CROI Update 2021: Cardiovascular and Metabolic Complications

Virginia A. Triant, MD, MPH
Massachusetts General Hospital
HOPE Conference

April 13, 2021

Disclosure

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

Cardiovascular and Metabolic Complications CROI 2021

- Adverse effects of ART
  - Weight gain
  - Metabolic effects
  - CVD outcomes
- Novel risk factors for CVD
  - Proteomics
  - Inflammation
- Epidemiology of aging and comorbidities

Cross-cutting themes:
Effects of age, race, sex, and geographic setting on the diagnosis, treatment, and prevention of aging-related complications of HIV

Cardiovascular and Metabolic Complications CROI 2021

- Adverse effects of ART
  - Weight gain
  - Metabolic effects
  - CVD outcomes
- Novel risk factors for CVD
  - Proteomics
  - Inflammation
- Epidemiology of aging and comorbidities

Cross-cutting themes:
Effects of age, race, sex, and geographic setting on the diagnosis, treatment, and prevention of aging-related complications of HIV

Context: INSTIs and Weight Gain

- INSTIs and TAF have been associated with weight gain in multiple studies
- Weight gain among suppressed patients switching therapy is less well described
- 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 INSTIs or following ART initiation
  - The clinical implications of weight gain (cardiometabolic disease or outcomes)

Weight Gain after INSTI Switch

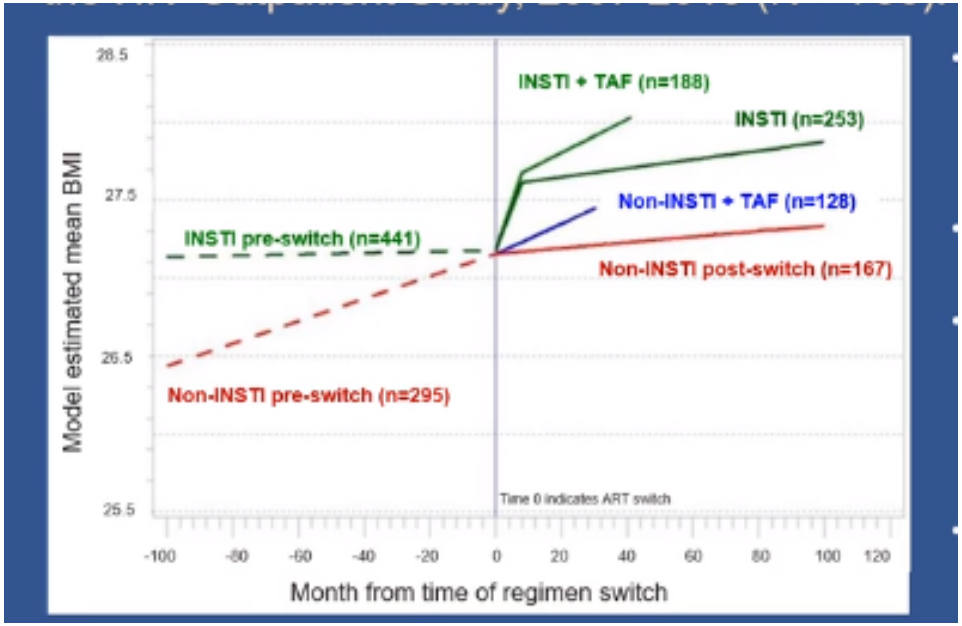
- Objective: To assess how INSTIs contribute to weight gain in real-world clinical practice
- Study design
  - Trio Health Research Network
  - Retrospective observational study
  - Switch to new INSTI from non INSTI or another INSTI
  - Accounted for concurrent TDF to TAF switch (47%)
  - Three multivariate models using ≥3, ≥5, and ≥ 10% cutoffs for increase in weight gain
- Mean increase in weight at 1 year was 1.3 kg
- Weight gain was not different among INSTIs
- Factors associated with weight gain in all 3 models:
  - Female
  - Baseline BMI underweight/normal
  - Black race
  - TDF-to-TAF switch

- **Type of INSTI was not associated with weight gain in any of the models**
- **Emphasized importance of controlling for TDF-to-TAF switch**

McComsey et al. vCROI 2021, abstract 503

Weight Gain with INSTIs versus TAF

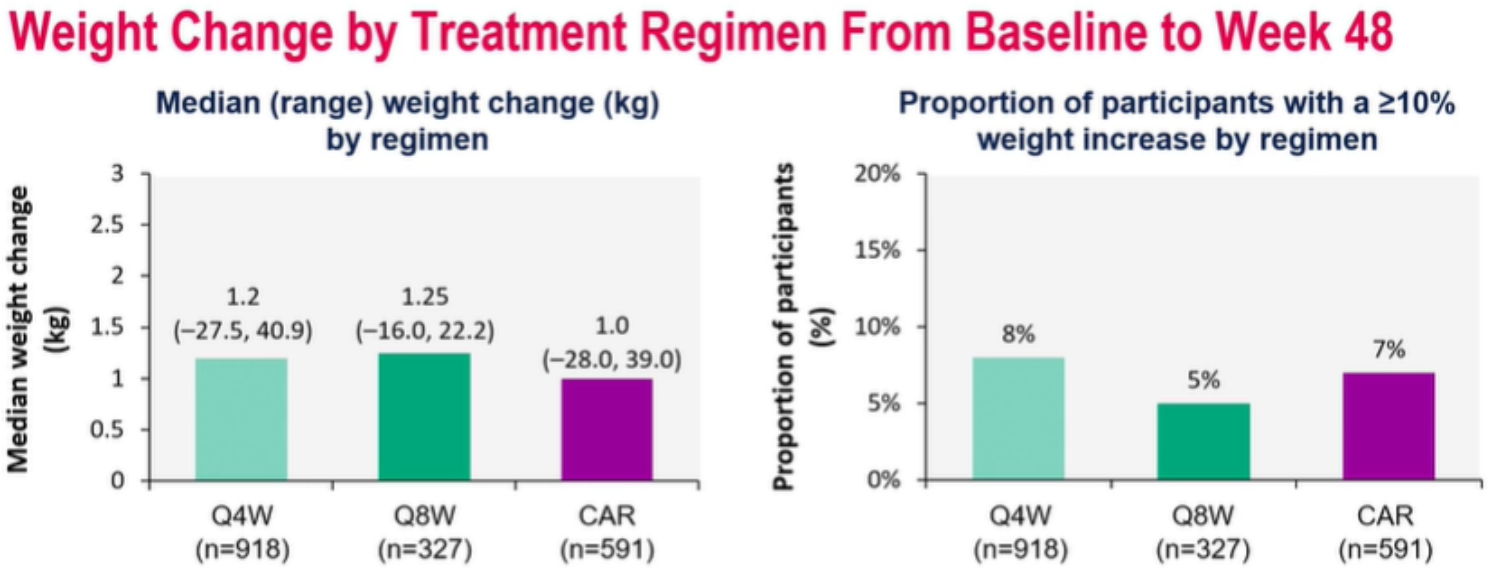
- Objective: To assess magnitude, timing, and persistence of weight change among virally suppressed patients switching to INSTIs or TAF
- Study design
  - HOPS study across 8 care sites
  - INSTI-naïve undergoing switch
- Switching to INSTI-based ART associated with more rapid weight gain compared with non-INSTI-based ART
- Receiving TAF associated with more rapid weight gain compared with no TAF
- Earlier weight gain attributable to INSTI and later to TAF. After 8 months:
  - Trajectory similar for INSTI and non INSTI patients
  - Trajectory steeper for TAF vs. non-TAF
- Unchanged findings after adjustment for age, gender, race, baseline BMI
- No significant differences between INSTIs
- Different trajectories of weight gain prior to switch



- **Both INSTIs and TAF were independently associated with weight gain**
- **Timing of weight gain differed by class**

Palella et al. vCROI, abstract 504

Weight Changes with Long-Acting Cabotegravir/Rilpivirine



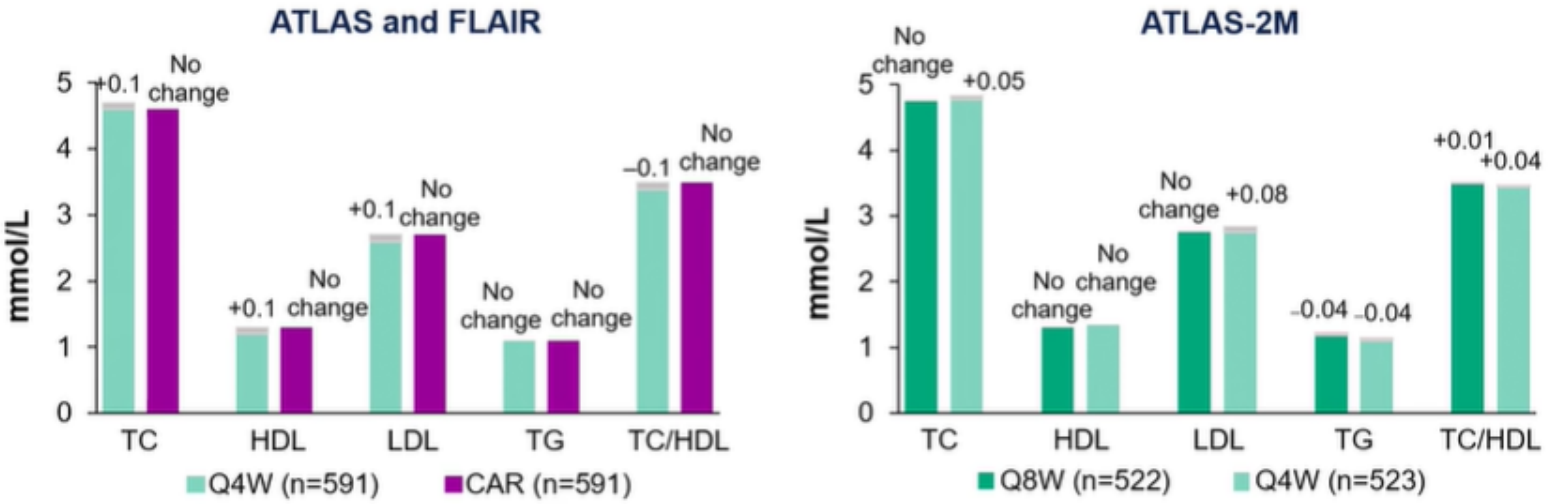
- Objective: To assess weight and lipid changes over 48 weeks in phase 3 study with pooled data from FLAIR, ATLAS, and ATLAS-2M (industry-sponsored)
- Median weight gain was 1.2 kg for both CAB and rilpivirine dosing arms (q4wk and q8wk)
- Proportion with ≥10% increase in weight was similar across groups

Patel et al. vCROI 2021, abstract 505

Lipid Changes with Long-Acting Cabotegravir/Rilpivirine

Baseline and Change From Baseline at Week 48 in Lipid Parameters

Median lipid parameters at BL (solid bars) and median change (mmol/L) from BL (grey bars) at Week 48

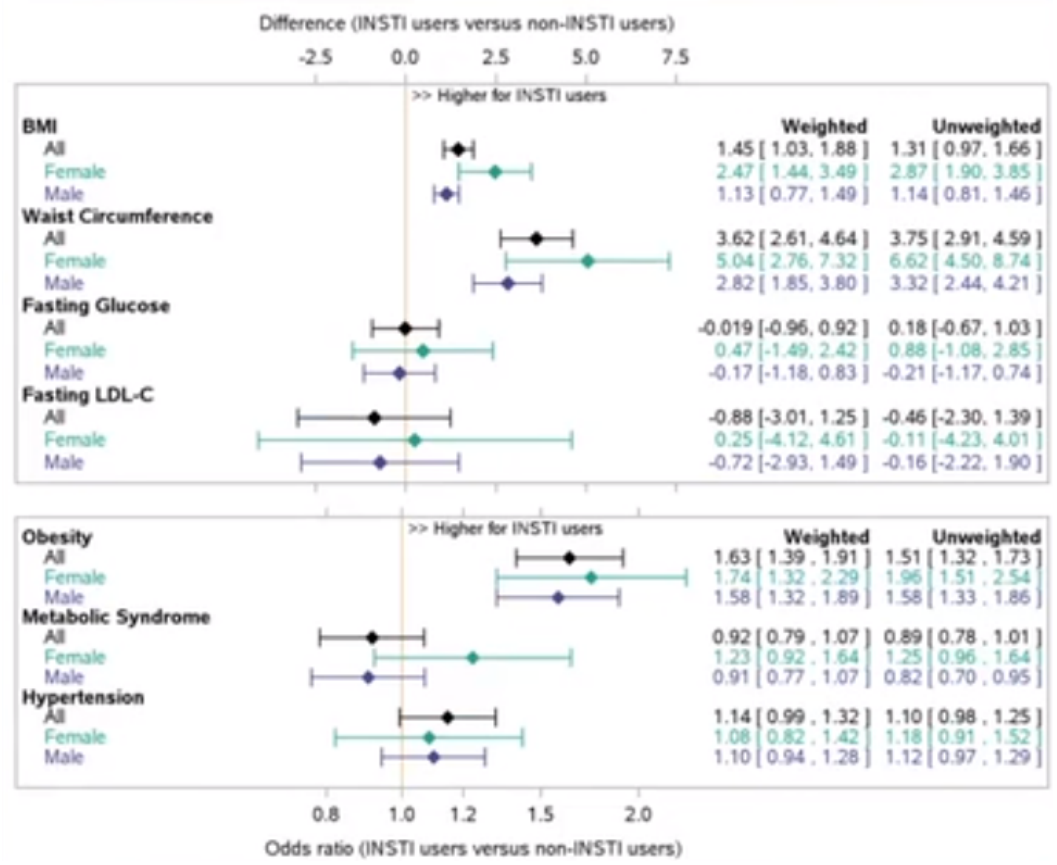


- Objective: To assess changes in lipid parameters similar across treatment arms
- No significant difference in lipids
- Data demonstrate overall favorable metabolic profile of long-acting cabotegravir and rilpivirine dosed every month or 2 months

Patel et al. vCROI 2021, abstract 505

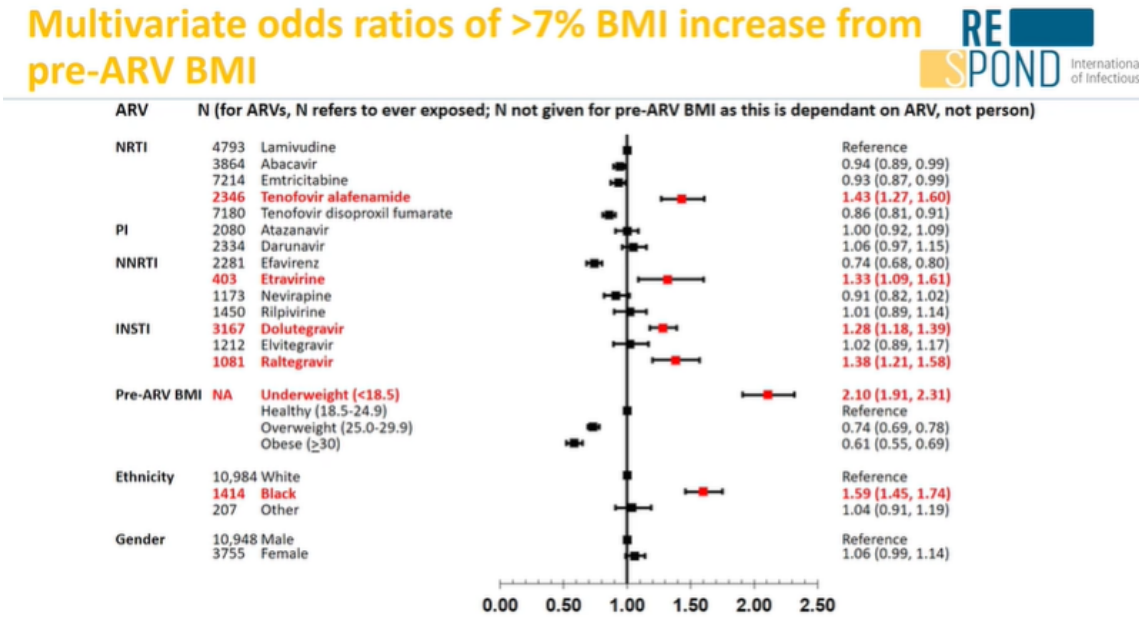
INSTIs and Metabolic Profile in REPRIEVE

