Analytical Treatment Interruption (ATI) Among African Women with Early ART Initiation with or without VRC01 Circulating at HIV Acquisition: Study Design and Early Observations of Viral Rebound and Control

Shelly Karuna[1], Katharine Bar[2], Allan DeCamp[3], Erika Rudnicki[3], Pei-Chun Yu[3], Phil Andrew[4], Catherine Orrell[5], Azwi Takalani[6], Simba Takuva[6], Lucio Gama[7], Tae-Wook Chun[8], Nyaradzo Mgodi[9], Sufia Dadabhai[10], Carrie-Anne Mathew[11], Joseph Makhema[12], Portia Hunidzarira[9], Fatima Laher[13], Mina Hosseinipour[14], Randall Tressler[15], Lydia Soto-Torres[15], Myron Cohen[16], Judith Currier[17], Joseph Eron[18], and Lawrence Corey[1] for the HVTN 805/HPTN 093/A5390 Study Team

[1]Fred Hutch Cancer Center, Vaccine & Infectious Disease Division, Seattle, United States, [2]University of Pennsylvania, Department of Medicine, Philadelphia, United States, [3]Fred Hutch Cancer Center, Statistical Center for HIV/AIDS Research and Prevention, Seattle, United States, [4]FHI360, Durham, United States, [5]Desmond Tutu Health Foundation, Cape Town, South Africa, [6]Hutch Centre for Research in South Africa, Johannesburg, South Africa, [7]Vaccine Research Center, NIAID, Bethesda, United States, [8]National Institute of Allergy and Infectious Diseases, Laboratory of Immunoregulation, Bethesda, United States, [9]University of Zimbabwe, Clinical Trials Research Centre, Harare, Zimbabwe, [10]Johns Hopkins Research Project, Blantyre, Malawi, [11]Wits Reproductive Health Institute, Johannesburg, South Africa, [12]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana, [13]Perinatal HIV Research Unit Vaccine Research Center, Johannesburg, South Africa, [14]University of North Carolina Project-Malawi, Lilongwe, Malawi, [15]National Institute of Allergy and Infectious Diseases, Division of AIDS, Bethesda, United States, [16]University of North Carolina, Institute for Global Health and Infectious Diseases, Chapel Hill, United States, [17]University of California, Division of Infectious Diseases, Los Angeles, United States, [18]University of North Carolina, Division of Infectious Diseases, Chapel Hill, United States

Background

Viremia rebounds rapidly in most people living with HIV upon ART cessation. Early ART initiation is associated with ART-free virologic control, and broadly neutralizing anti-HIV-1 antibodies (bnAbs) may modulate immune responses to HIV (eg, as depicted in Fig 1). Durable ART-free virologic control has been observed in 20-25% of African women in some cohorts, significantly higher than in other populations. The HVTN 703/HPTN 081 AMP trial evaluated VRC01 bnAb-mediated HIV-1 prevention among African women; those who acquired HIV were linked to early ART. An AMP ATI (HVTN 805/HPTN 093/A5390, Fig 2) was designed in alignment with international consensus recommendations and in partnership with African community, investigator, ethics and regulatory collaborators. The trial aims to evaluate whether early ART +/- VRC01 circulating at HIV acquisition is associated with virologic control post-ATI and to assess underlying immunologic and virologic dynamics.

