Prevention at CROI 2022

Kevin L. Ard, MD, MPH

I have no financial conflicts of interest.

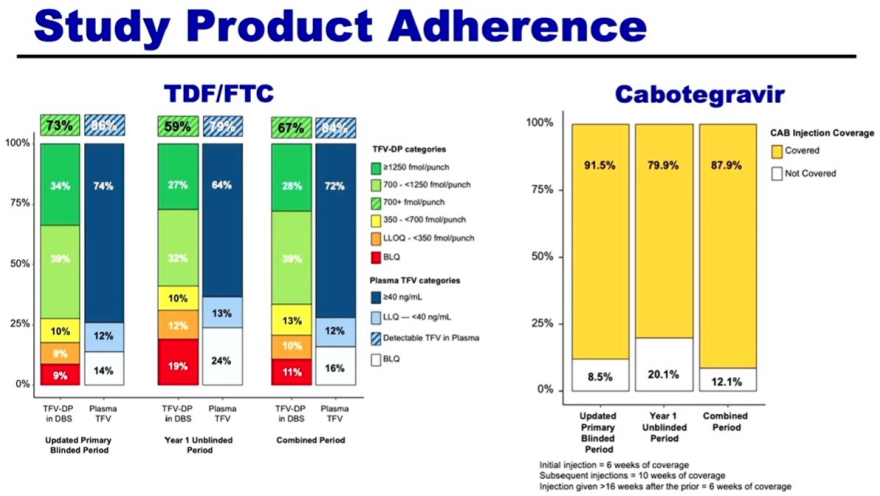
Agenda

1. New data about currently-available PrEP
2. New PrEP methods
3. Posters

Currently-available PrEP

Updates from HPTN 083 (CAB-LA vs. TDF/FTC for PrEP)

- Updated efficacy analysis from the first unblinded year
- HR 0.33 for HIV in CAB-LA versus TDF/FTC, consistent with the primary blinded results
- However, HIV incidence rose in both CAB-LA and TDF/FTC arms with declines in adherence in both arms



Landovitz R, Abstract 96

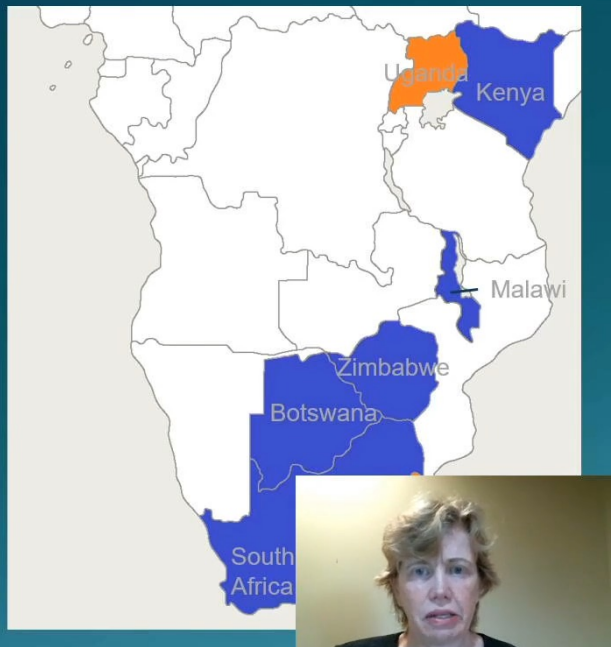
HIV RNA assays for those receiving CAB-LA for PrEP

- Low viral load INSTI genotypes for people who acquired HIV despite CAB-LA
- Among 7 cases, RNA assays would have detected HIV before a major INSTI mutation was detected in 4 cases and before additional major INSTI mutations in 2 cases
- Authors' recommendation: CAB-LA is still a good option for PrEP even when resources do not permit RNA assays

Eshleman S, Abstract 95

Counterfactual efficacy of CAB-LA versus placebo among women

Counterfactual study	CAB-LA Incidence	Counterfactual Placebo Incidence	Efficacy of CAB-LA versus Placebo (95% CI)
Five Country (AMP Women)	0.19	2.62	**93% (76%-98%)**
Three Country (ECHO)	0.23	4.47	**95% (79%-99%)**
South Africa (HVTN 702 Vaccine)	0.28	4.21	**93% (73%-98%)**



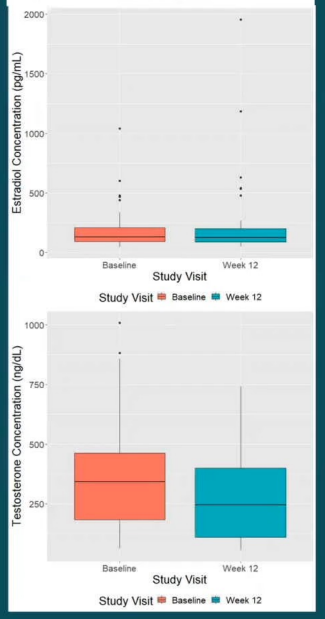
Donnell D, Abstract 86

No bidirectional effects of TDF/FTC and hormone therapy among transgender people

Results: Hormone Concentrations

- N=114; mean age 32.7y (SD 9.6); 14% Black, 44% White, 31% Latinx
- 49 TGW on stable estrogen, estradiol concentrations did not change significantly between Weeks 0 and 12 in those taking PrEP (185.2 vs 221.8 pg/mL, p=0.53).
  - Cohen's d: -0.09116937 (very small)
- 39 TGM on stable testosterone, testosterone concentrations were lower between Weeks 0 and 12 in individuals taking PrEP (373.2 vs 274.3 ng/dL, p=0.052).
  - Cohen's d: 0.4639996 (small)

Figure 2: Box plots of h
concentrations before a
TDF/FTC PrEP dosing.