- Objective: To evaluate effects of INSTIs on weight and clinically relevant cardiometabolic parameters
- Study design
  - REPRIEVE: multi-center CVD prevention trial
  - N=4500 (1848 on INSTI)
- INSTI use associated with:
  - Higher mean BMI (1.5 kg)
  - Higher odds of obesity (63%)
  - Higher waist circumference
- Differences most pronounced among females
- INSTIs not associated with fasting glucose, LDL, metabolic syndrome, HTN



Lo et al. vCROI 2021, abstract 506

Newer ARVs and BMI Association



- Objective: To assess factors associated with BMI increase following ARV initiation
- Study design: RESPOND cohort, N=14703
- Factors associated with >7% BMI increase after ARV initiation:
  - DTG, etravirine, raltegravir, and TAF independently
  - Combined use of DTG and TAF (stronger association than with either alone)
  - Low pre-ARV BMI
  - Black race

Bansu-Matharu et al. vCROI 2021, abstract 507

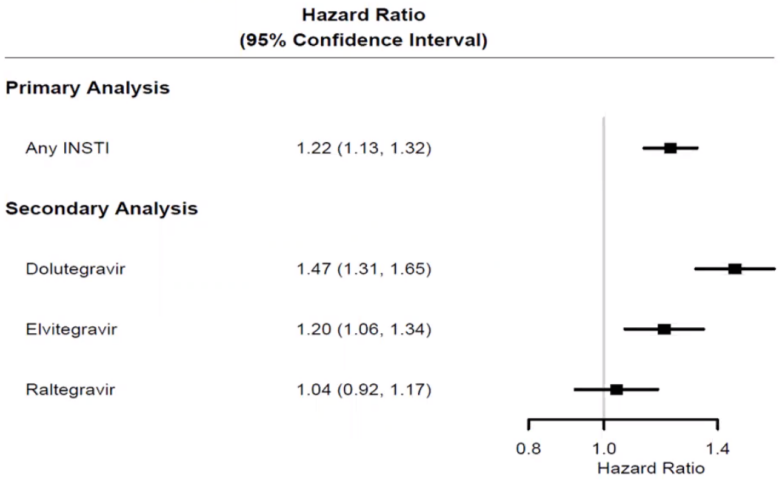
Potential Mechanism of INSTI-Associated Weight Gain

- Study of metabolomic profiles from MACS/WIHS showed changes in amino acid pathways reflecting insulin resistance and in bioenergetic pathways suggesting altered mitochondrial fuel utilization and metabolic inflexibility after switch to INSTI (Lahiri)
- INSTI exposure modifies adipocyte biology related to weight gain (Pickering)
- INSTIs may interrupt adipose function via inhibition of estrogen action (Kim)

Lahiri et al. vCROI 2021, abstract 512; Pickering et al. vCROI 2021, abstract 514; Kim et al. vCROI 2021, abstract 515

DM and INSTI Initiation

- Objective: To assess the risk of new-onset diabetes and hyperglycemia at 6 months in PWH initiating INSTIs
- Study design:
  - Data from IBM MarketScan databases
  - Adults with commercial insurance and Medicaid on ARVs
  - Outcomes ascertained by ICD and CPT codes
- Patients on INSTIs 22% more likely to develop DM or hyperglycemia
- Risk of DM/hyperglycemia greatest with DTG
  - Not able to study bictegravir
- Not able to study TAF, but effects likely attributable to INSTIs since <5% were on concurrent TAF



Adjusted for age, male gender, Elixhauser co-morbidities, gestational diabetes, pancreatitis, pancreatitis malignancy, Hepatitis B & C, cardiovascular disease, hypoglycemia

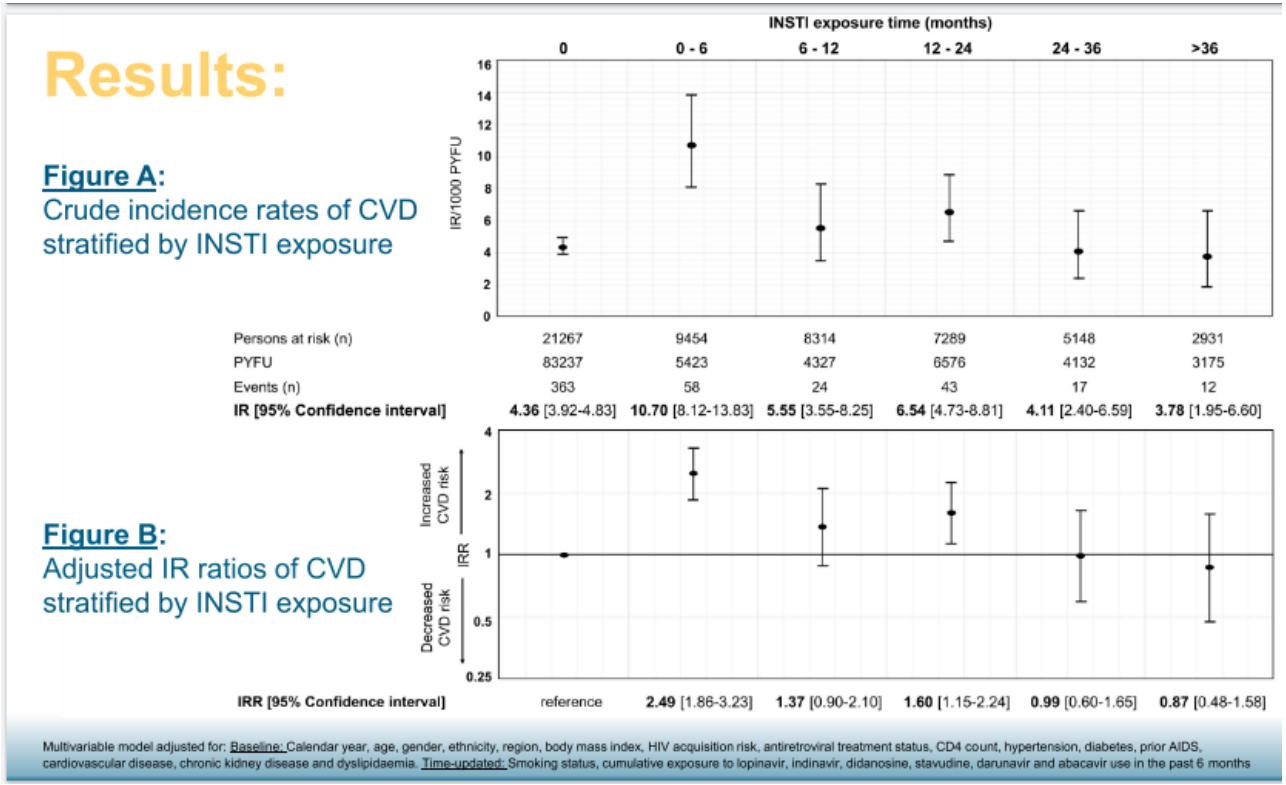
O'Halloran et al. vCROI 2021, abstract 516

INSTIs and CVD Risk

- Objective: To assess whether exposure to INSTIs is associated with increased risk of CVD
- Study design:
  - RESPOND, international collaboration of 17 cohorts
  - Composite endpoint of MI, stroke and invasive cardiovascular procedure; adjudicated events
  - N=21267 (46% exposed to INSTI)
  - 517 CVD events, 4.9/1000 PY
- Sensitivity analyses:
  - Interaction between INSTI exposure group and CVD
  - Interaction between INSTI exposure group and age
  - Excluded individuals with prior CVD
  - Excluded invasive cardiovascular procedures from the composite CVD endpoint
  - Restricted time period to after 2016
- Could not specifically examine ART-naive

Neesgaard et al. vCROI 2021, abstract 488

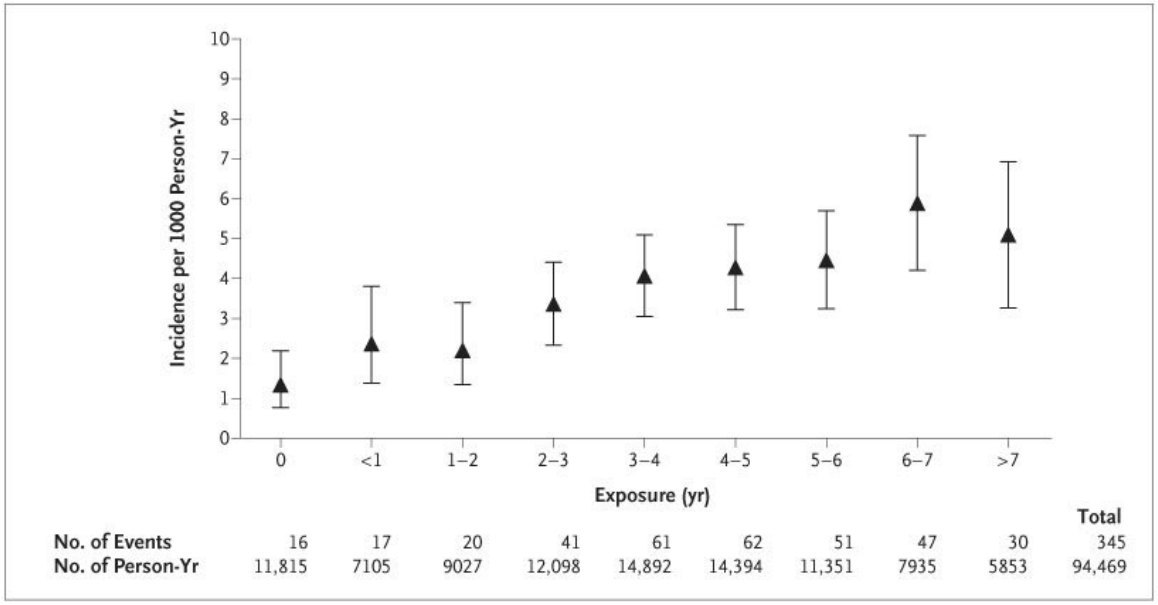
INSTIs and CVD Risk



- INSTI exposure associated with a 2.5-fold greater incidence of CVD within first 6 months of exposure compared to no exposure in adjusted analyses

Neesgaard et al. vCROI 2021, abstract 488

Context: AMI Incidence Increased with PIs

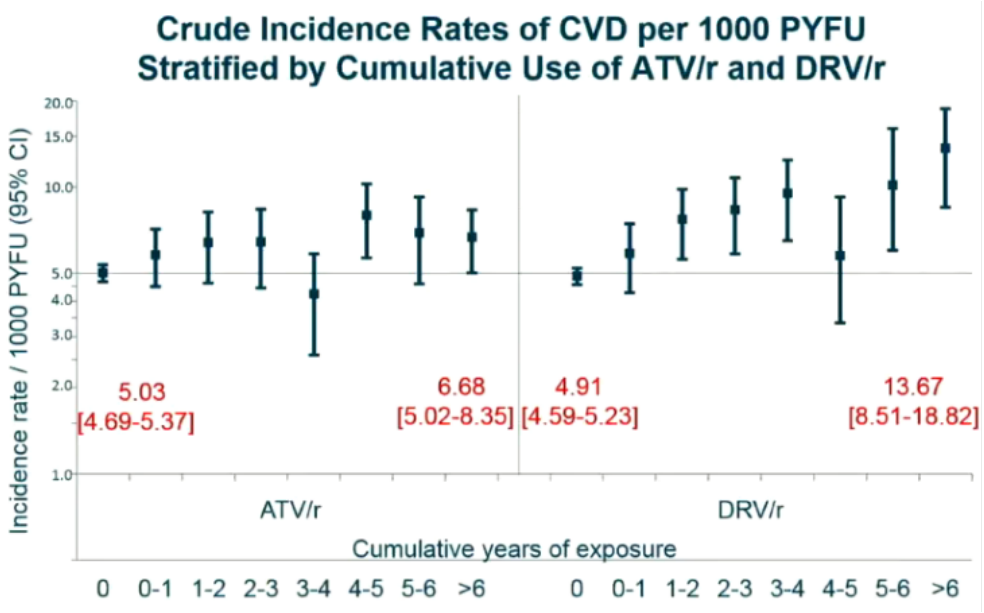


										Total
No. of Events	16	17	20	41	61	62	51	47	30	345
No. of Person-Yr	11,815	7105	9027	12,098	14,892	14,394	11,351	7935	5853	94,469

- D:A:D - prospective observational cohort of 33,347 patients
- Relative risk of AMI 1.16 per year ART exposure
- PIs but not NNRTIs conferred increased risk
- Cumulative exposure to indinavir (RR 1.12 per year) and lopinavir-ritonavir (RR 1.13 per year) associated with increased risk of AMI
- No increased risk observed with atazanavir

Friis-Moller NEJM 2007.

Context: Darunavir and CVD Risk

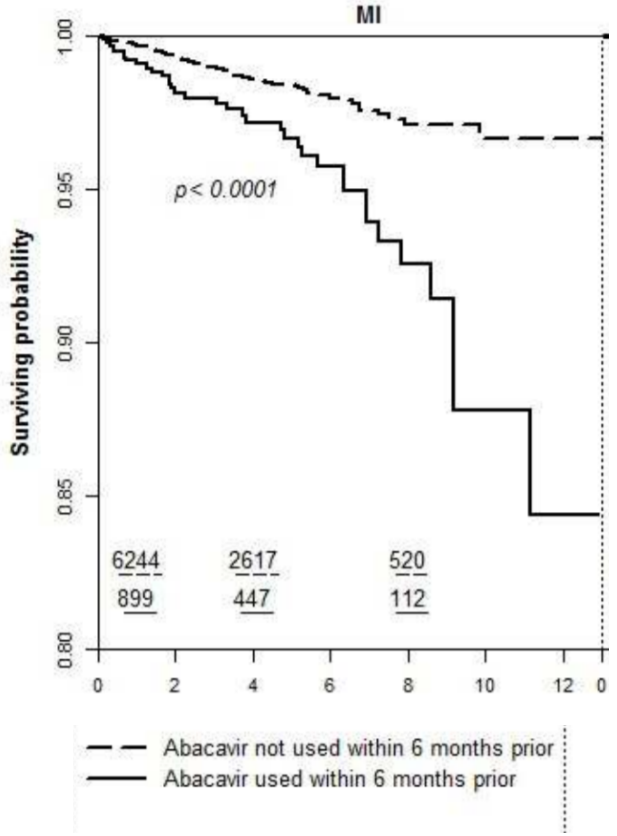


- Increasing CVD risk with cumulative exposure to DRV/r but not ATV/r in multivariate models
- 59% increased risk CVD per 5 years exposure to boosted darunavir
- Strength of association similar to that of IDV and LPV/r but not modified by dyslipidemia
- Multiple sensitivity analyses performed with unchanged results
- Suggests possible PI class effect
  - Atazanavir is exception: hyperbilirubinemia associated with decreased CVD risk
- Clinical implications potentially significant → further studies likely

Ryom et al. Lancet HIV 2018; Marconi et al. JAHA 2018.

Context: Abacavir and MI Risk in the NA-ACCORD

- N=8265 NA-ACCORD participants
- Recent abacavir use in prior 6 months associated with increased risk of MI after adjustment for known CVD risk factors
  - Adjusted HR 1.84



- Kaplan Meier estimates for time from ART initiation to first myocardial infarction, by recent (within the last 6 months) abacavir use

Elion et al. JAIDS 2018.

Clinical Questions

Do you switch off an INSTI if a patient experiences weight gain? If so, do you use a threshold for weight gain?

