Impacts of ART Initiation in Acute and Early HIV Results from the *Sabes* study in Peru

Rachel Bender Ignacio, MD MPH
Assistant Professor, University of Washington and Fred Hutch
Director, UW Positive Research

May 4, 2023

Disclosures

Consulting for Abbvie on HIV remission/cure research, unrelated to this presentation content

All risks have been mitigated

Disclaimer

Funding for this presentation was made possible by U1OHA29296 from the Human Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. *Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.*

AETC AIDS Education & Training Center Program Mountain West

Antiretroviral therapy in acute or early HIV

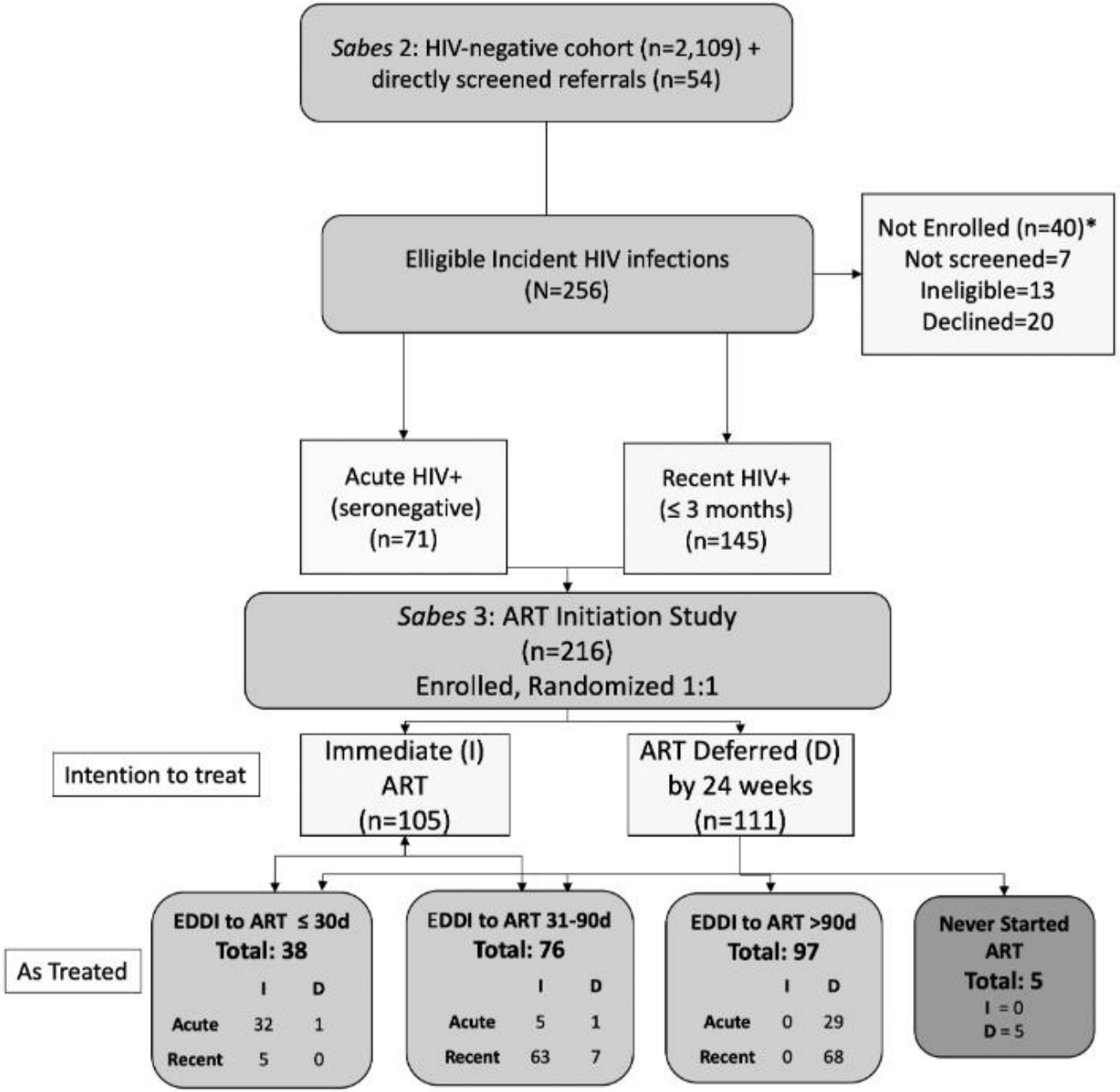
What was known prior to this study:

- Since 2016, the WHO has recommended ART on diagnosis for everyone with HIV
- Most people diagnosed with HIV worldwide have prevalent HIV
  - Data on the individual health benefits of ART were studied in prevalent HIV
  - Infection of unknown or long duration, stratified by CD4 count
- Public health benefit of Treatment as Prevention (TasP) high
  - especially for acute HIV with high VLs
- No clear data on individual health benefits of starting ART in primary HIV
  - Some non-randomized data on impact on HIV reservoir and inflammation