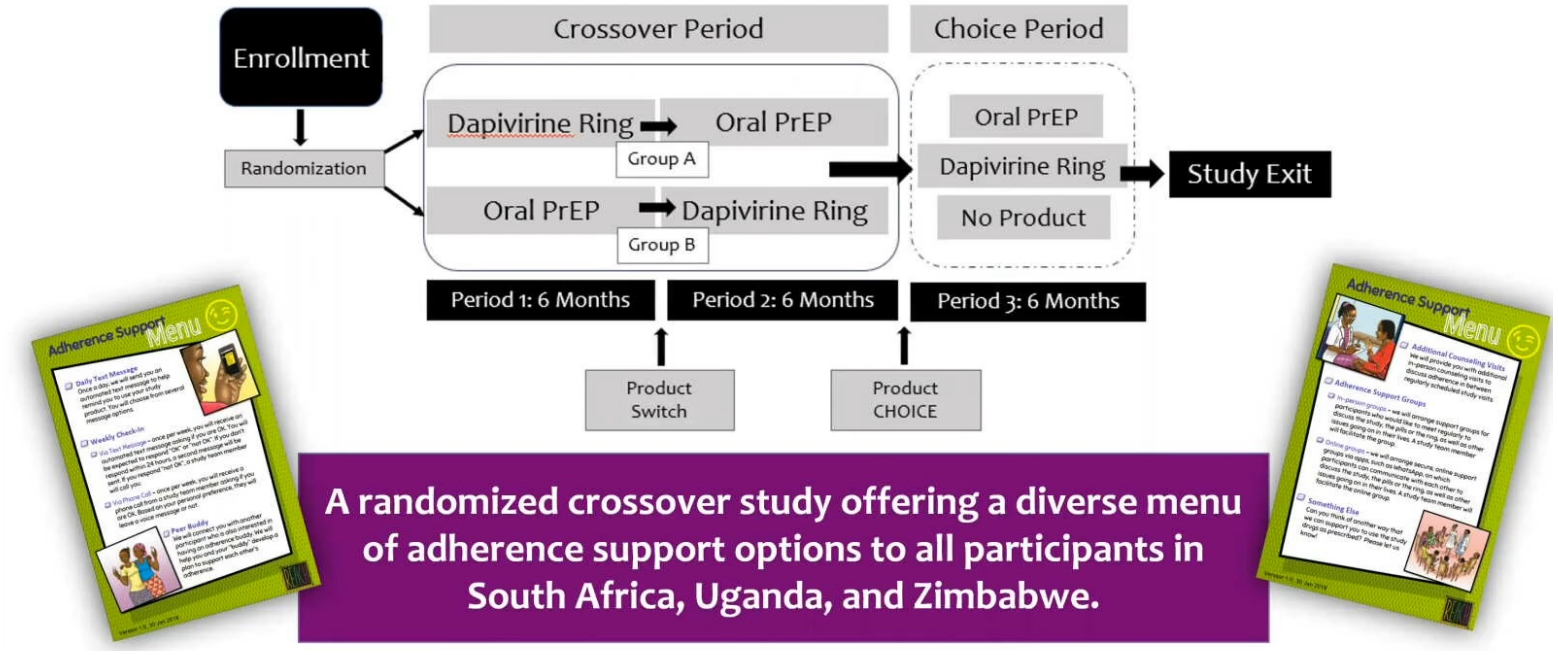


No significant changes in TFV-DP in DBS between weeks 0 and 12

No changes in body image or satisfaction with hormone therapy

Blumenthal J

REACH Study Design

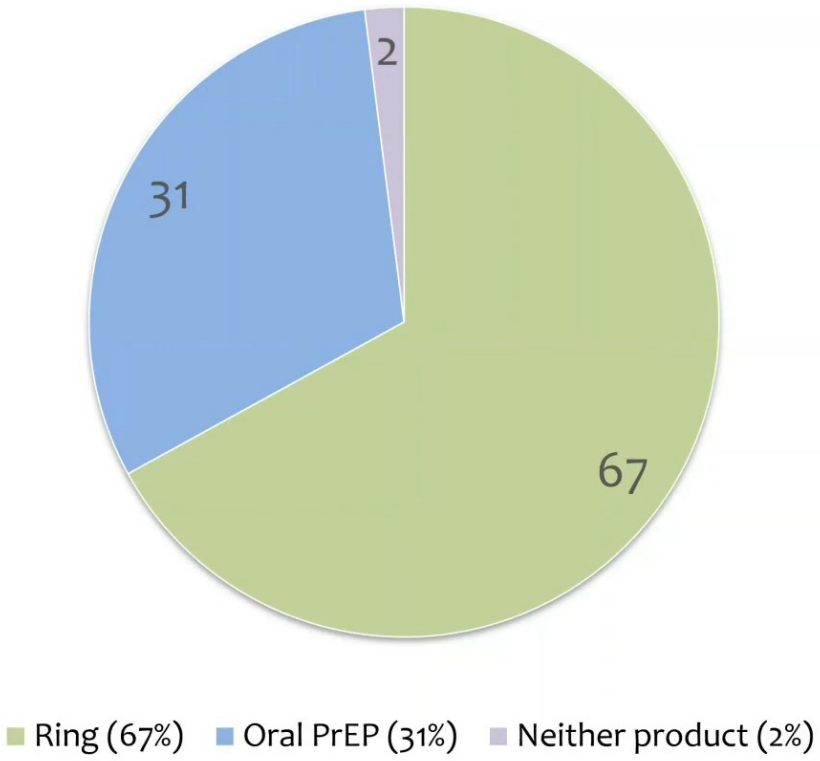


Ngure K

Product Choice in Period 3

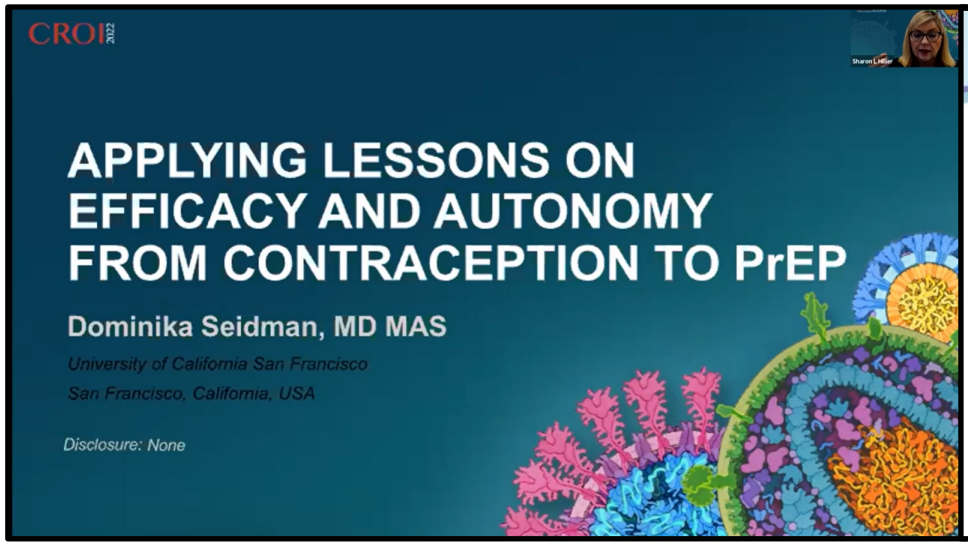
Of 227 (92%) participants who reached the choice period, more than 2/3 (152) chose the ring

Randomization sequence in the crossover period was not associated with product choice



Higher adherence to oral PrEP predicted choice of oral PrEP; the same relationship was not seen for the ring

Theme: The importance of choice

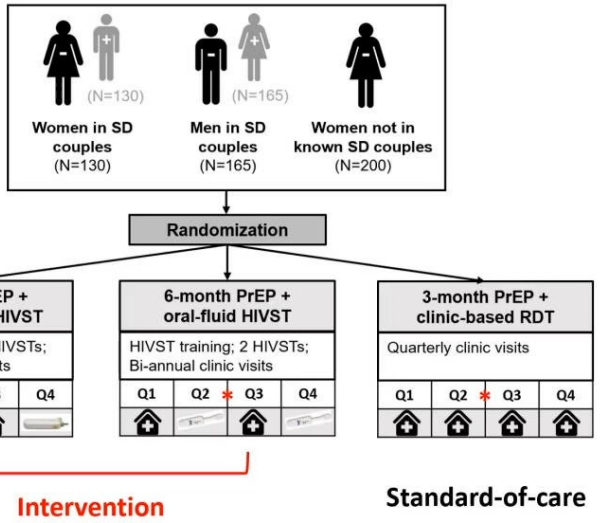


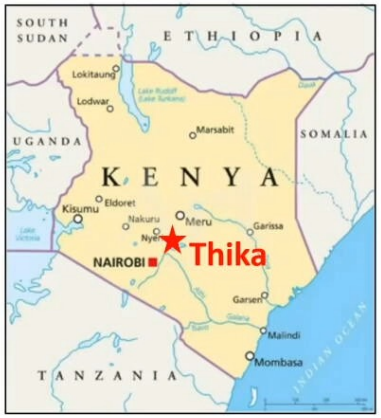
RCT of providing 6 months of PrEP with HIV self tests

Study design & setting

1:1:1 non-inferiority individual-level randomized trial:

Inclusion criteria:
- ≥18 years
- Using PrEP 1 month

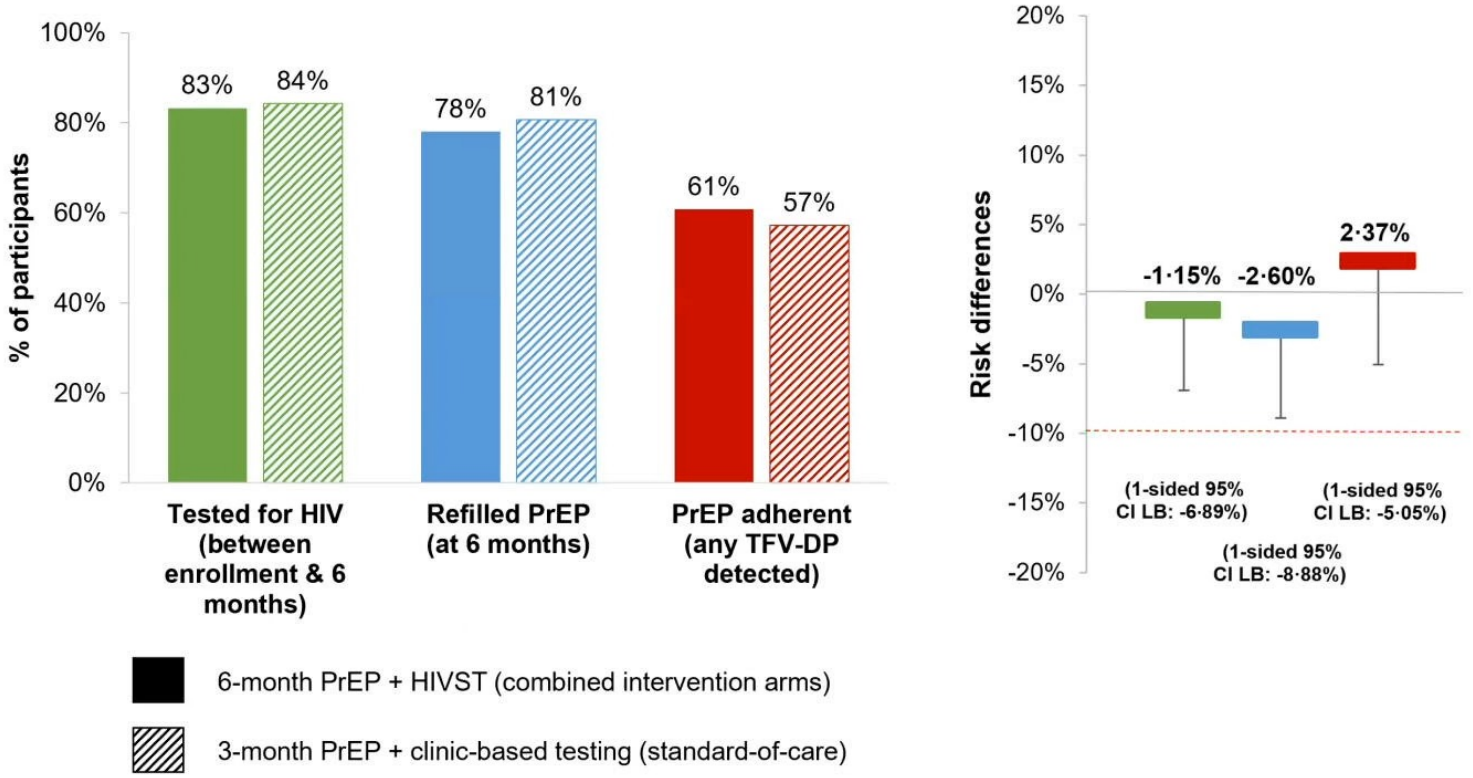




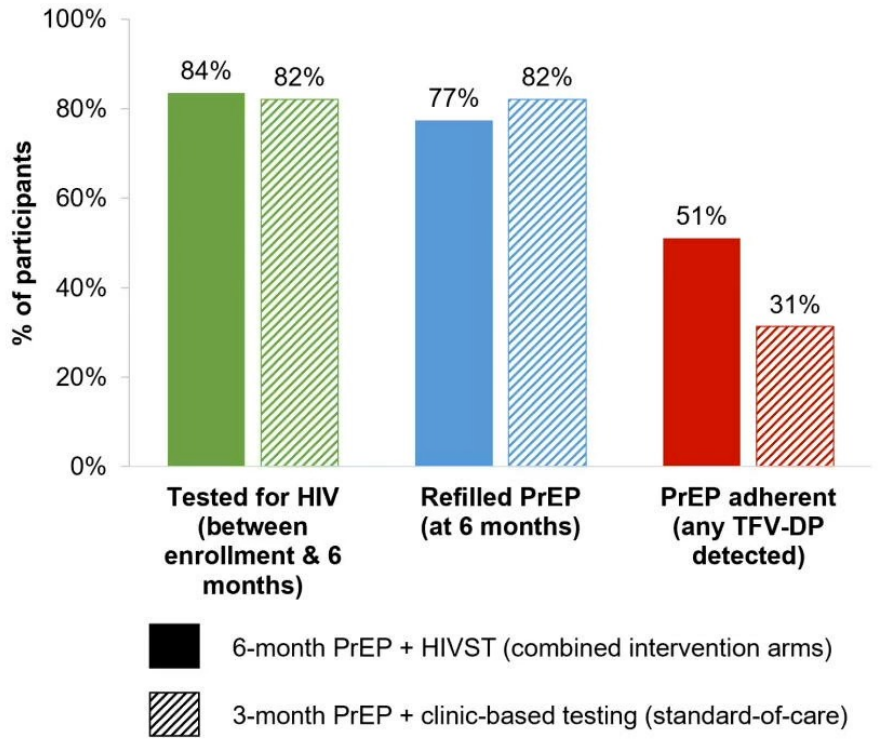
(Ortblad et al, Trials 2019)

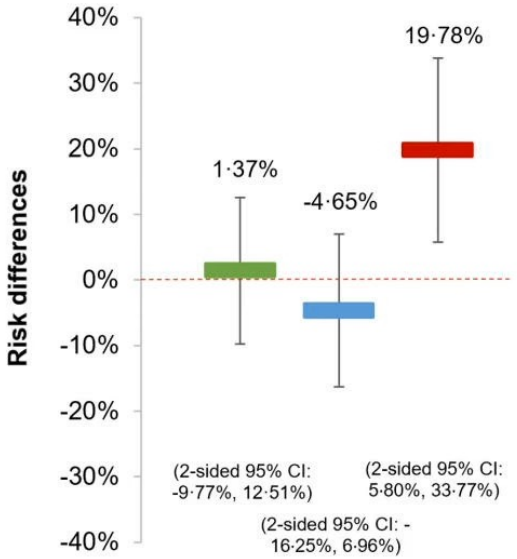
Ngure K

Results: all participants, N=495 (primary)



Results: women not in known serodifferent couples, N=200





Traditional male circumcision does not prevent HIV in sub-Saharan Africa.

Male circumcision status and HIV incidence during HPTN 071 follow-up

Circumcision status	Incidence HIV infections (rate per 100 person-yr)	Adjusted hazard ratios[1] (95% CI)	P value
Medical	11/3458 (0·31)	0·30 (0·16, 0·55)	<0·0001
Traditional	39/4166 (0·94)	0·84 (0·54, 1·31)	0·45
Uncircumcised	92/9402 (0·97)	Ref.	Ref.

