Antibody Mediated Prevention (AMP) ATIs
&
Analytical Treatment Interruption Studies in Africa

Shelly Karuna, MD, MPH ▪ 18 February 2023

Summary for Community

- What is the main issue or key question(s) your work addresses?
  - Can ATIs in Africa be conducted safely?
  - Can ATIs help us address key questions in HIV prevention, treatment & cure?

- What was the key finding or "take home message"?
  - ATIs can be conducted safely and very well in Africa.
  - African women are a unique population with & from whom we can learn a great deal through ATIs.

- How is this important for HIV cure research?
  - AMP ATI participants can demonstrate how ATIs can be successfully conducted throughout the world.
  - AMP ATI participants can help us learn about immune responses and virus characteristics that may be associated with post-treatment control. This knowledge may help us identify potential cure strategies more efficiently.

- Background: ATIs in Africa
- The AMP studies
- Post-AMP ATI in sub-Saharan Africa
  - Development
  - Screening Outcomes
  - Viral Rebound & Control

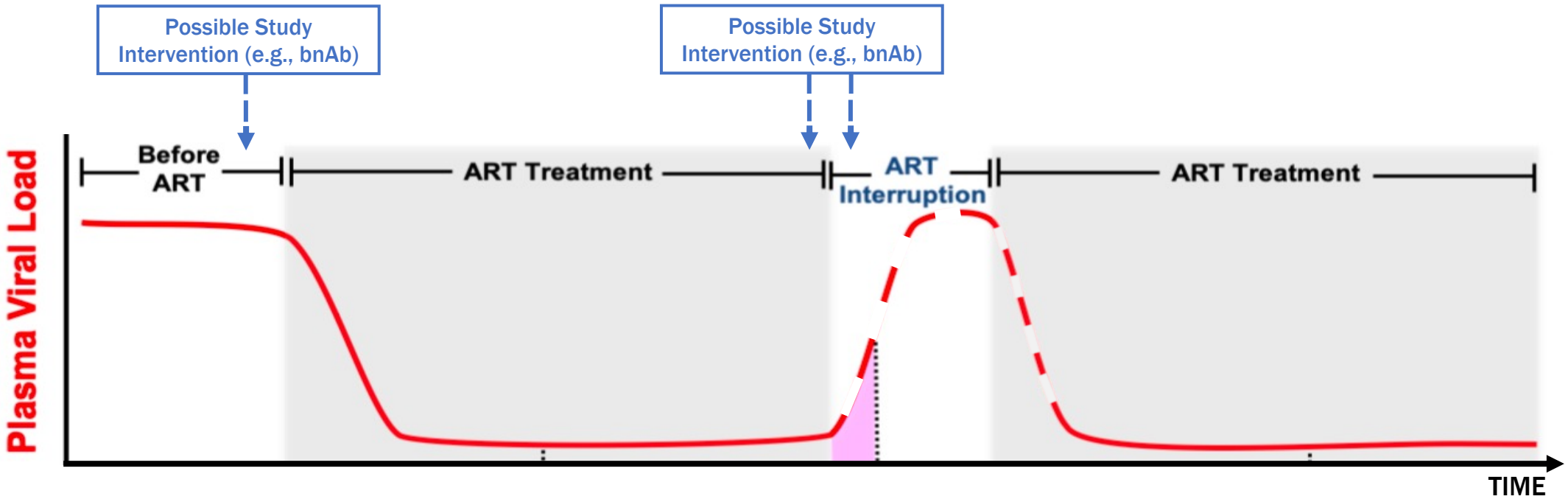
Special Thanks

- Fatima Laher
- Glenda Gray
- Nigel Garrett
- Catherine Orrell
- Sufia Dadabhai
- Ian Sanne
- Joseph Makhema
- Mina Hosseinipour
- Rachel Kawalazira

BACKGROUND

ATIs in Africa

Analytical Treatment Interruption (ATI)



- A carefully monitored ART pause by people living with HIV
- Historically used as part of therapy, in hopes of minimizing ARV toxicities & addressing multi-resistant virus & treatment failure
- Now used in research to evaluate options for HIV viral suppression, including for sustained, ART-free virologic remission (SVR); safe & well-tolerated "design of choice" in HIV cure research

Sample Treatment Interruptions in Africa

- Trivacan, ANRS 1269, CD4-guided STI* in west Africa
  Danel C et al, Lancet 2006
- SMART CD4-guided STI*
  The SMART Study Team NEJM, 2006
- Nested STI in DART in Uganda & Zimbabwe
  DART Trial Team, AIDS 2008
- RCT of Short-Cycle Intermittent vs Continuous ART in Uganda
  Reynolds SJ et al, PLoS ONE 2010
- RCT of STI* vs. Continuous ART for PI-based ART in RSA
  Firnhaber C et al, PLoS One 2011
- SPARTAC Short-course ART
  The SPARTAC Trial Investigators, NEJM 2013
- Optimizing Pediatric HIV-1 Treatment Study in Kenyan infants
  Pankau MD et al, Open Forum Infectious Diseases 2017

*STI: Structured Treatment Interruption

THE SPARTAC STUDY


The NEW ENGLAND JOURNAL of MEDICINE

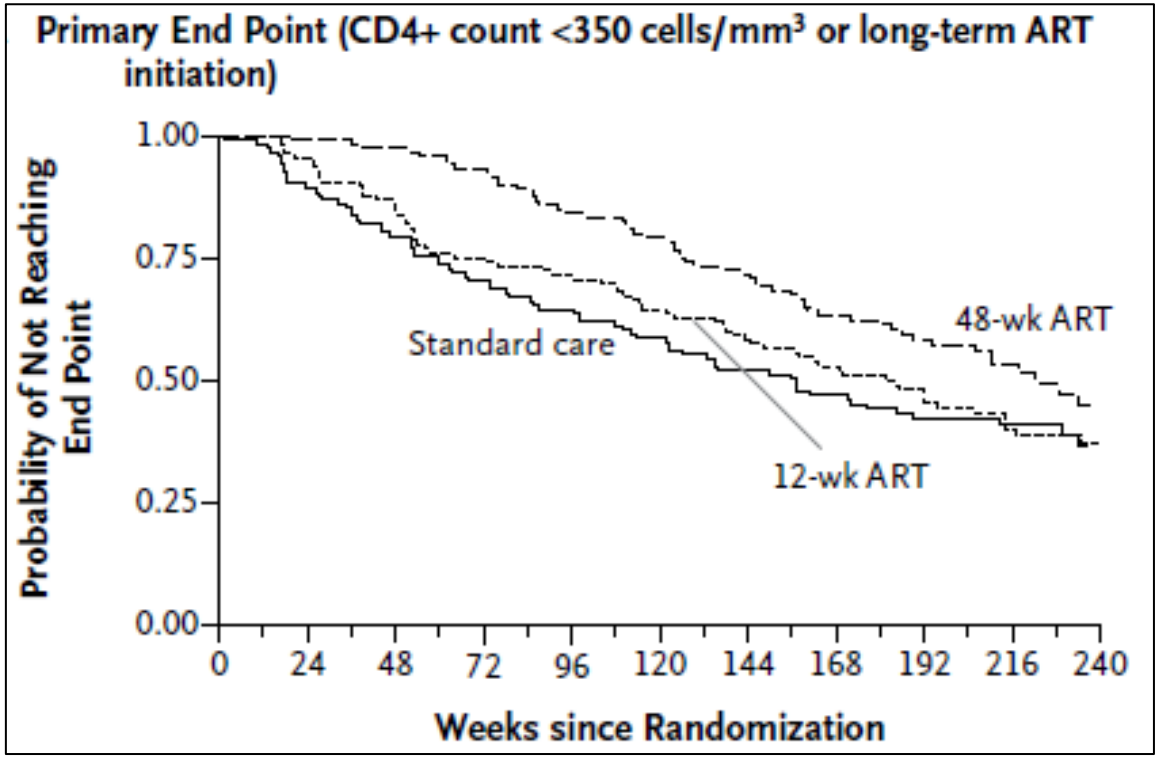
ESTABLISHED IN 1812 JANUARY 17, 2013 VOL. 368 NO. 3

Short-Course Antiretroviral Therapy in Primary HIV Infection

The SPARTAC Trial Investigators*

Does short-term ART during primary HIV infection lengthen the time to CD4+ < 350 or requirement of long-term ART?

