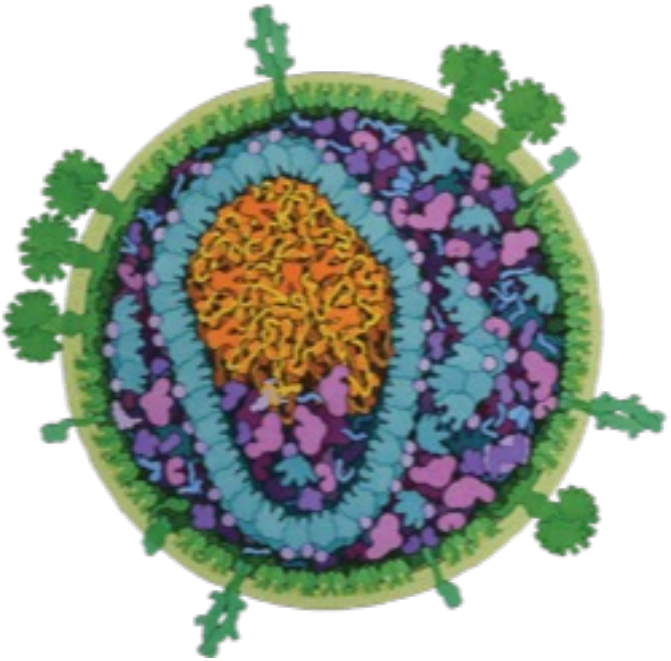
# ACTG Cure TSG: Priorities and Pathways

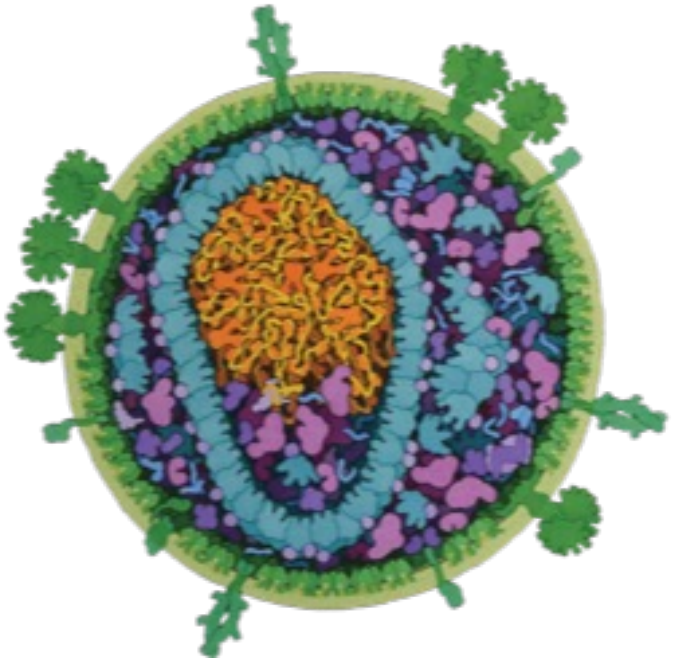
# Pre-CROI Community HIV Cure Workshop



**Chair: Marina Caskey**

**Vice Chair: Katie Bar**

**Ex Officio: Pablo Tebas**



# Outline

- ACTG Cure TSG Priorities overview
- Studies: open and opening soon
- Challenges
  - enrollment, equity, ATI studies
- International ATI studies
- Discussion

# ACTG Cure TSG Priorities

## 1. Characterize HIV reservoirs

- **A5321:** Cohort study of ART-treated PWH (early, chronic, low-level viremia, acq on CAB)
- **A5345**: Non-interventional ATI study
- **A5354**: Early initiation of ART (US, S America, Thailand)