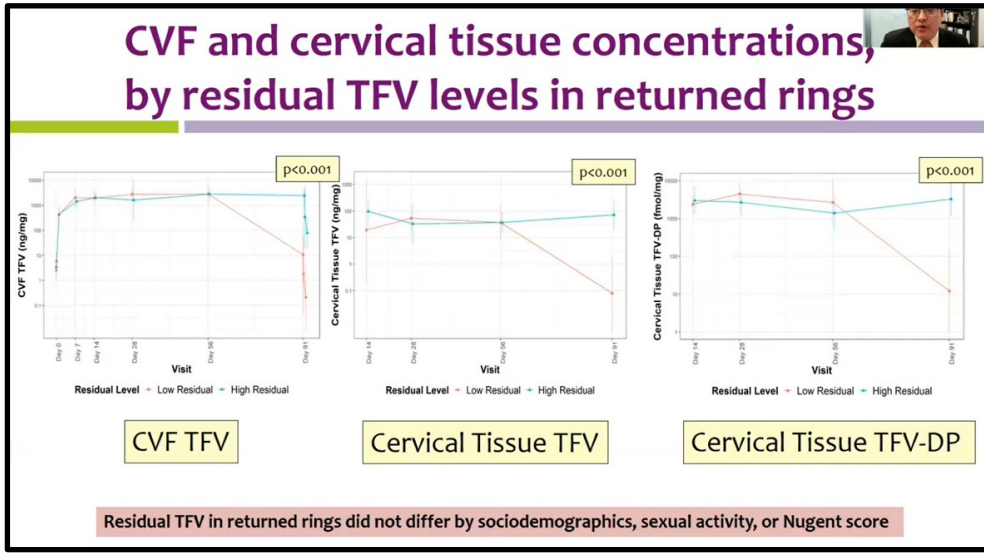
[1]Adjusted for community and age.

Belay Zewdie K, Abstract 87

New PrEP methods

A 90-day tenofovir ring may not last 90 days.

- Safety, PK, and acceptability study
- Participants randomized to tenofovir ring versus placebo
- No increased risk of adverse events
- Ring highly acceptable, and most participants indicated they would use it if available/effective
- 13 of 32 returned rings had low/no TFV

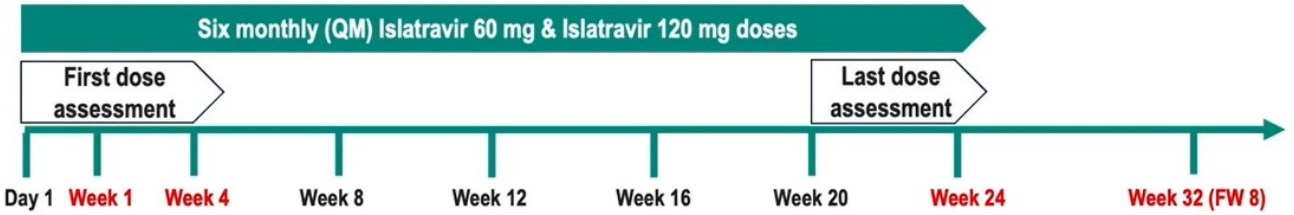


Liu A, Abstract 82

Islatravir has excellent distribution to tissues that may be of importance for PrEP.

Tissue PK Study Design

Sub-study of a Phase 2a, double-blind, randomized, placebo-controlled trial in adults at low risk for HIV-1 (NCT04003103)

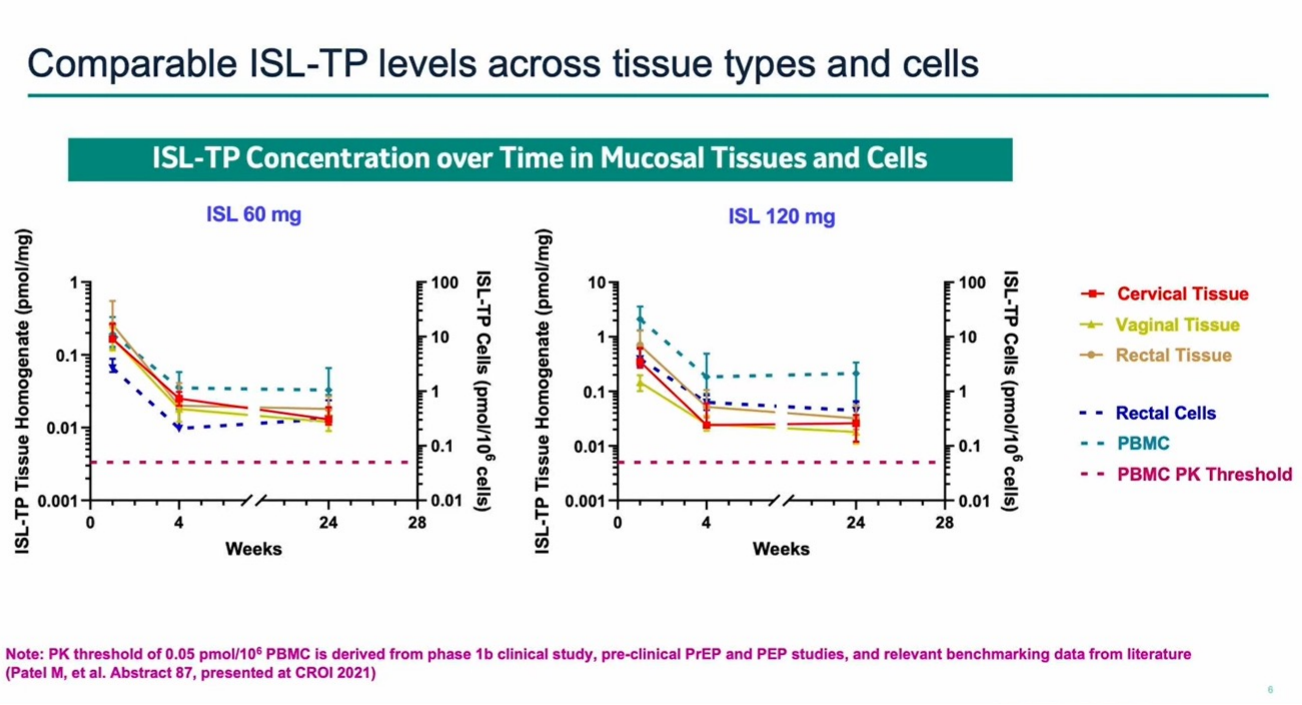


	Day 1	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32 (FW 8)
Study drug	X		X	X	X	X	X		
Rectal tissue*		X	X					X	X
Cervical tissue		X	X					X	X
Vaginal tissue		X	X					X	X
Plasma/PBMC		X	X					X	X

* Total cells isolation from rectal tissue was also performed in some participants.

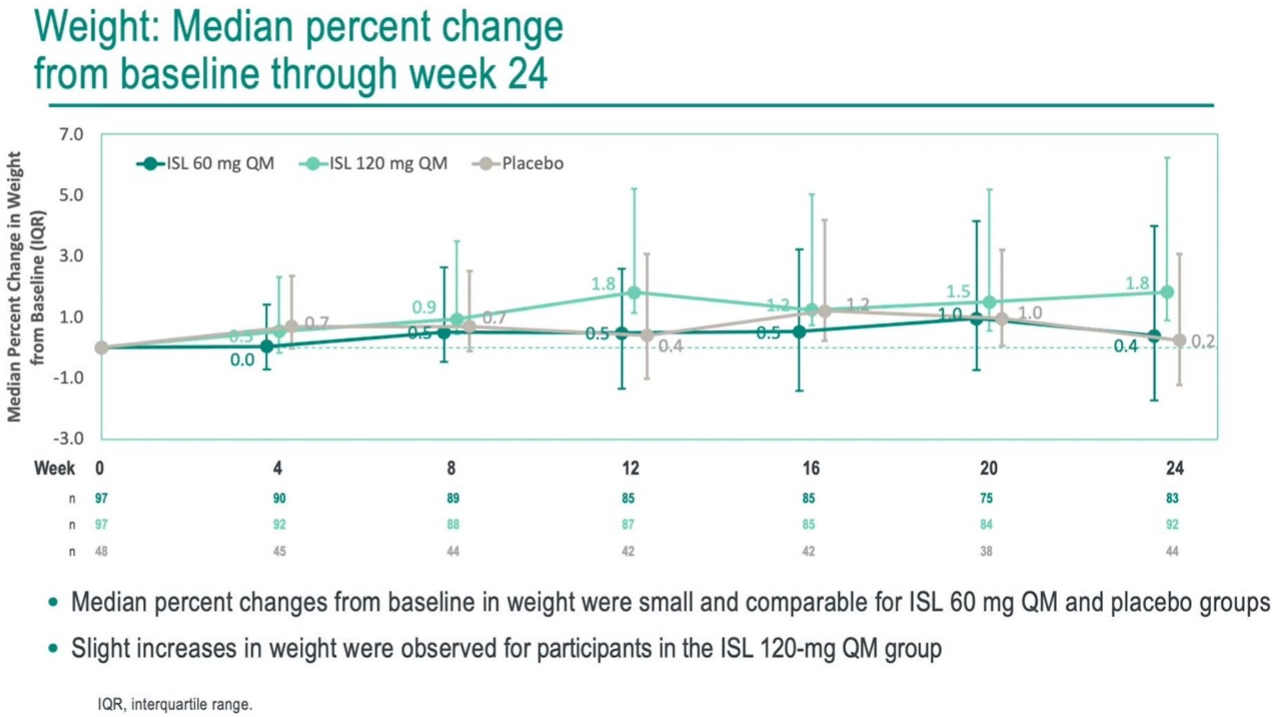
Hendrix CW, Abstract 83

Islatravir has excellent distribution to tissues that may be of importance to PrEP.



Hendrix CW, Abstract 83

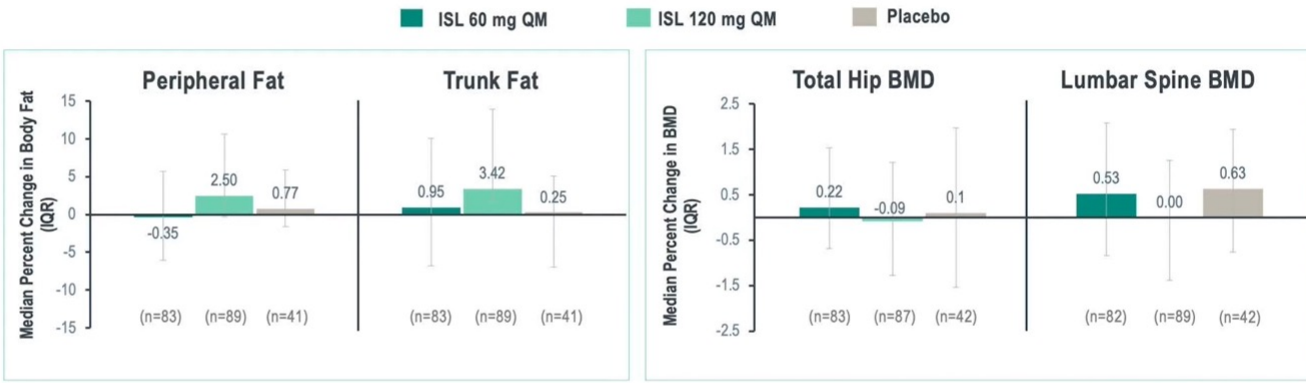
Islatravir at 60 mg does not promote weight gain over 24 weeks.



Macdonald P, Abstract 85

Islatravir does not decrease bone mineral density.