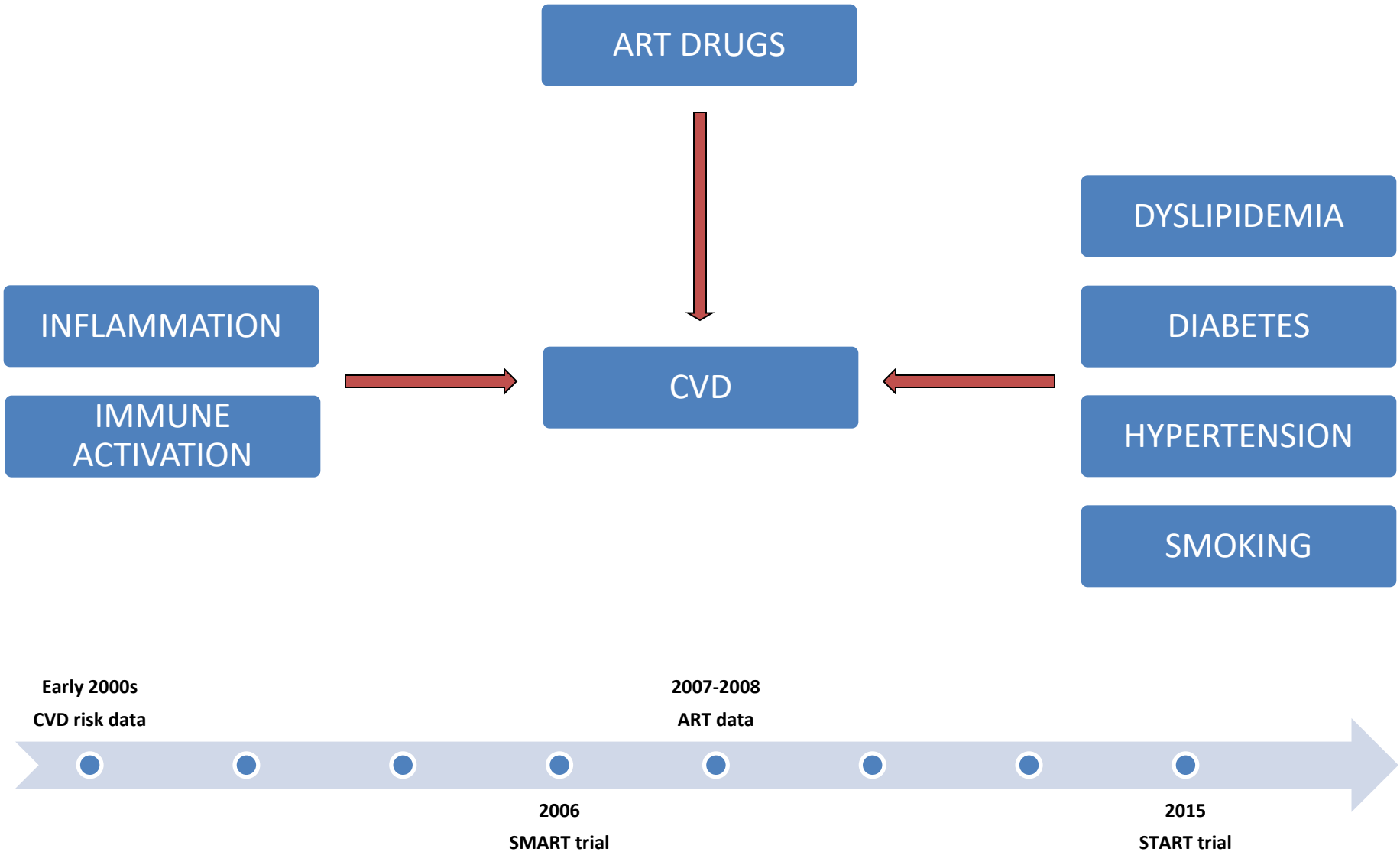
How do you counsel patients starting INSTIs regarding possible side effects including weight gain?

Cardiovascular and Metabolic Complications CROI 2021

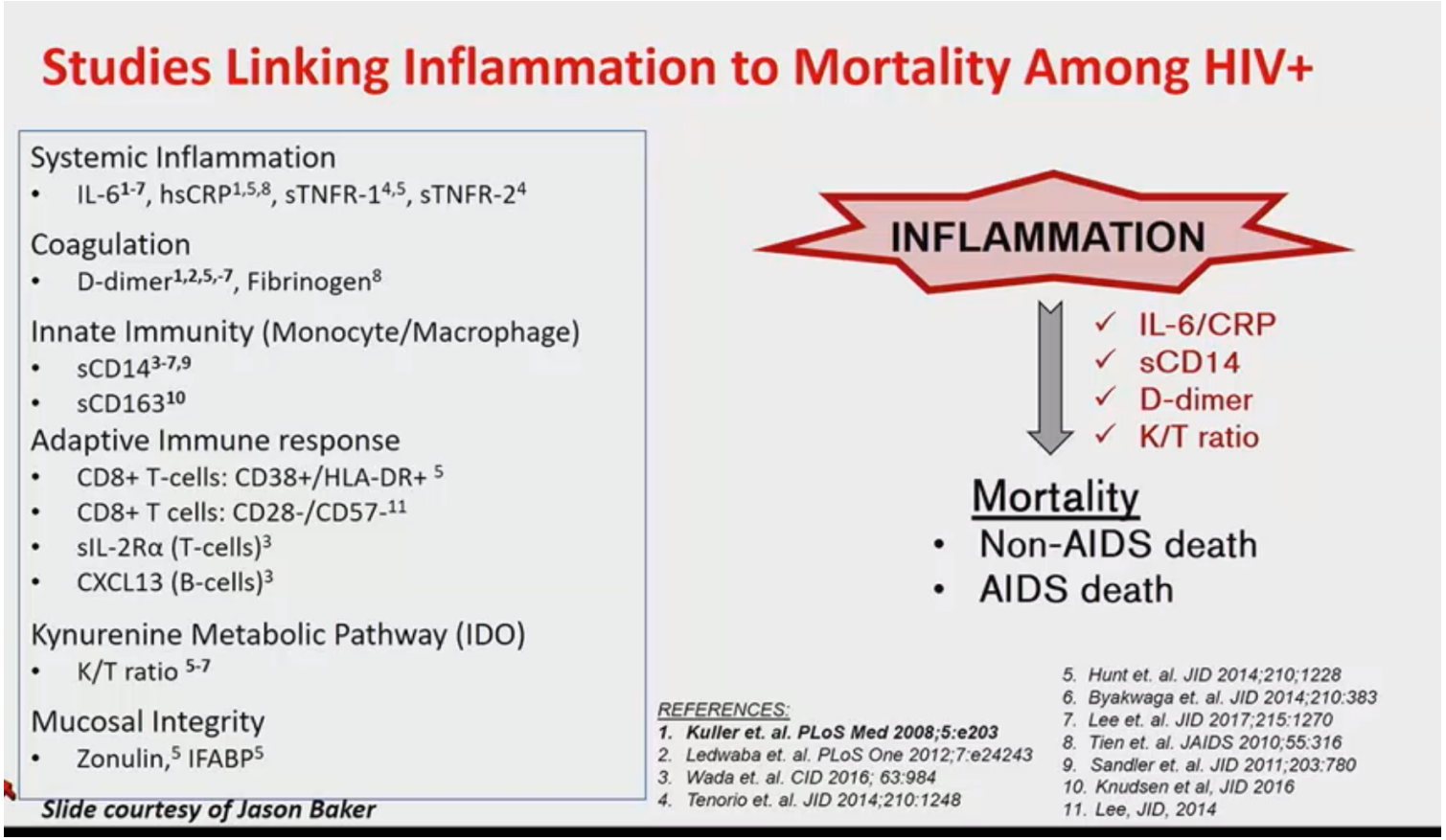
- Adverse effects of ART
  - Weight gain
  - Metabolic effects
  - CVD outcomes
- Novel risk factors for CVD
  - Proteomics
  - Inflammation
- Epidemiology of aging and comorbidities

Cross-cutting themes:
Effects of age, race, sex, and geographic setting on the diagnosis, treatment, and prevention of aging-related complications of HIV

Pathophysiology of HIV-Associated CVD



Inflammation and HIV



- Many pathways may be involved in HIV-related comorbidities and may be targets for intervention
- Do mechanisms for HIV-related CVD and other complications extend beyond traditional risk factors and beyond inflammation/immune dysregulation?

Sereti. Abstract 13. CROI 2019.

Proteins as Predictors of Mortality in HIV

- Do other mechanisms beyond inflammation/coagulation impact risk of comorbidities and mortality in HIV?
- In general population, protein-based scores improve CVD risk prediction
- Large scale proteomics studies are scarce in HIV
- Objectives:
  - Use large scale proteomics to identify novel protein biomarkers associated with mortality in HIV
  - Compare associations of novel proteins with those of HIV-related factors, inflammation and coagulation markers to mortality

Hsue et al. vCROI 2021, abstract 99

Proteins as Predictors of Mortality in HIV

- Stud design
  - VACS BC cohort
  - 1525 HIV veterans, 97% men
- Multiple proteins strongly associated with mortality in prediction models
  - After allowed to complete with age, CD4 and VL
  - After allowed to compete with IL-6, d-dimer, and sCD14
- Risk score based on 10 proteins had good discrimination
- Proteins have varied biologic function
- Many proteins have known therapeutic targets

Top Ten Prognostic Proteins for Mortality Among HIV+ Individuals in VACS

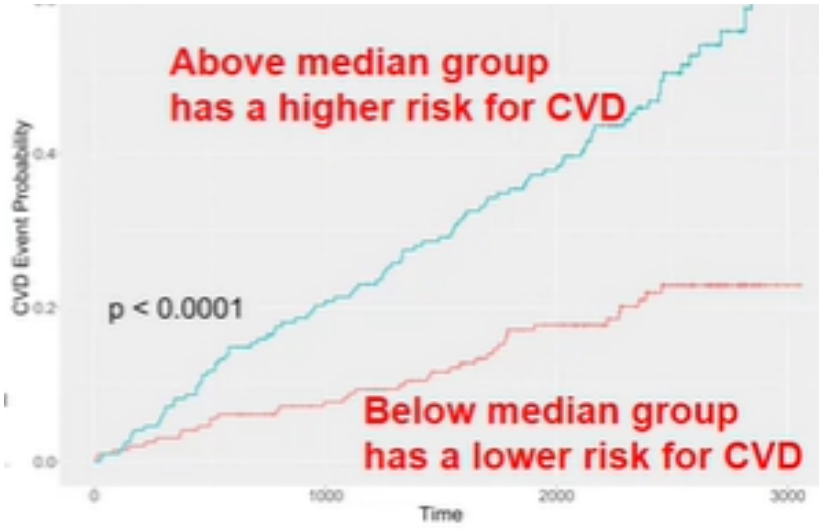
Protein name	HR	P value	Q value	Biological Function	Known Therapeutic Target
EGF containing Fibulin-like Extracellular Matrix Protein 1	2.78	1.76e-45	3.89e-42	Cell adhesion, migration, growth	
Sushi, vWF Type A, EGF and pentraxin domain-containing protein 1	2.04	2.08e-35	2.303e-32	Cell adhesion	
N-acetylglucosamine-1-phosphotransferase subunit gamma	3.99	2.14e-33	7.88E-31	Carbohydrate phosphorylation, lysosomal targeting	
Follistatin like 3	2.37	8.41E-31	2.65E-18	Antagonist to TGF-β superfamily ligands; body composition, islet cell function	
Monocyte differentiation antigen CD14, soluble	2.60	2.11e-30	5.18e-28	Immunity	Yes
WAP four-disulfide core domain protein 1	2.12	1.34e-29	2.95e-27	Cell growth	
Hepatitis A virus cellular receptor 2	2.34	1.88e-29	3.22e-27	Immunity	Yes
Epidermal growth factor receptor	0.161	9.73e-34	5.37e-31	Cell growth, differentiation	Yes
Histone lysine N-methytransferase SET	0.161	1.33e-33	5.80e-31	Histone methylation	Yes
Vitamin K-dependent protein C	0.295	2.01e-30	5.18e-28	Blood coagulation	Yes

Model	C-statistic Training Set (95%CI)	C-statistic Testing Test (95%CI)
Proteins only	0.71 (0.65, 0.77)	0.69 (0.56, 0.79)
Proteins competing with age, CD4 count, CD4 nadir, HIV RNA	0.71 (0.65, 0.77)	0.69 (0.56, 0.79)

Hsue et al. vCROI 2021, abstract 99

Role of Protein Biomarkers in CVD Risk Prediction

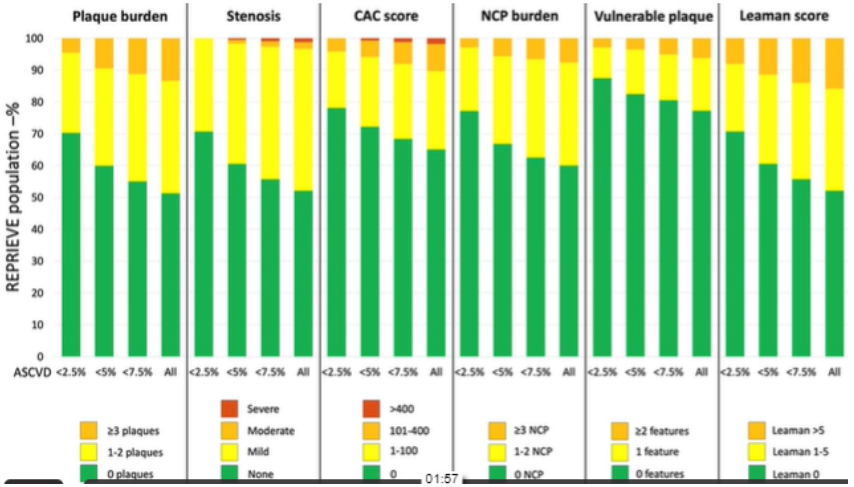
- Objective: To use proteomics to identify protein biomarkers that discriminate between CVD cases and controls in HIV
  - Non-traditional risk factors such as proteins may enhance CVD risk prediction in HIV
- Study design
  - Data from 4 INSIGHT clinical trials
  - Outcome: MI, coronary revascularization, stroke
- Developed protein score from 8 proteins
- AUC changed from 0.69 to 0.73 when protein score was added to model
  - Could not adjust for smoking
- Patients with protein score above the median were three times more likely to develop CVD



Safo et al. vCROI 2021, abstract 492

Inflammation in REPRIEVE

- Objective: To assess association of inflammatory biomarkers with coronary plaque
- Study design
  - Mechanistic substudy of REPRIEVE, a large international trial of statins for primary prevention in HIV
  - N=755
- Plaque increases with predicted ASCVD risk
- Inflammatory biomarkers associated with plaque in adjusted models



	Multivariate Model 3***		
	aOR	95%CI	p-value
Biomarker*			
MCP-1	1.10	1.00 - 1.21	0.047
IL-6	1.06	1.01 - 1.11	0.025
LpPLA2	1.18	1.09 - 1.26	<0.001
oxLDL	1.07	0.97 - 1.18	0.176
ASCVD risk	1.16	1.10 - 1.22	<0.001
Total ART Use duration (years)			
<5	Base		
5-10	0.84	0.51 - 1.37	0.478
>10	1.03	0.65 - 1.62	0.904
CD4			
<350	Base		
350-499	0.83	0.49 - 1.42	0.504
≥500	0.97	0.60 - 1.57	0.906
Nadir CD4			
<50	Base		
50-199	0.62	0.40 - 0.96	0.033
200-349	0.72	0.45 - 1.14	0.160
≥350	0.69	0.40 - 1.16	0.163
Unknown	0.54	0.21 - 1.40	0.204