HR, 48-wk ART vs. Standard Care = 0.63 (0.45-0.90, p=0.01)

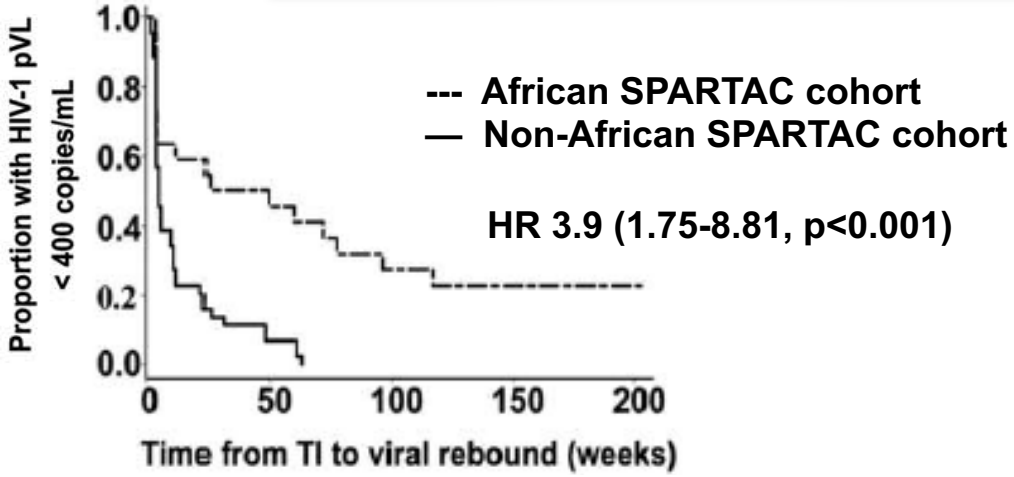


THE SPARTAC SUB-STUDY:
Virologic Control After Early ART Initiaion in African Women

Virological remission after antiretroviral therapy interruption in female African HIV seroconverters

Morgane Gossez[a], Genevieve Elizabeth Martin[a], Matthew Pace[a], Gita Ramjee[b], Anamika Premraj[b], Pontiano Kaleebu[c], Helen Rees[d], Jamie Inshaw[e], Wolfgang Stöhr[e], Jodi Meyerowitz[a], Emily Hopkins[a], Mathew Jones[a], Jacob Hurst[a], Kholoud Porter[f], Abdel Babiker[e], Sarah Fidler[g], John Frater[a,h,i], on behalf of the SPARTAC Trial Investigators

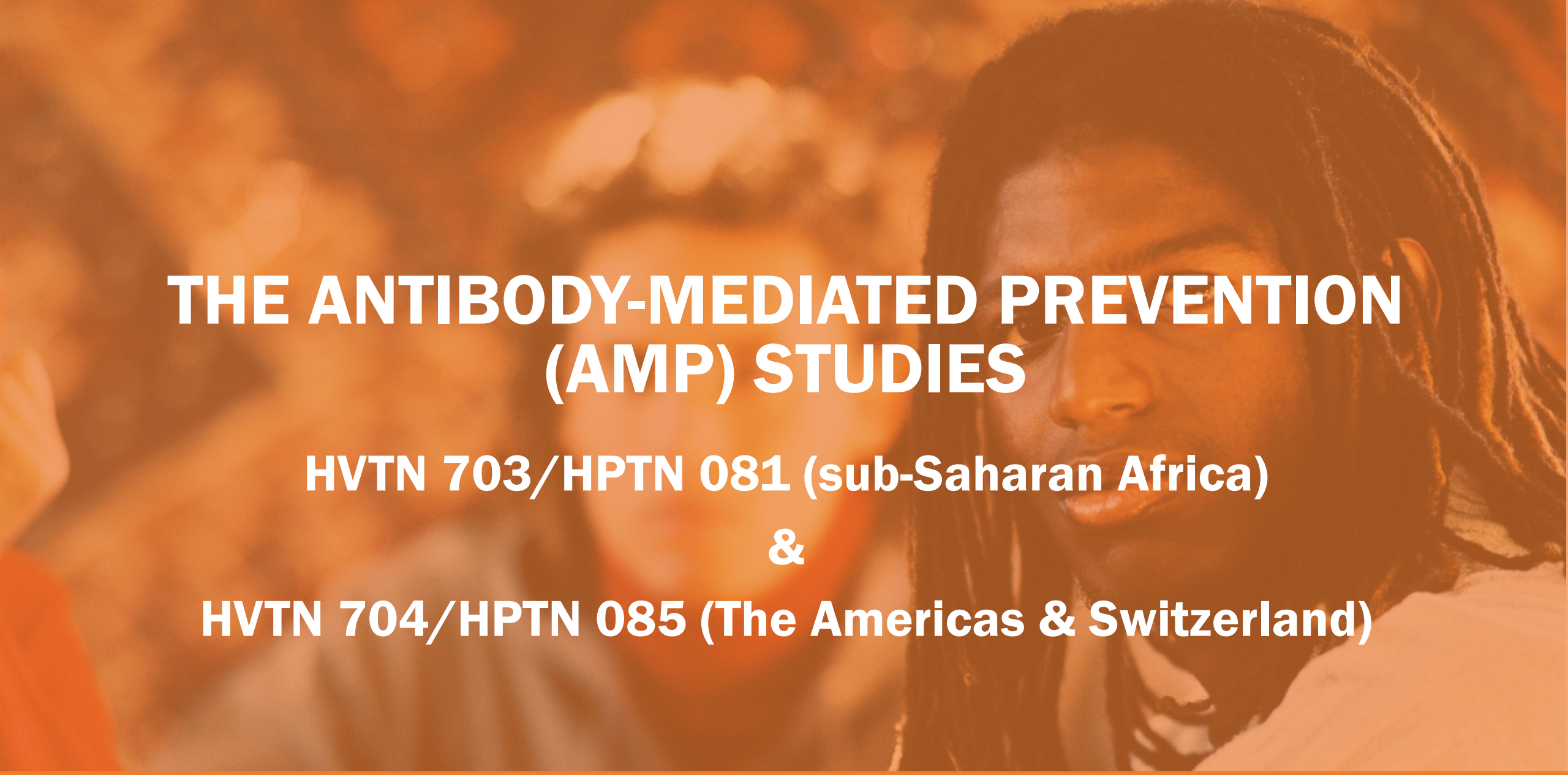
AIDS 2019, 33:185–197



--- African SPARTAC cohort
— Non-African SPARTAC cohort

HR 3.9 (1.75-8.81, p<0.001)

- SPARTAC ppts from Uganda & South Africa were included in the analysis; all female, all non-B (most C) sub-types
- Evaluated: CD4+ T-cell count; Viral Load; cell-associated HIV RNA & DNA; T-cell activation & exhaustion
- 5/22 (23%) African ppts in the 48-week "early ART" pre-ATI arm maintained VL< 400 copies/mL over a median of **188 weeks post-ATI**



THE ANTIBODY-MEDIATED PREVENTION (AMP) STUDIES

HVTN 703/HPTN 081 (sub-Saharan Africa)

&

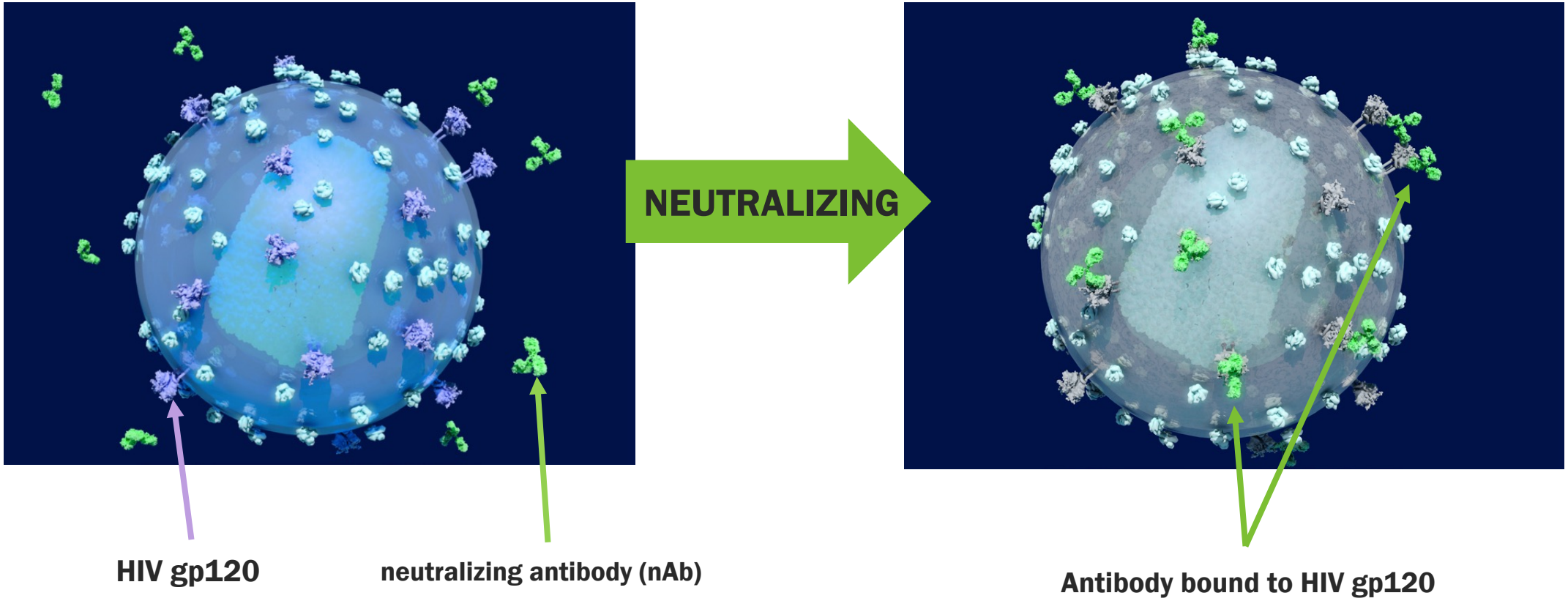
HVTN 704/HPTN 085 (The Americas & Switzerland)