INSIGHT START and TEMPRANO both NEJM 2015, and others, WHO 2016

MWAETC

SABES 3: Randomized ART Timing in Primary HIV



Participants were randomized to start ART on diagnosis or wait 24 weeks

All participants diagnosed seronegative or 3 mos from last negative test

As-treated analysis: participants reclassified by time between **E**stimated **D**ate of **D**etectable HIV **I**nfection (EDDI) and ART initiation

Facente et al, Epi & Infection, 2020
Lama, Bender Ignacio, Duerr et al, CID 2020

MWAETC

Sabes 3 study demographics

	Immediate N = 105	Deferred N = 111
Age (median, IQR)	26.8 (22, 31)	24.5 (21, 30)
Gender identity (N, %)		
Cisgender male	95 (90.5)	92 (82.9)
Transgender female	10 (9.5)	19 (17.1)
Education (N, %)		
Primary	4 (3.8)	5 (4.5)
Secondary	21 (20.0)	31 (27.9)
Postsecondary	80 (76.2)	75 (67.6)
Income (median, IQR) in Peruvian soles/month	750 (200, 1000)	750 (200, 950)
HIV diagnosis (N, %)		
Acute	37 (35.2)	34 (30.6)
Recent	68 (64.8)	77 (69.4)
Initial ART (N, %)		
EFV/FTC/TDF	92 (87.6)	96 (86.5)
EGV/co/FTC/TDF	13 (12.4)	15 (13.5)
Days from enrollment to ART (mean, range)	0 (0, 6)	158 (0, 200)
CD4 count at enrollment (median, IQR)	449 (272, 586)	406 (280, 544)
CD8 count at enrollment (median, IQR)	920 (625, 1314)	938 (639, 1450)
Initial HIV-1 RNA (median $\log_{10}$ copies/ml, IQR)	5.94 (5.04, 6.79)	5.76 (5.18, 6.51)

- All participants male at birth
- Any gender identity
- Enrolled at 2 sites in Lima, Peru
- ART was sponsored:
  - Co-formulated EFV/TDF/FTC 2013-15
  - Co-formulated EVG/cobi/TDF/FTC 2015-16

- All participants enrolled prior to Peru adopting the WHO treat all recommendations in 2016
- Anyone with an OI or CD4 < guideline threshold started ART per clinicians rather than wait

- Immediate: all participants started ART within 6 days
- Deferred:
  - 23% started ART early (CD4 or symptoms)
  - 5% never initiated ART and 5% started late

Lama, Bender Ignacio, CID 2020

MWAETC

Immediate ART prevents OIs and ARS symptoms

Adverse Event Type	Immediate Arm N (%)	Deferred Arm N (%)	*P* value (log-rank)
Bacterial STI	38 (40.0)	57 (60.0)	.17
Total events (non-STI)	78 (42.9)	104 (57.1)	.19
Neurologic/psychiatric disorders	18 (48.6)	19 (51.4)	.63
Gastrointestinal disorders	17 (40.5)	24 (59.5)	.43
Infections/infestations (non-STI)	13 (25.8)	35 (74.2)	**.005**
Skin/subcutaneous	12 (57.1)	9 (42.9)	.44
Systemic/general disorders	3 (25.0)	9 (75.0)	.12
Laboratory abnormalities	8 (80.0)	2 (20.0)	**.03**

Intent to treat Incidence rate of adverse events per 100PY (95% CI)	Immediate Arm	Deferred Arm	Incidence Rate Ratio for Immediate Arm	*P* value (log rank)
All adverse events	117 (93, 146)	141 (116, 170)	0.83 (.61, 1.13)	.22
Nonrelated events (entire study)	83 (63, 108)	123 (100, 151)	0.67 (.47, .95)	**.02**
ART-related events (during ART)	35 (23,52)	39 (23, 68)	0.88 (.42, 1.89)	.13
Nonrelated events (during ART)	83 (64, 108)	133 (99, 179)	0.62 (.41, .95)	**.0003**

As Treated Incidence of adverse events per 100PY (95% CI)	≤30 days from EDDI to ART N = 38	31–90 days from EDDI to ART N = 76	>90 days from EDDI to ART N = 97	*P* value (log-rank)
All adverse events	85 (56, 129)	163 (129, 205)	125 (102, 154)	**.03**
ART-related events	35 (18, 67)	32 (19, 54)	44 (25, 75)	.07
Nonrelated events	50 (29, 86)	131 (101, 170)	107 (85, 133)	**.007**