## 2. Evaluate therapeutic interventions

- Studies to reduce, control and/or eliminate HIV reservoirs

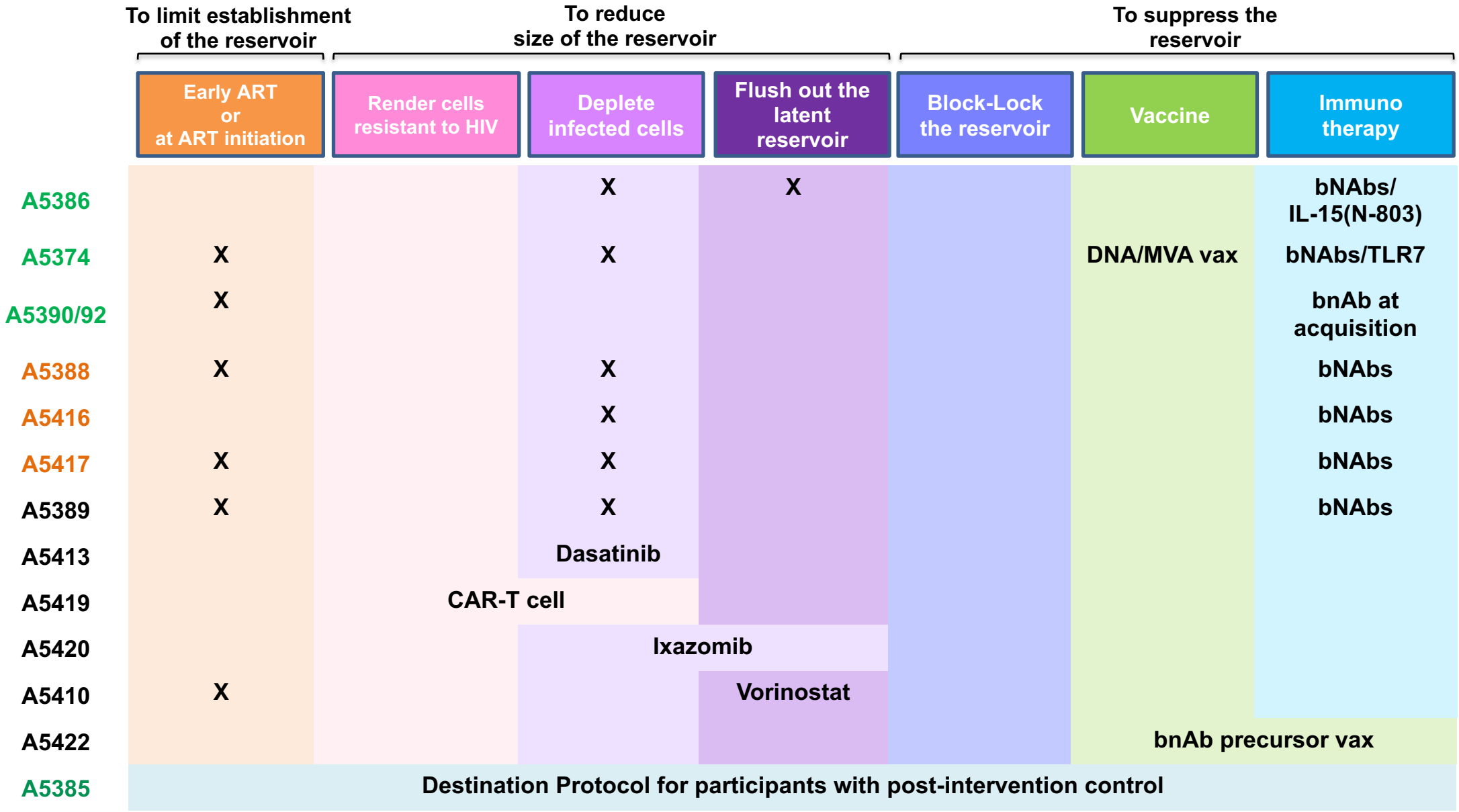
## 3. Collaborate with community partners

- On priorities; ethical and efficient conduct of studies; sociobehavioral implications

# Cure intervention strategies: concepts

- **Immunotherapies**
  - Broadly neutralizing antibodies
  - Therapeutic vaccination (T & B cells)
  - Immunomodulatory drugs
  - CAR T cells
- **Disrupt latency**
  - Shock-and-kill
  - Interference with homeostatic proliferation
  - Block-and-lock
- **Gene editing strategies**
  - Viral excision by CRISPR
  - CCR5-Δ32 mutation
- **Timing of ART and intervention**
  - ART initiation: bnAbs, LRA, others
  - Early ART
- **Study populations**
  - Treated early
  - Intervention during early HIV
  - Sex at birth, gender, pre/peri/post-menopausal status
  - Geographic diversity,including in viral clades
- **Combination approaches**
  - *eg,* bnAb + vaccine + LRA

