Considerations for Analytical Treatment Interruption (ATI)

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IMPAACT Community & Science
September 22nd 2024.

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Background

- Combination antiretroviral therapy (ART) revolutionized HIV care
  - Began in 1995 in high income settings
  - Available in Africa from 2004
  - Over time: ART more effective, simpler, better tolerated
- Many have living memory of how bad HIV can be
- Adherence, adherence, adherence, adherence
- **U**ndetectable) = **U**ntransmissable

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Landscape is changing with increased desire to stop ART safely – Why?

- Adherence
- Stigma
- Want a HIV-free life
- The few HIV cure success stories are noted in communities globally

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HIV Cure = HIV clearance from one's body

1. How many people have cleared HIV from their bodies?
2. What are the entry criteria for Clearance Cure?
3. How feasible is this?

How many people have cleared HIV from their bodies?

- 3 confirmed
- 4 probable

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Entry Criteria for intervention to clear HIV from one's body

1. Adult with HIV
2. Relapsed acute myeloid leukemia (1st round of chemotherapy ineffective)
3. Bone marrow or stem cell transplant center available
4. Donor cells resistant to HIV (Δ32 CCR5 co-receptor: HIV cannot enter cells)
5. Active transplant program
6. Funding

Stem cell transplant survival 60%

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What is Analytic Treatment Interruption (ATI)?

- Stopping ART in a trial aimed at HIV clearance (Cure) or Control
- Strict viral load monitoring
- Specimen collection to understand:
  - Effects of the intervention
  - How the immune system reacts
  - How the virus adapts

Why is ATI necessary?

- After acquisition, HIV establishes a reservoir that is hard to eradicate
- Currently the only way to determine if an intervention to clear HIV or control HIV replication is successful
- If better markers are found, ATI may not be necessary in the ‘testing’ or ‘discovery’ phase.

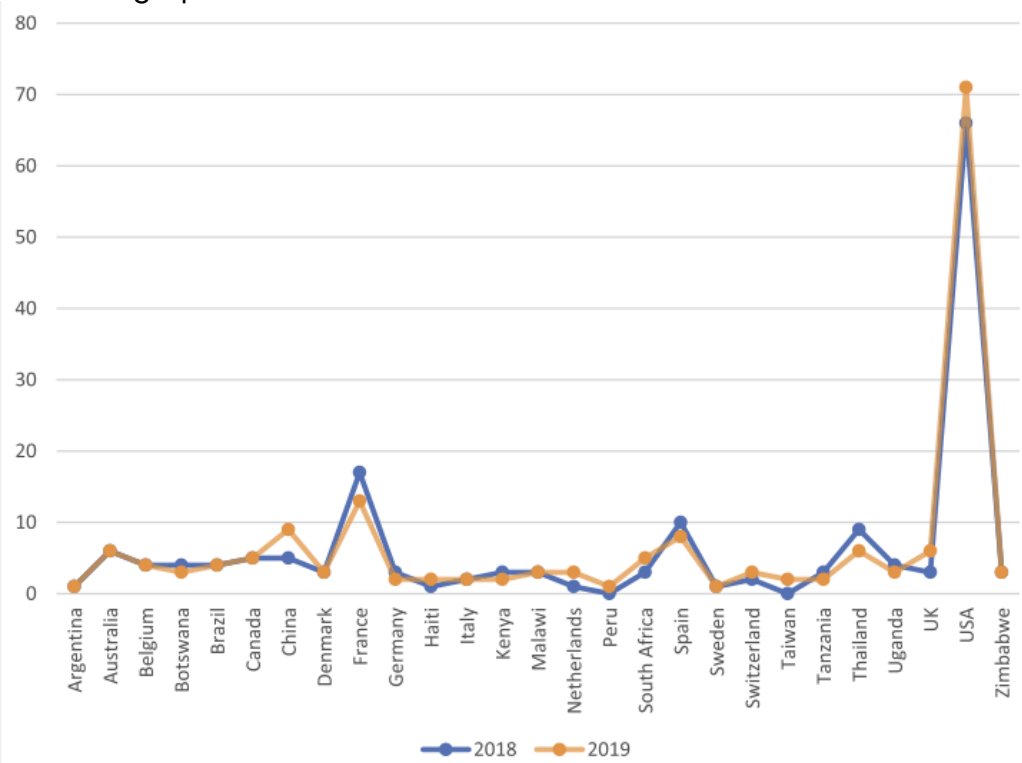
HIV cure research landscape

- Cure research mainly in low HIV prevelance settings

- Well resourced academic institutions, in Global North

- Less research in Global South: lack of:
  - Local expertise?
  - Infrastructure?
  - Regulatory systems?
  - Political will?
  - Advocacy?