DEXA parameters: Median percent change from baseline at week 24



- Changes from baseline in peripheral and trunk fat were small and comparable for ISL 60-mg QM and placebo groups
- Slight increases in peripheral and trunk fat were observed for participants in the ISL 120-mg QM group
- Median percent changes from baseline in total hip and lumbar spine BMD were small and comparable across all groups

n, number of participants at week 24; peripheral and trunk fat measured in grams; BMD measured in grams per centimeters squared.

Macdonald P, Abstract 85

Islatravir does not impact serum creatinine.

Serum creatinine and eGFR: Median percent change from baseline at week 24

	ISL 60 mg QM N=97	n	ISL 120 mg QM N=97	n	Placebo QM N=48	n
Renal parameters, median percent change (IQR)						
Serum creatinine, mg/dL	0.0 (−11.8 to 12.8)	84	0.0 (−5.8 to 11.1)	92	0.0 (0.0-14.3)	44
eGFR, mL/min/1.73 m^2	0.0 (−12.9 to 15.6)	84	0.0 (−11.5 to 7.2)	92	0.0 (−14.3 to 0.0)	44

- No changes from baseline in serum creatinine or eGFR were observed across treatment groups

Macdonald P, Abstract 85

But, islatravir may reduce lymphocyte/CD4 counts.

Program update

- Based on changes in lymphocytes as observed in clinical trials of islatravir, the PrEP program has been placed on clinical hold by the US Food and Drug Administration[1]
  - No new participants are being screened or randomly assigned at this time
  - Dosing of investigational product has been stopped for all participants
  - All participants already enrolled in the phase 3 efficacy trials are being offered open-label daily PrEP

MSD news release. https://www.merck.com/news/merck-announces-clinical-holds-on-studies-evaluating-islatravir-for-the-treatment-and-prevention-of-hiv-1-infection/. Accessed January 19, 2022.

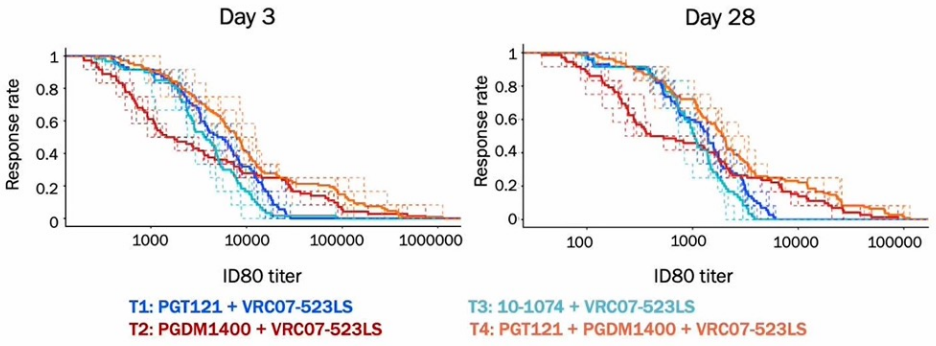
Combinations of bnAbs for PrEP

HVTN 130/HPTN 089: Study Design (Total N=27)

Study arm	N	Dose	Month 0	Month 4
Treatment 1 (T1)	6	20+20 mg/kg	PGT121 VRC07-523LS	–
Treatment 2 (T2)	6	20+20 mg/kg	PGDM1400 VRC07-523LS	–
Treatment 3 (T3)	6	20+20 mg/kg	10-1074 VRC07-523LS	–
Treatment 4 (T4, T4)	9	20+20+20 mg/kg	PGDM1400 PGT121 VRC07-523LS	PGDM1400 PGT121 VRC07-523LS

Study Sites:
New York, NY (Columbia, Harlem Prevention Center); Boston, MA (Fenway); Nashville, TN
Data unavailability was mostly caused by missed/remote visits due to the COVID-19 pandemic

Greater Neutralization Magnitude and Breadth of Triple vs. Dual bnAb Combinations against 12 multi-clade virus panel



T2: PGDM1400 + VRC07-523LS combination had lower breadth at lower titers

Sobieszczyk M, Abstract 81

Posters

Selected posters

- At Fenway, HIV/STI testing and PrEP starts had rebounded by the delta surge but were below pre-pandemic levels. (Mayer KH, 939)
- 56% of cisgender women initiating PrEP at health centers stopped within one year; discontinuation is associated with lack of insurance and lower income. (Irie W, 925)
- Among 997 pregnancies in South Africa, there were no differences in adverse birth outcomes between PrEP-exposed and unexposed pregnancies, but adverse birth outcomes were common (~14%). (Davey DJ, 705)

Sexual Health Clinic Outcomes And PrEP Linkage In A Large Urban Emergency Department

Aniruddha Hazra, MD, Ruby Massey, Michelle Moore, AGPCNP-BC, Damaris Garcia, Richard Rogers, Jessica Schmitt, LCSW

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02344

Background

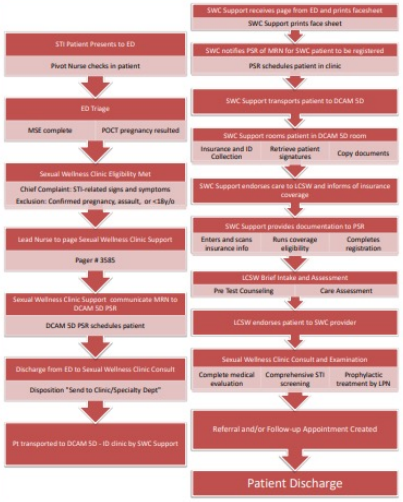
- Closure of municipal sexually transmitted infection (STI) clinics has caused patients to rely on the Emergency Department (ED) for their sexual health needs.
- The Sexual Wellness Clinic (SWC) was created to provide comprehensive sexual health care and primary care linkage to patients presenting to the ED with STI complaints

Methods

- SWC-eligible patients are identified at ED intake and undergo a Medical Screening Exam (MSE) by a triage physician before transport to clinic
- Once at the SWC, patients undergo a complete history and physical examination, comprehensive STI testing, and, if indicated, empiric treatment as well as same-day initiation of Pre-Exposure Prophylaxis (PrEP)
- Social services within the clinic also assist in arranging primary care follow-up either at the medical center or an affiliated Federally Qualified Health Center (FQHC)
- We performed a retrospective review of SWC patients from February 20, 2019 through September 30, 2021.

Transferring ED patients to a **specialized sexual health clinic** is **feasible** and **identifies unique target populations** for STI and HIV elimination efforts.

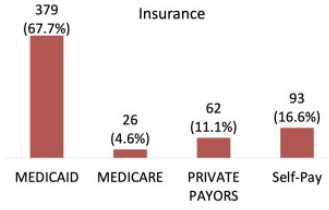
SWC Workflows

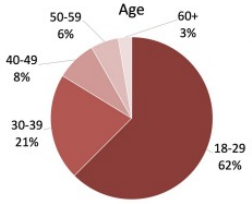


Results

560 patients seen 2/20/2019 through 9/30/2021

- 50.5% cis-male, 49.5% cis-female
- Age range 18-82, median 30 (IQR 12.42)
- 72.3% of patients use Medicaid/Medicare





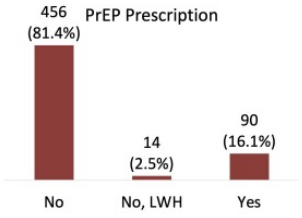
STI Positivity Rates	
Gonorrhea	82 (14.6%)
Chlamydia	75 (13.4%)
Syphilis	132 (23.5%)
HSV	5 (0.89%)
HIV	3 (0.54%)

Same-Day PrEP Starts

- 90 same day PrEP starts (16.1%)
- 56.7% cis-female and 43.4% cis-men

Primary Care Linkage

- All new PrEP starts had a follow-up scheduled
- At 3 months 18 patients continued to take PrEP (20%) and at 6 months only 10 patients continued (11.1%)



Conclusions

- This unique workflow is feasible at a large urban ED
- Majority of PrEP starts in cis-women, differing from metropolitan STI clinics
- Room to improve adherence to PrEP
- Identifying new at-risk populations is integral to support local and national HIV/STI elimination efforts

Acknowledgements

SWC consists of an interdisciplinary team who are integral to its efforts. Special thanks to Richard Rogers, LPN, Michelle Taylor, LCSW, Paul Djuricich, PharmD, Robert Stafford, PharmD, Lindsey Wesley-Madgett, Damaris Garcia, Xavier Burgos, and Cheryl Scott.

Summary

- Monitoring with HIV RNA assays for those on CAB-LA may permit identification of HIV infection before INSTI resistance occurs.
- TDF/FTC is compatible with gender affirming hormone therapy for transgender and gender diverse people.
- In the REACH Study, a majority of women chose the dapivirine ring over oral PrEP.
- Monthly oral islatravir achieves good levels in multiple tissues, but its development is on hold because of adverse effects on lymphocytes.

PREGNANCY AND BIRTH OUTCOMES IN PREP EXPOSED & UNEXPOSED PREGNANT SOUTH AFRICAN WOMEN

00705

D. Joseph Davey[1, 2] , D. Nyemba [2], R. Mvududu [2], N. Mashele [2], LG Bekker[3], P. Gorbach[1], TJ. Coates[1], L. Myer [2]
[1]University of California, Los Angeles, CA, USA, [2]University of Cape Town, South Africa, [3]Desmond Tutu HIV Centre, University of Cape Town, South Africa

BACKGROUND

- There are few safety data on the use of oral PrEP in pregnancy presenting a barrier to implementation in some settings

METHODS

- Based at a primary care facility in Cape Town, the **PrEP in pregnancy and postpartum (PrEP-PP) study** offered HIV prevention counseling and PrEP to consenting pregnant women (≥16 years) without HIV from their first antenatal care (ANC) visit through 12 months' postpartum
- We compared **pregnancy and birth outcomes including pregnancy loss** (miscarriage, stillbirth, termination) and **birth outcomes** (birthweight [median], low-birth weight [<2500 grams], pre-term [<37 weeks' gestation] and neonatal death) between PrEP exposed (any PrEP use while pregnant) vs. unexposed (no PrEP use in pregnancy), abstracted from routine health records, and compared these with clinic-wide statistics from the same period
- Analysis of miscarriage and stillbirth were restricted to women who entered before 20 and 28 weeks, respectively
- Analysis of birth outcomes included all women with available data

Rate of adverse pregnancy and birth outcomes high in the population

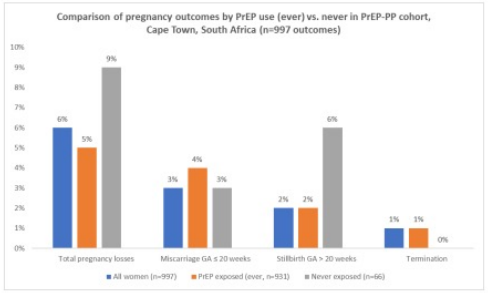
PrEP exposure in pregnancy is not associated with any increased adverse pregnancy or birth outcomes

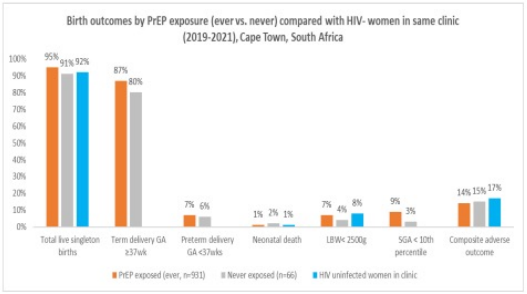
Oral PrEP should be integrated into PMTCT and ANC care in high HIV incidence communities

PrEP-PP
Pre-exposure Prophylaxis in Pregnancy & Postpartum

RESULTS

- Between August 2019 and January 2022, we ascertained n=997 pregnancy outcomes
  - Median gestation at first ANC= 23 weeks [IQR, 14-31]
  - Median maternal age=26 years [IQR, 22-31]
- 93% (n=931) were PrEP exposed
- Overall, 94% had singleton live births
- We recorded 5% miscarriages or stillbirths in the PrEP exposed group vs. 9% in the unexposed group (p=0.06)
- **There were no differences in birth outcomes between the PrEP-exposed vs. unexposed (composite adverse birth outcome=14% in both groups; p=0.99).**
- **Among the PrEP exposed, there was no association with duration of antenatal exposure and birth outcomes (p=0.84).**
- Comparing statistics on birth outcomes in HIV-uninfected women, the frequency of adverse birth outcomes was similar to levels in the PrEP exposed cohort (p>0.05).