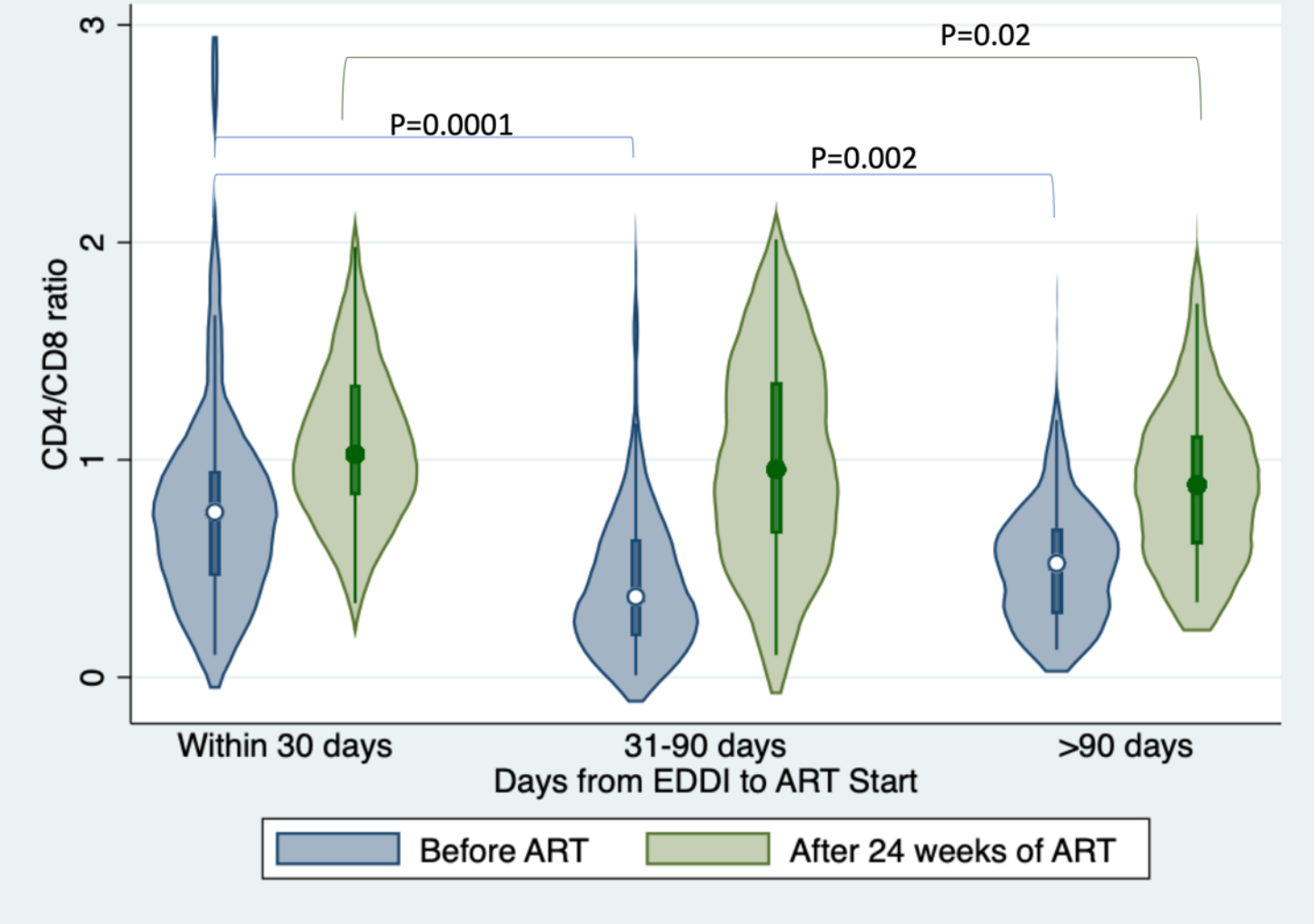
Lama, Bender Ignacio, CID 2020

MWAETC

Immunologic benefits of ART in primary HIV

MWAETC

CD4/CD8 ratio by time since EDDI in *Sabes*

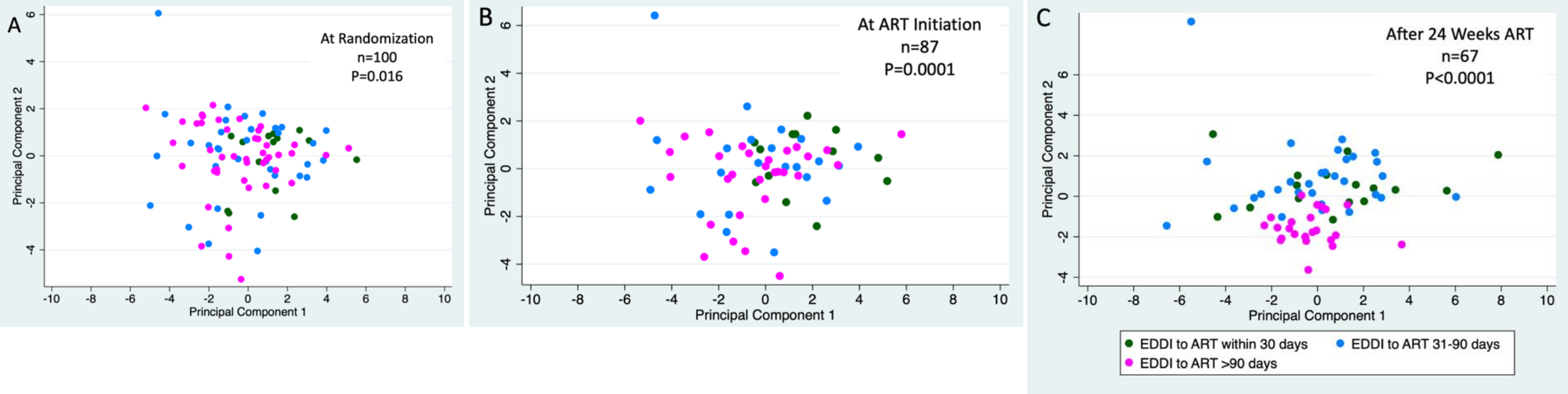


CD4/CD8 ratio differences persist at 4 years on ART

Treatment group	Mean CD4 ratio
≤30 days	1.37