HIV VACCINE TRIALS NETWORK

ACTG AIDS CLINICAL TRIALS GROUP

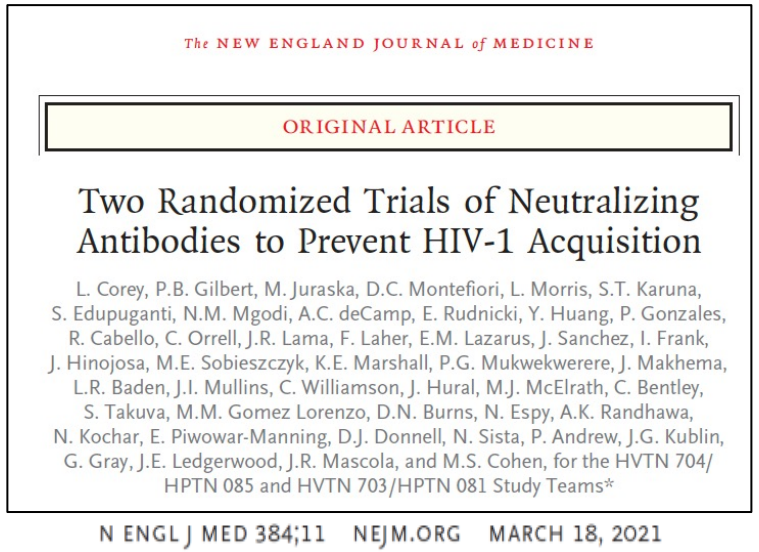
HPTN HIV Prevention Trials Network

Neutralizing Antibodies



Thanks to Lisa Donohue for these images.

The AMP Studies



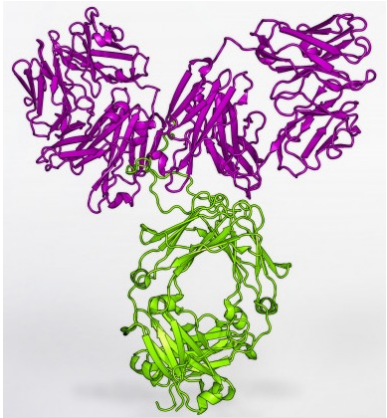
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

L. Corey, P.B. Gilbert, M. Juraska, D.C. Montefiori, L. Morris, S.T. Karuna, S. Edupuganti, N.M. Mgodi, A.C. deCamp, E. Rudnicki, Y. Huang, P. Gonzales, R. Cabello, C. Orrell, J.R. Lama, F. Laher, E.M. Lazarus, J. Sanchez, I. Frank, J. Hinojosa, M.E. Sobieszczyk, K.E. Marshall, P.G. Mukwekwerere, J. Makhema, L.R. Baden, J.I. Mullins, C. Williamson, J. Hural, M.J. McElrath, C. Bentley, S. Takuva, M.M. Gomez Lorenzo, D.N. Burns, N. Espy, A.K. Randhawa, N. Kochar, E. Piwowar-Manning, D.J. Donnell, N. Sista, P. Andrew, J.G. Kublin, G. Gray, J.E. Ledgerwood, J.R. Mascola, and M.S. Cohen, for the HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams*

N ENGL J MED 384;11 NEJM.ORG MARCH 18, 2021



Model of the VRC01 HIV antibody
NIAID

Trial	Cohort	VRC 01 10 mg/kg	VRC 01 30 mg/kg	Placebo	Total
HVTN 704/ HPTN 085 	**Americas & Europe: US, Peru, Brazil, Switzerland** MSM & TG people (Clade B)	**900**	**900**	**900**	**2,700**
HVTN 703/ HPTN 081 	**Sub-Saharan Africa: Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, Zimbabwe** Heterosexual women (Clades A, C, D, & CRFs)	~633	~633	~634	1,900
	Total	~1,533	~1,533	~1,534	4,600

HIV VACCINE TRIALS NETWORK

ACTG AIDS CLINICAL TRIALS GROUP

HPTN HIV Prevention Trials Network

The AMP Trials: Outcomes

PROOF OF CONCEPT

- ~75% protection against bnAb-sensitive viruses

BENCHMARK

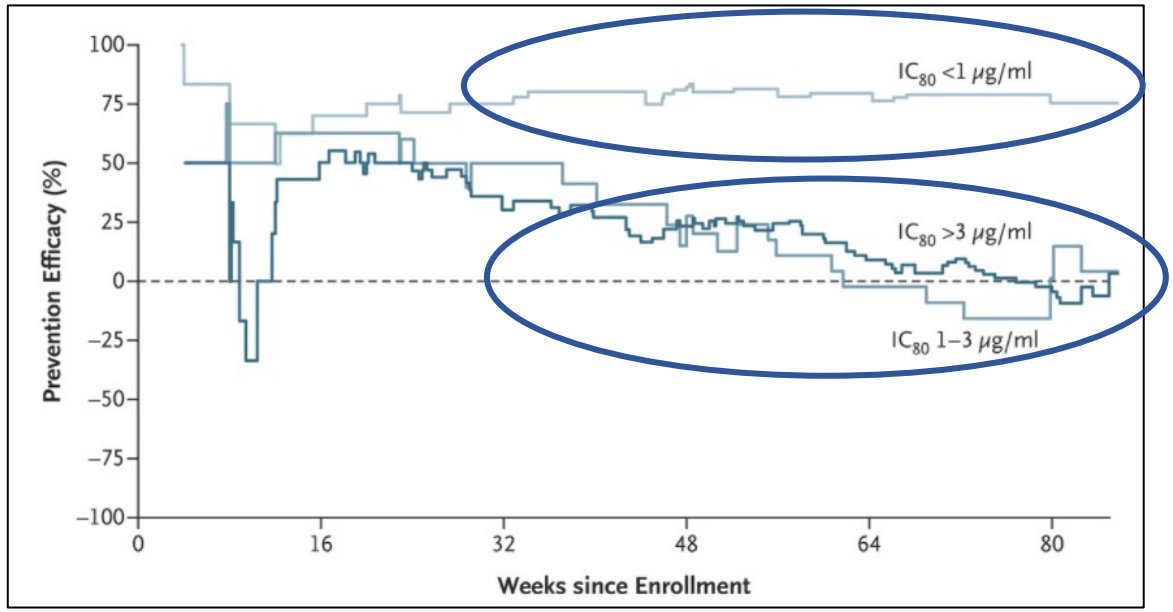
- Informs our understanding of the antibody breadth & potency needed for protection

ASSAY VALIDATION

- TZM-bl pseudovirus assay provided a sharp cutoff for neutralization-based prevention efficacy assessment

MECHANISTIC CORRELATE OF PROTECTION

- protection achieved with a neutralization titer of ~1:250, which also corresponds to NHP/SHIV model



HVTN 704/HPTN 085: PE 26.6% [95% CI -11.7 to 51.8]

HVTN 703/HPTN 081: PE 8.8% [95% CI -45.1 to 42.6]