Grinspoon et al. vCROI 2021, abstract 494

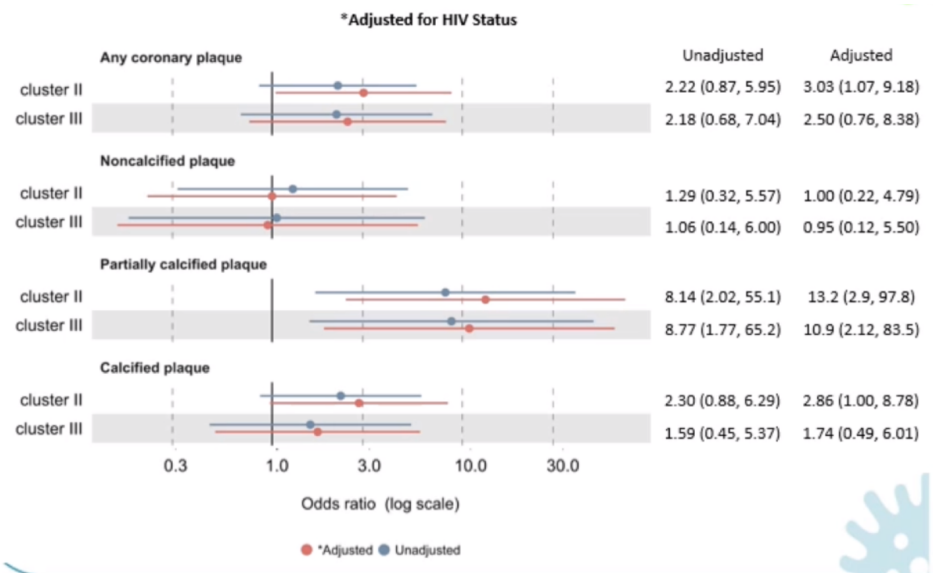
Biological Profiles and CAD

- Objective: Is there an inflammatory profile associated with CAD in HIV?
- Study design:
  - HIV UPBEAT cohort: prospective longitudinal cohort
  - HIV without CAD and propensity score matched controls
  - N=51 HIV, 50 controls
  - CT angiography to assess for subclinical atherosclerosis
- Studied 28 protein biomarkers to reflect pathways
- Studied 10 T cell immunological markers

Protein Biomarkers			
Coagulation		**Microbial translocation**	
sCD40L	D-dimer	LBP	
sP-sel		I-FABP	
Endothelial function		**Systemic inflammation**	
sICAM-1	E-selectin	hsCRP	IL1RA
sVCAM-1	vWF	IL-6	TNF
Innate immune activation		IFN	IL1 beta
sCD14	MCP1	TNF R I/II	
sCD163	MIP1 alpha	**Immune regulation**	
Th1 response		IL-10	TSLP
IL-18	IL-2	IL-4	
IL-12	IFN	**Atherosclerosis**	
		Lp-PLA2	

McGettrick et al, vCROI 2021, abstract 100

Biological Profiles and CAD



- 36% had subclinical atherosclerosis
- 3 distinct inflammatory clusters/biological profiles identified
  - Cluster III: higher systemic inflammation
  - Clusters II and III strongly associated with partially calcified plaque
- HIV did not alter the association between inflammatory profile and plaque
  - Suggests that inflammatory profiles rather than additional effect of HIV are driving risk of subclinical atherosclerosis

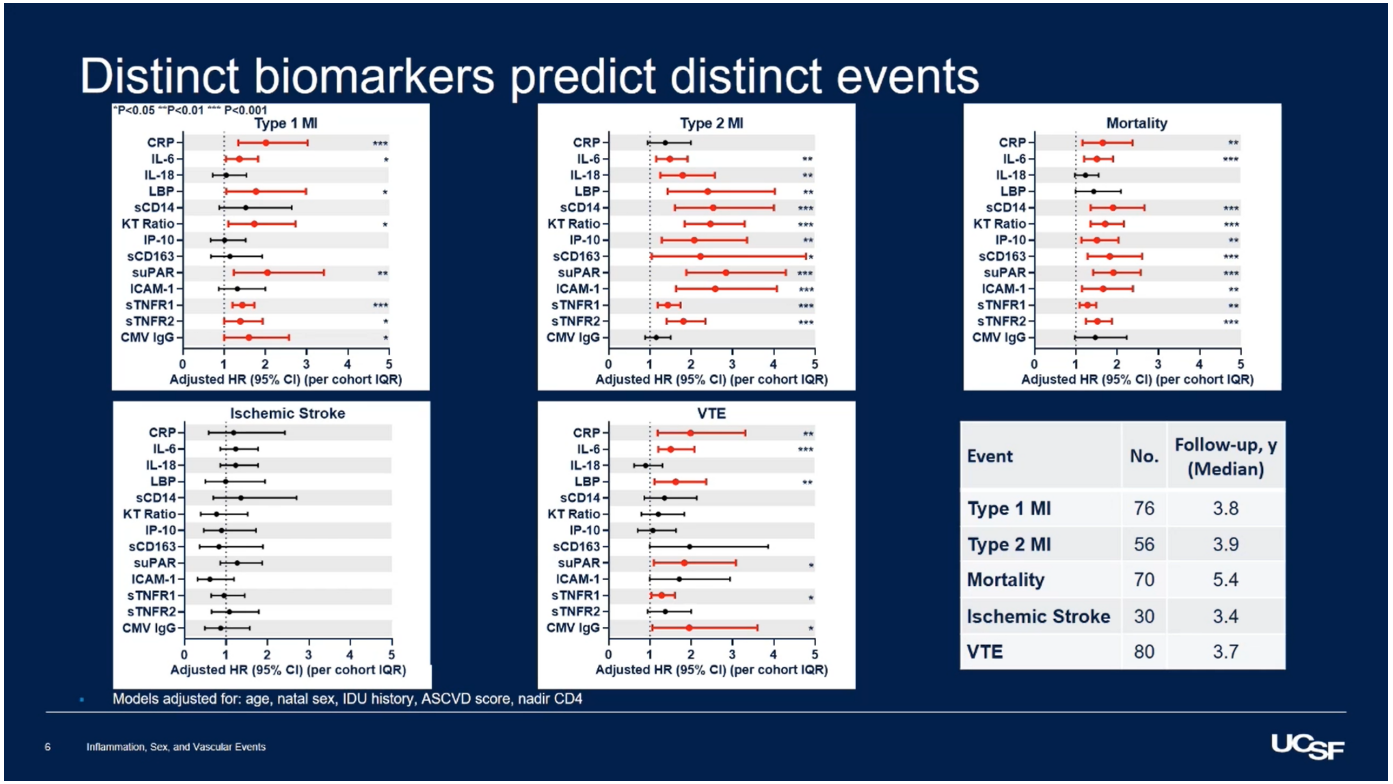
McGettrick et al, vCROI 2021, abstract 100

Sex Differences in Inflammation and Vascular Events

- Objective: To investigate
  - Immunologic predictors of vascular events
  - How sex affects immune activation and its relationship to clinical outcomes
- Study design:
  - CNICS: large multicenter cohort
  - Case cohort study
  - Sampled cases of type 1 and type 2 MI, ischemic stroke, and VTE
  - N=979 virally suppressed at least 1 year

Schnittman et al. vCROI 2021, abstract 98

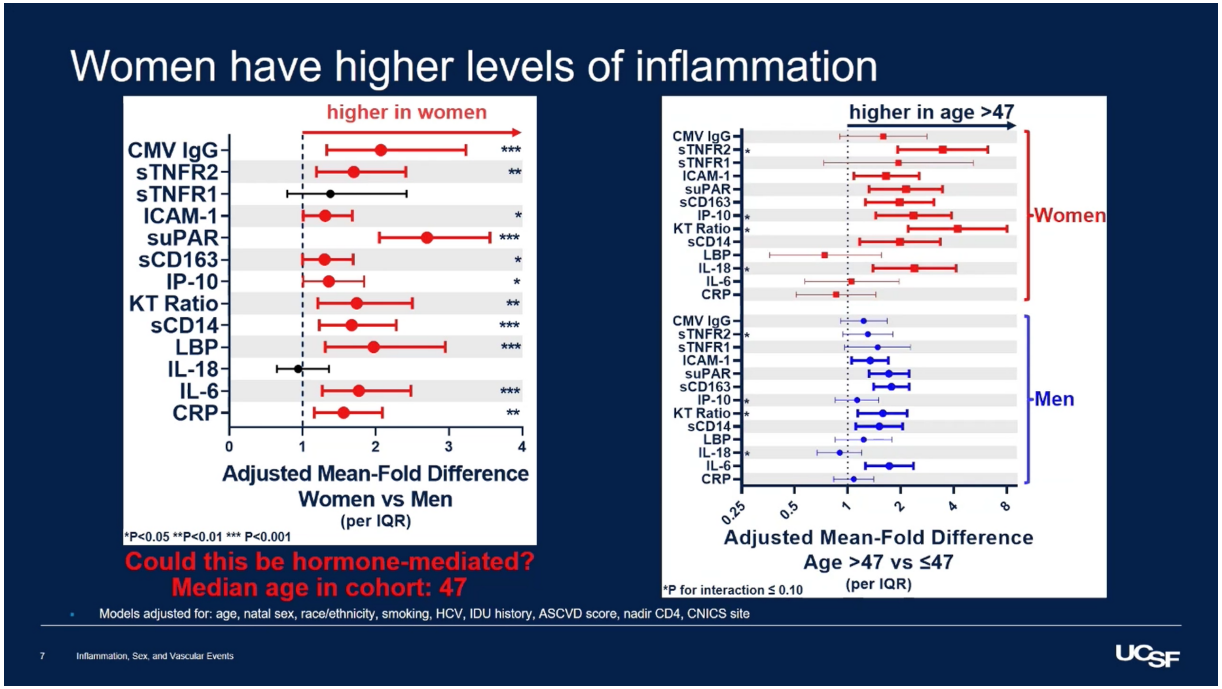
Sex Differences in Inflammation and Vascular Events



- Distinct biomarkers predict distinct all cause events → implications for intervention
  - Type 2 MI and mortality: all pathways
  - Type 1 MI: generalized inflammation, microbial translocation, kynurenine pathway, CMV
  - VTE: generalized inflammation, microbial translocation, CMV

Schnittman et al. vCROI 2021, abstract 98

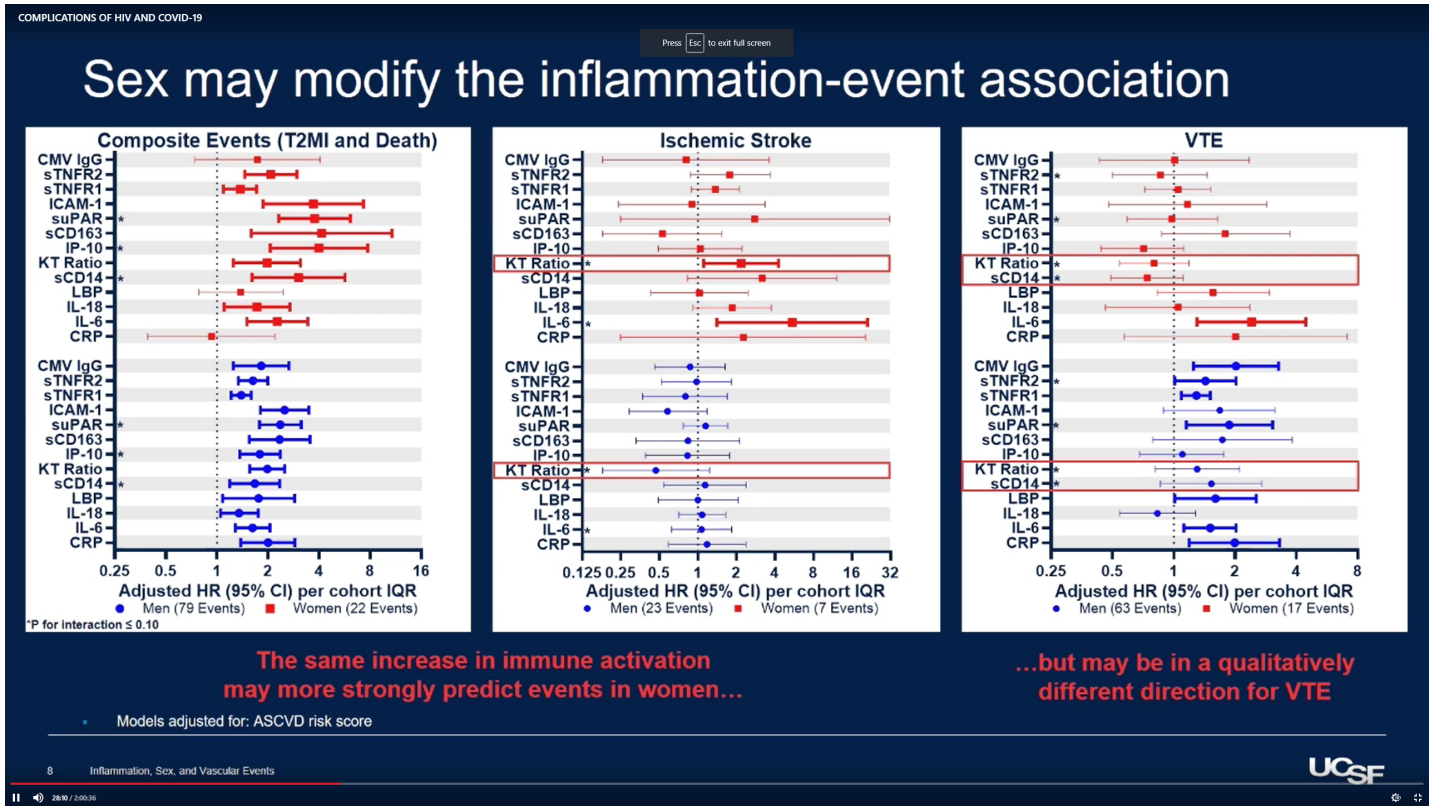
Sex Differences in Inflammation and Vascular Events



- Levels of inflammation are higher in women
- Men and women have higher biomarkers after age 47 (cohort median and surrogate for menopause)
- Women have larger relative increases in biomarkers after age 47

Schnittman et al. vCROI 2021, abstract 98

Sex Differences in Inflammation and Vascular Events



- In women with HIV, immune activation is both higher and more strongly associated with vascular events
  - Effect modification by sex differs depending on the outcome
  - For composite of Type 1 MI and death, for increase in any biomarker, the hazard of incident event is higher in women (in red on the top)
  - For VTE, increase in biomarkers is associated with a higher hazard of the outcome in men than women

Schnittman et al. vCROI 2021, abstract 98

Clinical Questions

What is your approach to CVD risk stratification in PLWH?

Should novel risk factors be incorporated into CVD risk stratification in HIV?