Geographic Distribution of Cure Studies 2018-2019



Communities remember severe HIV in early 2000's & beyond

Barr et al, *J Virus Eradication*, 2020

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What is the HIV reservoir?

Discovered in 1989

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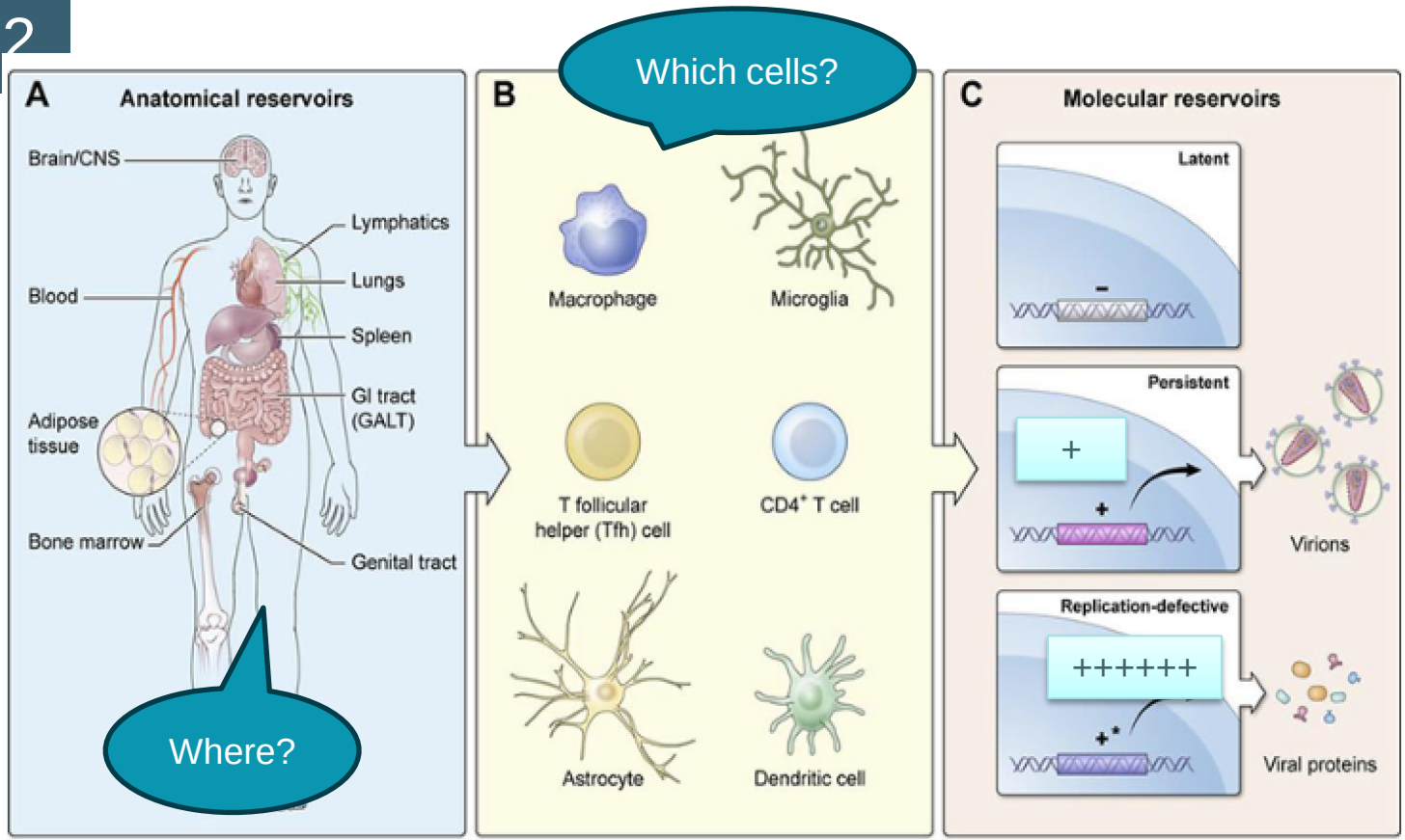
HIV Reservoir

- HIV DNA in cells
- Lower in children after early ART
- Only a small number of cells with HIV can divide
- Can be very hard to demonstrate
- In adults, viral rebound even after billions of cells negative for HIV

Viral load

- In plasma
- RNA copies
- Driven by cells in Reservoir

HIV reservoirs



Henderson, L. J., et al. J. Virology Jan 2020, 94 (3) e00375-19; DOI: 10.1128/JVI.00375-19