31-90 day	1.16
>90 days	1.18

Lama, Bender Ignacio, CID 2020

Multivariate Variation in Immune Activation Markers Between As-Treated Groups



Principal Component Analysis (PCA) Plots from the *Sabes Study*

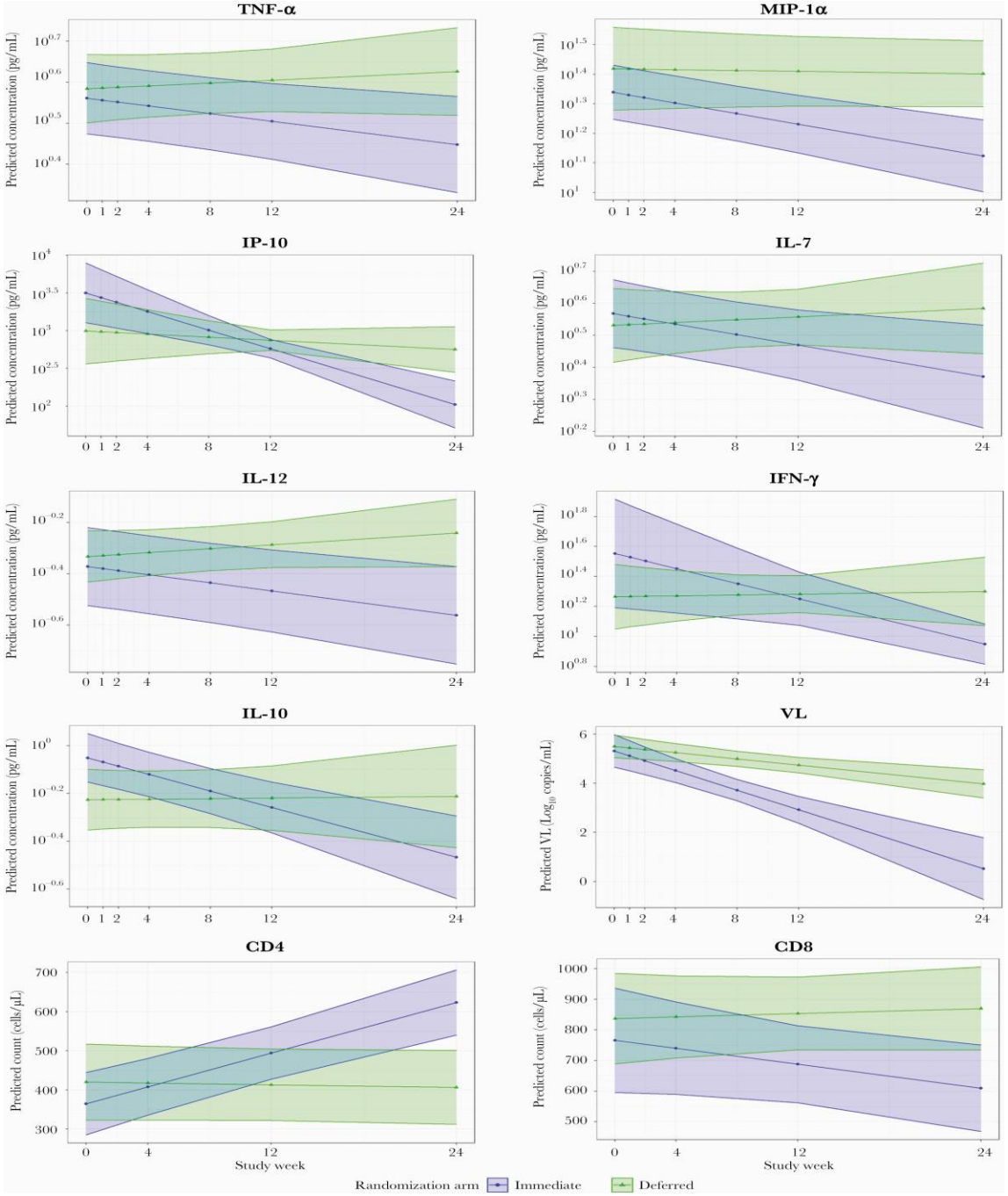
PCA undertaken on 20 biomarkers tested in plasma (first 8 PCs, 2 shown in figures)