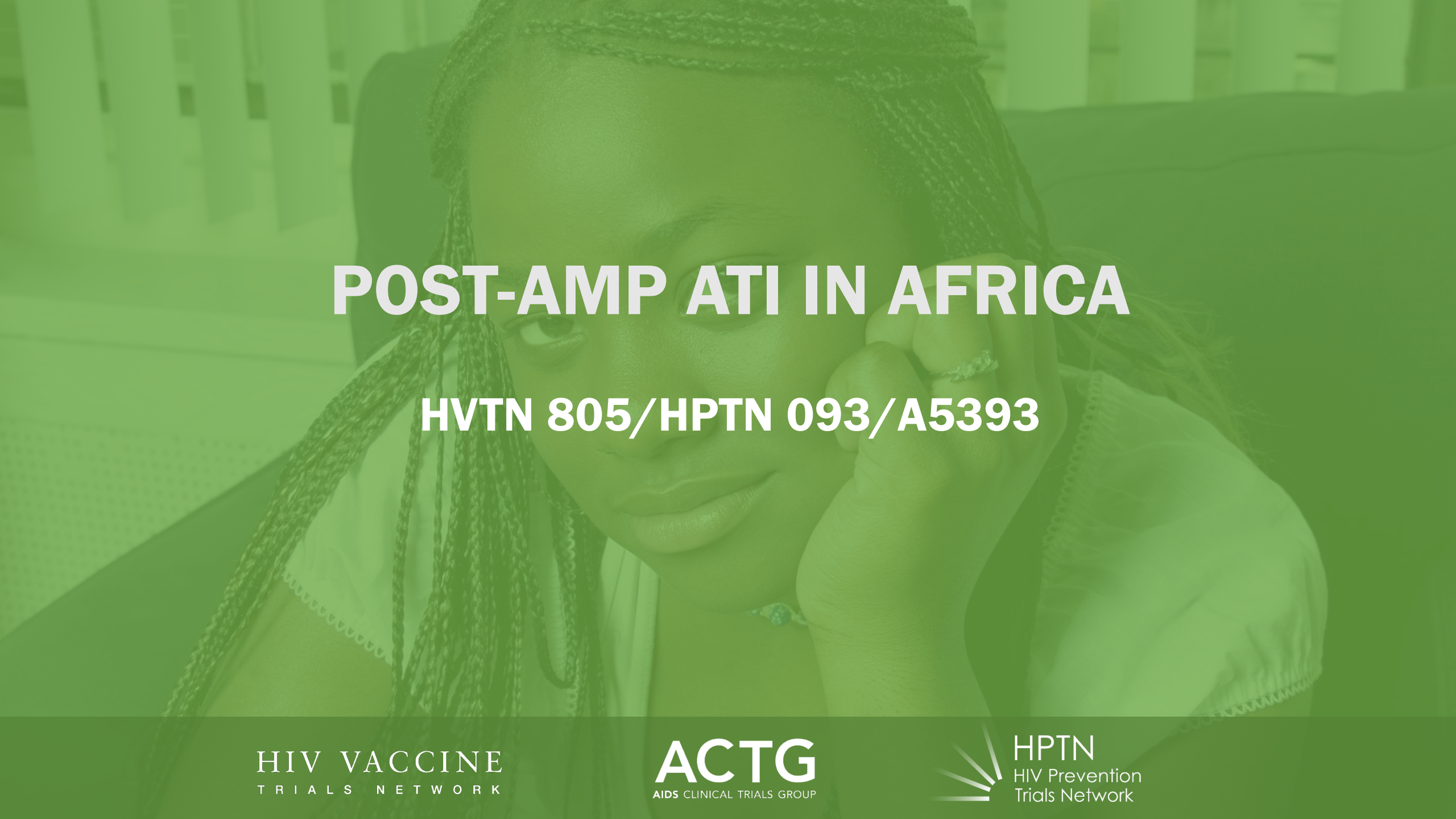
PE= Prevention Efficacy

Corey et al., NEJM, 2021.

AMP Participants are Unique

- Early ART initiation due to frequent HIV diagnostics and CRS-facilitated entry into HIV care
- Broadly neutralizing antibodies present at the time of HIV acquisition

Each of these factors may have (1) favorable effects on the participant's immune system, or (2) unfavorable effects on the participant's virus, or both, to set the stage for possible later ART-free durable virologic control.



POST-AMP ATI IN AFRICA

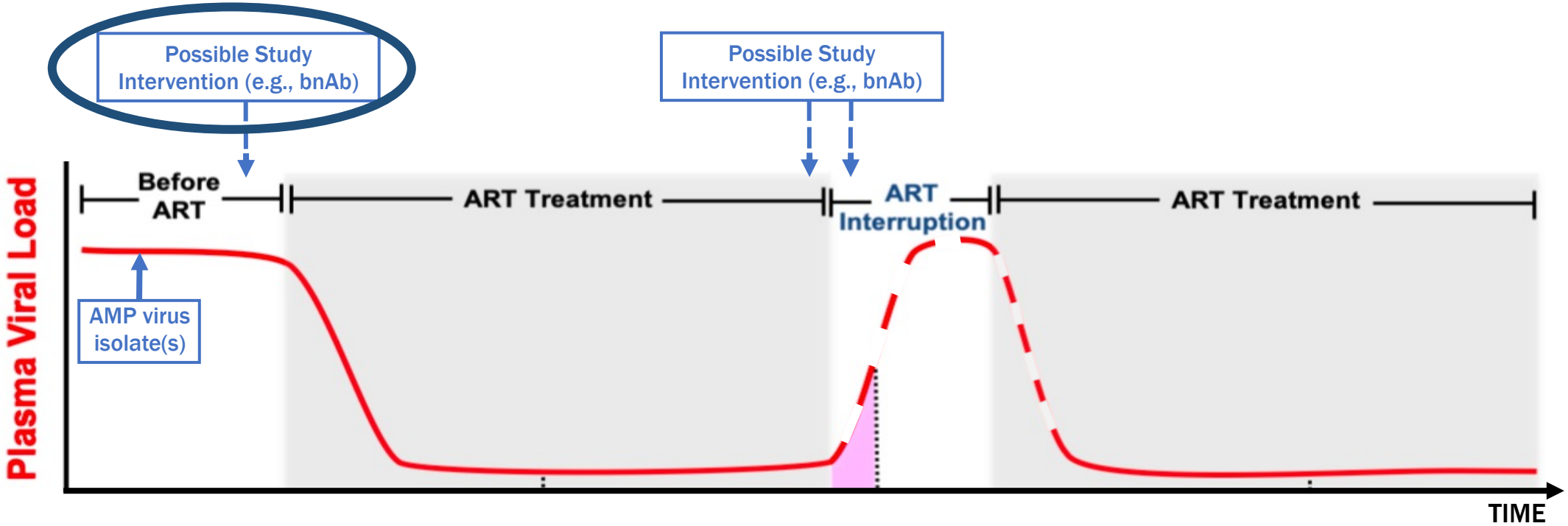
HVTN 805/HPTN 093/A5393

HIV VACCINE TRIALS NETWORK

ACTG AIDS CLINICAL TRIALS GROUP

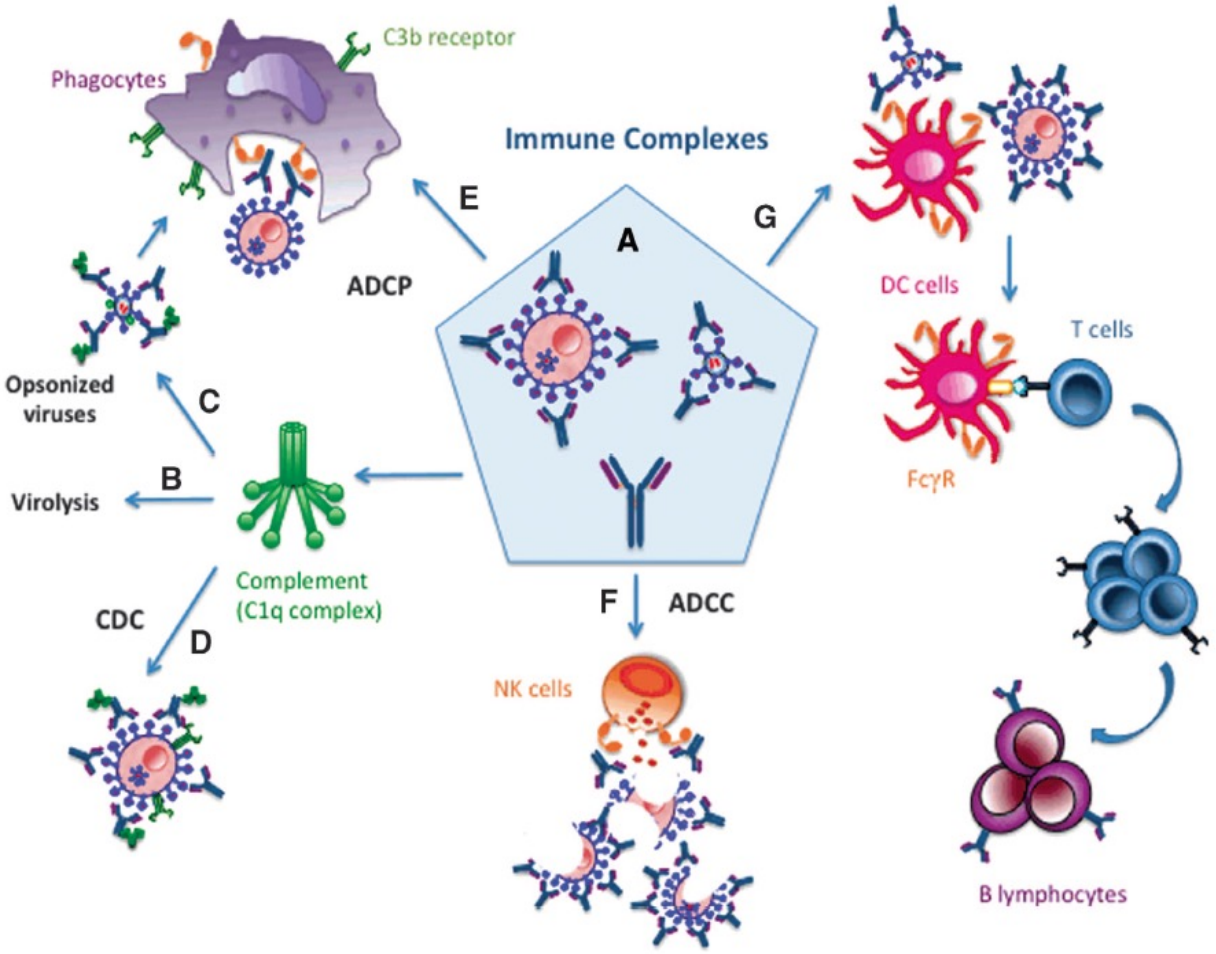
HPTN HIV Prevention Trials Network

Analytical Treatment Interruption (ATI)



