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

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- 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**

- **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
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 Initiation in African Women

- 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)
Neutralizing Antibodies

HIV gp120  neutralizing antibody (nAb)  Antibody bound to HIV gp120

Thanks to Lisa Donohue for these images.
# The AMP Studies

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

Before ART

ART Treatment

ART Interruption

ART Treatment

Plasma Viral Load

Possible Study Intervention (e.g., bnAb)

Possible Study Intervention (e.g., bnAb)

AMP virus isolate(s)

TIME
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

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

- Spring/Summer 2019: Teleconferences
  - Martin Delaney Collaboratory & IAS Working Groups for HIV Cure

- August 2019: Washington, DC & Johannesburg
  - Symposium with global investigators and funders re: HIV sustained virologic remission/cure research agenda & next steps, including AMP ATI
  - Further consultation with HVTN 703/HPTN 081 (AMP Africa) site & community representatives re: AMP ATI design

- February 2020: Cape Town
  - Investigators; Ethicists; Ethics Committee & other Regulatory & Public Health representatives; Community representatives

AMP ATI concept development begins
Recent Consensus ATI Design Recommendations

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


analytical antiretroviral treatment (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.

Panel Key recommendations

Inclusion criteria:
- Stable CD4 count >500 cells/μL
- HIV RNA undetectable on stable ART
- Otherwise healthy individuals without major comorbidities

Key exclusion criteria:
- Active or chronic hepatitis B or C infection, with detectable hepatitis B/C surface antigen, hepatitis B virus DNA, or both
- Active hepatitis C virus infection, with detectable hepatitis C virus RNA
- Active Mycobacterium tuberculosis infection
- History of systemic cancers, such as lymphoma and leukemia, or other major malignancies
- History of HIV-associated dementia or progressive multifocal leukoencephalopathy
- Resistance to two or more classes of antiretroviral drugs
- History of cardiovascular event or high risk of an event (eg, previous cardiovascular disease score >15%)
- History of AIDS defining illness according to Centers for Disease Control and Prevention criteria
- History of CD4 <200 cells/μL during chronic stages of infection
- Women who are pregnant or breastfeeding
- Advanced non-alcoholic fatty liver and advanced non-alcoholic steatohepatitis, if evidence for substantial fibrosis (Metavir score ≥2) or evidence of cirrhosis
- HIV-related kidney disease or moderate to severe decrease in estimated glomerular filtration rate (eGFR) ≤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 of people who started ART during the hypertensive HIV phase
- Monitoring of patients’ psychosocial experiences

ATI start criteria:
- If requested by the participant or the site’s HIV care provider
- If participant becomes pregnant
- If ART is deemed medically necessary for non-HIV related causes
- Symptomatic HIV disease
- Confirmed absolute CD4 <250 cells/μL or CD4% <10%
- HIV RNA >100,000 copies per mL for 4 weeks
- Absolute CD4 <200 cells/μL or CD4% <10%

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

Additional information on the manuscript and its results may be found in the supplementary material.

Lozouet HIV 2019
Published Online March 15, 2019
http://dx.doi.org/10.1093/hiv/52352-302815033052-5
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**

- **SCREEN**
- **PRE-DISCONTINUE ART**
- **ATI WEEKS 0-8**
- **ATI WEEKS 10-24**
- **ATI WEEKS 28-52**

**SCHEDULE 1**

- **ATI WEEKS 0-8**
- **ATI WEEKS 10-36**
- **ATI WEEKS 40-52**

**SCHEDULE 2**

- **ART RE-INITIATION CRITERIA MET**

**SCHEDULE 3**

- **FOLLOW UP ON ART 52 WEEKS**

**PRE-ENTRY**

- **Plasma HIV RNA**
  - CHECK WEEKLY
  - CHECK Q2 WEEKS
  - CHECK Q4 WEEKS

- **CD4+ & CD8+ T cell counts**
  - CHECK WEEKLY
  - CHECK Q2 WEEKS
  - CHECK Q4 WEEKS

- **Hematology & Chemistries**
  - CHECK WEEKLY
  - CHECK Q4 WEEKS
  - CHECK Q8 WEEKS

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

3. OR Q2 WEEKS FOR WEEKS 10-24 IF VL≥200 copies/mL

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Thanks to Lisa Donohue
ART Re-initiation Criteria

- Viral load $\geq 1,000$ copies/mL for $\geq 4$ 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
  - 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?