CONCLUSIONS

While the overall frequency of adverse pregnancy and birth outcomes is high in this setting, **these reassuring data suggest no differences in pregnancy outcomes comparing women exposed to PrEP to women with no exposure to PrEP.**

ADDITIONAL KEY INFORMATION

Clinical trials reference: NCT03902418

Funding: DJD, TJC and LM have funding from NIMH (R01MH116771) and NICHD (R01HD106821). DJD has funding from Fogarty International Center/NIH (K01TW011187).

Acknowledgements: We would like to thank the PrEP-PP study participants, study staff, Western Cape Department of Health healthcare workers.

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CROI Update 2022: Cardiovascular and Metabolic Complications

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Massachusetts General Hospital

April 5, 2022

Disclosure

- Virginia A. Triant, MD, MPH: no disclosures

Cardiovascular and Metabolic Complications CROI 2022

- Impact of ART on cardiometabolic risk
  - INSTIs and weight gain
- Role of inflammation in HIV-associated CVD
  - Pathophysiology
  - Risk prediction
  - Interventions
- Epidemiology, subpopulations, and additional cardiovascular outcomes
  - Women
  - Perinatally-infected youth
- Disparities in diagnosis and management of cardiometabolic disease
  - Impact of COVID-19

Summary and Implications

- Impact of ART on cardiometabolic risk continues to be delineated
  - Priority research questions:
  - What factors predict weight gain when initiating INSTIs?
  - Do metabolic effects including weight gain translate to increased outcome event rates?

- Inflammation plays a key role in HIV-associated CVD
  - Priority research questions:
  - What interventions can safely reduce inflammation and immune activation?
  - Will immunomodulatory interventions translate into decreased rates of CVD?

- Disparities in prevention and management of cardiometabolic disease in PWH persist
  - Priority research questions:
  - How can we optimally implement guideline-concordant prevention and management practices for CVD, cancer, and other comorbidities?
  - Are HIV-specific screening tools needed?
  - Will early HIV treatment reduce chronic diseases of aging in PWH?

Cardiovascular/Metabolic Sessions: CROI 2022

Opening session

MARTIN DELANEY PRESENTATION: WE'RE STILL HERE: HIV, AGING, AND THE INVISIBLE GENERATION

(CROI COMMUNITY LIAISON SUBCOMMITTEE)

Symposia

HIV AND AGING

Oral abstract sessions

MALIGNANCIES AND COMORBIDITIES: AN INCREASING BURDEN

Poster sessions

RISK FACTOR AND INFLAMMATORY MEDIATORS OF CARDIOVASULAR DISEASE

HIV INFECTION AND INFLAMMATION

WEIGHT GAIN AND ADIPOSE TISSUE BIOLOGY

BIOMARKERS AND COMORBIDITIES

HYPERTENSION, HEART FAILURE, AND OTHER CARDIOVASCULAR DISEASE OUTCOMES

OTHER COMORBIDITIES

METABOLIC COMPLICATIONS

COMORBIDITIES AND COMPLICATIONS OF HIV AND ART IN CHILDREN AND YOUTH

Cardiovascular and Metabolic Complications CROI 2022

- Impact of ART on cardiometabolic risk
  - INSTIs and weight gain
- Role of inflammation in HIV-associated CVD
  - Pathophysiology
  - Risk prediction
  - Interventions
- Epidemiology, subpopulations, and additional cardiovascular outcomes
  - Women
  - Perinatally-infected youth
- Disparities in diagnosis and management of cardiometabolic disease
  - Impact of COVID-19

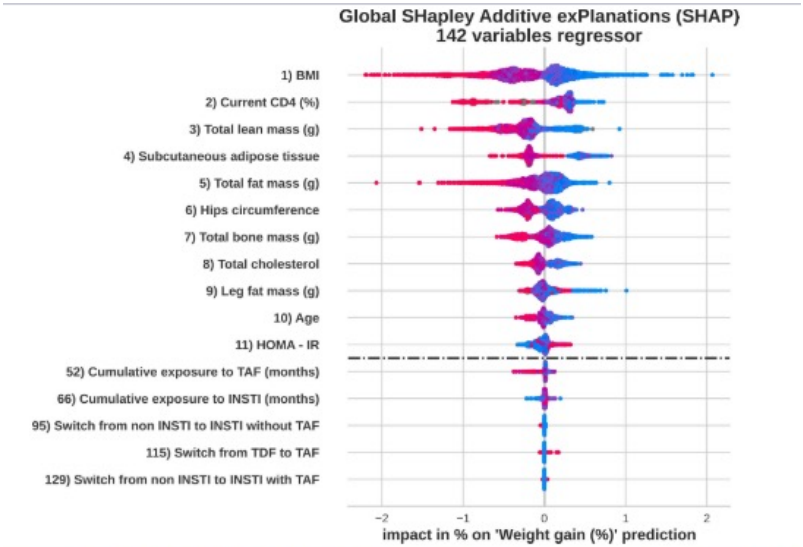
Context: INSTIs and Weight Gain

- INSTIs have been associated with weight gain in multiple studies, including switch studies

- Questions that remain incompletely understood:
  - The relative contributions of INSTIs and TAF to weight gain
  - The effects of different INSTIs on weight gain
  - The risk factors for weight gain with INSTI initiation
  - The clinical implications of weight gain (cardiometabolic disease or outcomes)

Machine Learning to Predict Weight Gain following INSTI Switch

- Objective: To develop a machine learning algorithm that predicts percentage weight gain in PWH switching ART to INSTI-containing regimen
- Results: An algorithm built from over 140 variables was highly accurate (>90%) in predicting weight gain
- An algorithm limited to routinely collected clinic variables was less accurate
- Switch to INSTI was relatively less important than other variables in predicting weight gain
- Implications: Predicting weight gain is complex and likely multifactorial

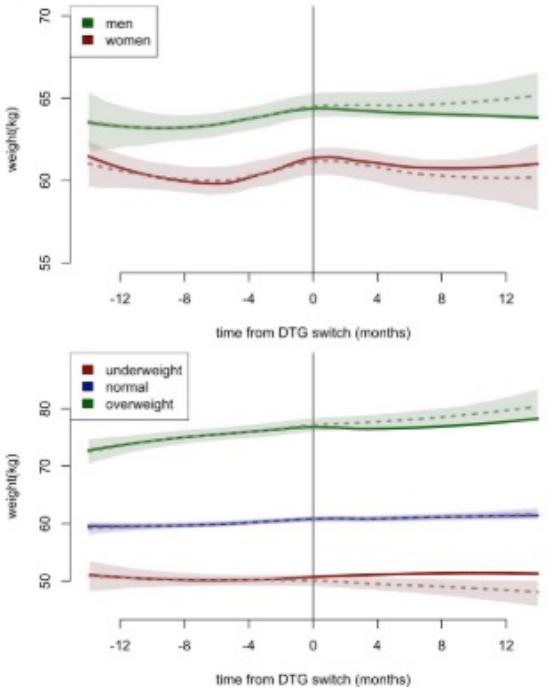


Guaraldi, Abstract 597, CROI 2022

INSTIs and Weight Gain: sub-Saharan Africa

- Background: Data on weight changes following switch to DTG in ART-experienced patients in low-income settings with lower prevalence of obesity are limited
- Objective: To determine whether PWH switching to DTG in rural Kenya experience weight gain
- Results: Switch to dolutegravir in rural Kenya was not associated with significant weight gain
  - Mean weight change 0.8kg in 12 months pre-switch and 0.4kg in 12 months post-switch
  - Observed weight gain less than predicted based on pre-switch trajectory
  - Similar results for those on TDF pre and post switch (exception 2.9kg gain if baseline underweight)
- Implications: Metabolic effects of INSTIs may differ depending on geographic location

Figure 1. Observed (solid line) vs. predicted (dashed line) weight trajectories among participants on TDF pre/post DTG switch (n=1850)



Hickey, Abstract 596, CROI 2022

INSTIs and Weight Gain

INSTIs and Body Composition

- Background: In the DOLAM study, weight at 48 weeks increased more in the 2-drug (DTG +3TC) arm versus 3-drug arm (1.5 kg)
- Objective: To assess body composition changes in PWH switching from 3-drug to 2-drug regimen using DEXA
- Results: No significant changes between arms in:
  - Body fat
  - Lean mass
  - Bone mineral density

INSTIs and Mitochondrial Effects

- Objective: to quantify changes in mitochondrial health and morphology following exposure to INSTIs
- Results: after 9 days of dolutegravir exposure, alternations in mitochondrial morphology observed
- Human telomerase reverse transcriptase (hTERT) did not confer protection against DTG-mediated stress
- Alterations reversed after 6 days of recovery from exposure
- Mitochondrial effects not seen with raltegravir