Dotted lines indicate potential interventions or outcomes

Immune Complex Modulation of Host Immune Responses



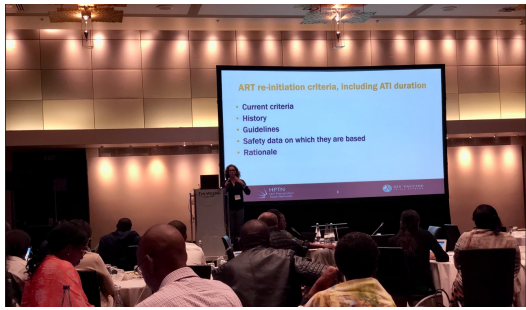
A. OPSONIZATION of virus & of infected cells
B. Complement-mediated VIROLYSIS
C. FcγR- and complement-mediated PHAGOCYTOSIS
D. Complement-dependent CYTOTOXICITY
E. Antibody-dependent cellular PHAGOCYTOSIS (ADCP)
F. Antibody-dependent cellular CYTOTOXICITY (ADCC)
G. Antigen recognition, uptake & presentation by antigen-presenting cells (APCs) like dendritic cells (DCs)

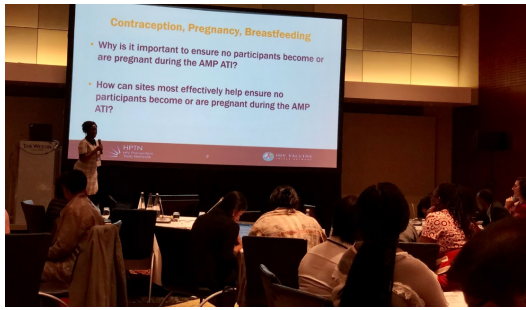
Lambour J et al, Emerging Microbes & Infections 2016
Dhodapkar KM et al, PNAS 2005

From the Beginning: Scientific & Stakeholder Engagement

AMP ATI concept development begins

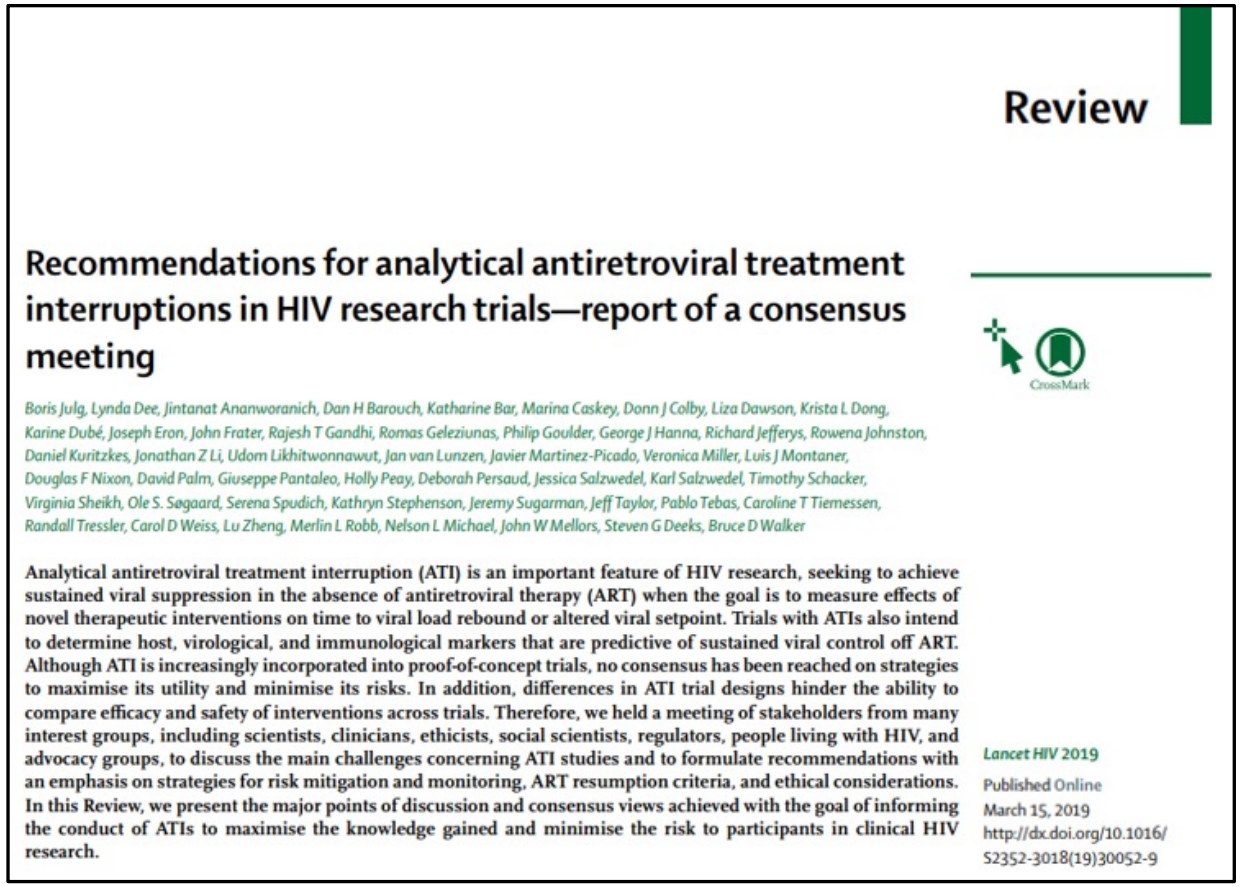
- March 2019: Johannesburg & Boston
  - Sub-Saharan Africa, North & South America
  - Investigators, Ethicists, Regulatory, Public Health & Community representatives





Photos thanks to Maija Anderson

Recent Consensus ATI Design Recommendations



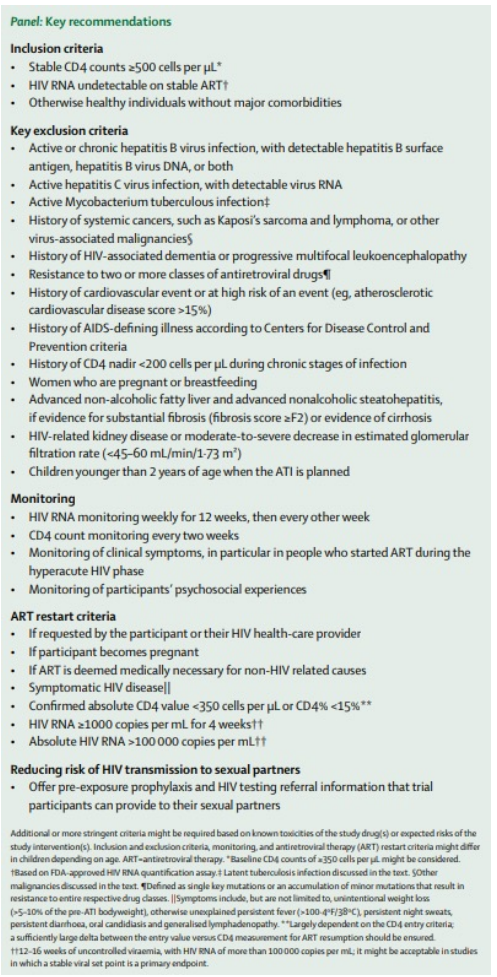
Review

Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting

Boris Julg, Lynda Dee, Jintanat Ananworanich, Dan H Barouch, Katharine Bar, Marina Caskey, Donn J Colby, Liza Dawson, Krista L Dong, Karine Dubé, Joseph Eron, John Frater, Rajesh T Gandhi, Romas Geleziunas, Philip Goulder, George J Hanna, Richard Jefferys, Rowena Johnston, Daniel Kuritzkes, Jonathan Z Li, Udom Likhitwonnawut, Jan van Lunzen, Javier Martinez-Picado, Veronica Miller, Luis J Montaner, Douglas F Nixon, David Palm, Giuseppe Pantaleo, Holly Peay, Deborah Persaud, Jessica Salzwedel, Karl Salzwedel, Timothy Schacker, Virginia Sheikh, Ole S. Søgaard, Serena Spudich, Kathryn Stephenson, Jeremy Sugarman, Jeff Taylor, Pablo Tebas, Caroline T Tiemessen, Randall Tressler, Carol D Weiss, Lu Zheng, Merlin L Robb, Nelson L Michael, John W Mellors, Steven G Deeks, Bruce D Walker