IL1a, IL1b, IL2, IL4, IL6, IL7, IL8, IL10, IL16, IL12 IL23, IP10, TNFa, TNFb, IFNa2a, IFNg,, MIP1a, MIP1b, MCP-1, SDF-1

At both time of ART start and after 24 weeks on ART, the >90-day group was different from each of the more-immediately treated groups

The ≤30 and 31-90 day groups were not distinguishable from each other

Lama, Bender Ignacio, CID 2020



Change in soluble biomarkers over the first 24 weeks among PWH who initiated ART immediately vs deferred by 24 weeks in *Sabes*

Most biomarkers higher within 30 days of EDDI vs >30 days
Modestly attenuated by baseline VL

Positive blood metabolites for ethanol (PEth) associated with higher IFN-γ, TNF-α, and IL-12p70

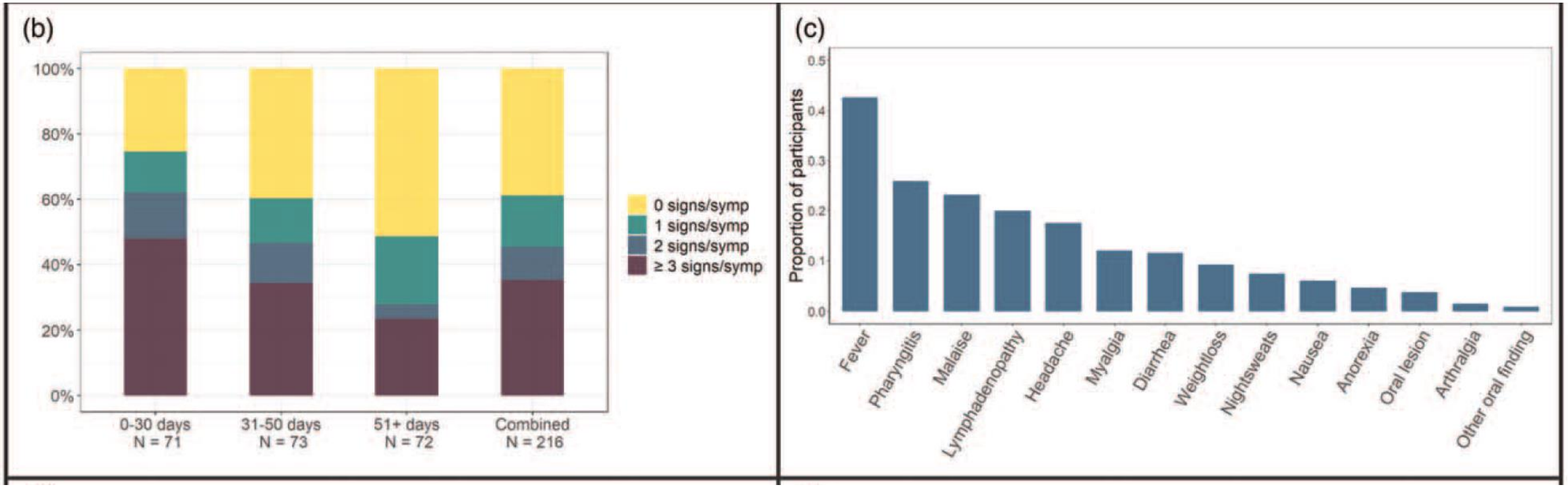
Smokers vs non-smokers had higher TNF-α, MIP-1α, and IL-12p70