Cardiovascular and Metabolic Complications CROI 2021

- Adverse effects of ART
  - Weight gain
  - Metabolic effects
  - CVD outcomes
- Novel risk factors for CVD
  - Proteomics
  - Inflammation
- Epidemiology of aging and comorbidities

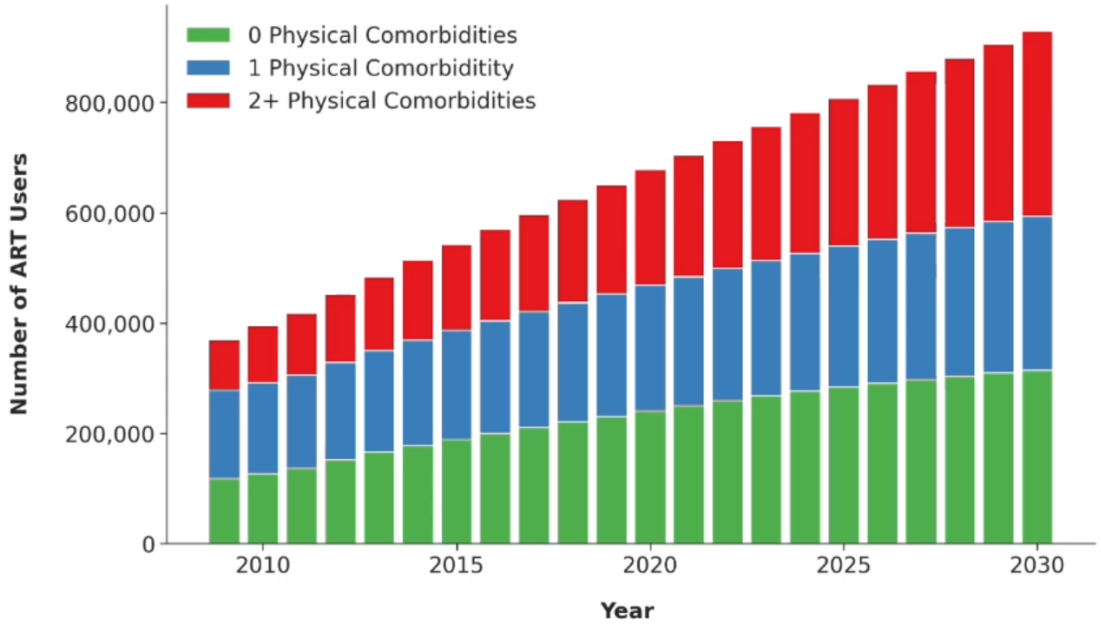
Cross-cutting themes:
Effects of age, race, sex, and geographic setting on the diagnosis, treatment, and prevention of aging-related complications of HIV

Multimorbidity and Aging

- Objective: To assess how the multimorbidity burden will grow as PWH on ART age in the next decade
  - The proportion of PWH >65 almost doubled 2013-2017
- Study design
  - PEARL simulation model
  - Tool for projecting aging, multimorbidity, and polypharmacy in HIV
  - Aggregate data from CDC surveillance and NA-ACCORD
  - Simulation starts in 2009 and projects to year 2030
- Projects increase in ART users with median age 50 in 2020 to 53 in 2030

Kasaie et al. vCROI 2021, abstract 102

Multimorbidity and Aging

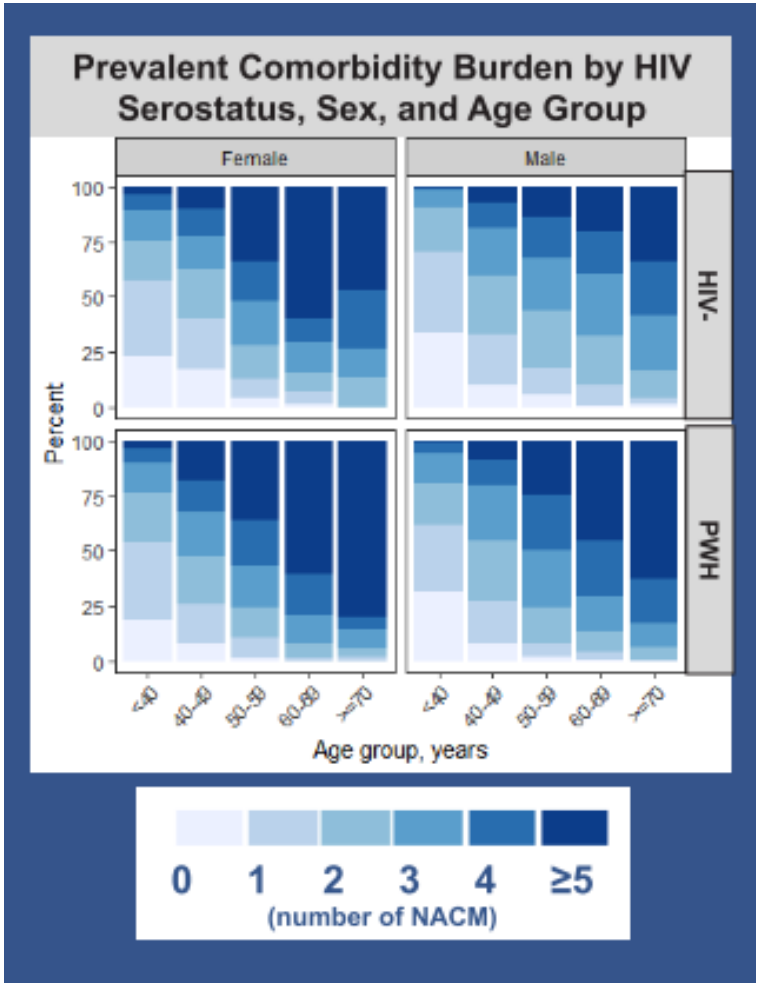


- Multimorbidity burden predicted to grow over time and differs by age and subgroup
- 30% with >1 comorbidity in 2020 vs. 36% in 2030
- 17% increase in Hispanic men who inject drugs and 24% increase in Hispanic women

Kasaie et al. vCROI 2021, abstract 102

Impact of HIV on Age-Related Comorbidities

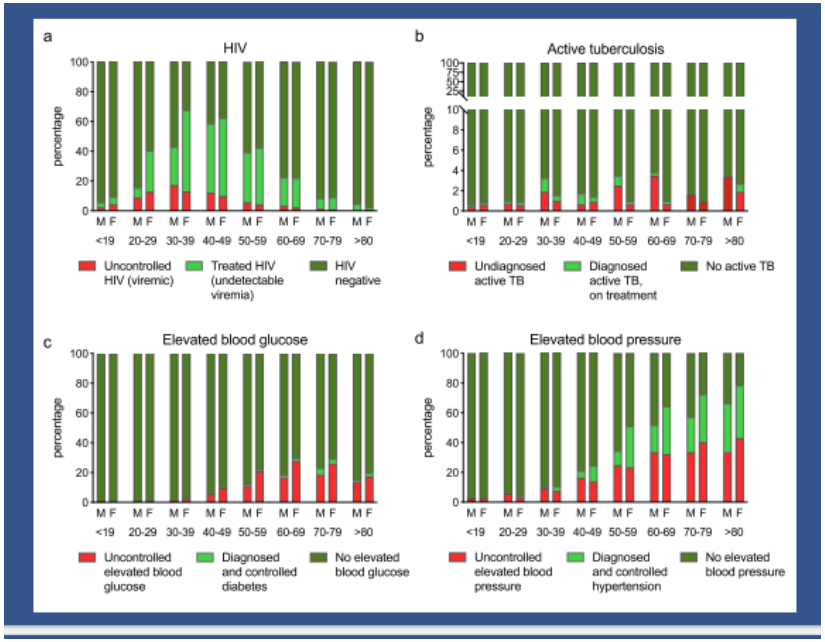
- Objective: To assess the differential impact of HIV on burden of non-AIDS comorbidities in women versus men
- Study design
  - MACS/WIHS combined cohort
- Comorbidity burden higher in
  - PWH
  - Advancing age
  - Women
- Effect of HIV on comorbidity burden persisted in adjusted analyses
- HIV and sex-specific screening and prevention strategies needed for non-AIDS comorbidities

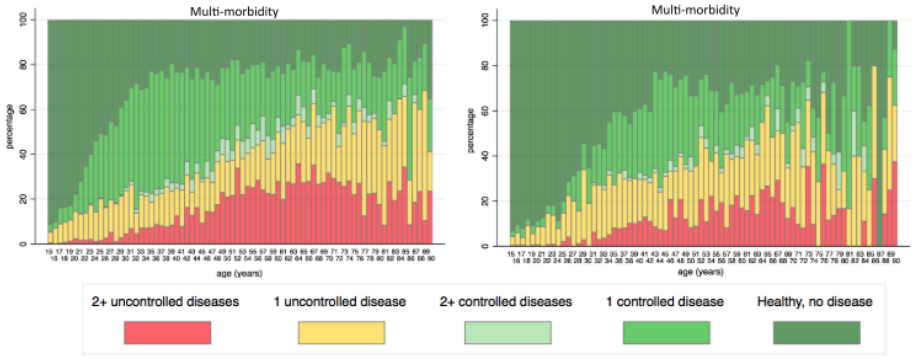


Collins et al. vCROI, abstract 526

Infectious and Noncommunicable Diseases in Rural South Africa

- Objective: To study population prevalence of HIV, TB, elevated blood glucose, and elevated blood pressure in KwaZulu-Natal
- Study design:
  - N=17118 (11618 women)
  - Used mobile health camps
- Prevalence of diagnosed and uncontrolled elevated glucose and BP increased with age
  - HIV well controlled but elevated blood glucose and BP poorly controlled
- Multimorbidity increased with age and at an earlier age for women
- Distribution of noncommunicable diseases does not overlap with HIV age distribution
- Public health response should expand on successes of HIV testing and treatment to provide noncommunicable disease care





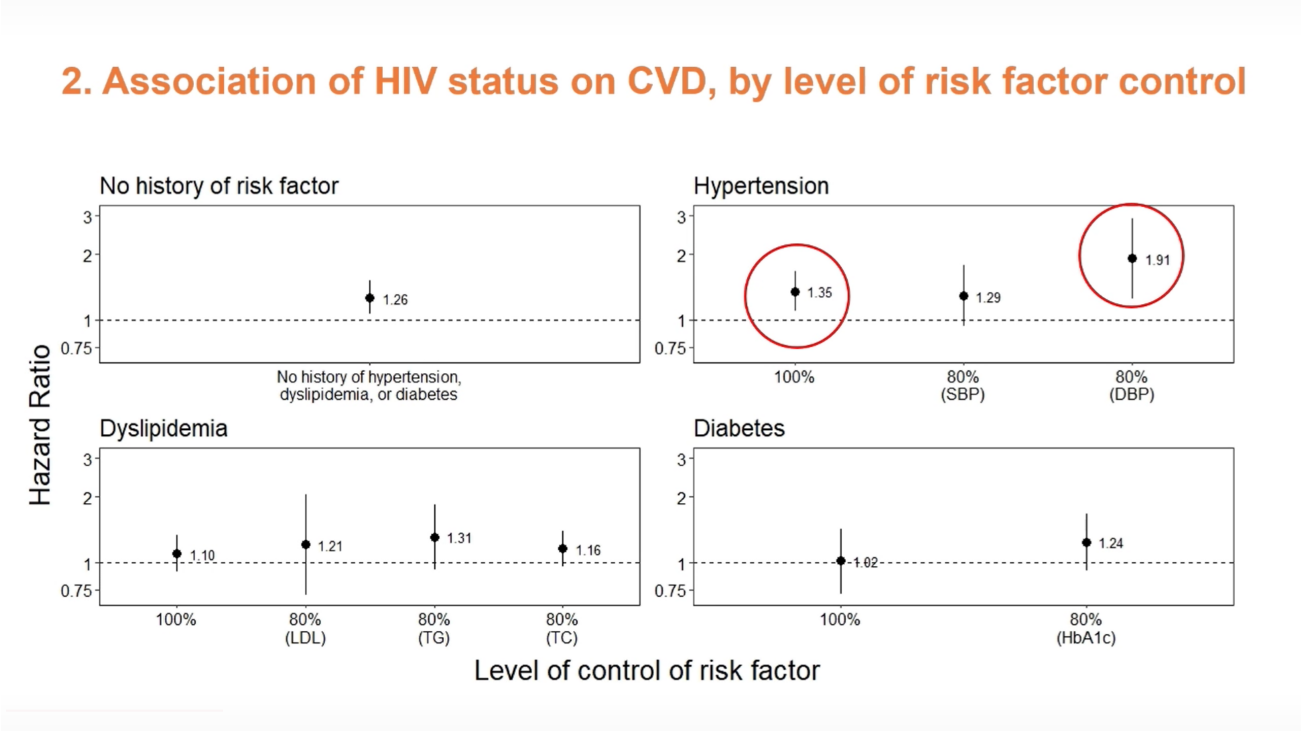
Wong et al. vCROI 2021, abstract 524

CVD Risk Factor Management

- Objective: To assess whether successful management of CVD risk factors reduces excess CVD risk
- Study design
  - Kaiser Permanente Northern California HIV cohort
  - N=8285, 90% men
  - Frequency-matched controls
- Disease management index
  - Measure of how effectively a condition is managed that incorporates time and level of control
  - DMI 100% = perfect control
  - DMI 0.81 = blood pressure that was in control for 81% of person time
- Assessed association of HIV status on DMI
  - Similar dyslipidemia, HTN, and diabetes control by HIV status
  - Slightly worse TG and better A1C control for HIV

Silverberg et al. vCROI 2021, abstract 97

CVD Risk Factor Management



- Assessed association of HIV status on CVD, stratified by level of risk factor control
- For patients with no history of HTN, dyslipidemia, or diabetes, 26% increased risk CVD in HIV vs. non-HIV
- For patients with dyslipidemia or diabetes and perfect control, risk of CVD was no different by HIV status
- For patients with HTN and perfect control, CVD risk was elevated by 35% in those with HIV vs. non-HIV
  - For those with inadequate HTN control, CVD risk was elevated by 91% in those with HIV vs. non-HIV
- Raises question whether more aggressive BP targets are needed for HIV

Silverberg et al. vCROI 2021, abstract 97

Clinical Questions

What challenges are you facing as your patients living with HIV age?

Will care delivery models need to be changed to care for patients with more comorbidities who are aging with HIV? How will care models depend on the clinical setting?

Summary and Implications

- Weight gain and associated metabolic abnormalities have increasingly been shown to be associated with INSTIs and TAF
- Inflammation plays a key role in HIV-related CVD
  - Interplay of traditional and novel CVD risk factors
  - Possibility of additional factors beyond inflammation
  - Optimal strategies to reduce chronic inflammation in treated and suppressed patients are still being defined
- Implementation research is needed to provide guideline-concordant CVD care
- Durable and early HIV treatment may help achieve both the US plan to end the epidemic and the reduction of non-communicable disease complications

THANK YOU


CROI
Conference on Retroviruses
and Opportunistic Infections

Prevention at vCROI 2021

KEVIN L. ARD, MD, MPH

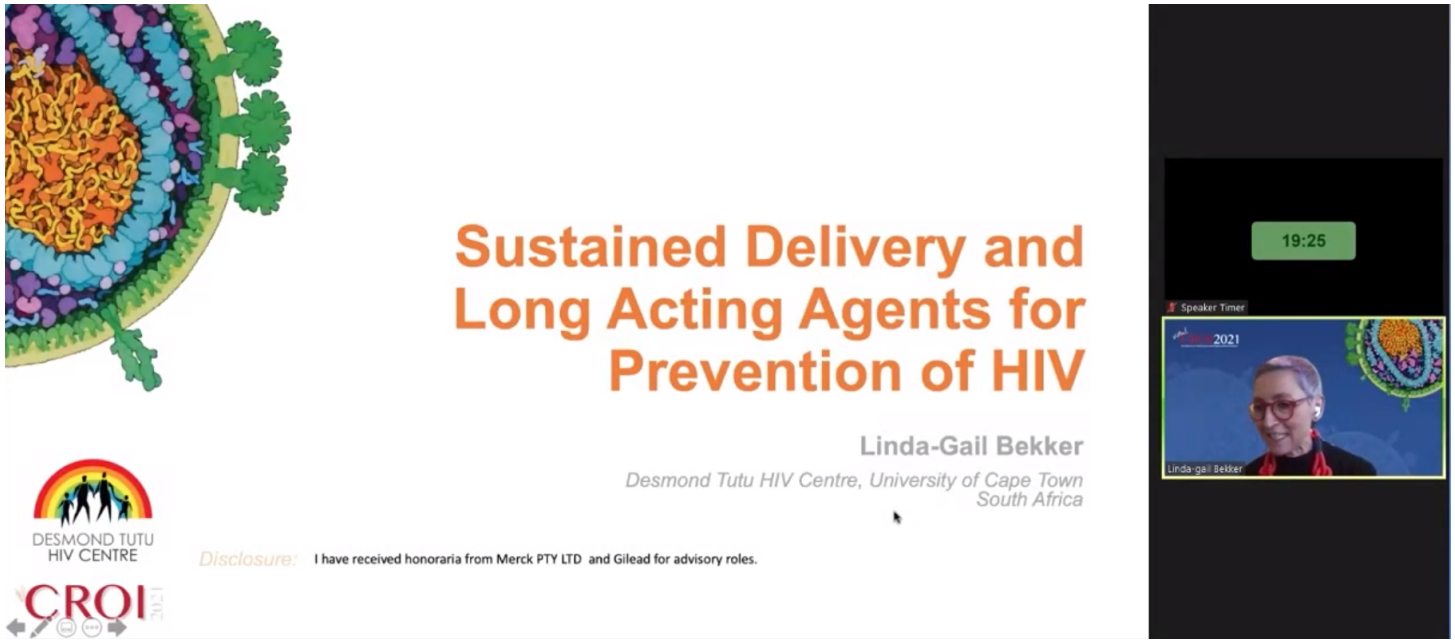
APRIL 13, 2021

Outline

1. New data about oral tenofovir-based PrEP

2. Long-acting PrEP formulations in various stages of development

Recommended plenary



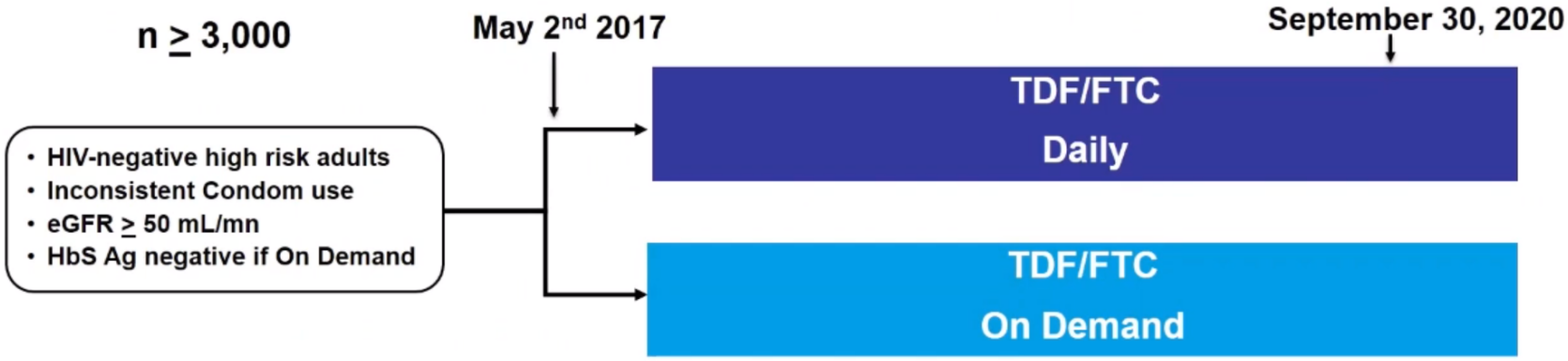
New data about oral tenofovir-based PrEP

