2025 Pre-CROI Community HIV Cure Research Workshop ~ 8 March 2025

Recommendations from the **2024 Analytical Treatment Interruption (ATI) Consensus Workshop**

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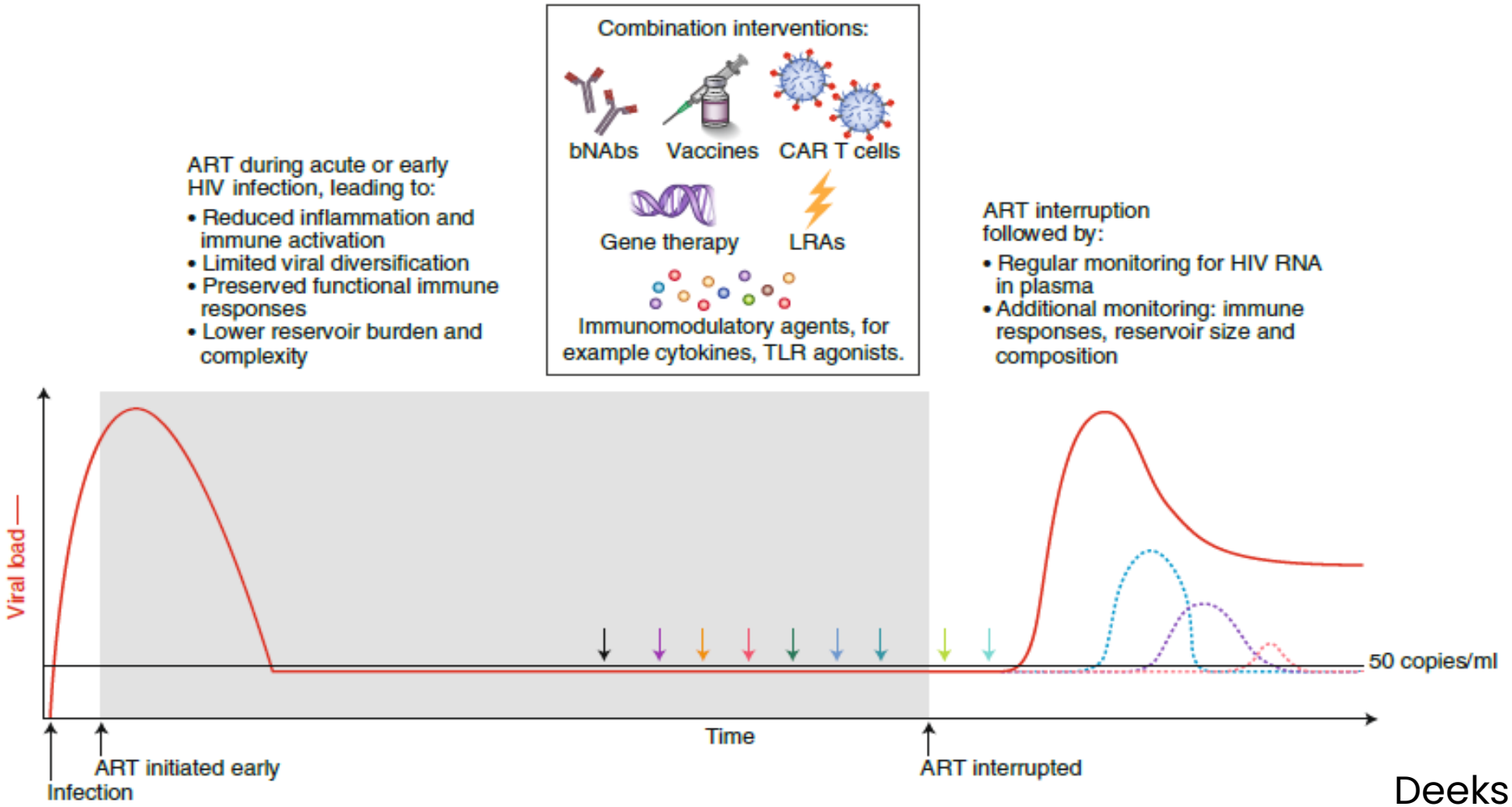
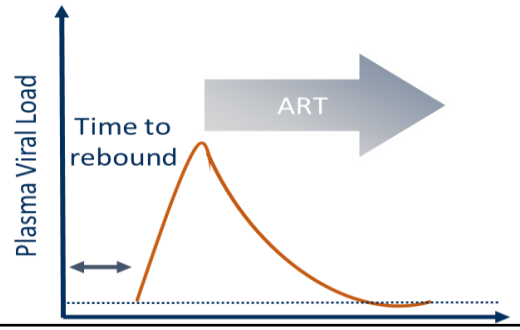
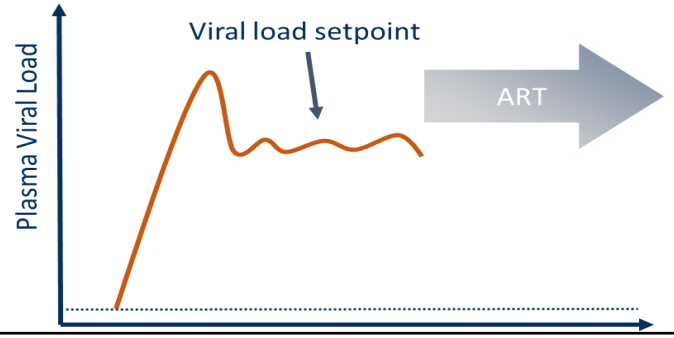
Many cure strategies involve combination approaches which may require a degree of viremia; *currently ATI provides the only reliable readout*