Gilada et al OFID 2022

Acute Retroviral Syndrome, ART, and outcomes

MWAETC

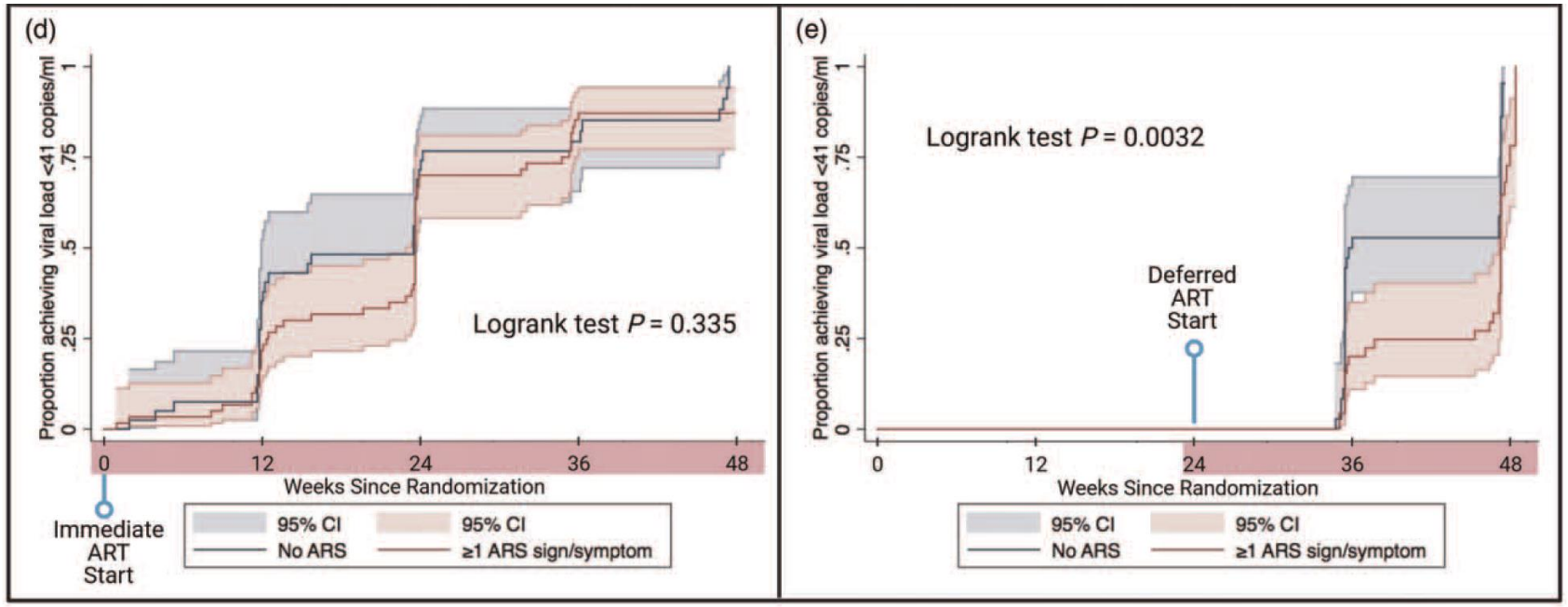
Incidence of Acute Retroviral Syndrome



61% of participants had at least 1 ARS sign or symptom
35% had 3 or more
ARS was more common within 1 month of EDDI
Presence of ARS associated with higher viral load at diagnosis

Gabert, AIDS 2023

Outcomes associated with ARS



Those with ARS took longer to suppress VL or failed to suppress, but only in those who did not start ART immediately

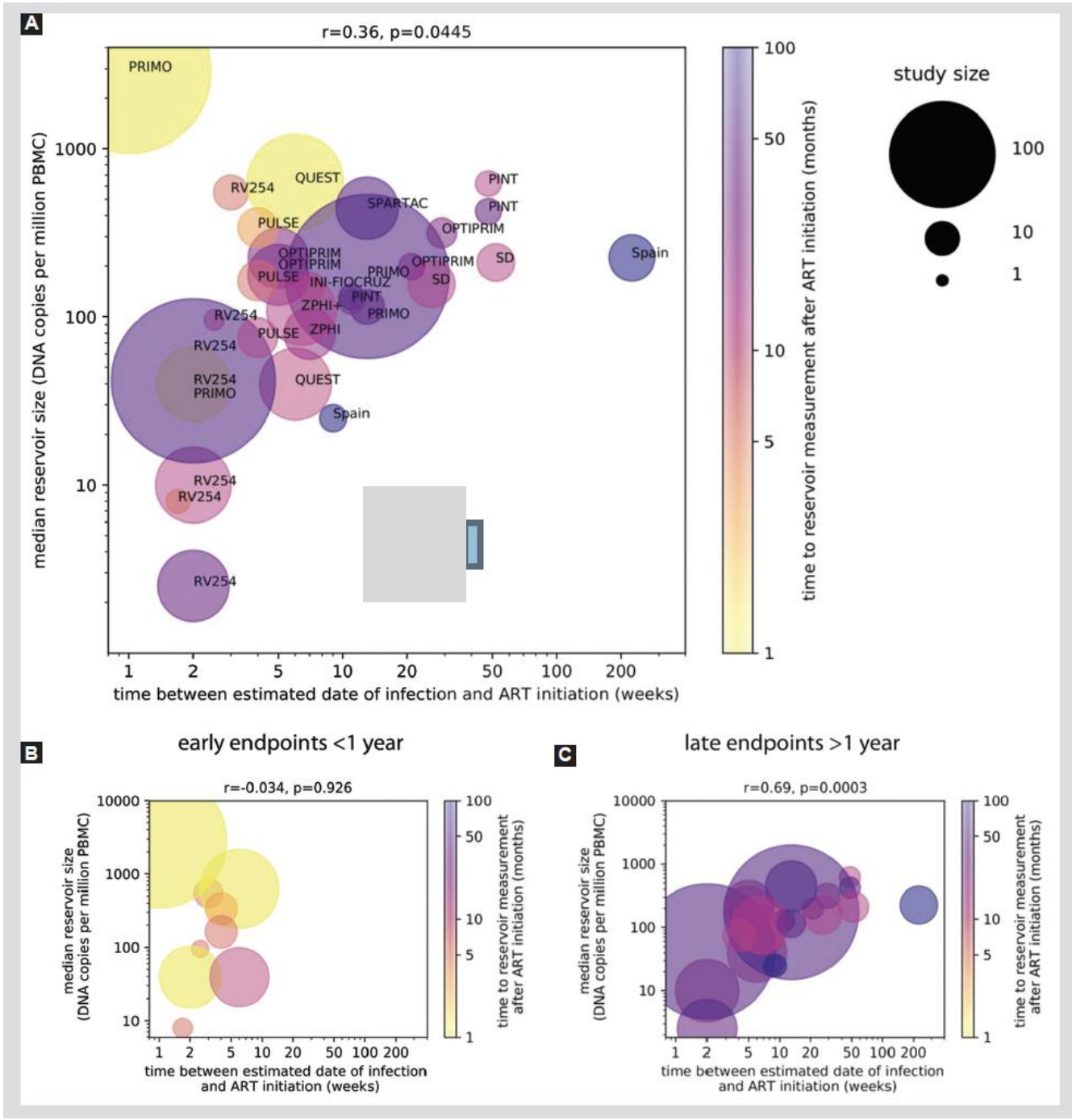
More ARS signs/symptoms was associated with risk of CD4 <350 within 6 months