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ATI trials - long history

1st ATI trial - 1995

408 THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 17, 1995

A CONTROLLED TRIAL OF ZIDOVUDINE IN PRIMARY HUMAN IMMUNODEFICIENCY VIRUS INFECTION

SABINE KINLOCH-DE LOËS, M.D., BERNARD J. HIRSCHEL, M.D., BRUNO HOEN, M.D., DAVID A. COOPER, D.SC., M.D., BRETT TINDALL, PH.D., ANDREW CARR, M.D., JEAN-HILAIRE SAURAT, M.D., NATHAN CLUMECK, M.D., ADRIANO LAZZARIN, M.D., LARS MATHIESEN, M.D., FRANÇOIS RAFFI, M.D., FRANCISCO ANTUNES, M.D., JAN VON OVERBECK, M.D., RUEDI LÜTHY, M.D., MICHEL GLAUSER, M.D., DAVID HAWKINS, M.D., CHRISTOPHE BAUMBERGER, PH.D., SABINE YERLY, M.S., THOMAS V. PERNEGER, M.D., PH.D., AND LUC PERRIN, M.D.*

- ZDV vs Placebo
- Shortly after acquiring (Acute) HIV
- Rx 6m & then stop
- Monitor:
  - CD4 /CD8 response
  - Opportunistic infections
- Could this preserve the immune system?

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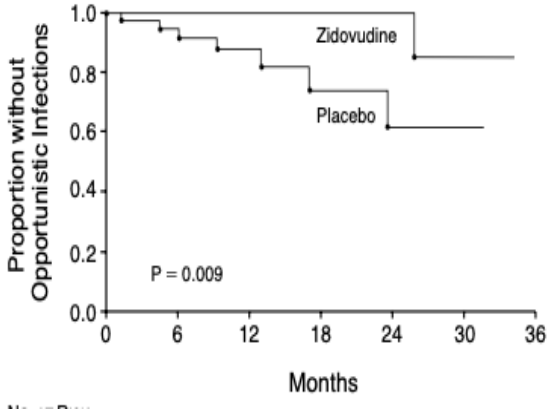
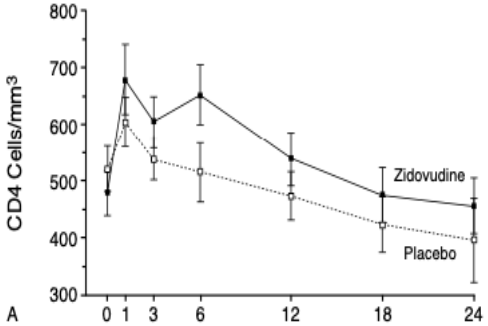
Outcomes supported ZDV in acute HIV



Fewer OIs



Trend to better CD4 counts

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Can one control HIV in absence of ART (Viral loads <50 copies/mL)?

Yes!

- 10% of adults who stop ART after early initiation
- Some with good immune systems control without ART - Elite controllers (including some children)

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Why are children good candidates for ATI studies?

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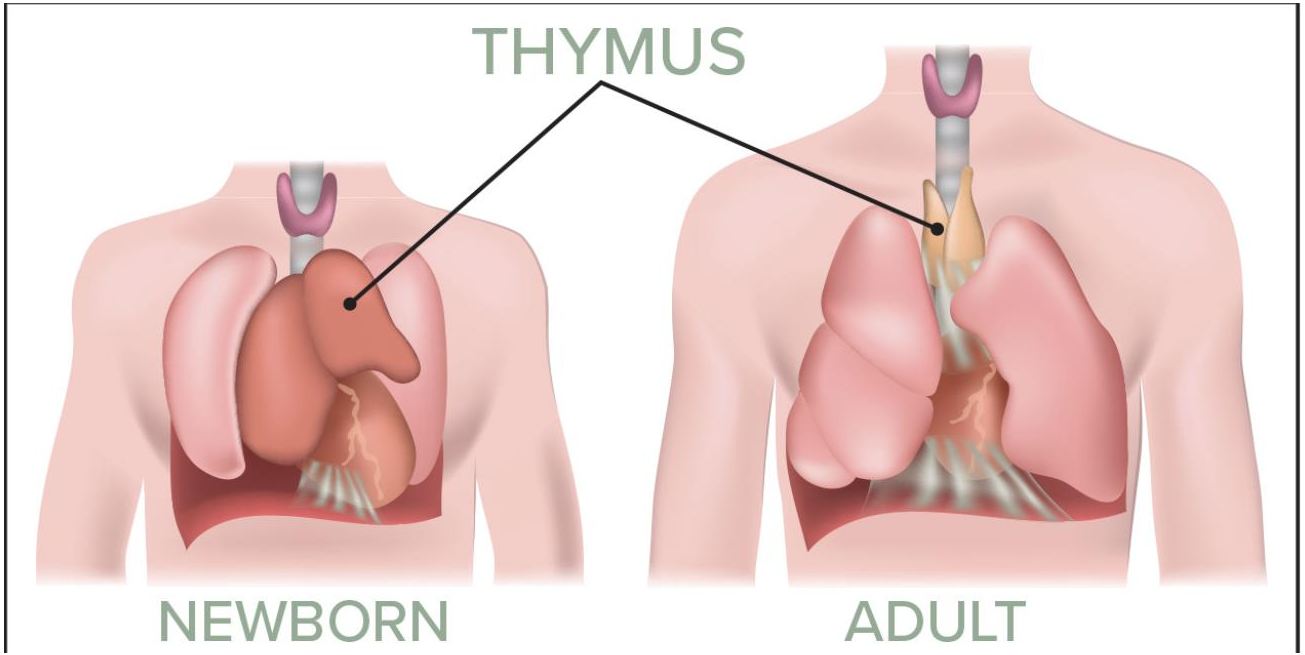
Thymus – produces naïve CD4 & CD8 T cells



