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, acquired 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

<table>
<thead>
<tr>
<th>Destination Protocol for participants with post-intervention control</th>
<th>To limit establishment of the reservoir</th>
<th>To reduce size of the reservoir</th>
<th>Flush out the latent reservoir</th>
<th>To suppress the reservoir</th>
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</thead>
<tbody>
<tr>
<td>Early ART or at ART initiation</td>
<td>Render cells resistant to HIV</td>
<td>Deplete infected cells</td>
<td>Block-Lock the reservoir</td>
<td>Vaccine</td>
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<td>A5386</td>
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<td>A5374</td>
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<td>A5390/92</td>
<td>X</td>
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<td>DNA/MVA vax</td>
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<td>A5388</td>
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<td>A5413</td>
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<td>Dasatinib</td>
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<td>A5419</td>
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<td>CAR-T cell</td>
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<td>A5420</td>
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<td>Ixazomib</td>
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<td>A5410</td>
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<td>Vorinostat</td>
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<td>Study</td>
<td>Study Population</td>
<td>Location</td>
<td>Projection to Open</td>
<td>Complete Accrual</td>
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<tr>
<td>A5386</td>
<td>N-803 +/- bNAbs on ART</td>
<td>Chronic treated (n=46; 2 active arms)</td>
<td>US</td>
<td>Enrolling</td>
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<tr>
<td>A5374</td>
<td>ChAd/MVA vac/ TLR7/bNAbs on ART</td>
<td>Early HIV (n=45; pbo)</td>
<td>US/non-US (Americas)</td>
<td>Open / enroll. Jan 2024</td>
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<tr>
<td>A5390/93</td>
<td>AMP ATI in Americas/Africa</td>
<td>AMP participants with acquisition (n=26; 13)</td>
<td>Non-US (S America; Africa)</td>
<td>Closed to enrollment; ongoing</td>
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<tr>
<td>A5388</td>
<td>bNAbs at ART initiation</td>
<td>Early HIV (n=48; pbo)</td>
<td>US/non-US (Americas)</td>
<td>Jan-2024 May-2025 Apr-2025</td>
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<td>A5416</td>
<td>bNAbs during ATI in SSA</td>
<td>Chronic treated (n=48; pbo)</td>
<td>Non-US (Africa)</td>
<td>Jan-2024 Oct-2024 Jan-2024</td>
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<td>A5417</td>
<td>bNAbs at ART start in SSA</td>
<td>ART naive (n=135; pbo)</td>
<td>Non-US (Africa)</td>
<td>Feb-2024 Aug-2025 May-2025</td>
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<td>A5389</td>
<td>bNAbs during ART vs ATI</td>
<td>Early treated (n=40; pbo)</td>
<td>US/non-US (Americas)</td>
<td>Apr-2024 Aug-2025 May-2024</td>
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<td>A5413</td>
<td>Dasatinib (anti-proliferative) on ART</td>
<td>Chronic (n=14)</td>
<td>US (site limited)</td>
<td>Jun-2024</td>
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<td>A5419</td>
<td>CD4 CAR-Ts expand w/ vac on ART</td>
<td>Chronic (n=12)</td>
<td>US (site limited)</td>
<td>Aug-2024</td>
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<td>A5420</td>
<td>Ixazomib (pro-apoptosis/LRA on ART</td>
<td>Chronic (n=40; pbo)</td>
<td>US</td>
<td>Jul-2024</td>
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<tr>
<td>A5410</td>
<td>Vorinostat at ART start</td>
<td>ART naive (n=48; pbo)</td>
<td>US</td>
<td>On hold</td>
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<tr>
<td>A5422</td>
<td>CH505 TF (bNAb precursor vac) on ART</td>
<td>Chronic (n=30/pbo)</td>
<td>US</td>
<td>Mar-2024</td>
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<tr>
<td>A5385</td>
<td>Post-intervention Control Cohort</td>
<td>Participants who experience PIC</td>
<td>US/non-US</td>
<td>Open Dec 2023</td>
</tr>
</tbody>
</table>

**Studies: Ongoing and Planned**
A5386: A Phase I Open Label study of **IL-15 Superagonist (N-803)** **with or without bNAb**s (VRC07.523LS+10-1074-LS) during suppressive ART
(Chairs: Wilkin/Jones/Caskey)

**Primary Objectives:**
- Safety and Tolerability
- Virologic control during ATI
  (HIV-1 RNA <200 copies/mL 8 weeks after ATI)

**Study Population** (n=46):
- 18 to 70
- Current CD4 > 500
- CD4 nadir > 200
- On ART w/ VL < LLOQ x > 2yrs

**Target: 46**
- Enrolled (Step 1): 17
- Entered ATI (Step 2): 3
- Re-started ART: 2
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)

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

**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

**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)

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 bNAb (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
**Study Population** (n=48):
- 18-70 yrs of age
- Current CD4 > 450
- On ART w/ VL < LLOQ x > 2yrs
- Goal to enroll ~ 50% women

**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)

**Primary Objectives:**
- Safety and Tolerability
- Prevent return of viremia x 24wks

**Expected to Open early 2024**
- 9 sites: South Africa, Malawi, Botswana
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)

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 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!