*Remained after multivariable adjustment only in the deferred ART arm

Minimal effects on CD4 or VL after 2 or 4 years, and blunted by immediate ART

Gabert AIDS 2023

Does earlier ART during Primary HIV influence establishment of the HIV latent reservoir?



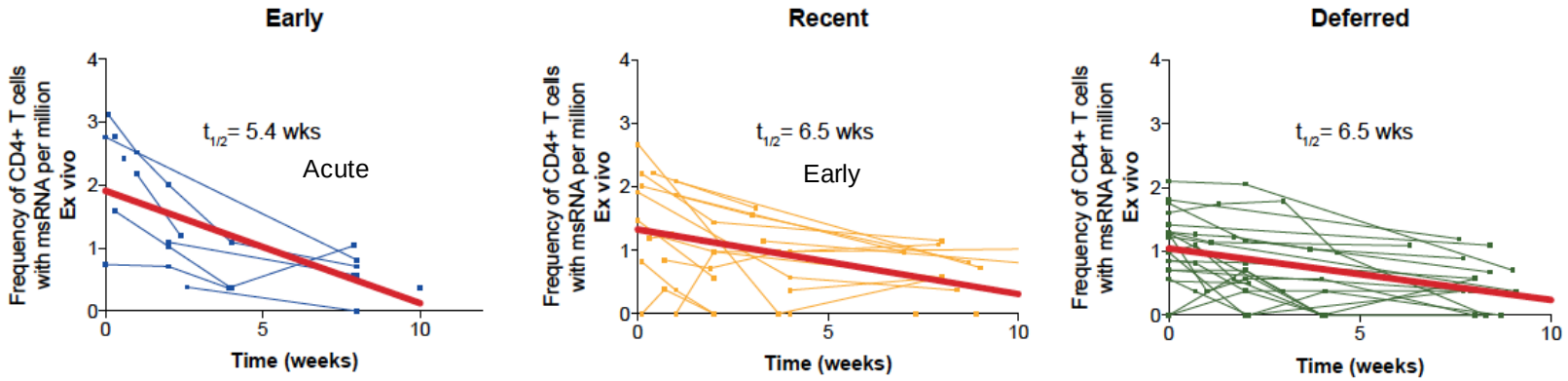
Eva Shelton

Dan Reeves

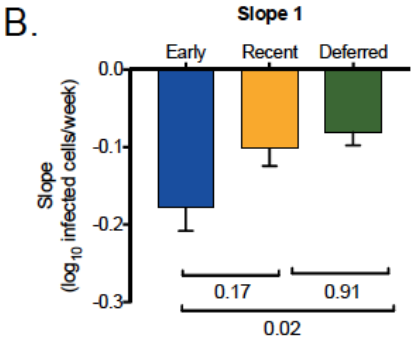
Shelton et al AIDS Reviews 2020

Steeper decay in markers of HIV latency when ART started within 30 days of Estimated Date of Infection (EDDI)