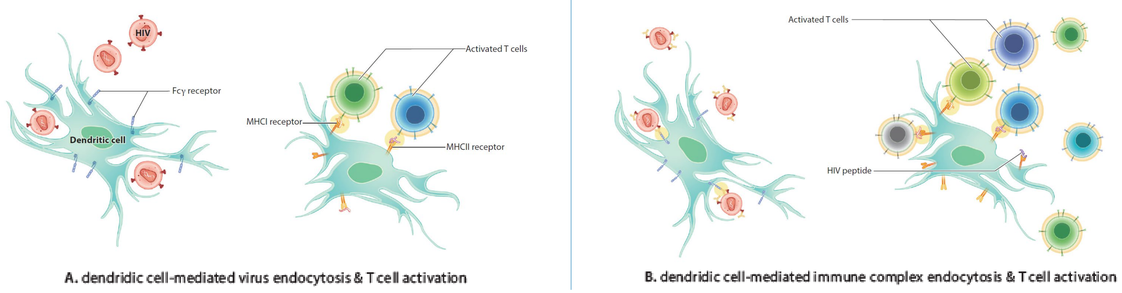
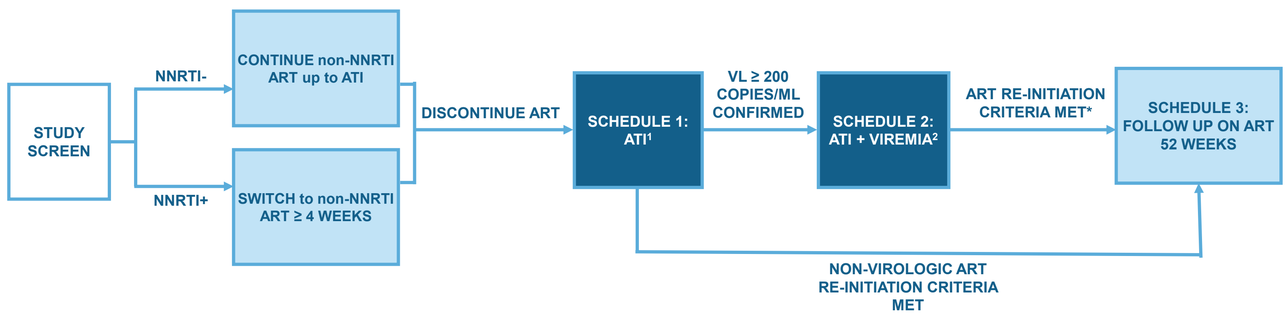


Fig 1. Vaccinal effect. Adapted from Karuna & Corey, Annu Rev Med 2020. In the absence (A) & presence (B) of bnAb-Env immune complexes, dendritic cells are among the first responders of the innate immune system.



	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

Fig 2. HVTN 805/HPTN 093/A5390 study schema and schedule of key virologic and safety lab monitoring.

Results

Eleven participants from South Africa, Malawi, Botswana and Zimbabwe have enrolled, thus far. Eight of 11 women met ART re-initiation criteria (n=5 for viral load [VL]; n=3 for participant/clinician request; see Fig 3). One participant requesting ART re-initiation had tenofovir levels consistent with ART use during ATI. Median time to confirmed VL>200 was 4.8 weeks (range 2.3 to 26.7+). Median time to meet virologic ART re-initiation criteria was 17.1 weeks (5.1+ to 30.7+). ART was re-initiated a median of 7 days later, followed by re-suppression. No SAEs or Grade ≥2 related AEs were reported.