Deeks et al, *Nat Med*, 2021

Two ATI Designs: *Time to rebound vs. Set point*

	ATI DESIGN	
	Time to rebound	**Set point**
ART restart	Resume ART immediately once VL detectable 	Resume ART if agreed set point not reached 
Duration of viremia	Minimal	Potentially prolonged
Risks Transmission Inflammation Reservoir reseeding	 • Low • Low • Negligible	 • Possible • Possible • Unknown
Knowledge gained	Limited • Size of the reservoir (?)	Significant • Insights into post-treatment control. • Viremia needed for some immunotherapies (?)

1st Consensus Workshop on ATI in HIV Cure Trials (2019)

Recommendations were very useful for the HIV cure field

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

Lancet HIV 2019; 6: e259–68

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

- In 2019, most ATI trials had been conducted in the US enrolling white men
- Since the 2019 ATI Workshop, many more ATI trials conducted in more representative populations and knowledge expanded
- An update was overdue:
  - Include perspectives and recommendations for HIV high-burden LMICs where multiple ATI trials are planned
  - Include recommendations for paediatric and adolescent populations

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WRAIR
Walter Reed Army Institute of Research
MILITARY HIV RESEARCH PROGRAM

2024 Analytical Treatment Interruption (ATI) Consensus Workshop

8-10 May 2024 ·Trademark Hotel, Nairobi, Kenya

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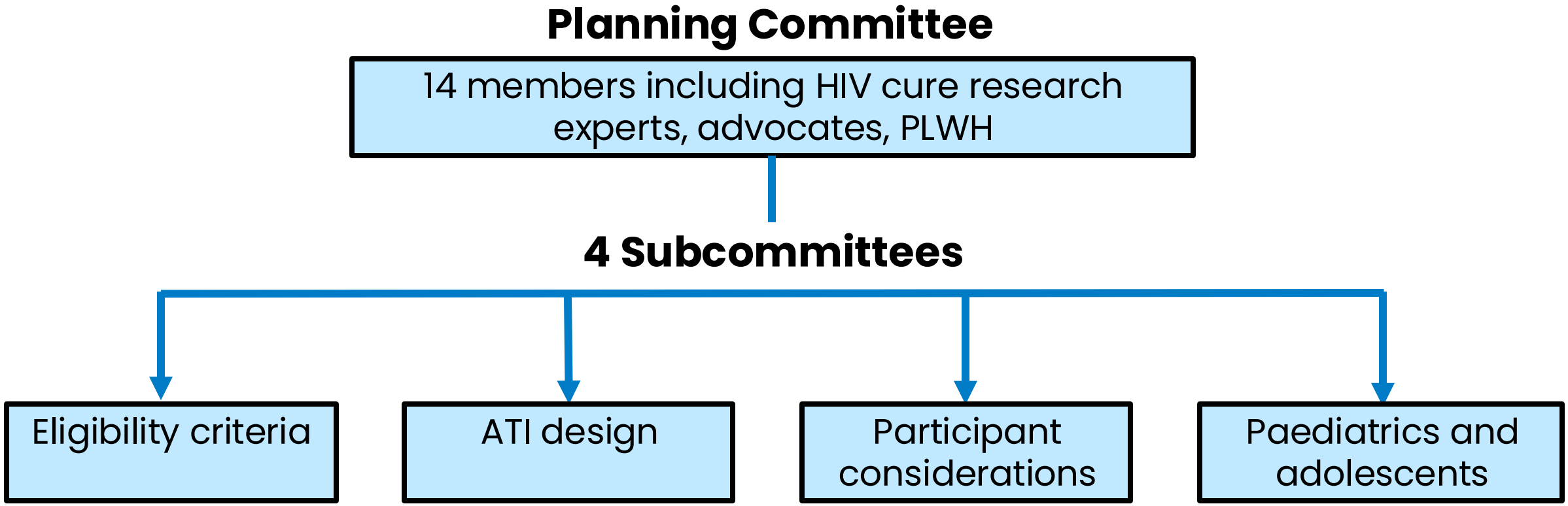
Preparation – *January to April 2024*



Planning committee and subcommittees

- Gathered evidence and met once every 2 weeks
- Consulted key stakeholders
- Conducted virtual community ATI workshops
- Formulated a list of key topics for consensus voting

2024 ATI Workshop Attendees

- 134 attendees from 5 continents (~ half from Africa) gathered in Nairobi, Kenya for 3 days

- Attendees included scientists, clinicians, community advocates, persons living with HIV, ATI participants; representatives from funding, regulatory, and industry organizations

ATI - *Basic Considerations*