- 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

1. Met criteria for Screening (n=52)
   - 20 Placebo, 32 VRC01
   n=32

2. Agreed to initiate Screening (n=20)
   - 6 Placebo, 14 VRC01
   n=5

3. Eligible (n=15)
   - 6 Placebo, 9 VRC01
   n=2

4. Enrolled (n=13)
   - 6 Placebo, 7 VRC01

   - Placebo (n=6)
     1 in ATI, 5 re-initiated ART
   - VRC01 (n=7)
     2 in ATI, 5 re-initiated ART

5. Reasons for exclusion:
   - 7 Pregnant or breastfeeding
   - 7 Unable to be contacted
   - 5 Relocated
   - 3 Not interested
   - 3 Ineligible: Unwilling to interrupt ART
   - 2 Ineligible: Unable to comply with visit schedule
   - 3 Ineligible: ART criteria
   - 2 Ineligible: VL criteria

6. Other reasons:
   - 2 Unable/unwilling to adhere to protocol
   - 1 Unwilling to interrupt ART
   - 1 Initiated ART too long after dx
   - 1 Clinically significant medical condition

7. Other exclusions:
   - 1 Unable to contact
   - 1 Changed mind

Thanks to Doug Grove
SSA AMP ATI Pre-Screening & Screening Outcomes

Met criteria for Screening (n=52)
- 20 Placebo, 32 VRC01

Agreed to initiate Screening (n=20)
- 6 Placebo, 14 VRC01

Eligible (n=15)
- 6 Placebo, 9 VRC01

Enrolled (n=13)
- 6 Placebo, 7 VRC01

Placebo (n=6)
- 1 in ATI, 5 re-initiated ART

VRC01 (n=7)
- 2 in ATI, 5 re-initiated ART

Outcomes:
1. Unable to contact
2. Unable/unwilling to adhere to protocol
   - 1 Unable/unwilling to adhere to protocol
   - 1 Unable/unwilling to adhere to protocol
   - 1 Clinically significant medical condition
3. Unable to be contacted
4. Unwilling/unable to interrupt ART
   - 2 Unable to interrupt ART
   - 2 Unable to interrupt ART
   - 1 Clinically significant medical condition
5. Relocated
6. Not interested
7. Ineligible: ART criteria
   - 1 Ineligible: ART criteria
   - 2 Ineligible: ART criteria
8. Ineligible: VL criteria
   - 2 Ineligible: VL criteria
   - 1 Ineligible: VL criteria
9. Ineligible: ART Criteria
10. Unable to comply with visit schedule
11. Unable/unwilling to adhere to protocol
12. Clinically significant medical condition

Placebo (n=6) outcomes:
- 1 in ATI, 5 re-initiated ART
- 1 Unable to contact

VRC01 (n=7) outcomes:
- 2 in ATI, 5 re-initiated ART
- 2 Unable/unwilling to adhere to protocol
- 3 Ineligible: VL criteria
- 2 Unable to comply with visit schedule
- 2 Unable/unwilling to adhere to protocol
- 1 Clinically significant medical condition

Graph showing distribution of outcomes.
AMP ATI Study Design

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

>300 visits (~20+ visits/ppt, & counting)
No Missed Visits
100% Retention

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

VL <200 for 319 days

early termination d/t relocation

(+) for ARVs

Now 18+ months

2 additional participants remain virologically suppressed at 4+ months

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

• ATIs can be conducted safely & well in Africa

• 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

*AMP ATI in Peru began in August 2022 with n=17 pts so far*
AMP ATI Studies Protocol Team Acknowledgements

**Chairs**
- Shelly Karuna
- Katharine Bar

**PTLs/CMMs**
- Phil Andrew
- Shelly Karuna
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- Simba Takuva
- Manuel Villaran

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- Maximina Jokonya

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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