# ACTG Cure TSG Studies: Approaches



# Studies: *Ongoing and Planned*

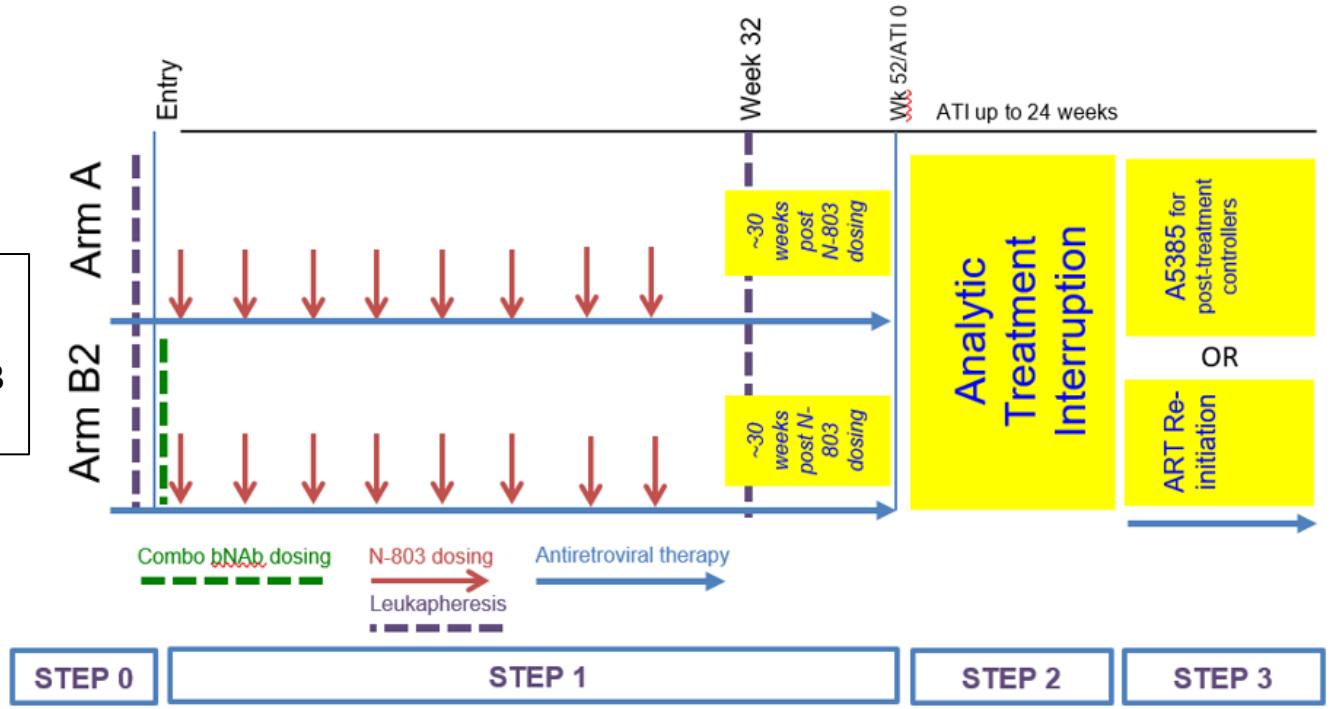
| Study | Study Population | Location | Projection to Open | Complete Accrual | ATI Start |
|---|---|---|---|---|---|
| **A5386**<br>N-803+/- bNAbs on ART | Chronic treated<br>(n=46 ; 2 active arms) | US | Enrolling | | 2023 |
| **A5374**<br>ChAd/MVA vax/ TLR7/bNAbs on ART | Early HIV<br>(n=45; pbo) | US/non-US<br>(Americas) | Open / enroll. Jan 2024 | | 2025 |
| **A5390/93**<br>AMP ATI in Americas/Africa | AMP participants with acquisition (n= 26; 13) | Non-US<br>(S America; Africa) | Closed to enrollment; ongoing | 2023 | 2021 |
| **A5388**<br>bNAbs at ART initiation | Early HIV<br>(n=48; pbo) | US/non-US<br>(Americas) | Jan-2024 | May-2025 | Apr-2025 |
| **A5416**<br>bNAbs during ATI in SSA | Chronic treated<br>(n=48 ; pbo) | Non-US (Africa) | Jan-2024 | Oct-2024 | Jan-2024 |
| **A5417**<br>bNAbs at ART start in SSA | ART naïve<br>(n=135; pbo) | Non-US (Africa) | Feb-2024 | Aug-2025 | May-2025 |
| **A5389**<br>bNAbs during ART vs ATI | Early treated<br>(n=40; pbo) | US/non-US<br>(Americas) | Apr-2024 | Aug-2025 | May-2024 |
| **A5413**<br>Dasatinib (anti-proliferative) on ART | Chronic<br>(n=14) | US (site limited) | Jun-2024 | | No |
| **A5419**<br>CD4 CAR-Ts expand w/ vax on ART | Chronic<br>(n=12) | US (site limited) | Aug-2024 | | N/A |
| **A5420**<br>Ixazomib (pro-apoptosis/LRA on ART | Chronic<br>(n=40; pbo) | US | Jul-2024 | | No |
| **A5410**<br>Vorinostat at ART start | ART naïve<br>(n=48;pbo) | US | On hold | | No |
| **A5422**<br>CH505 TF (bNAb precursor vax) on ART | Chronic<br>(n=30/pbo) | US | Mar-2024 | | No |
| **A5385**<br>Post-intervention Control Cohort | Participants who experience PIC | US/non-US | Open Dec 2023 | N/A | N/A |

# **A5386:** A Phase I Open Label study of **IL-15 Superagonist (N-803)** with or without **bNAbs (VRC07.523LS+10-1074-LS)** during suppressive ART

(Chairs: Wilkin/Jones/Caskey)