Martinez, Abstract 598, CROI 2022; Caloren, Abstract 601, CROI 2022

INSTIs and Weight Gain: Pharmacogenetics

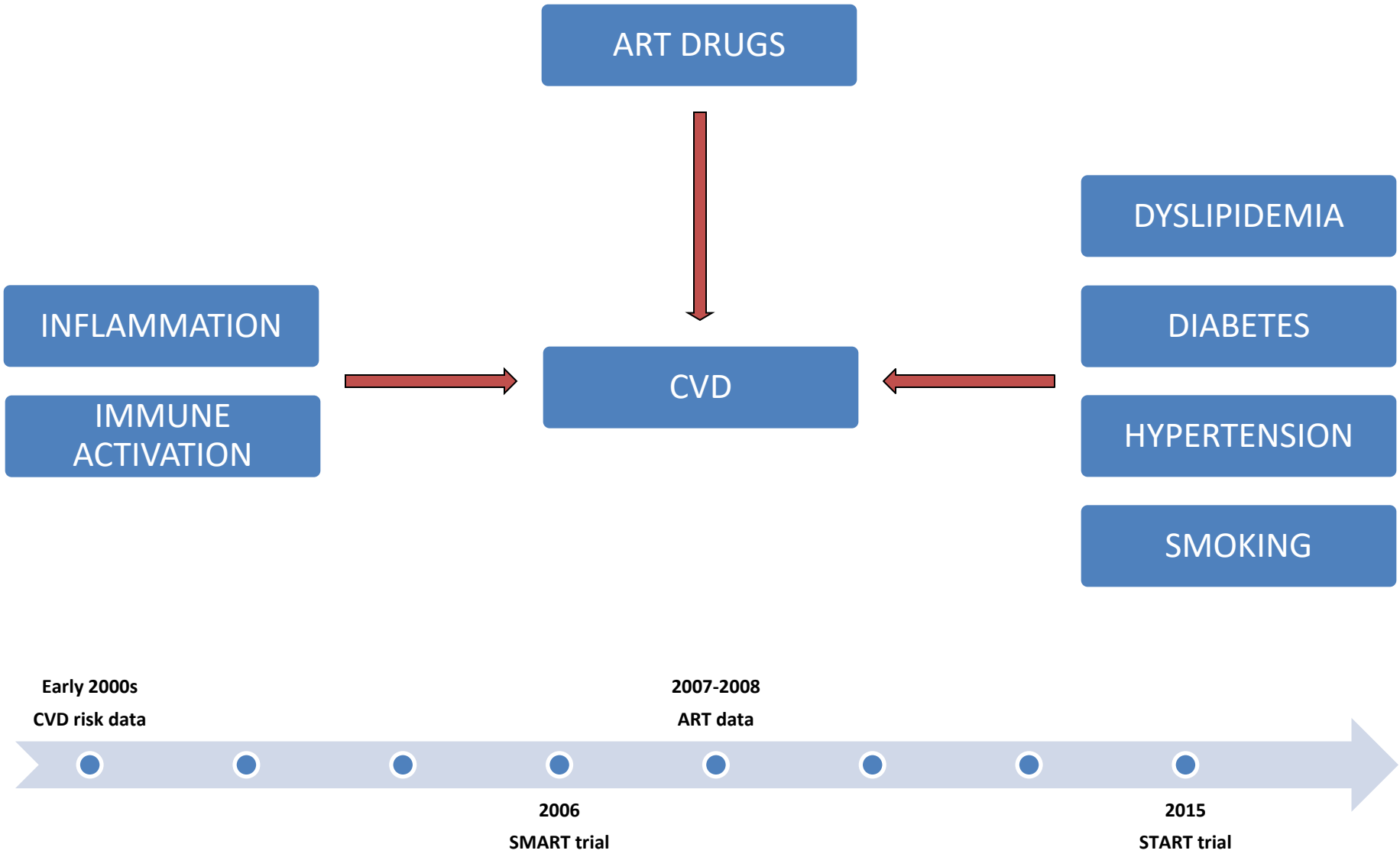
- Background: CYP2B6 genotypes have been associated with greater weight gain after switch from EFV- to INSTI-based ART
- Objective: To assess association of CYP2B6 genotype and weight change following switch from EFV- to INSTI-based ART
  - Hypothesis that CYP2B6 slow metabolizer genotype associated with greater weight gain
- Results: N=5968, ACTG cohorts
- CYP2B6 poor metabolizer genotype associated with greater weight gain
  - Among poor metabolizers, weight gain reached significance only in Hispanic and elvitegravir subgroups
  - Small N
  - Results inconsistent
- Implications: Weight gain likely complex and multifactorial

Haas, Abstract 595, CROI 2022

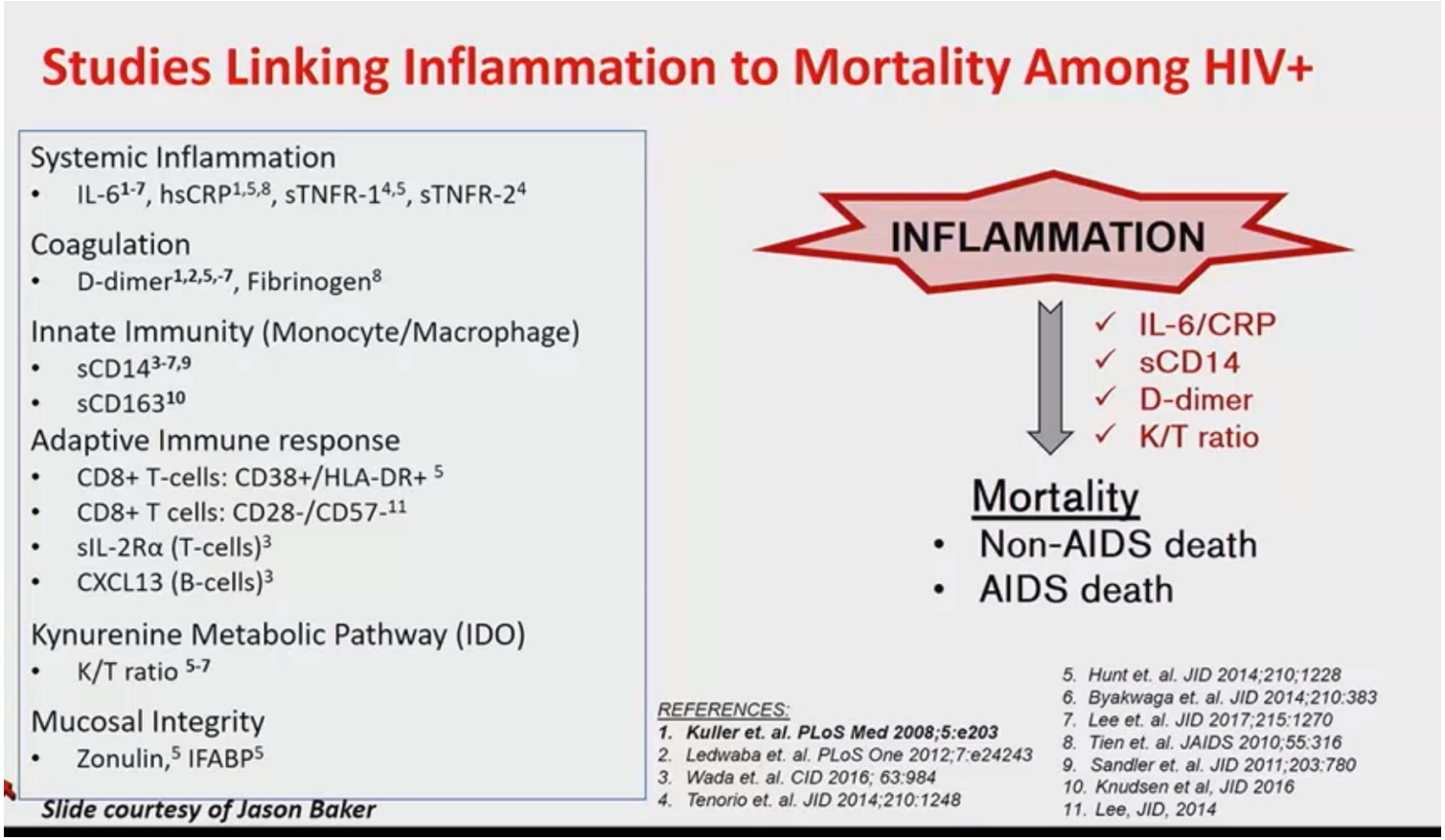
Cardiovascular and Metabolic Complications CROI 2022

- Impact of ART on cardiometabolic risk
  - INSTIs and weight gain
- Role of inflammation in HIV-associated CVD
  - Pathophysiology
  - Risk prediction
  - Interventions
- Epidemiology, subpopulations, and additional cardiovascular outcomes
  - Women
  - Perinatally-infected youth
- Disparities in diagnosis and management of cardiometabolic disease
  - Impact of COVID-19

Context: Pathophysiology of HIV-Associated CVD



Context: Inflammation and HIV

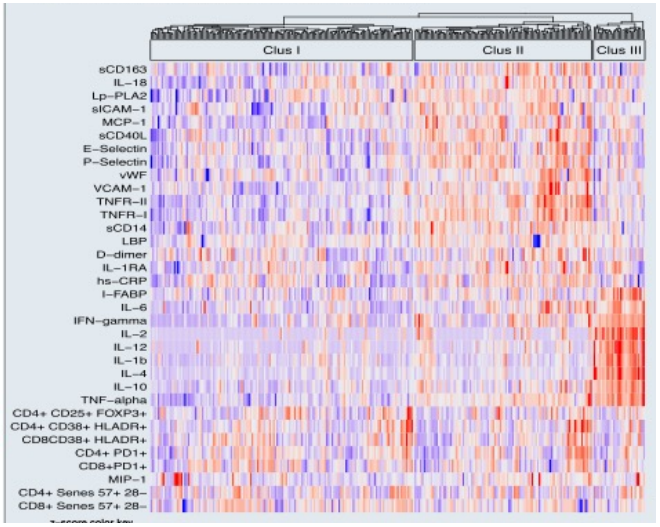


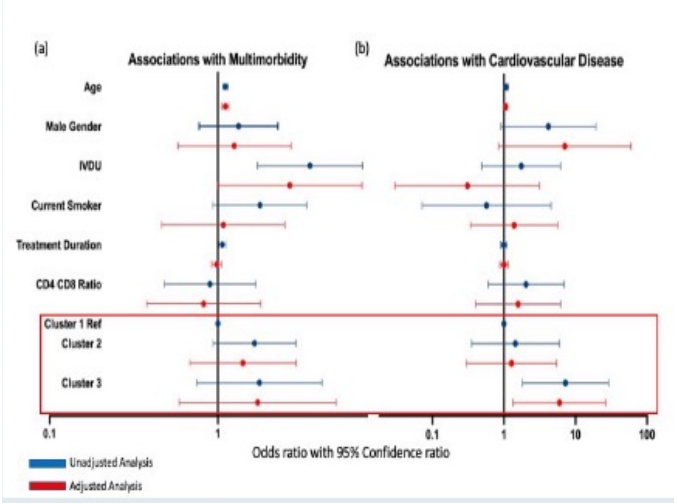
- Many pathways may be involved in HIV-related comorbidities and may be targets for intervention
- Does combining or clustering groups of inflammatory and immune markers, analogous to grouping individual traditional CVD risk factors to generate an overall risk score, improve our ability to risk-stratify?

Sereti, CROI 2019.