- **Are ATI studies appropriate?**
  98% - Yes, if participants are informed and understand the risk, risks are minimized and the study is designed to answer an important scientific question that cannot be answered without an ATI

- **Should Placebo groups be included in ATI studies?**
  91% - support inclusion depending on study hypothesis and trial design; if no historical control available, and scientifically justified by sample size analysis

- **Adverse Events related to ATIs**
  Consensus - that AEs that related to ATI should be part of standardized reporting of ATI-inclusive trial results (specific criteria listed, 71%-94%)

- **What to do with participants who do not meet ART restart criteria by end of trial**
  98% - If the participant(s) choose to remain off ART, they should be enrolled in a separate protocol for close monitoring

Percentages represent the majority options voted on by the workshop attendees

Eligibility Criteria - *Recommendations (in review)*

	2019	2024	Comments
ELIGIBILITY	• Stable CD4 >500	• Only 21% favored keeping CD4>500 • CD4 T-cell count varies by region, thus consensus to allow region-specific CD4 inclusion criteria - CD4 >350 (25%) - CD4 >400 (37.5%)	Favoured more relaxed CD4 criteria (baseline and nadir)
	• CD4 nadir >200	• **No nadir** CD4 count criterion	In many LMICs, CD4 nadir is not known, or record is inaccessible
	• Exclude VL blips	• **Allow VL blips** if not within the past year	
	• Exclude if history of **past cardiovascular disease** (CVD) or high risk for CVD	• Exclude only **active CVD,** allowing region-specific CVD risk assessment	Consensus to allow region specific criteria when significant differences exist
	• Exclude if past history of AIDS defining illnesses	• Exclude only if history of **severe immunodeficiency** (cryptococcal meningitis-CMV retinitis, virus-associated cancers)	
	• Exclude if past history of cancer	• Exclude current cancers, allow past history of non-viral cancers	More relaxed allowing past history of comorbidities, immunodeficiency and non-HIV related cancer
		• No age limit, exclude pregnancy and breastfeeding women	