***Target: 46***

- **Enrolled (Step 1): 17**
- Entered ATI (Step 2): 3
- Re-started ART: 2




***Study Population*** (n=46):

- 18 to 70
- Current CD4 > 500
- CD4 nadir > 200
- On ART w/ VL < LLOQ x > 2yrs

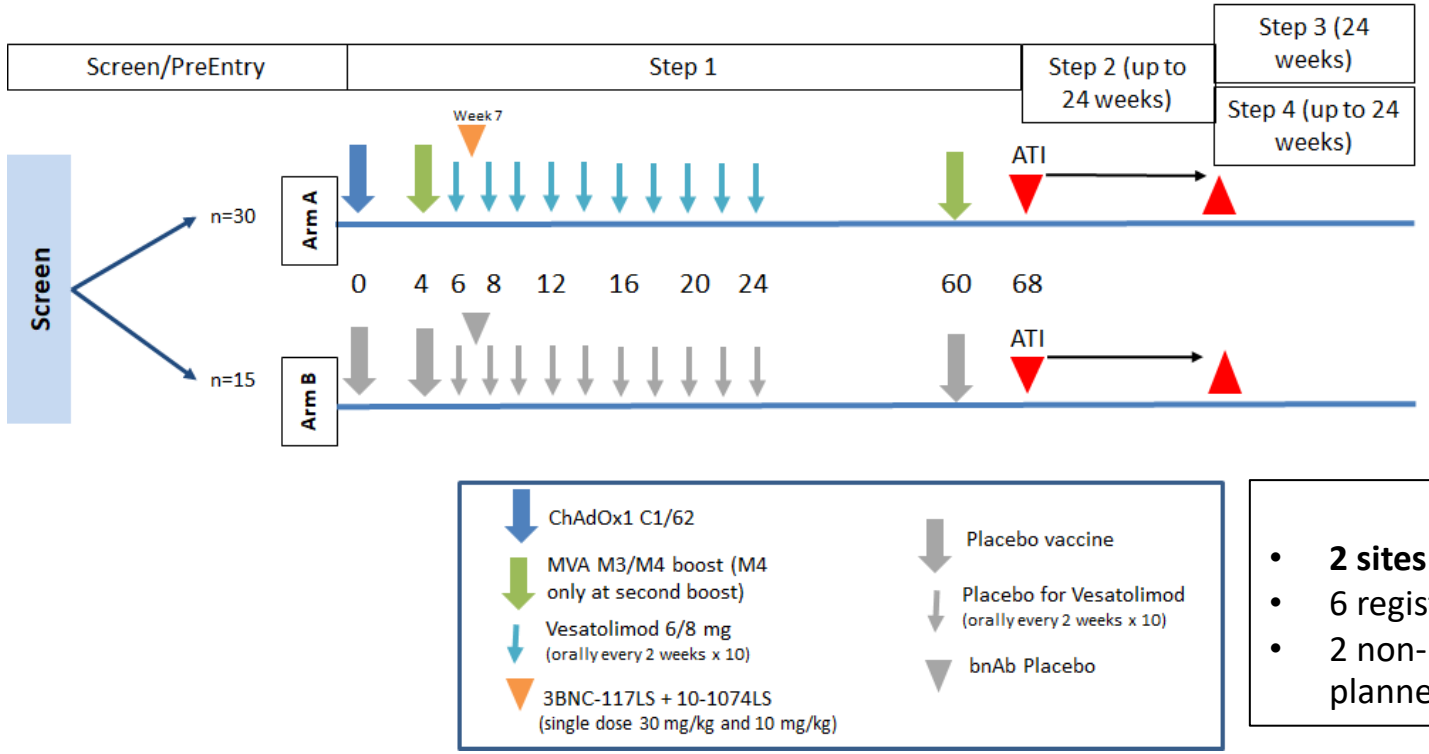
***Primary Objectives:***

- Safety and Tolerability
- Virologic control during ATI

(HIV-1 RNA <200 copies/mL 8 weeks after ATI)

# **A5374:** A Phase I/IIa Randomized, Placebo-Controlled Trial of **Conserved-Mosaic ChAdOx/MVA T-cell Vaccines** with **Vesatolimod, bNAbs** (3BNC117-LS and 10-1074-LS) in early treated adults

(Chairs: Riddler/Gay/Mellors)




***Sites***

- **2 sites activated**
- 6 registered
- 2 non-US sites planned (Brazil)

***Study Population*** (n=45):

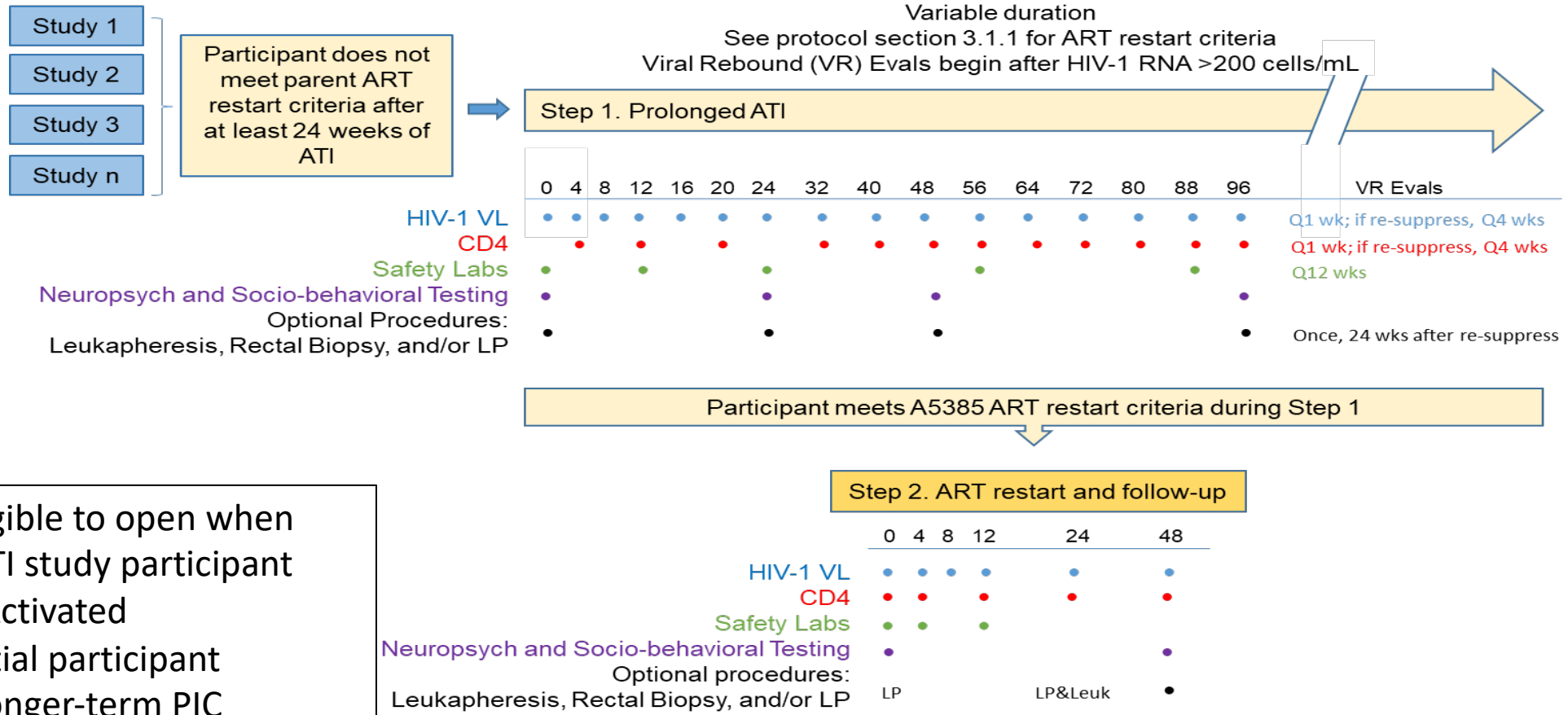
- 18 or older
- Current CD4 > 500
- **ART start within 28d of infection (Fiebig V)**
- On ART w/ VL < LLOQ x > 1yr
- **Stratified randomization by HLA**