Prévenir ANRS

http://prevenir.anrs.fr/

Study Design

Open-Label Prospective Cohort Study in the Paris Region



- **Participants opted for either Daily or On Demand PrEP and could switch regimen**
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- STI screening at physician's discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

Prévenir ANRS

Baseline Characteris

Characteristics (Median, IQR) or (n, %)	Daily N=1544 (50.5%)	On Demand N=1515 (49.5%)	P-value
Age (years)	35 (28 – 43)	36 (30 – 44)	<.0001
MSM	1511 (97.9)	1503 (99.2)	0.0002
Heterosexual men or women	20 (1.3)	11 (0.7)	
Transgender	13 (0.8)	1 (0.1)	
2-year university degree or more	1086 (83.8)	1126 (87.8)	0.0033
Employed	1101 (85.2)	1106 (86.4)	0.3620
History of PrEP use	843 (54.6)	868 (57.3)	0.1333
Use of Chemsex*	223 (14.4)	203 (13.4)	0.4045
No. condomless sex acts in prior 4 weeks	2 (0 – 6)	2 (0 – 4)	<.0001
No. sexual partners in prior 3 months	12 (6 - 25)	10 (5 - 15)	<.0001

* at last sexual intercourse : cocaine, GHB, MDMA, mephedrone..

Prévenir ANRS

HIV Incidence

Global HIV Incidence: 0.11/100 PY (95% CI: 0.04-0.23) (6 cases)

Mean Follow-up of 22.1 months and 5633 Person-Years

Rate of study discontinuation: 14.4/100 PY

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)	IRR (95%CI)
TDF/FTC Daily	2583.25	0.12 (0.02 – 0.34)	**0.99** (0.13-7.38)
TDF/FTC On Demand	2553.68	0.12 (0.02 – 0.34)	

361 HIV-infections averted*

* assuming an incidence of 6.6/100 PY as observed in the Placebo group of the ANRS Ipergay study

The adverse event profiles did not favor on-demand dosing.

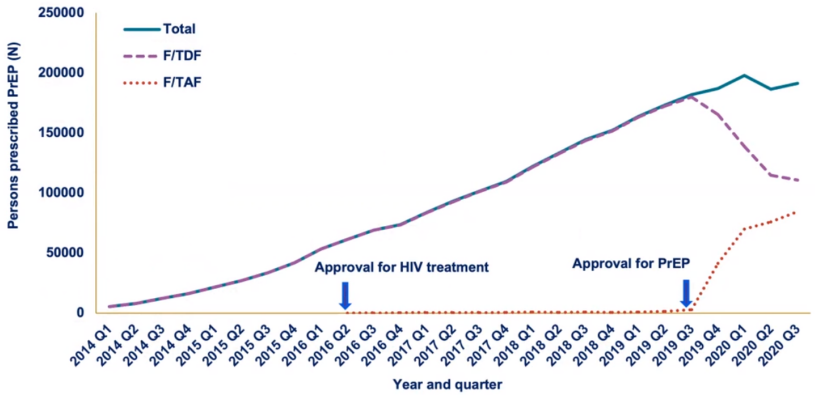
- Drug-related adverse events significantly ***less common*** with daily versus on-demand dosing (IRR 0.78 [0.63-0.97])
- Driven by **more gastrointestinal side effects** with on-demand use (generally mild)
- But, **more grade 1 or 2 ALT elevations** with daily dosing (IRR 1.21 [1.07-1.37])
- No differences in nephrotoxicity

When will on-demand dosing gain acceptance?

Do you use on-demand dosing for patients? If so, in what scenarios?

Many switched from TDF/FTC to TAF/FTC after the latter's FDA approval.

Results



- 36% of new PrEP users after 10/3/2019 started TAF/FTC
- 29% of TDF/FTC users switched to TAF/FTC
- Switchers more likely to be older, male, living in the Midwest, South, or West compared to the Northeast
- Switchers less likely to have cash or "other" payers compared to public insurance

How many of these were driven by medical considerations versus the need to maintain DAP access?

PrEP/early ART during acute HIV affect HIV diagnostic testing.

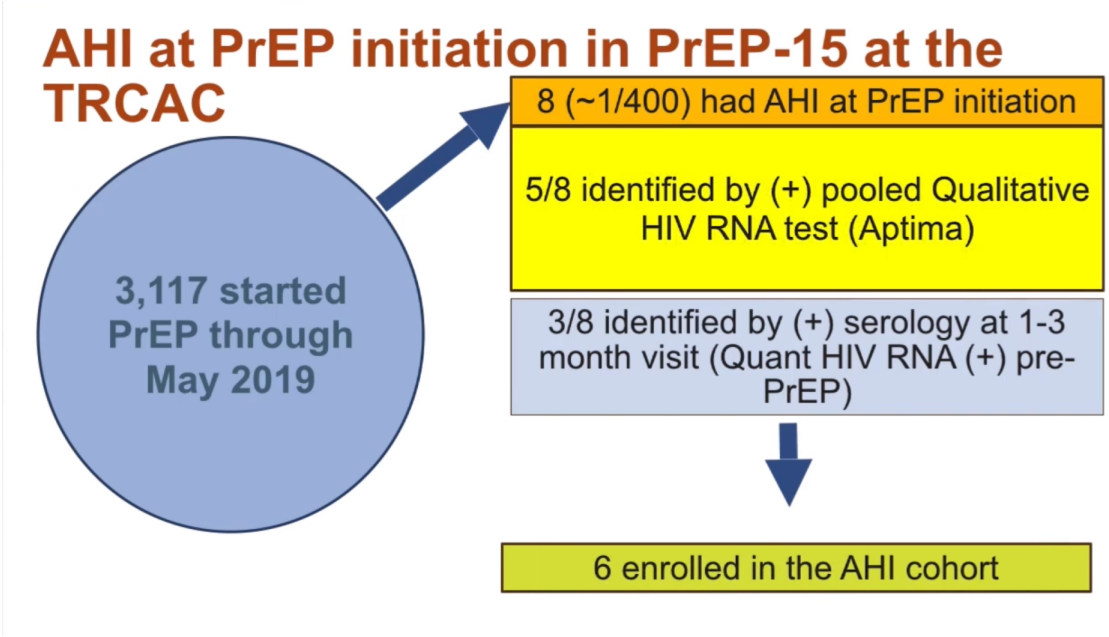


Table: Clinical and diagnostic test results from 6 Thai MSM who started PrEP during acute HIV infection.
xG=x generation HIV antibody test, Gn= Geenius, □=nonreactive, ■=reactive, ND=not done

Partici-pant	# days on PrEP	HIV diagnosis	Pre-PrEP VL (cps/mL)	Pre-ART VL (cps/mL)	Pre-ART CD4 (cells/µL)	Week 0			Week 24			Week 48			
						2G	3G	4G	2G	3G	4G	2G	3G	4G	Gn
3145	7	NAAT	16,780	216	685	□	■	□	□	■	□	ND	ND	□	□
4634	2	NAAT	219	2,317	528	□	□	□	□	■	□	□	ND	□	□
5803	29	Ab	58	37,222	302	□	■	□	■	■	□	ND	ND	■	□
6313	91	Ab	223,361	389	690	■	■	□	■	■	□	ND	ND	□	□
6934	2	NAAT	32	276	739	□	□	□	□	□	□	□	□	□	□
7167	15	NAAT	317	8,802	521	□	□	□	■	■	■	ND	ND	ND.	□

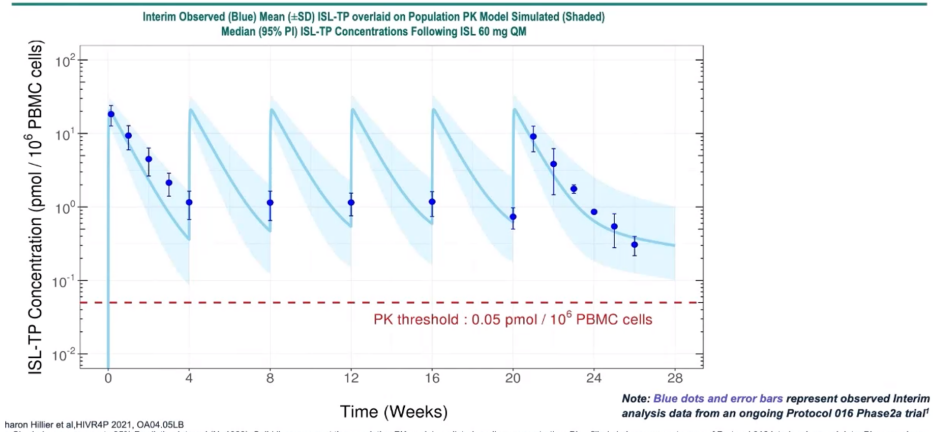
WB = Indeterminate or NEG at all time points in all participants

MHRP

Long-acting PrEP

Islatravir as a long-acting pill or implant

Monthly oral dose of ISL 60 mg is expected to maintain systemic ISL-TP concentrations above the PK threshold

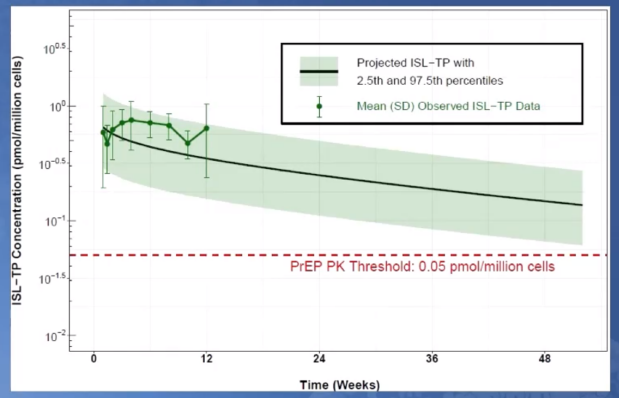


Note: Blue dots and error bars represent observed Interim analysis data from an ongoing Protocol 016 Phase2a trial[1]

haron Hillier et al,HIVR4P 2021, OA04.05LB

: Shaded area represents 95% Prediction Interval (N=1000); Solid line represent the population PK model predicted median concentration; Blue filled circles represent mean of Protocol 016 interim observed data; Blue error bars esent standard deviation of Protocol 016 interim observed data; Previously built Population PK model of ISL was leveraged for population PK simulations (CROI 2020, Abstract 462)

56 mg implant projected to lead to concentrations above threshold for 52 weeks



- 56 mg implant projected to release adequate ISL-TP (above the PK threshold) for almost all individuals for >52 weeks

Higher-dose DPV rings provide superior DPV levels over 13 weeks.

Phase 1 randomized trial with 3 arms:

- 25 mg DPV ring replaced every 4-5 weeks
- 100 mg DPV ring worn for 13 weeks
- 200 mg DPV ring worn for 13 weeks

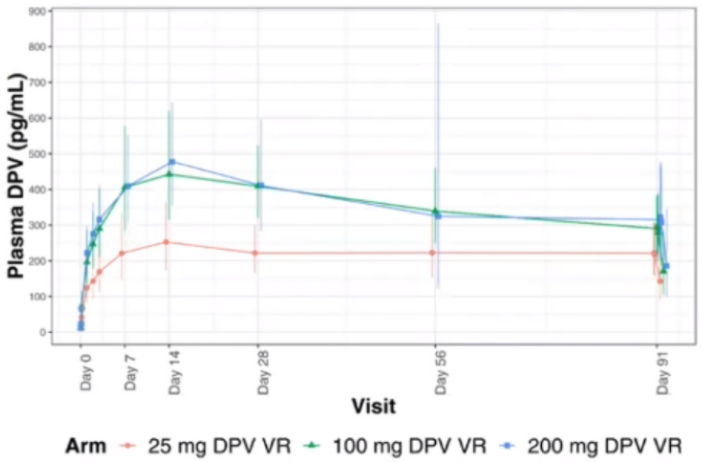
Population: 49 HIV-uninfected people assigned female sex at birth

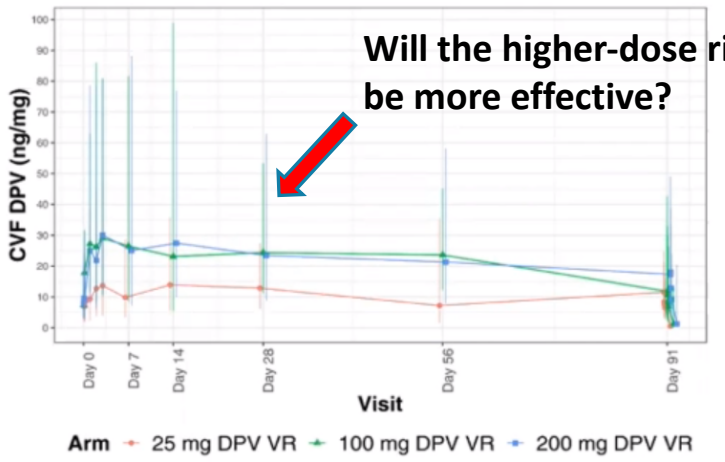
Outcomes: Safety, DPV concentrations in plasma and cervicovaginal fluid, residual drug in rings, acceptability

Results:

- Safety: Most AEs mild to moderate and not different among the arms
- Acceptability:
  - Participants liked the rings more than male condoms
  - Acceptability was highest for the 25 mg (monthly) ring

Geometric mean DPV concentrations in plasma and cervicovaginal fluid



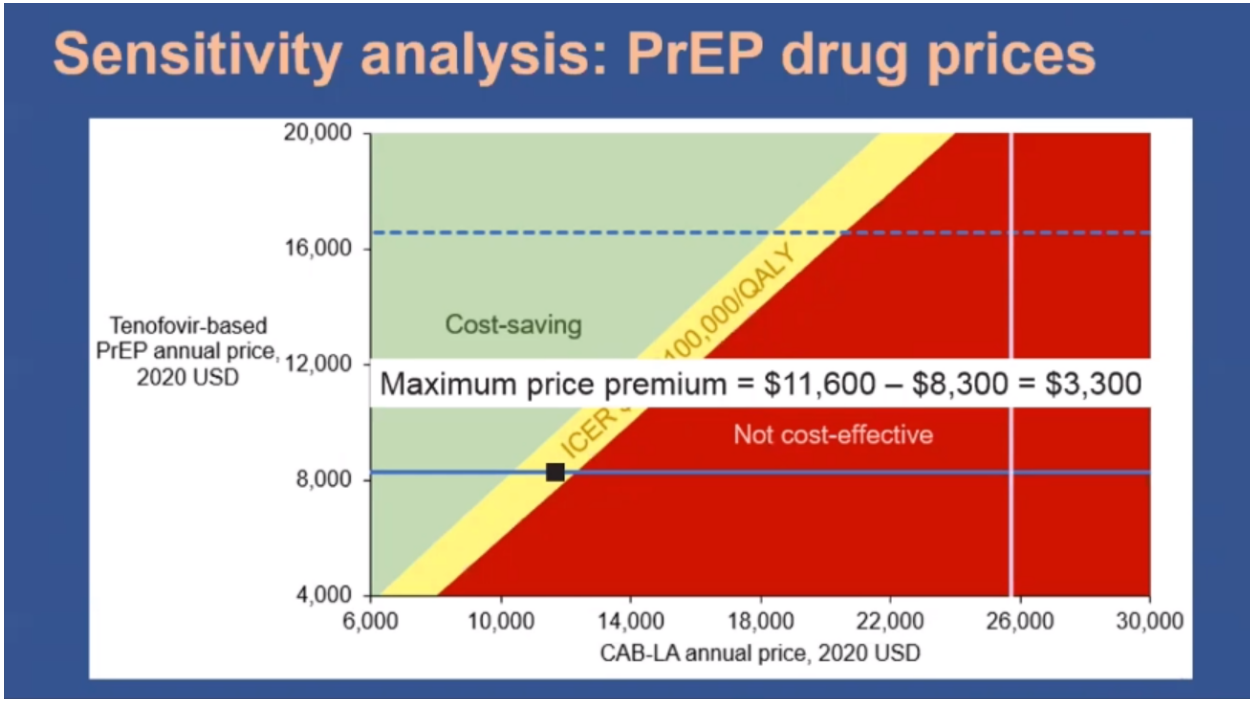


Will the higher-dose rings be more effective?

