. CROI 2019; Abstr. 82

Slide #25

Early Bactericidal Activity (EBA) of High-Dose INH in MDR-TB

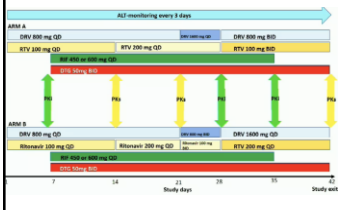


- 58/59 randomized pts (98%) completed treatment
- 9 pts had grade 3 AEs unrelated to INH
- There were no grade 4 SAEs or deaths
- Conclusion: High dose (up to 15 mg/kg/d) INH can safely be used in MDR-TB treatment

Dooley KA, et al. CROI 2019; Abstr. 82

Slide #26

Double Dose Darunavir/Ritonavir + Rifampin for TB Treatment



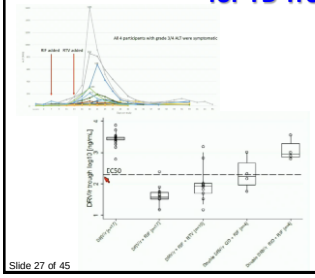
- Rationale
  - Rifabutin expensive and not widely available
  - LPV/RTV double dose + rifampin effective but not well tolerated
  - Darunavir/RTV better tolerated than LPV/RTV
- Dosing arms:
  - DRV/RTV 800 mg/100 mg BID
  - 1600 mg/200 mg once daily
  - Each included DTG 50 mg BID + rifampin 450mg or 600 mg

Maartens G, et al. CROI 2019; Abstr. 81

Slide 26 of 45

Slide #27

Double Dose Darunavir/Ritonavir + Rifampin for TB Treatment



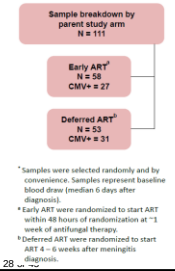
- Double dose DRV/RTV + rifampin has unacceptable hepatotoxicity risk in PLWH without TB
- Rifampin co-administration markedly reduced DRV concentrations
- Twice daily, but not once daily DRV/RTV may achieve adequate DRV trough concentrations

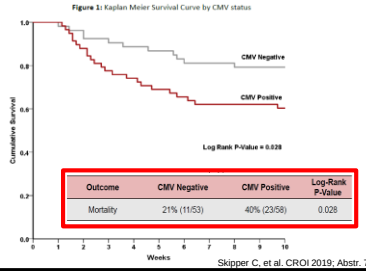
Maartens G, et al. CROI 2019; Abstr. 81

Slide 27 of 45

Slide #28

CMV Viremia and Mortality in Patients with Cryptococcal Meningitis





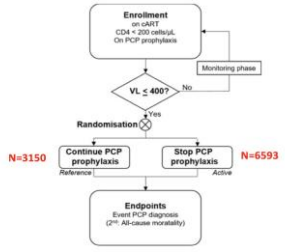
Outcome	CMV Negative	CMV Positive	Log-Rank P-Value
Mortality	21% (11/53)	40% (23/58)	0.028

Skipper C, et al. CROI 2019; Abstr. 709

Slide 28 of 45

Slide #29

Primary PJP Prophylaxis in Virally Suppressed PLWH



- COHERE Cohort of 9,743 pts with 18,550 person/yrs of followup eligible for 3 simulated trials:
  - Trial A = Continuation of PJP prophylaxis vs. stopping
  - Trial B = Starting PJP prophylaxis vs. no prophylaxis
  - Trial C = On PJP prophylaxis vs. off PJP prophylaxis

Atkinson A, et al. CROI 2019; Abstr. 712

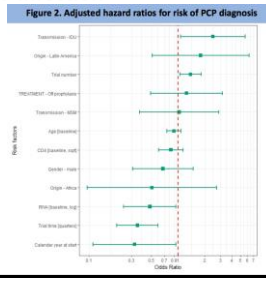
Slide 29 of 45

Slide #30

Primary PJP Prophylaxis in Virally Suppressed Persons with HIV Infection

- Overall low incidence of PJP
  - 0.15/100 py on and 0.28/100 py off prophylaxis
- HR estimates for occurrence of PJP for:
  - Trial A = HR 2.0 (0.61, 6.4); P = 0.3
  - Trial B = HR 2.8 (0.8, 9.9); P = 0.1
  - Trial C = HR 1.2 (0.5, 3.2); P = 0.8
- Conclusion: In virally suppressed pts, irrespective of CD4 cell count, the risk of PJP is low and similar for pts on and off prophylaxis

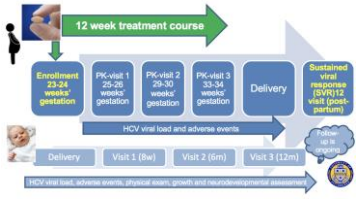
Figure 2. Adjusted hazard ratios for risk of PCP diagnosis



Slide 30 of 45

Slide #31

Sofosbuvir/Ledipasvir HCV Treatment in HCV/HIV-Coinfected Pregnant Women



- 170 HCV+ pregnant women
- 29 pts screened to enroll 9 pts who completed study medication and delivered 9 infants
  - 100% SVR in 8 pts, 1 still in followup
  - 5 infants completed 12 months F/U; 4 still ongoing

Chappell CA, et al. CROI 2019; Abstr. 87

Slide 31 of 45

Slide #32

Pregnancy and Delivery Outcomes Following Maternal HCV Treatment

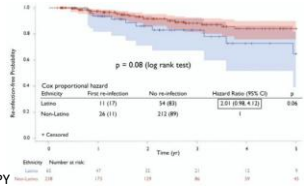
Outcome	N (%) or Median (IQR)
Maternal Related Adverse Events	5 (56%)
Maternal Related Adverse Events Grade >2	**0 (0%)**
Vaginal Delivery	5 (56%)
Gestational age at delivery (weeks + days)	**39+2 (36+6, 41+0)**
Birth weight (g)	3,290 (2,600, 4,160)
Infant Length of Hospital Stay (days)	3 (2, 12)
Infant Related Adverse Events	**0 (0%)**
Infant HCV RNA at Last Visit (copies/mL)	**0 (0, 0)**

Chappell CA, et al. CROI 2019; Abstr. 87

Slide #33

HCV Reinfection Among MSM with HIV Infection in NY

- NY Acute Hepatitis C Surveillance Network longitudinal study
  - HCV clearance by either SVR 12 after treatment or spontaneous clearance with undetectable VL for ≥ 12 weeks post infection
  - Acute reinfection → 1st noted ALT elevation or HCV viremia
- 304 cleared HCV
  - 33 reinfected and cleared → incidence rate 4.4/100 PY (primary rate 1.4/100 PY
  - 6 second reinfections → incidence rate 8.7/100 PYs



Fierer DA, et al. CROI 2019; Abstr. 86

Question-and-Answer