***Primary Objectives:***

- Safety and Tolerability
- Virologic control during ATI (does not meet ART restart criteria for 16wks after ATI)

# A5385: An Observational Post-Intervention Control Destination Cohort

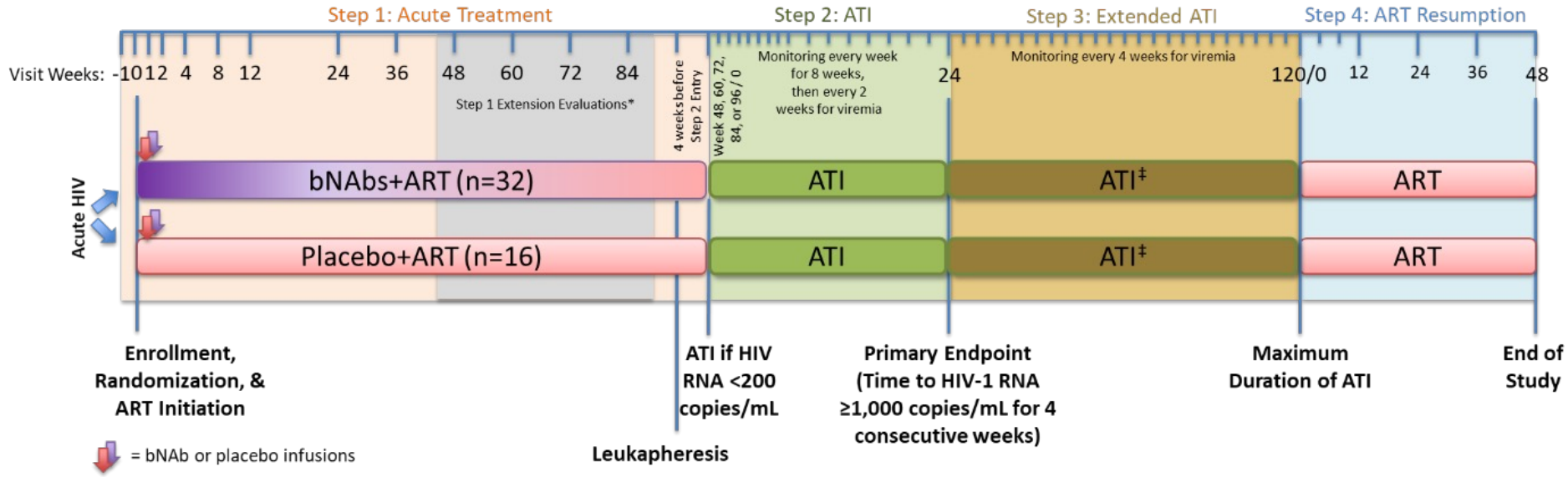
Chairs: Bar/Caskey/Crowell




- Sites eligible to open when enroll ATI study participant
- 3 Sites Activated
- 1 potential participant
  - 2 longer-term PIC declined interest

# **A5388:** A Double-Blind, Randomized, Placebo-Controlled Study of a Combination of HIV bNAbs (**VRC07-523LS and PGT121.414.LS**) plus ART Initiation during Acute HIV Infection to Induce HIV Remission

(Chairs: Trevor/Mellors/Tebas)




* If observed VRC07-523LS and PGT121.414.LS concentrations are within expected ranges to reach <1 µg/mL by the start of the ATI, or if there is a shorter observed half-life for the antibodies, then the ATI (Step 2) will be initiated at 48 weeks. If the concentrations are higher than expected, then Step 1 will be extended and the ATI will be started at week 60, 72, 84, or 96, depending on the real-time PK modeling.

‡ Participants who do not meet ART resumption criteria at the completion of Step 2 (i.e. post-treatment controllers) will proceed to Step 3 for continued monitoring; this step could be adapted to follow-up in A5385 or another relevant ACTG cohort.