- Geometric mean T_{max} ranged from 16-25 days in plasma and 1-7 days in CVF
- Decrease in DPV concentrations 4 hours after ring removal was comparable across arms, in both plasma and CVF

MTN microbicide trials network

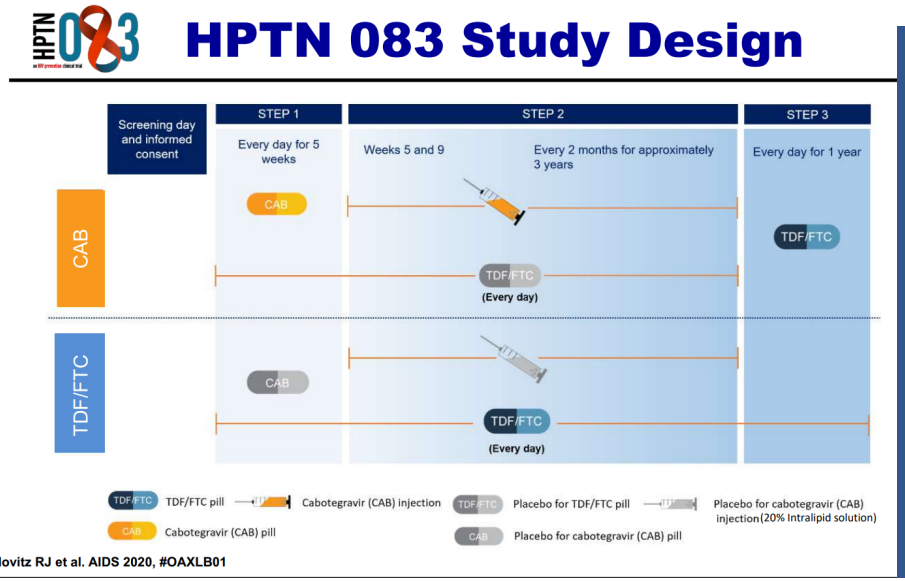
Compared to oral PrEP, CAB-LA is worth more, but not much more.



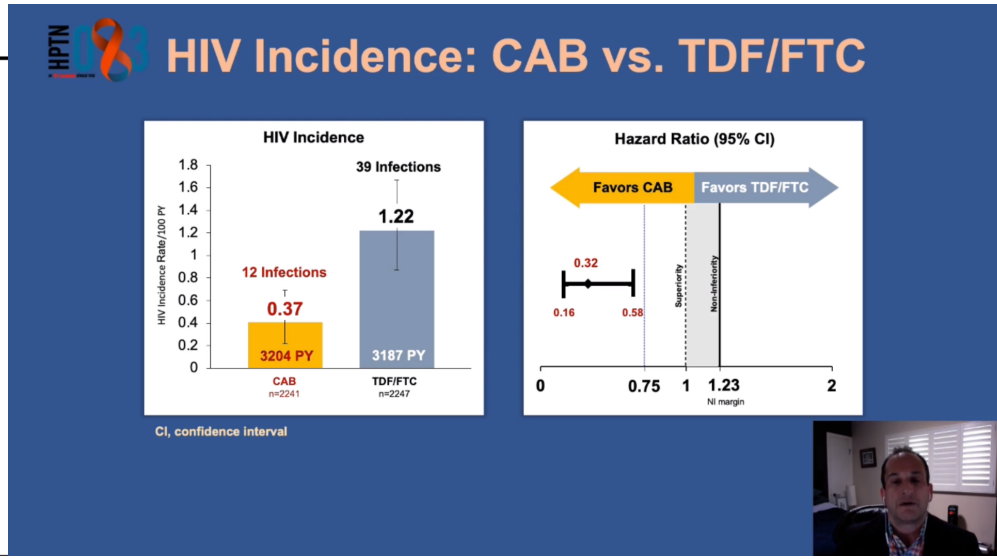
Scenario analyses

Scenario	Impact on CAB-LA price premium	Maximum price premium, 2020 USD
Resistance due to CAB-LA	—	$3,100
HIV diagnostic testing sensitivity and costs in CAB-LA	—	$3,300 - $3,400
Among a population of all potential MSM/TGW PrEP users at lower risk for HIV	↓	$1,000

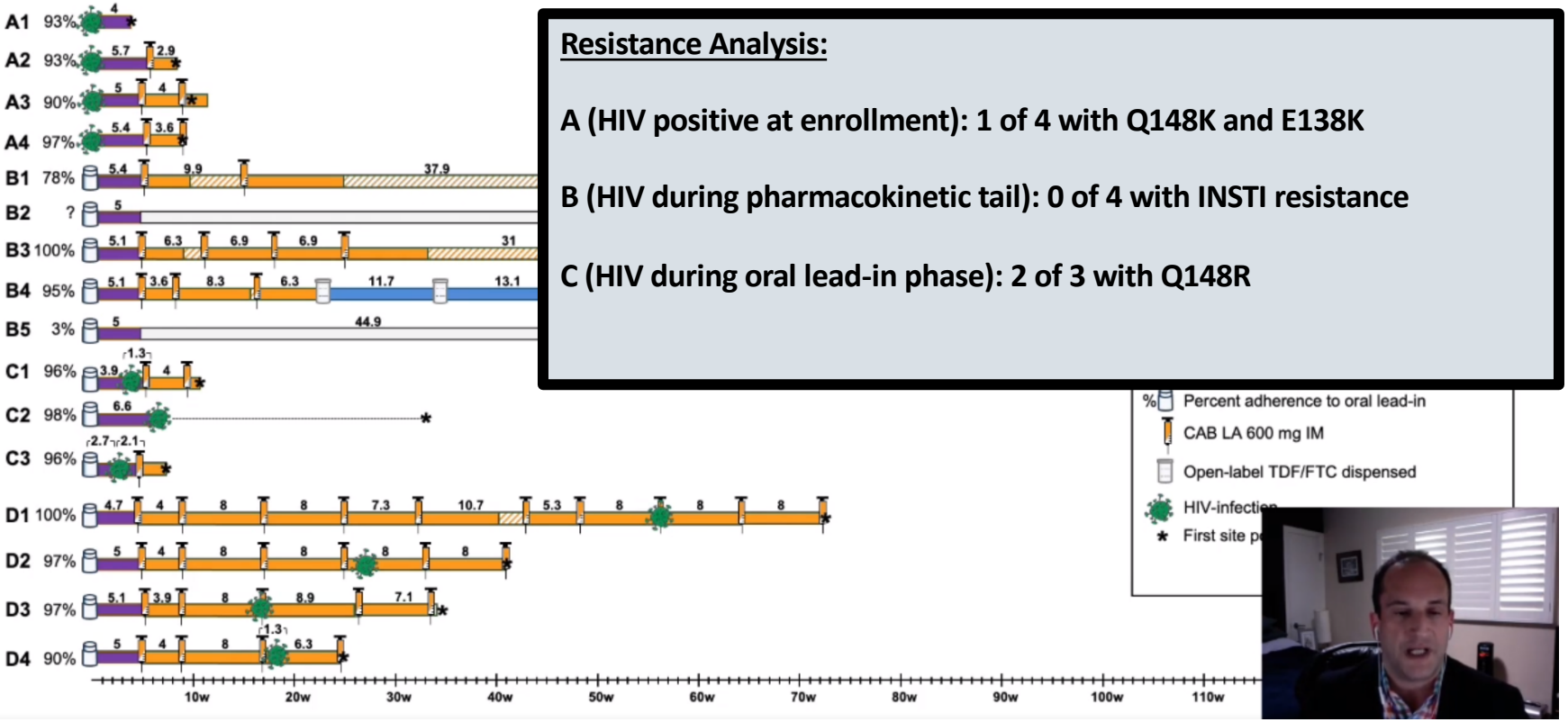
Detailed analysis of HIV infections in HPTN 083



Landovitz RJ et al. AIDS 2020, #OAXLB01



12 Incident, 4 baseline Infections: Cabotegravir



Resistance Analysis:

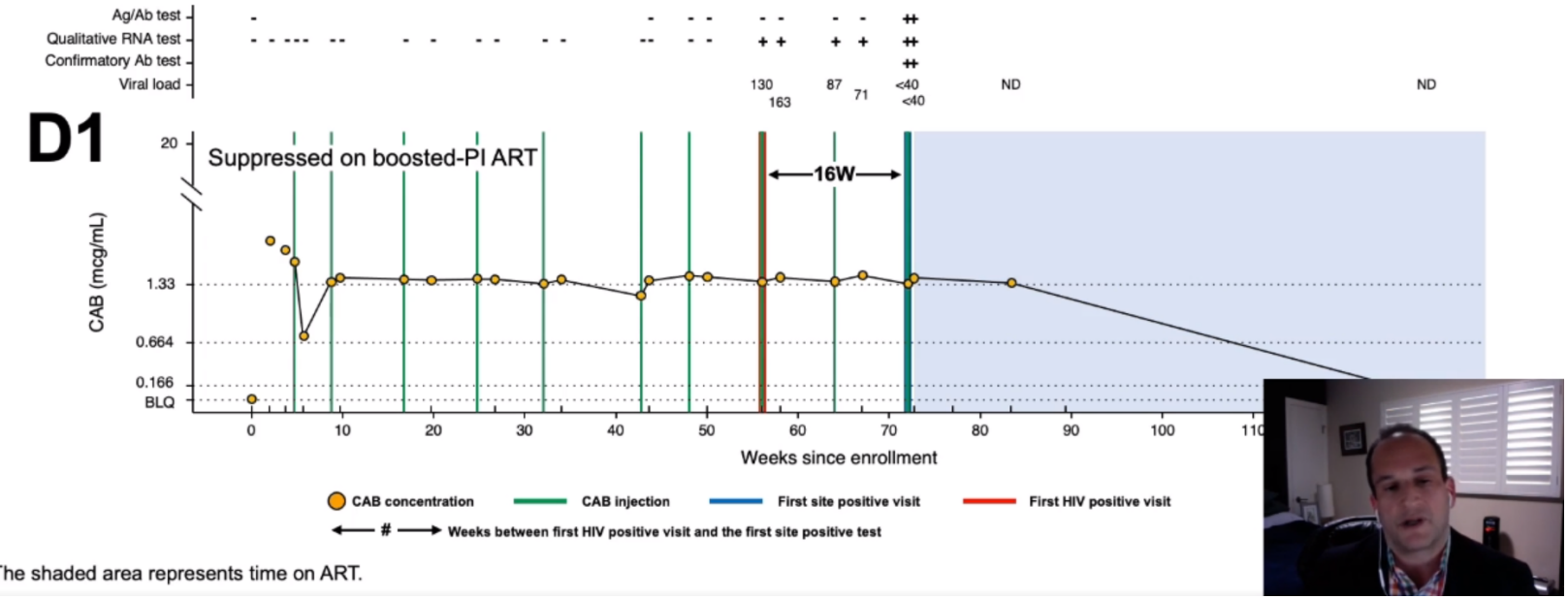
A (HIV positive at enrollment): 1 of 4 with Q148K and E138K

B (HIV during pharmacokinetic tail): 0 of 4 with INSTI resistance

C (HIV during oral lead-in phase): 2 of 3 with Q148R

Note:

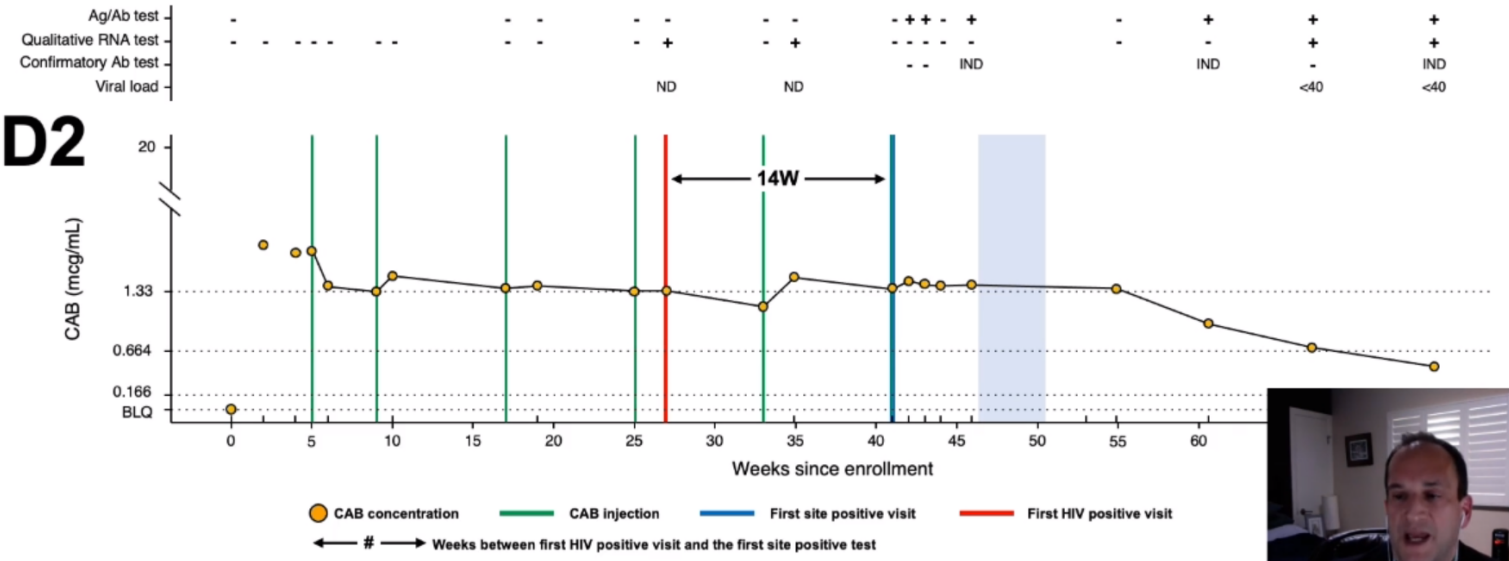
- **Initial drop in cabotegravir concentrations**
- **Delay between RNA and antibody positivity**
- **Low viral loads**