Analytical antiretroviral treatment interruption (ATI) is an important feature of HIV research, seeking to achieve sustained viral suppression in the absence of antiretroviral therapy (ART) when the goal is to measure effects of novel therapeutic interventions on time to viral load rebound or altered viral setpoint. Trials with ATIs also intend to determine host, virological, and immunological markers that are predictive of sustained viral control off ART. Although ATI is increasingly incorporated into proof-of-concept trials, no consensus has been reached on strategies to maximise its utility and minimise its risks. In addition, differences in ATI trial designs hinder the ability to compare efficacy and safety of interventions across trials. Therefore, we held a meeting of stakeholders from many interest groups, including scientists, clinicians, ethicists, social scientists, regulators, people living with HIV, and advocacy groups, to discuss the main challenges concerning ATI studies and to formulate recommendations with an emphasis on strategies for risk mitigation and monitoring, ART resumption criteria, and ethical considerations. In this Review, we present the major points of discussion and consensus views achieved with the goal of informing the conduct of ATIs to maximise the knowledge gained and minimise the risk to participants in clinical HIV research.

Lancet HIV 2019
Published Online
March 15, 2019
http://dx.doi.org/10.1016/S2352-3018(19)30052-9



Panel: **Key recommendations**

Inclusion criteria
- Stable CD4 counts ≥500 cells per μL*
- HIV RNA undetectable on stable ART†
- Otherwise healthy individuals without major comorbidities

Key exclusion criteria
- Active or chronic hepatitis B virus infection, with detectable hepatitis B surface antigen, hepatitis B virus DNA, or both
- Active hepatitis C virus infection, with detectable virus RNA
- Active Mycobacterium tuberculous infection‡
- History of systemic cancers, such as Kaposi's sarcoma and lymphoma, or other virus-associated malignancies§
- History of HIV-associated dementia or progressive multifocal leukoencephalopathy
- Resistance to two or more classes of antiretroviral drugs¶
- History of cardiovascular event or at high risk of an event (eg, atherosclerotic cardiovascular disease score >15%)
- History of AIDS-defining illness according to Centers for Disease Control and Prevention criteria
- History of CD4 nadir <200 cells per μL during chronic stages of infection
- Women who are pregnant or breastfeeding
- Advanced non-alcoholic fatty liver and advanced nonalcoholic steatohepatitis, if evidence for substantial fibrosis (fibrosis score ≥F2) or evidence of cirrhosis
- HIV-related kidney disease or moderate-to-severe decrease in estimated glomerular filtration rate (<45–60 mL/min/1·73 m^2)
- Children younger than 2 years of age when the ATI is planned

Monitoring
- HIV RNA monitoring weekly for 12 weeks, then every other week
- CD4 count monitoring every two weeks
- Monitoring of clinical symptoms, in particular in people who started ART during the hyperacute HIV phase
- Monitoring of participants' psychosocial experiences

ART restart criteria
- If requested by the participant or their HIV health-care provider
- If participant becomes pregnant
- If ART is deemed medically necessary for non-HIV related causes
- Symptomatic HIV disease||
- Confirmed absolute CD4 value <350 cells per μL or CD4% <15%**
- HIV RNA ≥1000 copies per mL for 4 weeks††
- Absolute HIV RNA >100 000 copies per mL††

Reducing risk of HIV transmission to sexual partners
- Offer pre-exposure prophylaxis and HIV testing referral information that trial participants can provide to their sexual partners

Additional or more stringent criteria might be required based on known toxicities of the study drug(s) or expected risks of the study intervention(s). Inclusion and exclusion criteria, monitoring, and antiretroviral therapy (ART) restart criteria might differ in children depending on age. ART=antiretroviral therapy. *Baseline CD4 counts of ≥350 cells per μL might be considered. †Based on FDA-approved HIV RNA quantification assay. ‡ Latent tuberculosis infection discussed in the text. §Other malignancies discussed in the text. ¶Defined as single key mutations or an accumulation of minor mutations that result in resistance to entire respective drug classes. ||Symptoms include, but are not limited to, unintentional weight loss (>5–10% of the pre-ATI bodyweight), otherwise unexplained persistent fever (>100·4°F/38°C), persistent night sweats, persistent diarrhoea, oral candidiasis and generalised lymphadenopathy. **Largely dependent on the CD4 entry criteria; a sufficiently large delta between the entry value versus CD4 measurement for ART resumption should be ensured. ††12–16 weeks of uncontrolled viraemia, with HIV RNA of more than 100 000 copies per mL; it might be acceptable in studies in which a stable viral set point is a primary endpoint.

AMP ATI Eligibility

SELECT* INCLUSION CRITERIA

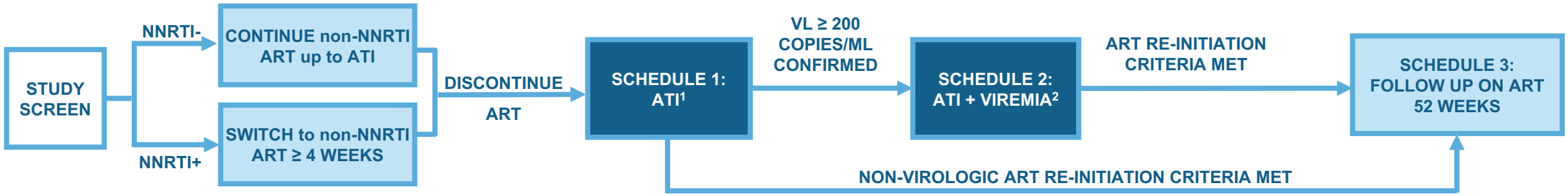
- Former AMP participant
- Initiated ART within ~ 6 months of HIV dx
- $CD4^+$ T cell count > 450 cells per mL
- VL suppressed on ART for ≥ 1 year
- If on an NNRTI-based regimen, willing to switch to protease or integrase inhibitor-based regimen ≥4 weeks pre-ATI
- Willing to be on effective contraception & use barrier protection throughout trial

SELECT* EXCLUSION CRITERIA

- Documented multi-class ART resistance that poses a risk of virologic failure if additional mutations develop during the study
- Reduced renal function
- HepBsAg (+) or (+) HCV RNA
- Elevated liver function tests
- Tuberculosis, untreated
- Pregnant or breastfeeding

*Not an exhaustive list

AMP ATI Study Design



	PRE-ENTRY		SCHEDULE 1			SCHEDULE 2				SCHEDULE 3		
	SCREEN	PRE-DISCONTINUE ART	ATI WEEKS 0-8	ATI WEEKS 10-24	ATI WEEKS 28-52[1]	ATI + Viremia WEEKS 0-8	ATI + Viremia WEEKS 10-36	ATI + Viremia WEEKS 40-52[2]	PRE-REINITIATE ART	FOLLOW UP ON ART WEEKS 0-12	FOLLOW UP ON ART WEEKS 12-28	FOLLOW UP ON ART WEEKS 40-52
Plasma HIV RNA	✓	✓	WEEKLY	Q2 WEEKS	Q4 WEEKS	WEEKLY	Q2 WEEKS[3]	Q4 WEEKS	✓	Q2 WEEKS	Q4 WEEKS	Q12 WEEKS
CD4+ & CD8+ T cell counts	✓	✓	Q2 WEEKS	Q4 WEEKS	Q8 WEEKS	Q2 WEEKS	Q4 WEEKS[4]	Q8 WEEKS	✓	Q4 WEEKS	Q8 WEEKS	Q12 WEEKS
Hematology & Chemistries	✓	✓	Q4 WEEKS		Q8 WEEKS	Q4 WEEKS		Q8 WEEKS	–	Q4 WEEKS	Q12 WEEKS	Q12 WEEKS

[1] QUARTERLY FOLLOW-UP VISITS MAY CONTINUE BEYOND WEEK 52 FOR PARTICIPANTS WHO DO NOT MEET CRITERIA FOR TRANSITION TO SCHEDULE 2.
[2] QUARTERLY FOLLOW-UP VISITS MAY CONTINUE BEYOND WEEK 52 FOR PARTICIPANTS WHO DO NOT MEET CRITERIA FOR ART RE-INITIATION
[3] OR WEEKLY FOR WEEKS 10-24, IF VL≥200 copies/mL
[4] OR Q2 WEEKS FOR WEEKS 10-24 IF VL≥200 copies/mL