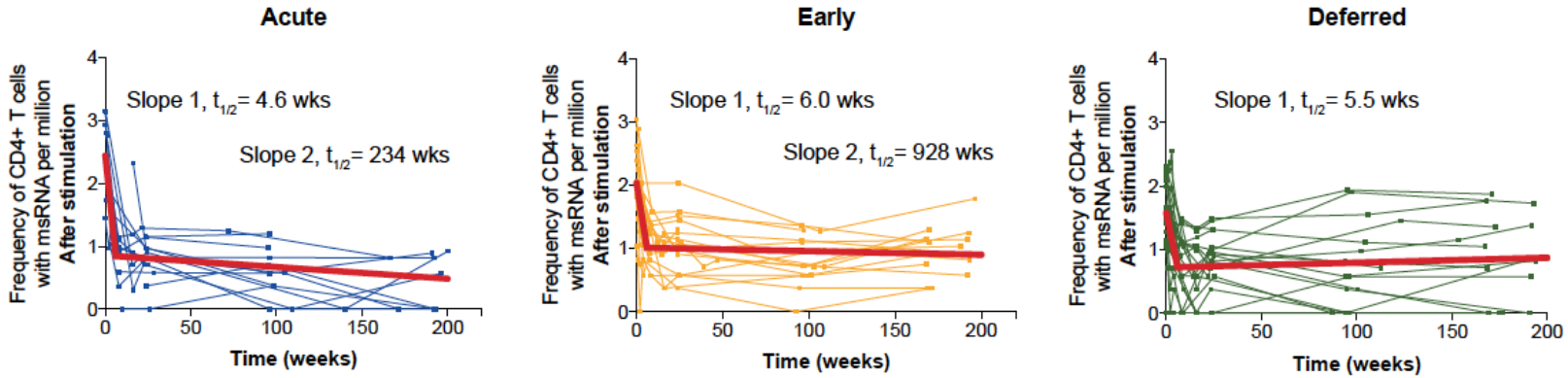
A. TILDA ex vivo



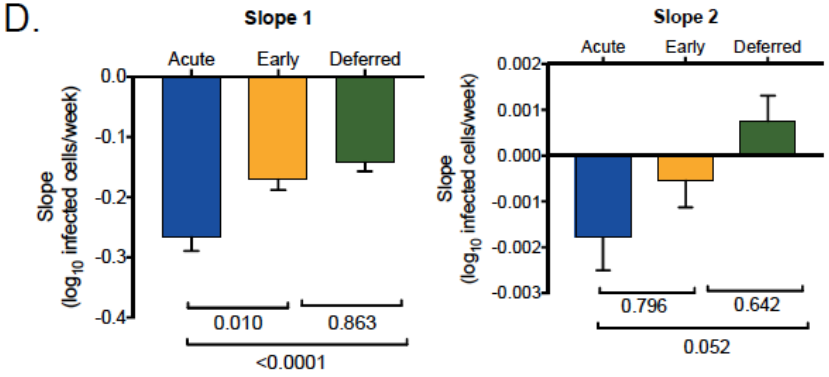
B.



C. TILDA after stimulation



D.



Summary

- Even within a closely followed randomized study, 10% of those randomized to defer ART started late or never → furthers rationale for same-day start
- ART in primary HIV decreases overall symptoms, including OIs and ARS
- Improved short term, and likely long term immunologic impacts
- Those who initiated ART within 30 days of HIV infection showed a steeper and more sustained decay in HIV reservoir measures, suggesting long-term benefit of acute ART initiation on reservoir clearance
- Strong data to support WHO guidelines to explicitly include treating during primary/acute HIV for the personal health benefits, in addition to TasP
  - Last/only randomized study prior to guidelines change

MWAETC

Appreciation

HOPE Group HIV Outcomes Prevention & Epidemiology

Delia Pinto-Santini PhD
Si Pasalar PhD
Ted White PhD
Alex Lankowski MD
Jessica Long PhD
Ina Montano PhD MPH
Trupti Gilada MD
Sam Schnittman MD
Rose Gabert MD-c
Ann Duerr MD PhD MPH

Nicolas Chomont, PhD
Marta Massanella, PhD

IMPACTA Peru
Javier Lama, MD MPH
Jessica Rios CNM
Jorge Gallardo MD
and many others

Florian Hladik MD PhD
Rogelio Valdez
Urvashi Pandey

National Institute of Allergy and Infectious Diseases

Thank you to the participants who were in this study for up to 6 years at NGO IMPACTA Peru

Merck and Gilead Sciences for donating study ART for the Sabes/MERLIN studies

NIAID K23AI129659
CFAR New Investigator Award *AI027757*
R01DA040532 MERLIN

UW Medicine
SCHOOL OF MEDICINE

MWAETC

Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $3,098,654 with 0% financed with non-governmental sources.

The content in this presentation are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, HRSA, HHS, or the U.S. Government.

AETC AIDS Education & Training Center Program
Mountain West