Inflammatory Biomarker Clusters

- Background: Inflammation thought to contribute to excess unmeasured CVD risk in PWH
- Objective: To investigate bioprofiling inflammatory pathways of PWH as novel strategy to identify risk of CVD and multimorbidity
- Results: Individuals in a cohort of PWH on ART (N=277) can be partitioned into groups of inflammatory profiles
- Cluster 3 with higher inflammation associated with CVD (adjusted odds ratio 7.07)
- Implications: Bioprofiling may be useful to risk-stratify for CVD



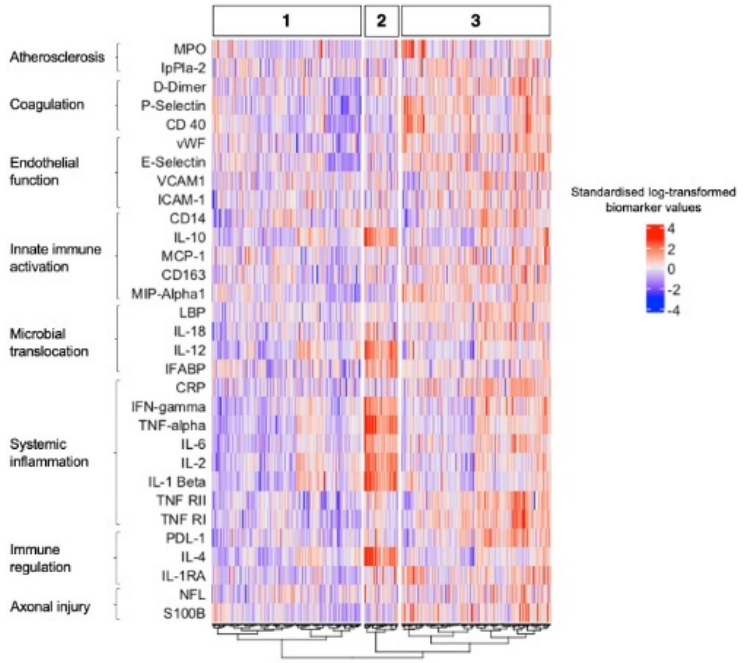


McGettrick, Abstract 578, CROI 2022

Inflammatory Biomarker Clusters

- Background: Chronic inflammation may contribute to comorbidities
- Objective: To validate previously identified biomarkers patterns and identify clinical and demographic associations
- Methods: POPPY cohort, N=465 (includes controls)
- Results: Three distinct inflammatory clusters identified
  - Cluster 1 low inflammation
  - Cluster 2 high T and B cell activation and proliferation
  - Cluster 3 elevated biomarkers across range
- No adjustment for confounders
- Implications: Biological phenotypes may contribute to clinical outcomes
- May enable personalized approach for prevention and treatment of comorbidities in PWH

Figure. Heatmap of clusters (n=465)



Note, log-transformed standardised biomarker values are used for the heatmap. Red represents relatively high biomarker values; blue represents relatively low biomarker values.

Bakewell, Abstract 622, CROI 2022

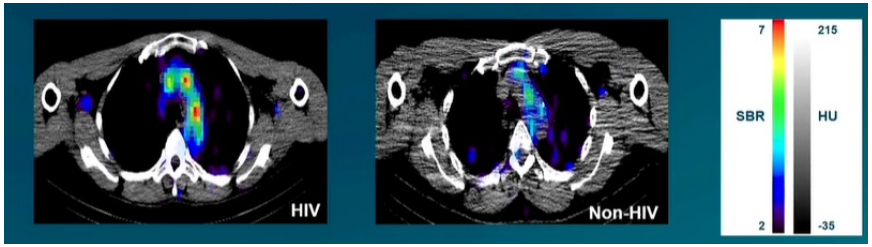
Pathophysiology: Arterial Inflammation and Plaque

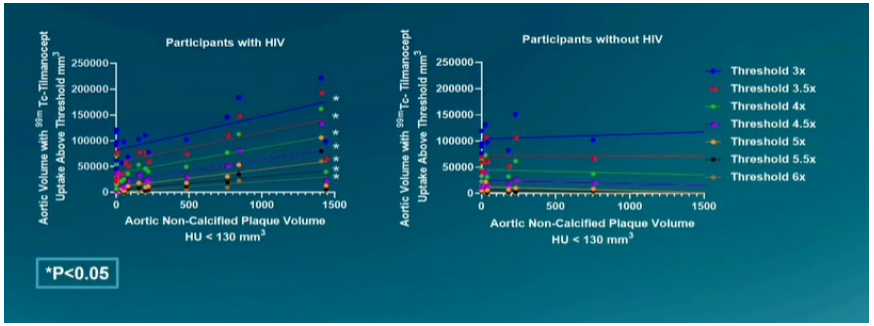
- Background: Macrophage specific radiotracer (technetium 99m tilmanocept), binds to CD206
- Higher CD206+ macrophages in high-risk plaque
- Determine feasibility for quantification of vascular inflammation
- First in-human application
- Objective:
  - Assessed macrophage specific arterial inflammation in people with vs. without HIV
  - Assessed relationship between macrophage specific arterial inflammation, atherosclerotic plaque, and immune activation in PWH

Toribio, Macrophage arterial infiltration relates to plaque type and immune activation in HIV, CROI 2022

Pathophysiology: Arterial Inflammation and Plaque

- Methods: Prospective cross-sectional, N=20
- Controls with similar CVD risk
- Results:
- Macrophage specific arterial inflammation was higher among PWH on ART compared to controls
  - Higher levels uptake indicated by higher signal to background ratio
  - Uptake of macrophage-specific tracer related to non-calcified aortic plaque volume in HIV only





Toribio, Macrophage arterial infiltration relates to plaque type and immune activation in HIV, Abstract 38, CROI 2022

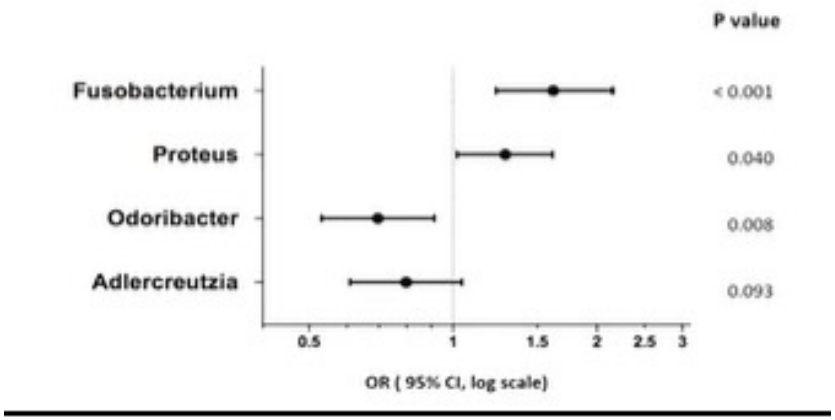
Pathophysiology: Microbiome and Plaque

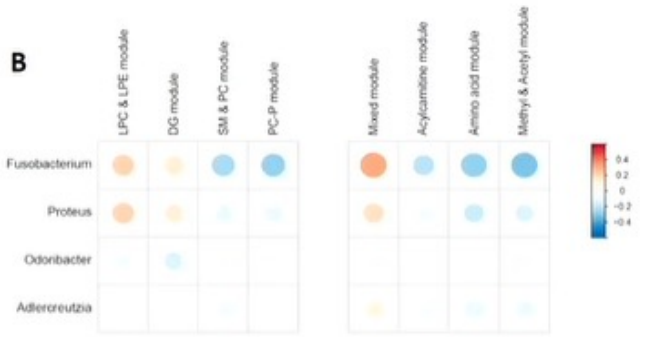
- Background: Alterations in gut microbiome and host metabolites have been implicated in HIV and cardiovascular disease
- It is unclear whether alterations in gut microbiome contribute to disrupted host blood metabolic profiles in relation to atherosclerosis in HIV
- Objective: To identify gut microbiome alterations associated with carotid artery plaque
- Methods: Plasma metabolomics and gut microbiome measurement
  - Cross-sectional: N=361 from WIHS
  - Prospective: N=737 from MACS/WIHS combined cohort

Wang, Gut microbiota, plasma metabolomics, and atherosclerosis in HIV infection, Abstract 37, CROI 2022

Pathophysiology: Microbiome and Plaque

- Results:
- 4 bacterial genre associated with plaque
  - Fusobacterium and Proteus positively associated
  - Odoribacter and Adlercreutzia inversely associated (produce beneficial metabolites)
- Fusobacterium associated with plasma metabolites involved in lipid metabolism
- No interactions by HIV status
- Implications: Changes in gut microbiome associated with carotid atherosclerosis, may be via disrupted lipid metabolism
- Raises concept of therapeutics to modulate gut microbiome to prevent atherosclerosis (e.g. dietary changes, probiotics, FMT)





Wang, Gut microbiota, plasma metabolomics, and atherosclerosis in HIV infection, Abstract 37, CROI 2022

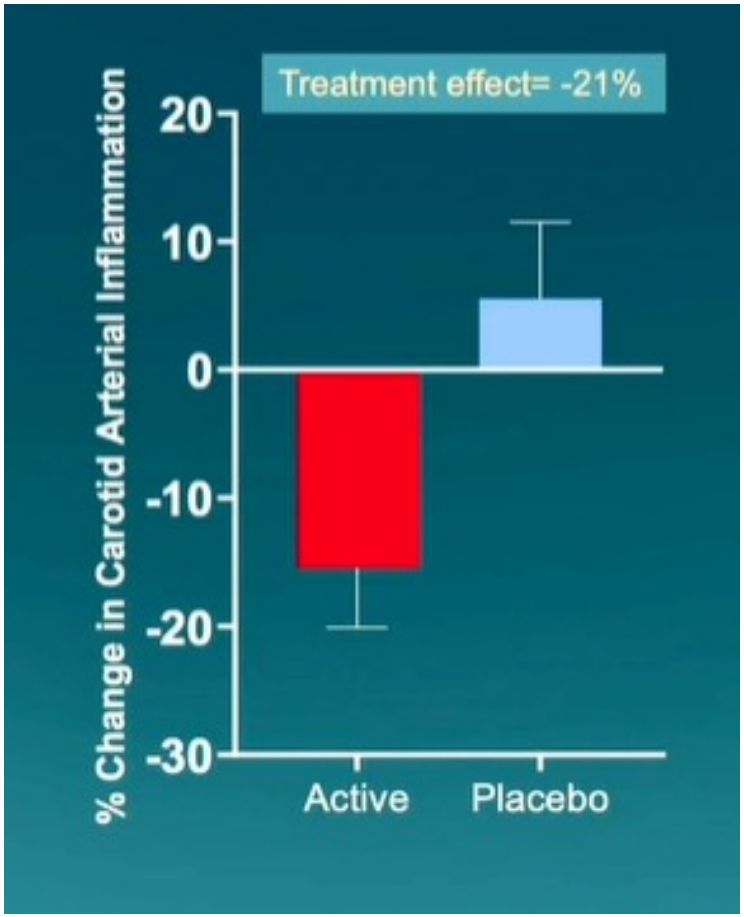
Interventions to Reduce Inflammation: GLP-2 analog

- Background: FDG, a measure of macrophage metabolic activity in atherosclerotic plaque that predicts CVD risk, is increased in PWH
- Intestinal permeability and microbial translocation cause systemic inflammation in HIV
- CD4 cells in GI tract remain depleted in PWH even on ART
- Glucagon-like peptide-2 (GLP-2) is a hormone that regulates intestinal epithelial cell growth and can restore intestinal epithelium
- Teduglutide is a GLP-2 analog
- Objective: GLP-2 analog will reduce systemic immune activation, macrophage activity, and cardiovascular inflammation in PWH

Lo, Improving intestinal Barrier using GLP-2 agonist reduces arterial inflammation in PWH, CROI 2022

Interventions to Reduce Inflammation: GLP-2 analog

- Methods: RCT proof-of-concept trial, N=32
- Primary outcome: carotid arterial inflammation as measured by FDG PET
- Results:
- GLP-2 analog teduglutide reduced:
  - Arterial inflammation
  - Circulating activated monocytes
  - Activated CD8 cells (not CD4)
  - Adjusted for statin and smoking
- Implications: Improving intestinal epithelial integrity may reduce cardiovascular inflammation



Lo, Improving intestinal Barrier using GLP-2 agonist reduces arterial inflammation in PWH, CROI 2022