ATI Design - *Recommendations (in review)*

ATI DESIGN

2019	2024	Comments
• **VL monitoring** VL weekly for 12w, then every 2w • **ART restart criteria:** - VL ≥1,000 x 4w - VL ≥100,000, confirmed • **CD4 monitoring** - Every 2 weeks - Restart ART if CD4 ≤350	• **VL monitoring - *unchanged*** Weekly for 8-12w, then every 2w • **ART restart criteria:** - VL ≥1,000 x 8w *(*extend if ≥0.3 log drop)* - VL ≥100,000, confirmed • **CD4 monitoring - *unchanged*** - Every 2 weeks - Restart ART if CD4 ≤350 • **Clinical monitoring** - for symptoms at every visit • **STI testing** every 8-12w • **Restart ART** if requested by study participant, healthcare provider, in case of pregnancy	• The impact of an ATI in persons with low CD4 nadir is not known • Mitigate participant risk with careful monitoring of CD4 and conservative ART restart requirements

Participant Considerations - *Recommendations (in review)*

	2019	2024	Comments
PARTICIPANT CONSIDERATIONS	• **PrEP for partners.** Refer for HIV testing and PrEP • **Psychosocial monitoring** recommended	• **PrEP for partners:** Refer to established reliable providers (or provide PrEP on site) • **Psychosocial monitoring.** Assess all visits during trial, especially during ATI. Provide on site counseling or refer depending on need and capacity • **Disclosure of HIV status and ATI participation.** Assess disclosure and provide onsite disclosure support at all visits to enable implementation of partner protection measures. • **ART adherence support.** After VL rebound and prior to ART restart, provide adherence support until VL undetectable. • **Socio-behavioral research.** Incorporate within ATI trials when there are important research questions to be answered related to participant experience, and for ATI trials at new sites/regions.	Expanded participant protection measures, including mental health & strategies to reduce transmission risk during ATI Onsite PrEP provision is complicated by responsibility for partners who are not enrolled in the trial. Many sites either do not have the capacity or funds to provide PrEP

Paediatric and Adolescents - *ATI Recommendations (in review)*

PAEDIATRICS and ADOLESCENTS

2019	2024	Comments
Exclude Age <2 years • No guidance on paeds and adolescents in ATIs	**Exclude** Age <2 years • **Include:** Stringent CD4 criteria • **Provide:** Disclosure support • **Allow:** HIV serostatus beyond 18 months and detectable reservoir • **Allow:** participants with history VL blips following ART suppression of viremia • **Allow:** VL >10,000 but <100,000 copies/ml for 4 consecutive weeks; or >1,000 but <10,000 copies/ml for 8 consecutive weeks • **Monitor:** for acute retroviral syndrome	Improved psychosocial support, clinical monitoring, age restrictions Recommendations now available to allow more representation of children and adolescents

Summary - *2024 ATI Recommendations*

- ATI trials are appropriate if risks are known and minimized, and answering a scientific question that cannot otherwise be answered. Placebos are appropriate depending on study hypothesis and trial design; if no historical controls available, and scientifically justified by sample size analysis

- More regional considerations, including guidance on ATI studies in LMICs

- Less restrictive recommendations in some areas based on current knowledge but may also depend on product being tested. In such cases more conservative monitoring is needed

- Inclusion of new recommendations e.g., TB co-infection, pediatrics and adolescents; more participant protection considerations

- ATI recommendations require frequent periodic updates as data is generated from additional trials and long-term findings

ATI recommendations to be published in 2025

Acknowledgements

PLANNING COMMITEE

Donn Colby
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