***Study population:***

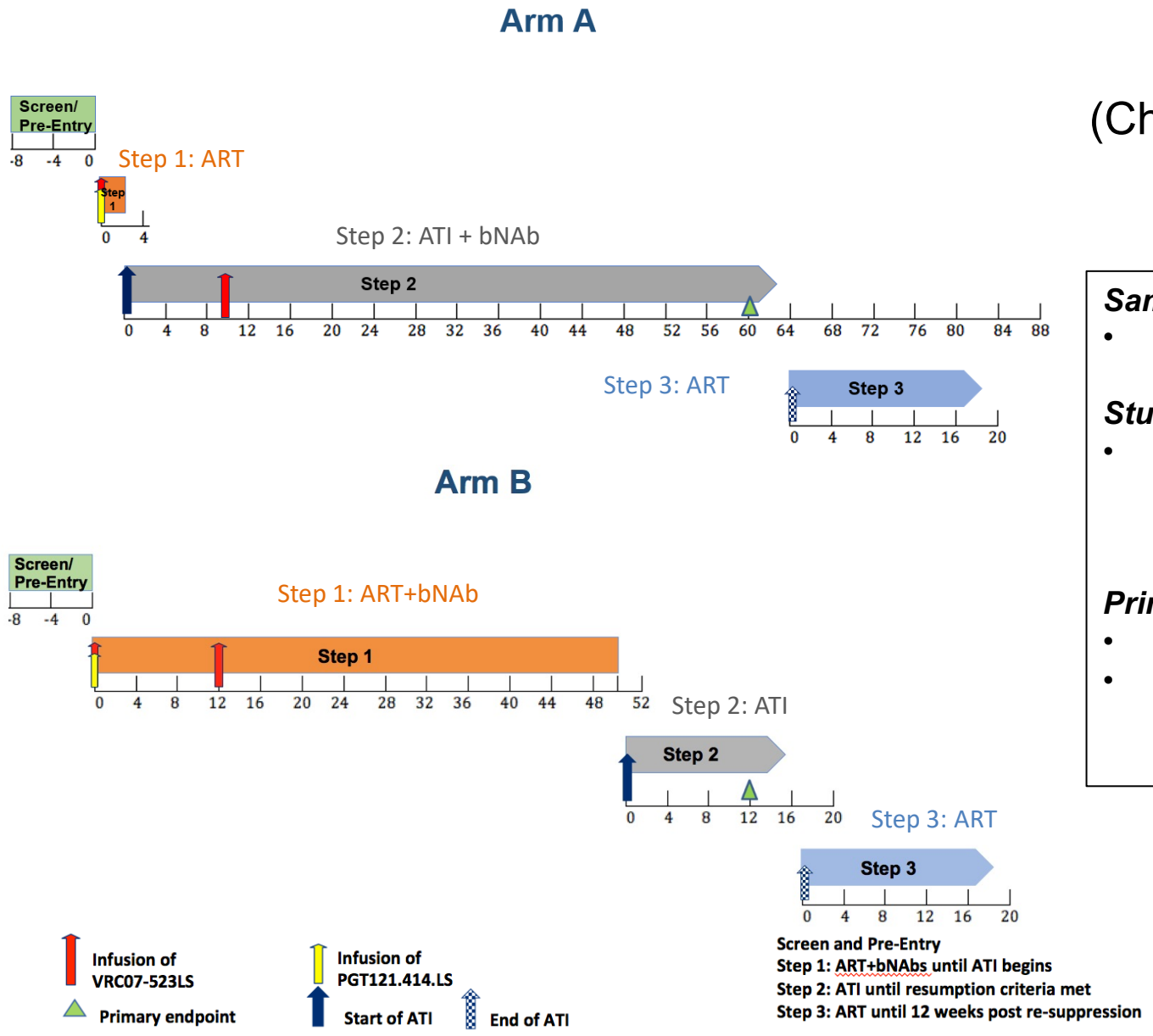
- ART-naïve adults with AHI
- ≥18 and ≤70 years old
- No history of receipt of any therapeutic HIV vaccine or monoclonal antibody therapy

***Primary Objectives:***

- Safety and Tolerability
- Time to HIV-1 RNA ≥1,000 copies/mL for 4 consecutive weeks after ATI.

# **A5389:** A Phase I Study of Two bNAbs (**VRC07-523LS and PGT121.414.LS**) During **Analytic Treatment Interruption** in PWH Who Initiated ART During **Acute HIV-1**

(Chairs: Malvestutto/Riddler/Mellors)




***Sample size:***

- 40 (20/arm).

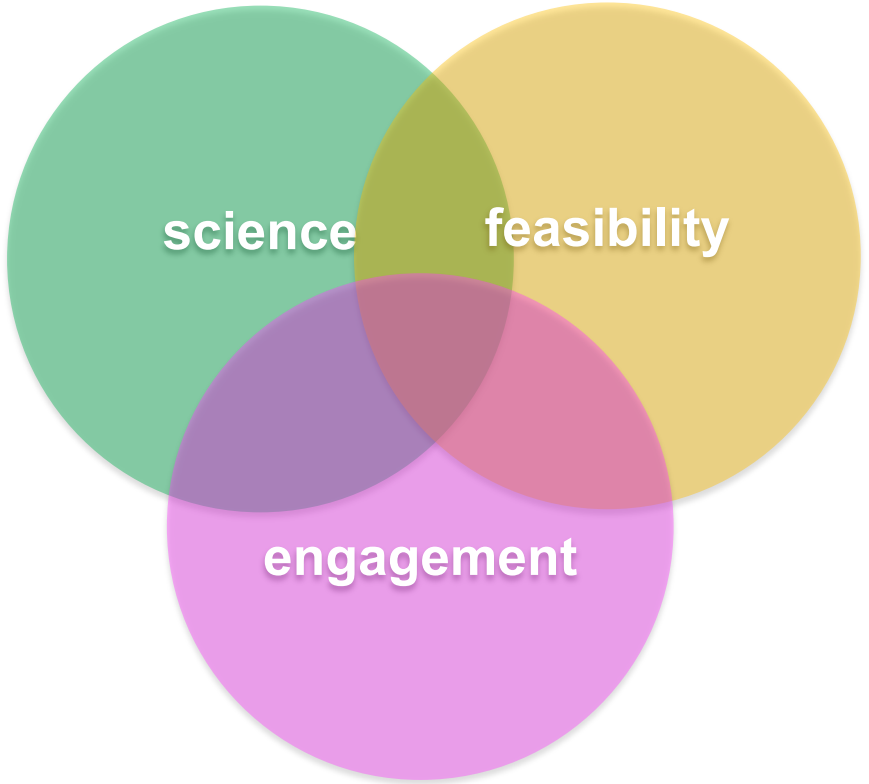
***Study Population:***

- Ages 18 to 70 years old, started ART during acute/early HIV, with suppressed VL x 24 months, current CD4+ count >450 cells/ml