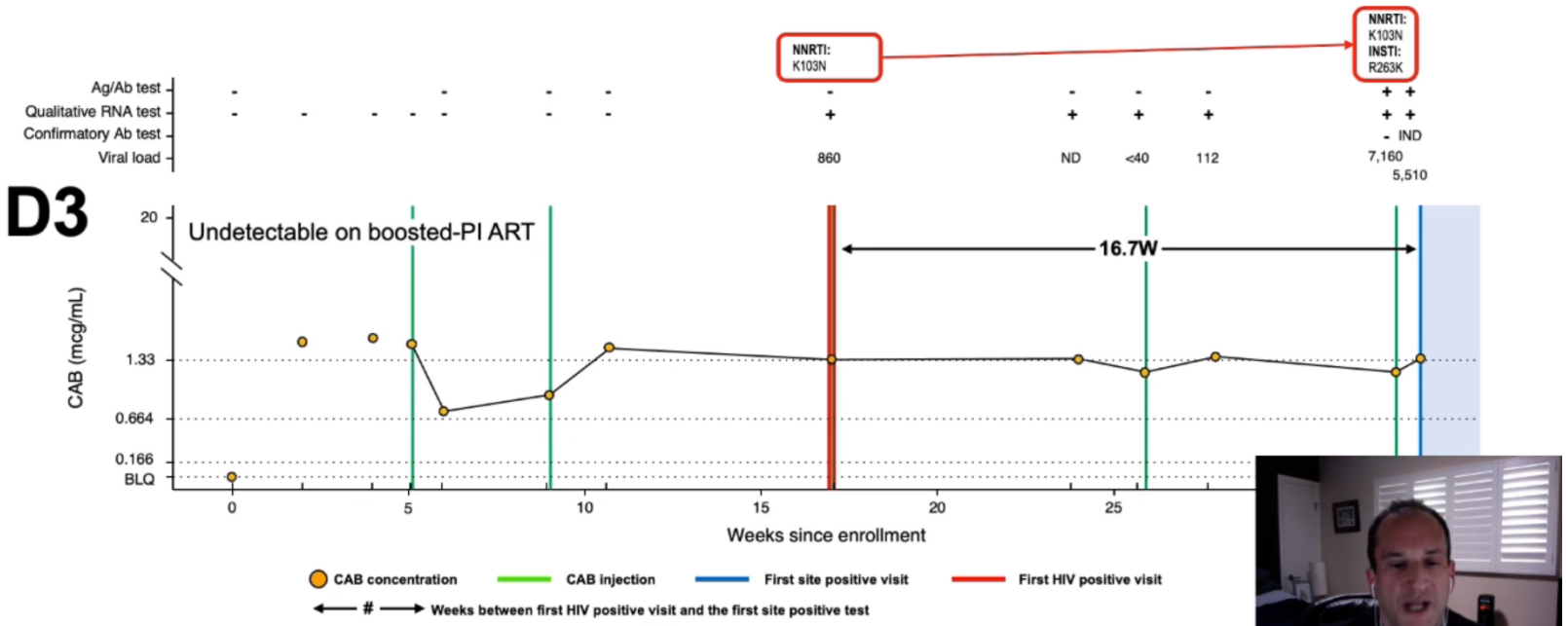
The shaded area represents time on ART.

Note:

- **Transient reversion of positive antibody/antigen test**
- **Virologic suppression without 3-drug ART**

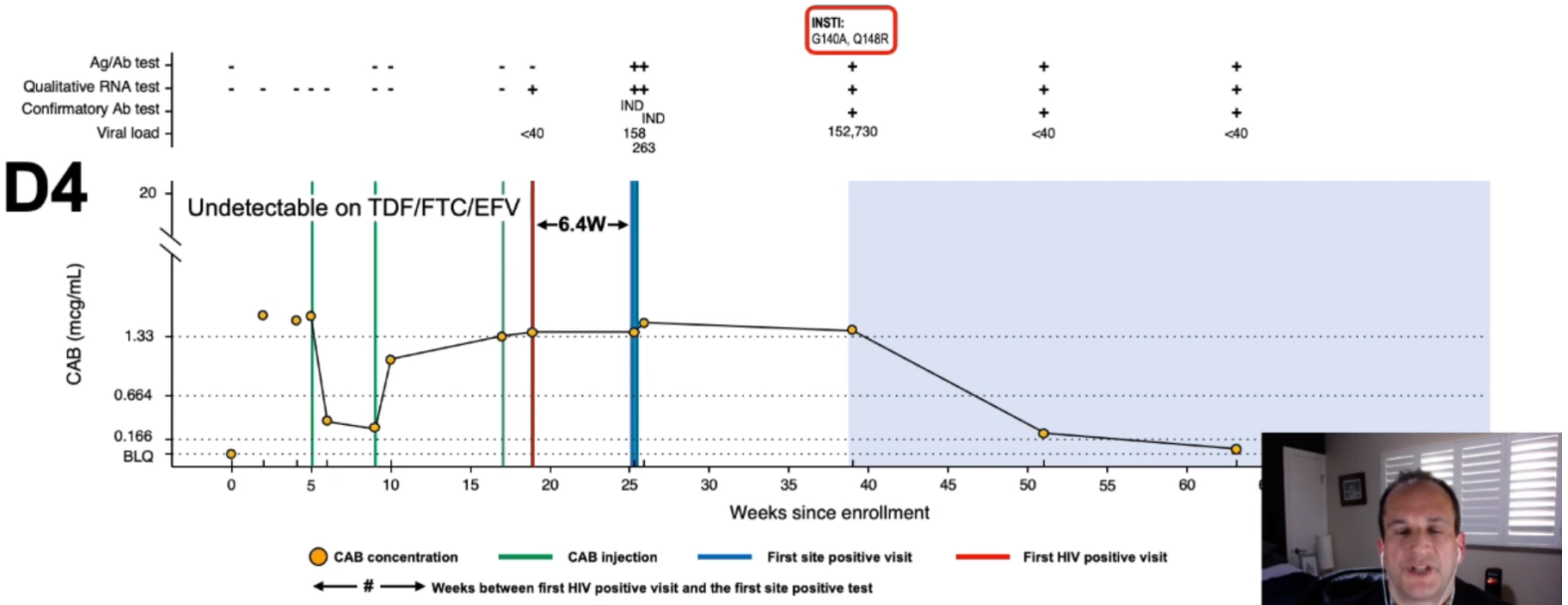


The shaded area represents time on ART.



The shaded area represents time on ART.

A Cautionary Tale



The shaded area represents time on ART.

Summary

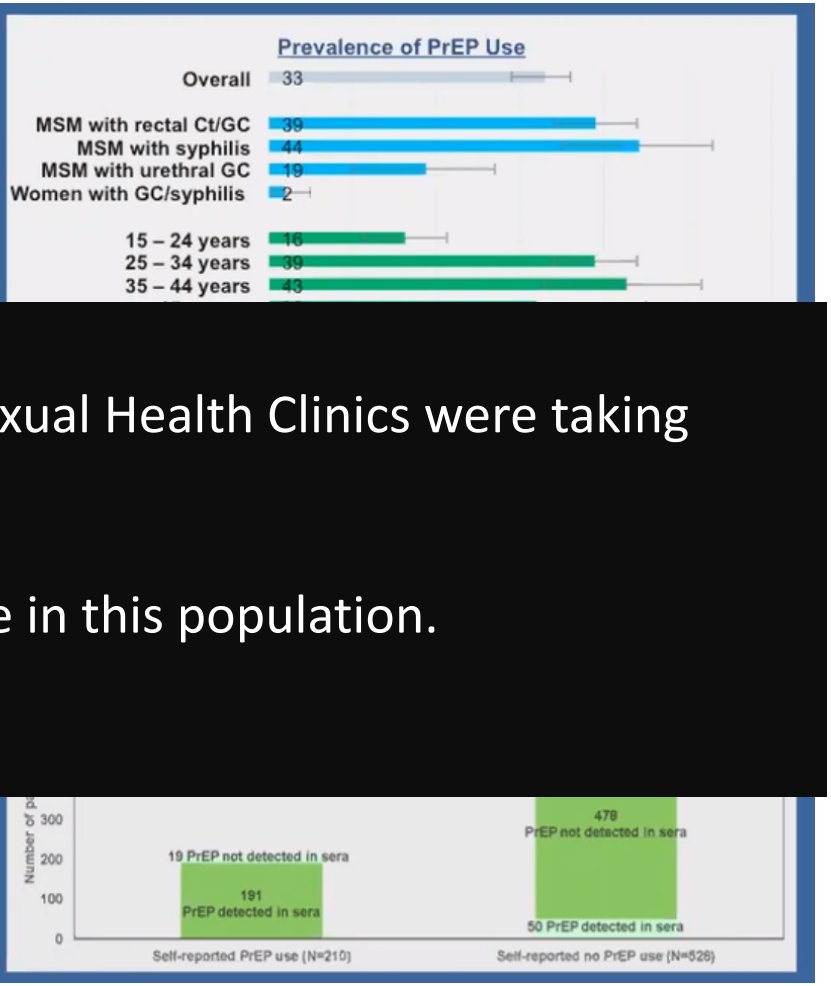
- On-demand TDF/FTC remains effective for MSM but is not necessarily safer than daily TDF/FTC.
- HIV diagnostic algorithms may need updated in the setting of PrEP, especially long-acting PrEP.
- Soon, multiple agents – including monthly pills, yearly implants, and long-acting injections – may be available for PrEP.

Results

Study Patients (N=744)

	MSM with rectal CT/GC	MSM with syphilis	MSM with urethral GC	MSM with co-infections	Women with GC/syphilis
	n=331 (45%)	n=122 (16%)	n=85 (11%)	n=97 (13%)	n=109 (15%)
Age (years)					
Bacterial STI history (past 12 months)					
Yes	32%	27%	25%	28%	15%
No	68%	73%	75%	72%	85%

* Low: <10% below FPL; medium: 10-<20% below FPL; high: 20-<30 below FPL; very high: >30% below FPL



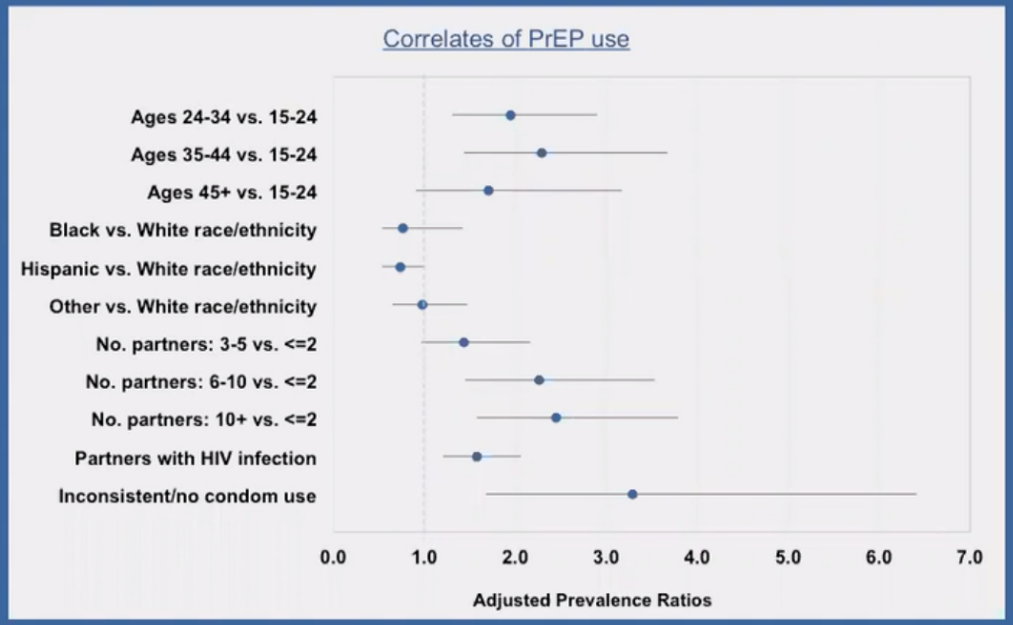
- 1/3 of people with a confirmed STI at Sexual Health Clinics were taking PrEP.
- Drug levels match self-reported PrEP use in this population.

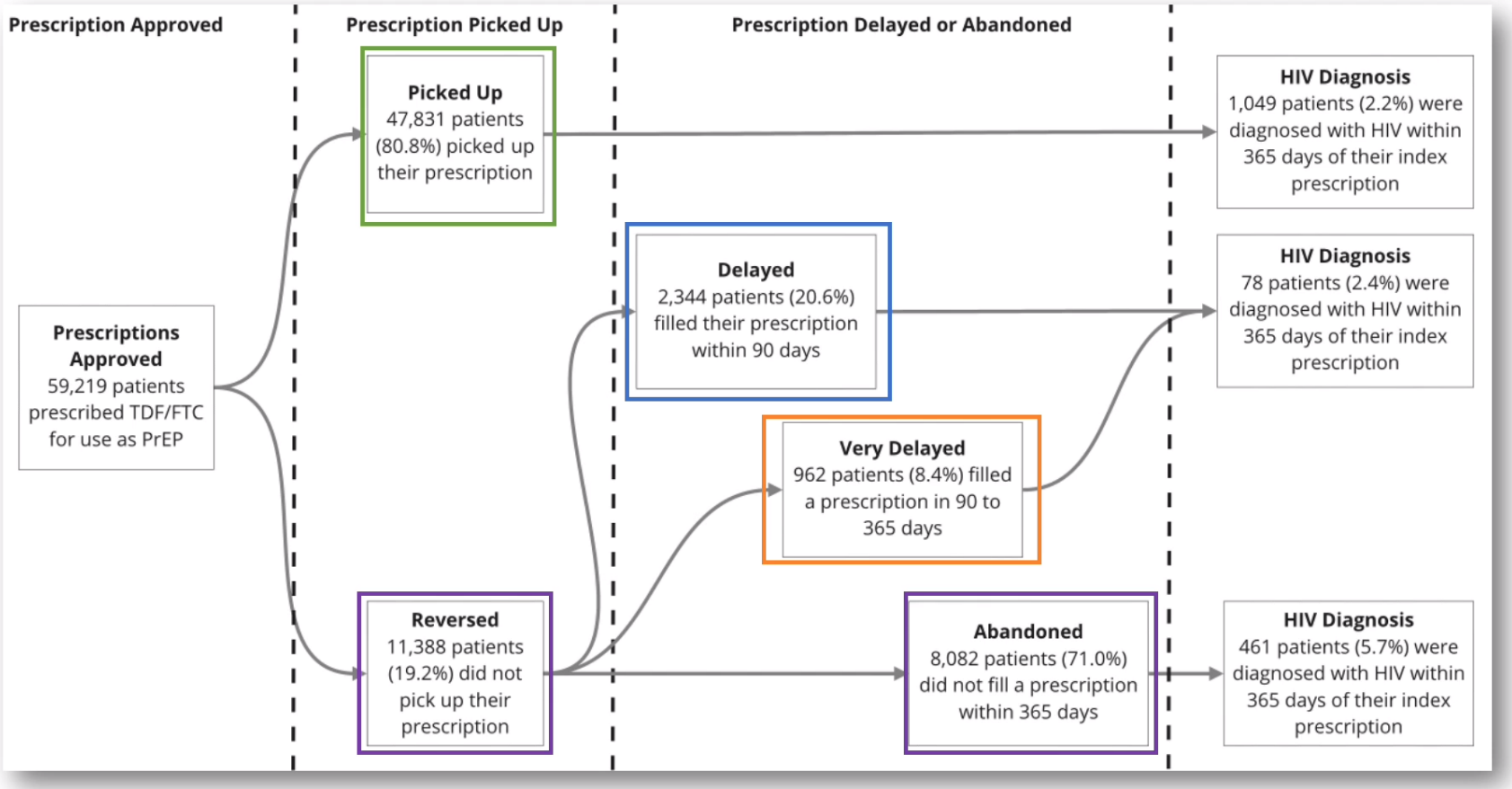
Results

Examined the following factors in bivariate analyses:

1. Age
2. Race/ethnicity
3. Neighborhood poverty level
4. Number of sex partners (past 3 months)
5. Any partners living with HIV infection (past 6 months)
6. Condom use
7. Prior bacterial STI (last 12 months)
8. Prior HIV post-exposure prophylaxis use

Factors significant at p<.05 included in multivariable models adjusted for race/ethnicity and age





Patients newly prescribed PrEP in 2016-2019, followed for up to one year