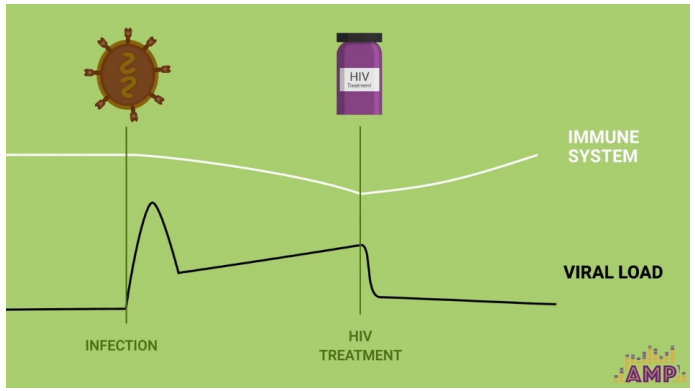
Thanks to Lisa Donohue

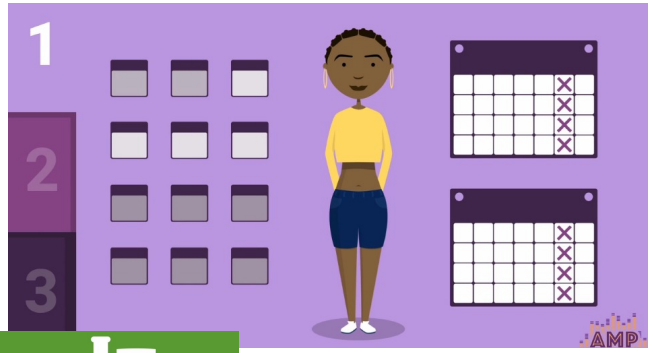
ART Re-initiation Criteria

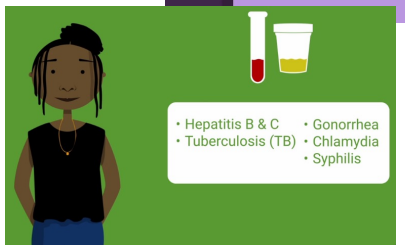
- Viral load ≥ 1,000 copies/mL for ≥ 4 consecutive weeks, confirmed on a second sample & not declining by 0.5 log from the previous week; OR
- $CD4^+$ T cell count < 350 cells/mm^3, confirmed on a second sample; OR
- Any HIV-related syndrome (eg, acute retroviral syndrome, an opportunistic infection); OR
- Participant or provider wish to re-initiate ART.

Additional Select Study-Specific Design Considerations

- **Robust informed consent process**
  - *Informed Consent Video* with *Informed Consent Form* & EC review
  - *Assessment of Understanding*
  - *Facilitated decision-making process* with an initial (& periodically repeated) decision aid & assessments: does your decision align with your values?







Additional Select Study-Specific Design Considerations

- **Robust informed consent process**
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  - *Assessment of Understanding*
  - *Facilitated decision-making process* with an initial (& periodically repeated) decision aid & assessments: does your decision align with your values?

"[participants] have shown a consistent & retained understanding over time"

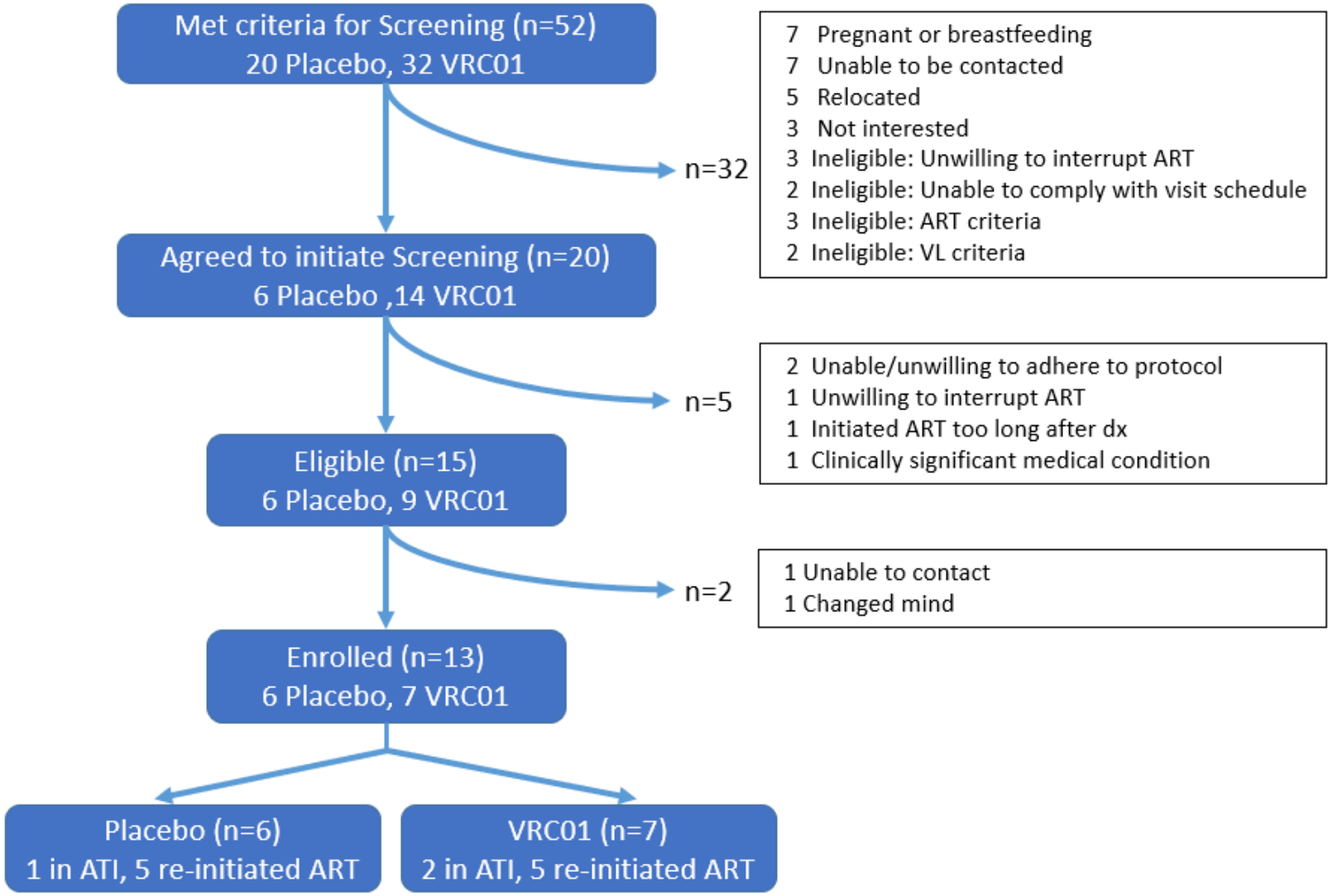
"it's not just one session of screening or counseling, you need to give people time to talk with family or a friend"

"this is another level of respecting a participant's decision"

- **STI testing q3 months and as clinically indicated**

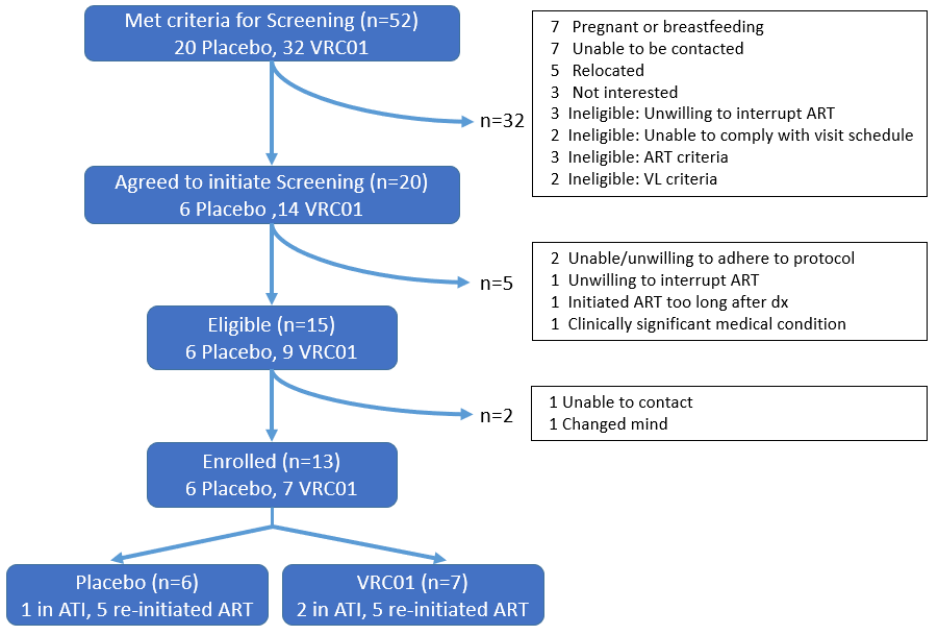
- **Weekly counseling on HIV transmission risk reduction and facilitated HIV testing and PrEP for sexual partners.**