***Primary Objectives:***

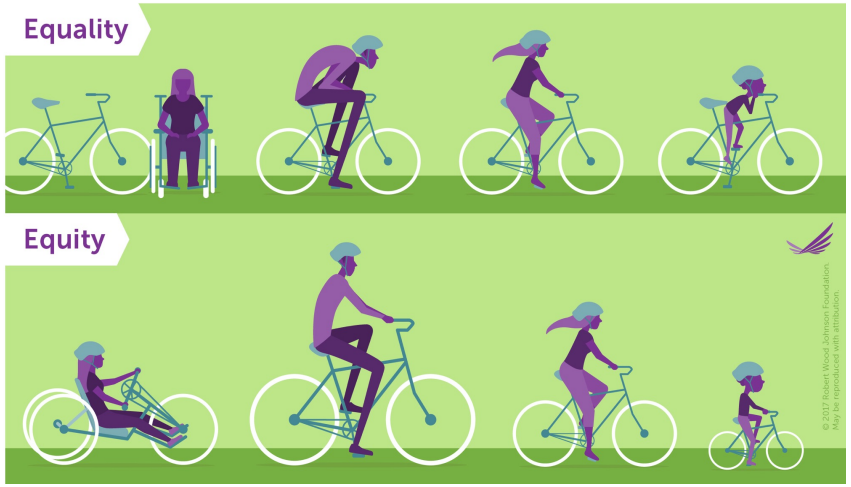
- Safety and tolerability
- Viral suppression during ATI (remain off ART by week 62 after Step 1 entry)

# Cure Trial Challenges: Enrollment




- Trial design is a balance between science and feasibility
- Trial success requires engagement of community, sites, providers
  - concept, design, recruitment, participant support
- Can be disconnect between trial experts and larger community

# Cure Trial Challenges: Equity and Representation

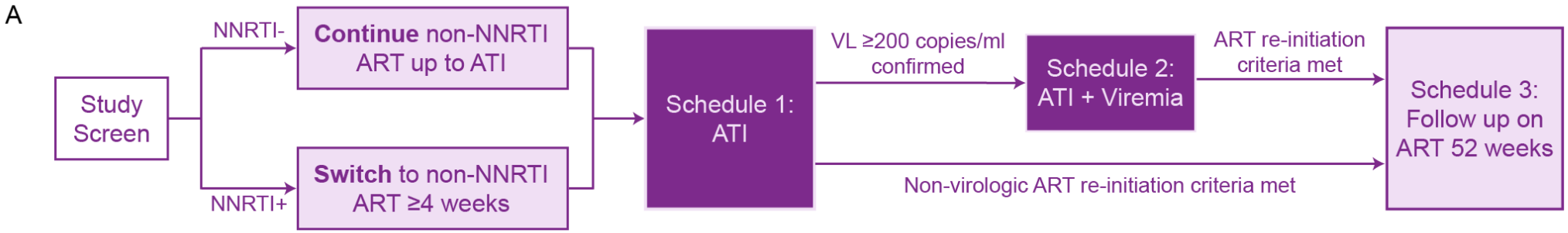



- **Sex/gender: cis-women**
  - *eg*, A5340 (2013): 15 enrolled participants, all cis-men
  - *eg*, A5386 (2023): 30% enrollment target, conditions in place. Currently <10% women enrolled
  - Obstacles: feasibility, linkage, engagement of providers, sites, potential participants, leukapharesis
- **Geography:**
  - Africa (A5393, A5416, A5417): studies in RSA, Zimbabwe, Malawi, Botswana
  - South America (A5374, A5388, A5389): Peru, Brazil
  - Obstacles: virus clade for bnAbs, export/product restrictions for products, inertia

# Cure Trial Challenges: ATI studies

- **Scientific value**: no alternative biomarker or surrogate endpoint
- **Experience to date**: Generally safe, but burdensome
- **Requires immense participant commitment**
  - Communication
  - Education for informed consent
  - Participant support
  - Partner protections
- **Sociobehavioral research for iterative improvements**
- **Research for improved design**
  - at home, point of care VL testing
  - biomarker for virus control

# HVTN 805/HPTN 093/A5393: AMP ATI in Africa

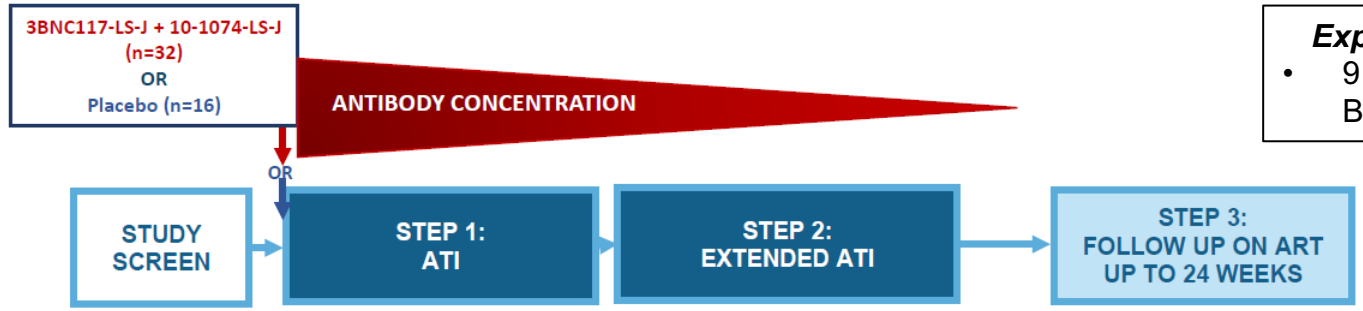



- **What is the impact of early ART +/- VRC01 at HIV acquisition on virus control post-ATI?**
  - AMP participants who acquired HIV, suppressed on ART
- Unique population: linked participants from AMP trial; HVTN/HPTN/ACTG sites
  - Stakeholder engagement process (2017-2020)
- Trial ongoing: all participants re-started ART
  - 2 participants with prolonged time off ART
  - No SAE
- ATI Stakeholder engagement, implementation & early clinical data, manuscript in preparation
  - Additional SBR, mechanistic studies ongoing