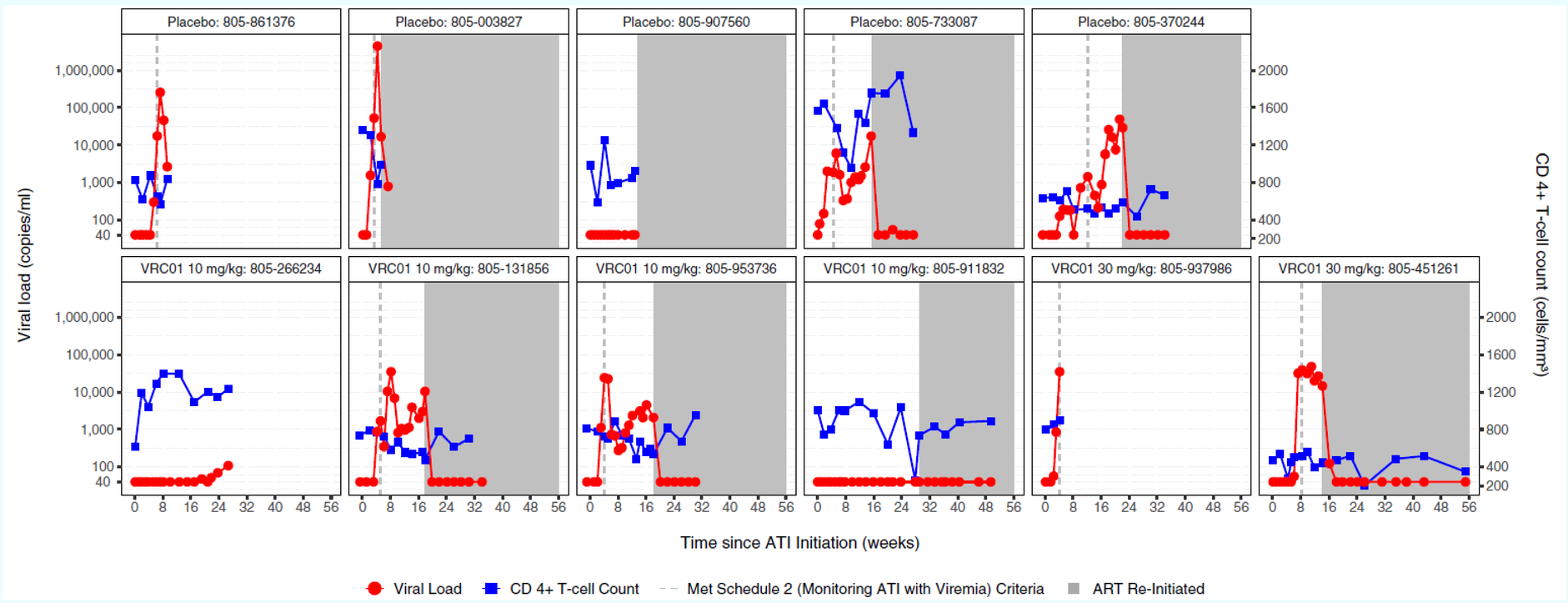


Fig 3. Individual participant viral load (red circles) and CD4+ T-cell counts (blue squares) over time during ATI. The treatment each participant received in the pre-ATI AMP study (i.e., Placebo or VRC01 10 mg/kg or 30 mg/kg) is indicated above each panel. Time of first viremia is indicated with the gray dashed line. Time of re-initiating ART is indicated by the beginning of the gray shaded areas. ART re-initiation criteria met are: viral load (805-003827, 805-733087, 805-451261, 805-953736, 805-131856, 805-370244), participant request (805-911832 due to participant concern about CD4 count and 805-907560 due to relocation), and CRS clinician request (805-907560) due to participant relocation. Participant 805-911832 had tenofovir levels in Dried Blood Spots that were consistent with ART use during ATI. Participants 805-861376, 805-370244, 805-131856 and 805-953736 each experienced ≥1 ART-free VL decline of ≥0.5 log, consistent with possible immune-mediated, temporary virologic control.

Methods

AMP ATI eligibility includes African women with an estimated HIV acquisition date within 8 weeks of receiving VRC01 or placebo in the AMP study, early ART initiation, and ≥1 year of viral suppression. Participants complete an NNRTI switch, as needed, then stop ART and receive frequent viral load (VL) and CD4+ T-cell count monitoring. See Fig 2. ART re-initiation criteria include CD4<250, VL>1,000 for 4 weeks without a ≥0.5 log decline, or participant/clinician request to restart ART.

Conclusions

In a safe and well-tolerated ongoing ATI developed with local stakeholder engagement, African women with early ART initiation +/- prior VRC01 exhibit evidence of viral rebound and control. Research to advance sustained virologic remission and HIV cure, including closely monitored ATIs, can be conducted safely among women in sub-Saharan Africa. Next steps include completion of assays to explore potential immunologic and virologic signals that may associate with observed viral rebound and control.

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Presenter email: mkaruna@fredhutch.org

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