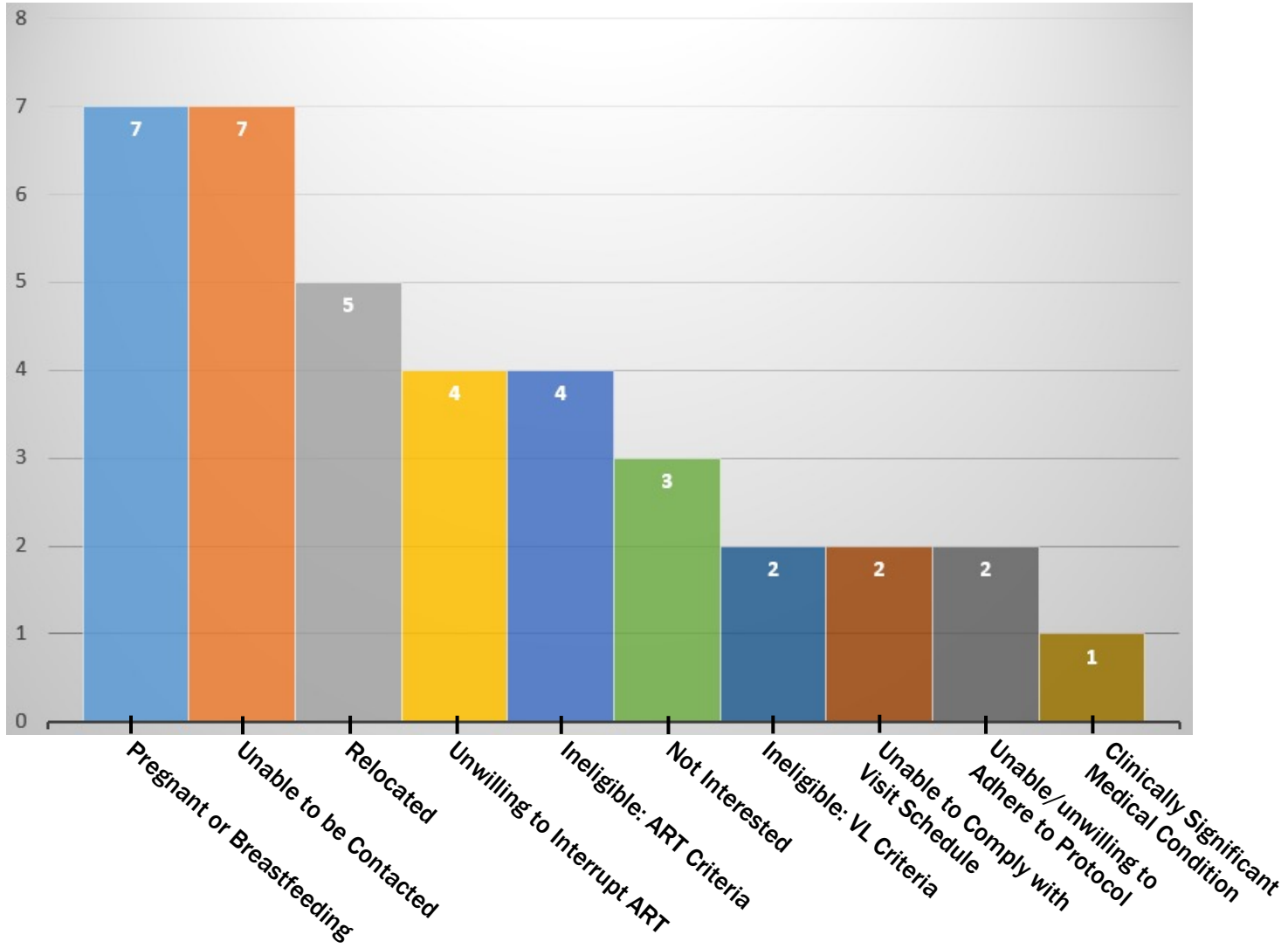
SSA AMP ATI Pre-Screening to Enrollment



Thanks to Doug Grove

SSA AMP ATI Pre-Screening & Screening Outcomes





AMP ATI Study Design

>300 visits (~20+ visits/ppt, & counting)

No Missed Visits

100% Retention

1 Early Termination (Relocation post-ART re-initiation)

	PR…	SCRE…	…E 3 FOLLOW UP ON ART WEEKS 40-52
Plasma HIV RNA	✓	✓	Q12 WEEKS
CD4+ & CD8+ T cell counts	✓	✓	Q12 WEEKS
Hematology & Chemistries	✓	✓	Q12 WEEKS

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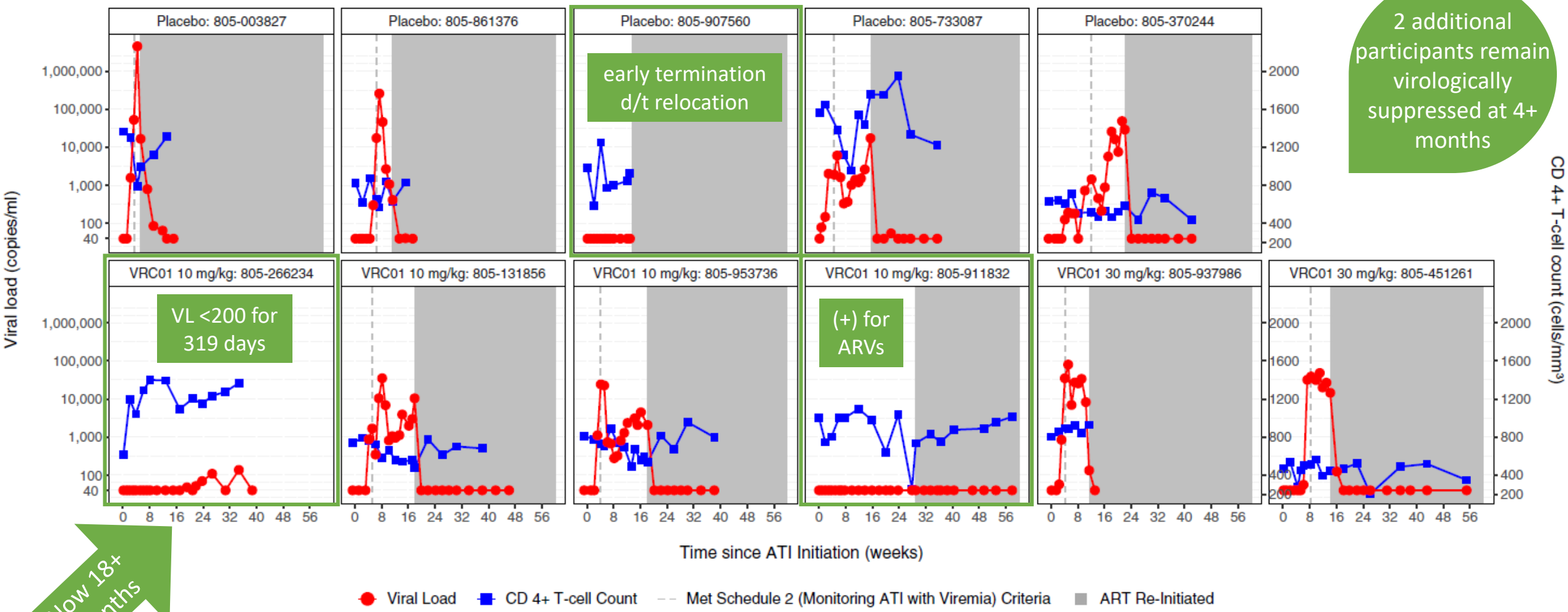
Thanks to Lisa Donohue

Viral Load & CD4+ T-cell Count Dynamics: Many Variables



Thanks to Doug Grove, Erika Rudnicki, Pei-Chun Yu & Allan deCamp

Summary

- ATIs can be conducted safely & well in Africa

& in Peru*

*AMP ATI in Peru began in August 2022 with n=17 ppts so far

- Authentic early-&-often stakeholder engagement is a key to ATI & HIV cure research success, irrespective of geography
- Among African women, consider *relationships*, pregnancy, autonomy & the role of a placebo group
- Robust informed consent, decision aids, psychological assessments and *non-punitive* ARV & STI testing can support success

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AMP ATI Site Acknowledgements

Thank you to all the site investigators, clinic coordinators, community engagement teams, and pharmacists.

HVTN 805/HPTN 093/A5393 Sites

- Blantyre
- Gaborone
- Harare – Seke South
- Harare - Spilhaus
- Johannesburg - Ward 21
- Lilongwe
- Rustenburg
- Soweto – Bara

HVTN 804/HPTN 095/A5390 Sites

- Iquitos
- Lima – Barranco
- Lima – San Marcos
- Lima – San Miguel
- Lima – Via Libre
- Rio de Janeiro – Manguinhos