# **A5416/HVTN806/HPTN108:** Phase I, Randomized, Placebo-Controlled Study of of **bNAbs** (3BNC117-LS-J and 10-1074-LS-J) in **ART-treated Adults** living with HIV-1 **in sub-Saharan Africa** during **ATI**

Short Title: Pausing ART Under Structured Evaluation (**PAUSE**)

(Chairs: Hosseinipour/Maboa/Hahn/Caskey)




| | SCREENING | STEP 1 ATI | | STEP 2 EXTENDED ATI | | | STEP 3 ART RE-INITIATION |
|---|---|---|---|---|---|---|---|
| | SCREEN | MONITORING WEEKS 0-8 | MONITORING WEEKS 9-24 | MONITORING WEEKS 25-52 | MONITORING WEEKS 53-72 | PRE-RESTART | MONITORING X 24 WEEKS |
| Plasma HIV RNA | ✓ | WEEKLY | Q2 WEEKS[1] | Q2 WEEKS[1] | Q4 WEEKS[1] | ✓ | WEEKS 4, 12 & 24 |
| CD4+ T cell counts | ✓ | Q2 WEEKS | Q4 WEEKS[1] | Q4 WEEKS[1] | Q4 WEEKS[1] | ✓ | WEEKS 12 & 24 |
| Hematology & Chemistries | ✓ | Q4 WEEKS | | Q8 WEEKS | | - | WEEKS 4, 12 & 24 |

[1]OR WEEKLY IF VL > LLQ

***Expected to Open early 2024***

- 9 sites: South Africa, Malawi, Botswana

***Study Population*** (n=48):

- 18 -70 yrs of age
- Current CD4 > 450
- On ART w/ VL < LLOQ x > 2yrs
- Goal to enroll ~ 50% women

***Primary Objectives:***

- Safety and Tolerability
- Prevent return of viremia x 24wks

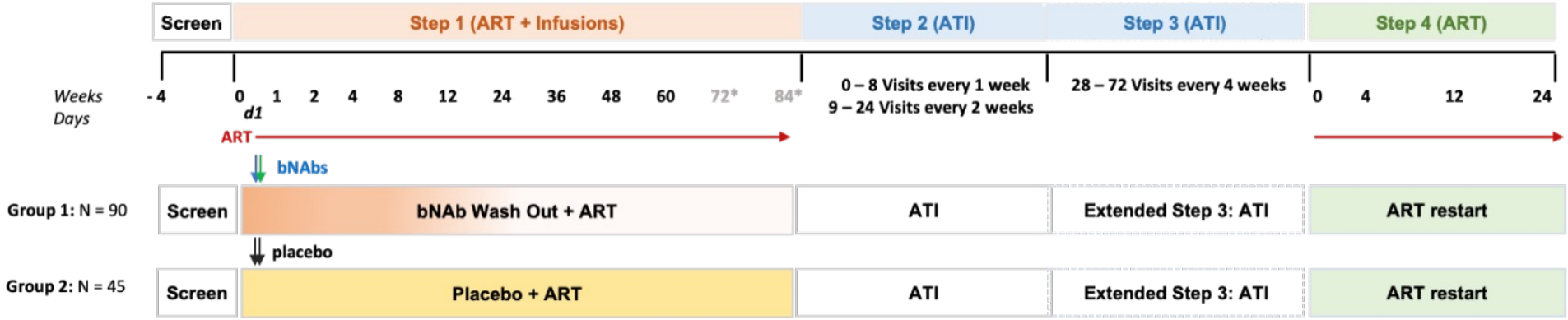
# **A5417:** A Randomized, Placebo-Controlled Study of two Long-Acting **bNAbs (3BNC117-LS and 10-10740LS) at ART Initiation** in Adults Living with HIV-1 in **sub-Saharan Africa**

*Short Title:* ART Combined with Antibodies for HIV-1 Cure In Africa **(ACACIA)**

(Chairs: Samaneka/Crowell/Bar/Caskey)

***Expected to Open mid 2024***

- 9 sites: South Africa, Malawi, Botswana, Zimbabwe




Group 1: 3BNC117-LS + 10-1074-LS + ART
Group 2: Placebos + ART
*ART regimen: Integrase inhibitor-based regimen

***Study Population*** (n=135):
- 18 -60 yrs of age
- ART naïve
- Plasma HIV-1 RNA > 1000 cp/ml
- Current CD4 >200
- Goal to enroll ~ 50% women

***Primary Objectives:***
- Safety and Tolerability
- Time to sustained viremia

# Cure Trial Challenges & Solutions

- **Cure TSG goals and approaches:**
  - **Open and enroll studies**
    - support sites, *eg*. centralized leukopak processing
    - incentivize Cure trial enrollment
  - **Support sites for ATI and other studies, US and international**
    - site surveys, central educational materials
  - **Comprehensive Cure Study Working Group**
    - Partner Protections Working Group Toolkit implementation
    - build on PPWG to include additional stakeholders to address holistic approach
- **Discussion**

Thank you!