Interventions to Reduce Inflammation: Statins

- Background: In SATURN-HIV, rosuvastatin lowered markers of monocyte activation in PWH on ART
- Objective: To assess whether rosuvastatin improves lipidomes and reduces the proinflammatory signatures in macrophages
- Results: Rosuvastatin downregulated immune activation signaling in monocyte-derived macrophages
  - Downregulation of inflammatory cytokines
  - Downregulation of complement signaling
- Implications: Statins may lead to a reduced inflammatory response and CVD risk by downregulating pro-atherosclerotic and immune activation signaling. These effects may complement lipid-lowering effects to reduce CVD risk

Ismail, Abstract 581, CROI 2022

Cardiovascular and Metabolic Complications CROI 2022

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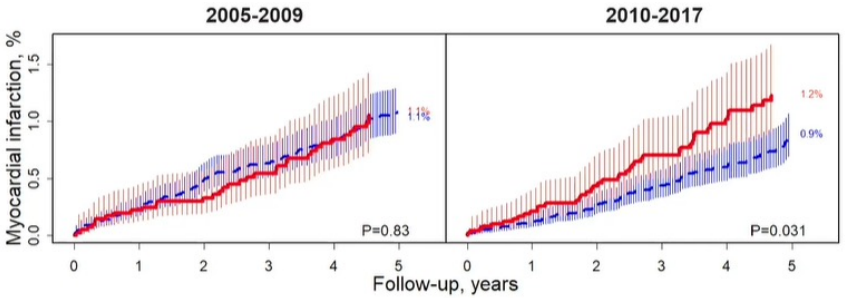
Myocardial Infarction Risk by HIV Status over Calendar Period

- Background: PWH have 40-80% increased risk of MI
- Pathophysiology likely due to increased traditional CVD risk factors, inflammation/immune dysregulation, and possible adverse effects of ART
- Objective: To quantify changes over time in MI incidence rates comparing PWH to PWoH
- Methods: Cohort study, two large healthcare systems in CA and MA
  - HIV and controls propensity score matched, similar baseline CVD risk
  - 2005-2009 vs. 2019-2017
  - Outcome: Incident MI

Silverberg, Trends in myocardial infarction risk by HIV status in two US healthcare systems, Abstract 39, CROI 2022

Myocardial Infarction Risk by HIV Status over Calendar Period

- Results: Cumulative incidence of MI similar in 2005-2009 but 60% higher for PWH in 2010-2017 calendar period
  - 1.2% risk of MI over 5 years in 2020-2017 for PWH vs. 0.9% vs. controls
  - Hazard ratio 1.6 in 2010-2017
- Implications: PWH may not have realized same improvements in CVD risk management due to HIV-specific factors
- Continued surveillance for CVD warranted



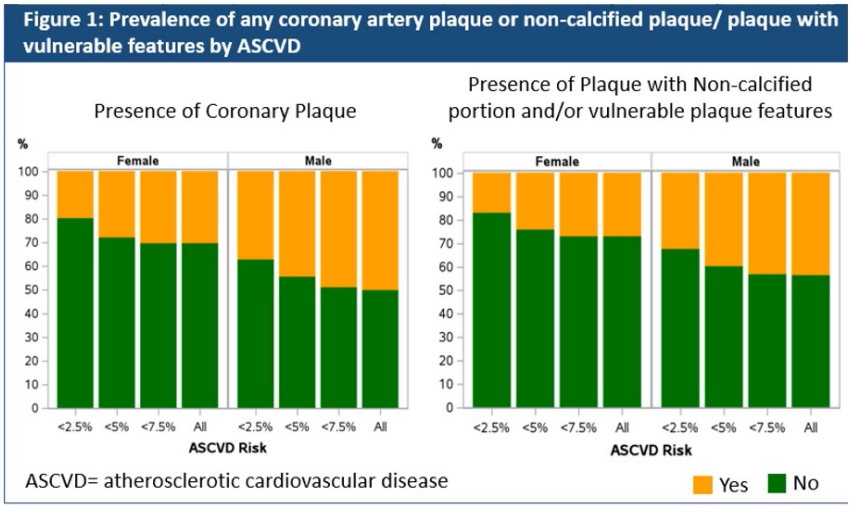
	KPNC		Partners		Overall	
Era	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
2005-2009	1.0 (0.7, 1.5)	0.90	1.2 (0.3, 5.8)	0.82	1.1 (0.8, 1.5)	0.61
2010-2017	1.6 (1.1, 2.4)	0.02	2.1 (0.6, 7.5)	0.28	1.6 (1.1, 2.4)	0.007

*Stepwise adjusted models considering demographics and Framingham risk score components.

Silverberg, Trends in myocardial infarction risk by HIV status in two US healthcare systems, Abstract 39, CROI 2022

Subclinical Atherosclerosis among Females

- Background: Women with HIV may have differing presentations of atherosclerosis
- Objective: To assess coronary plaque features and immune activation markers among women versus men
- Results: Among 755 women in REPRIEVE:
  - Lower prevalence coronary plaque
  - Lower prevalence plaque with non-calcified/vulnerable features
- For immune activation markers, women had:
  - Higher IL-6, hsCRP, d-dimer
  - Lower total monocytes
  - Shift toward higher inflammatory monocyte subsets
- Associations between immune markers and plaque did not differ by sex (exception d-dimer)
- Implications: Understanding sex-specific immune drivers of subclinical coronary pathology will be key to tailoring ASCVD preventive therapies to PWH



Zanni, Abstract 577, CROI 2022

Cardiovascular Disease in Children with Perinatally-acquired HIV

Subclinical Vascular Disease

- Objective: To investigate the progression of subclinical vascular disease in children with perinatally-acquired HIV (PHIV) versus HIV-uninfected in Uganda
- Results: At week 96 in children on stable ART
  - IMT decreased
  - Pulse wave velocity increased
  - BMI and longer abacavir use associated with IMT
- Implications: This study adds new data on CVD risk in children with perinatally-acquired HIV in sub-Saharan Africa

PDAY Risk Score

- Objective: To calculate the Pathological Determinant of Atherosclerosis in Youth (PDAY) risk score and assess factors associated with elevated risk in South African youth living with perinatally-acquired HIV
  - PDAY components are traditional CVD risk factors
- Results: 28% had an elevated coronary artery PDAY risk score, driven by low HDL cholesterol
- Sustained and transient viremia and longer ART duration were associated with increased PDAY score
- Implications: Understanding atherosclerotic risk in youth living with perinatally-acquired HIV is important for prevention and management

Dirajlal-Fargo, Abstract 727, CROI 2022; Mahtab, Abstract 726, CROI 2022

Additional Cardiovascular Outcomes

Atrial Fibrillation

- Objective: To assess the association of traditional risk factors and HIV-related factors with incident atrial fibrillation in CNICS
- Results: Atrial fibrillation associated with
  - Lack of ART
  - 2 or more core (non-NRTI) ART classes
  - Lower CD4 count
  - Traditional AF risk factors
- Implications: Analogous to coronary heart disease, both traditional and HIV-specific risk factors appear to contribute to risk in atrial fibrillation

Heart Failure

- Background: Data on pathogenesis of myocardial injury in HIV are lacking globally
- Objective: To estimate myocardial fibrosis and associations with inflammatory markers among PWH on ART in South Africa
- Results: HIV-associated activated monocyte phenotypes were positively associated with myocardial fibrosis
- Implications: Monocyte activation may contribute to heart failure risk in HIV via myocardial fibrosis

Nance, Abstract 587, CROI 2022; Peterson, Abstract 589, CROI 2022

Cardiovascular and Metabolic Complications CROI 2022

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HTN Care Cascade during COVID-19

- Background: HTN management in PWH is suboptimal
- Objective: To define the HTN care cascade over two years to identify gaps in care and assess impact of the COVID-19 pandemic in a national cohort of veterans with HIV
- Results: Gaps in HTN care in PWH were exacerbated by the COVID-19 pandemic
  - HTN monitoring and control decreased in 2020 versus 2019
- Implications: Disparities already existed in comorbidity prevention and management in HIV, and the COVID-19 pandemic is likely to have exacerbated them

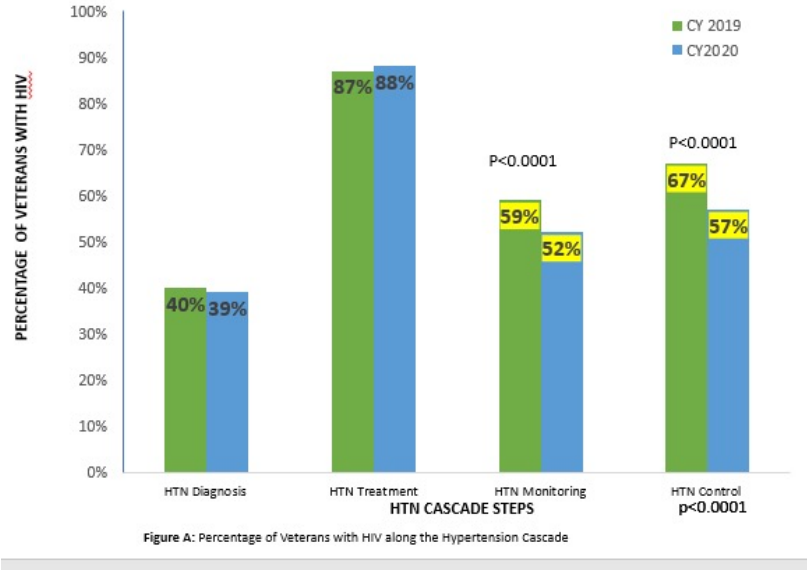

Figure A: Percentage of Veterans with HIV along the Hypertension Cascade

Musoke, Abstract 585, CROI 2022

Summary and Implications

- Impact of ART on cardiometabolic risk continues to be delineated
  - Priority research questions:
  - What factors predict weight gain when initiating INSTIs?
  - Do metabolic effects including weight gain translate to increased outcome event rates?

- Inflammation plays a key role in HIV-associated CVD
  - Priority research questions:
  - What interventions can safely reduce inflammation and immune activation?
  - Will immunomodulatory interventions translate into decreased rates of CVD?

- Disparities in prevention and management of cardiometabolic disease in PWH persist
  - Priority research questions:
  - How can we optimally implement guideline-concordant prevention and management practices for CVD, cancer, and other comorbidities?
  - Are HIV-specific screening tools needed?
  - Will early HIV treatment reduce chronic diseases of aging in PWH?

THANK YOU


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and Opportunistic Infections

Novel Biomarker of CVD

- Growth differentiation factor-15 (GDF-15) is a novel stress-induced cytokine that is emerging as a marker of poor CVD outcomes in the general population
- GDF-15 levels were higher in PWH versus controls
- In PWH and controls GDF-15 levels were higher in individuals with coronary plaque
- GDF-15 represents a new marker of high-risk coronary plaques in both PLWH and HIV-uninfected people

Royston, Abstract 579, CROI 2022

Abdominal Aortic Aneurysm

- Objective: To assess the association between HIV and incident AAA in a large cohort of U.S. veterans (VACS)
- Results: HIV was not associated with increased risk of AAA
- Among PWH, increased viral load (>500) and low CD4 (<200) were associated with increased risk of AAA
- Traditional risk factors predicted AAA in PWH
- Implications: Monitoring for aortic vascular disease in individuals with advanced or poorly controlled HIV is warranted

Filipkowski, Abstract 584, CROI 2022