Very active in 1st 6 months of life

Still quite active at puberty

Children do not have non-communicable diseases (common in adults)

- Heart disease
- High blood pressure
- Kidney disease

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Can ART be safely stopped in children?

YES!!!

3 older trials safely used CD4 to guide restart -

- CHER trial in infants
  - <12W of age for 40 or 96W vs deferred continuous
  - 2005 – 2011
  - 252 children interrupted ART

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2 other CD4-guided trials in children

- PENTA 11 – Europe
  - Interrupted for 48W vs continuous
  - 2004 – 2006
  - Safe
  - No neurodevelopment impairment
- OPH-3 – Kenya
  - Interrupted vs continuous
  - 21 interrupted
  - All back on ART within 3m
  - Safe

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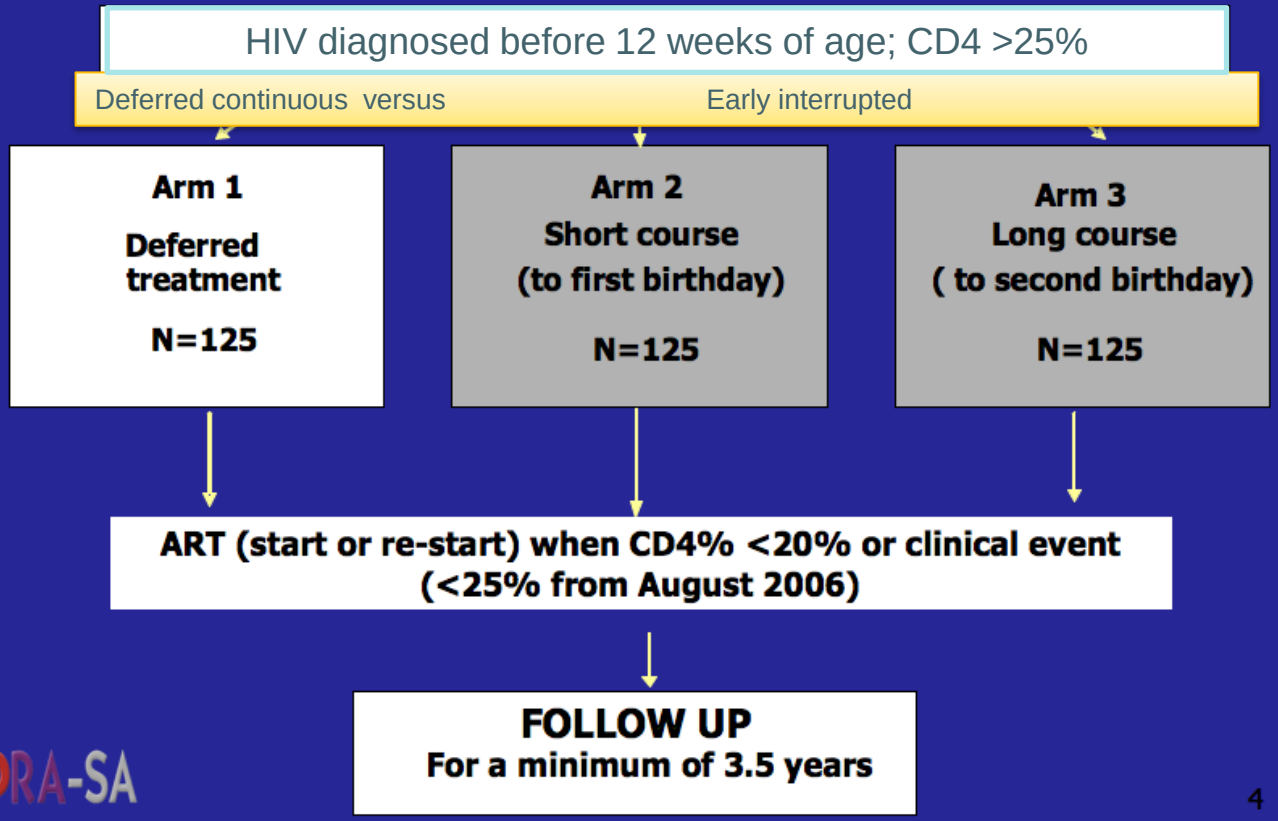
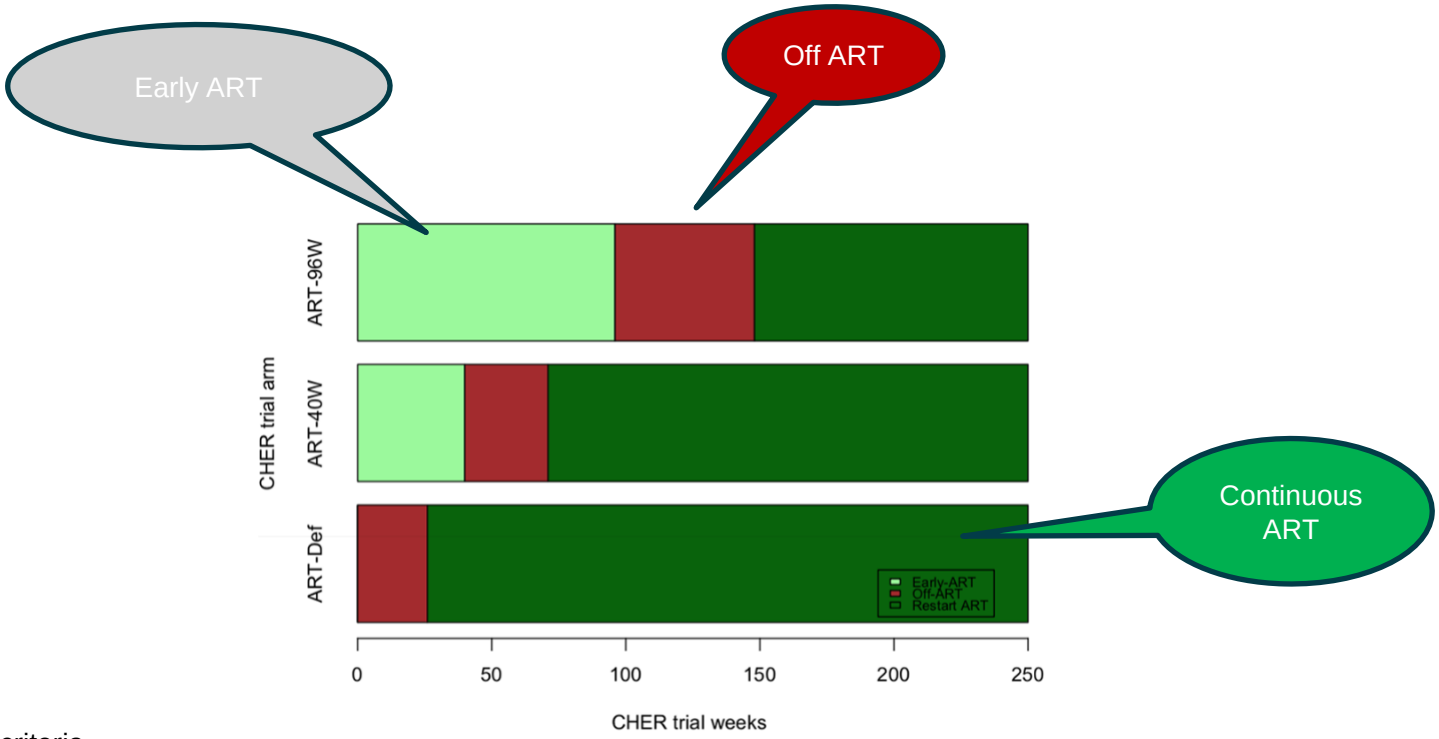
CHER Trial
Part A n= 375



CIPRA-SA

245 children on CHER safely stopped ART close to 1st or 2nd birthday

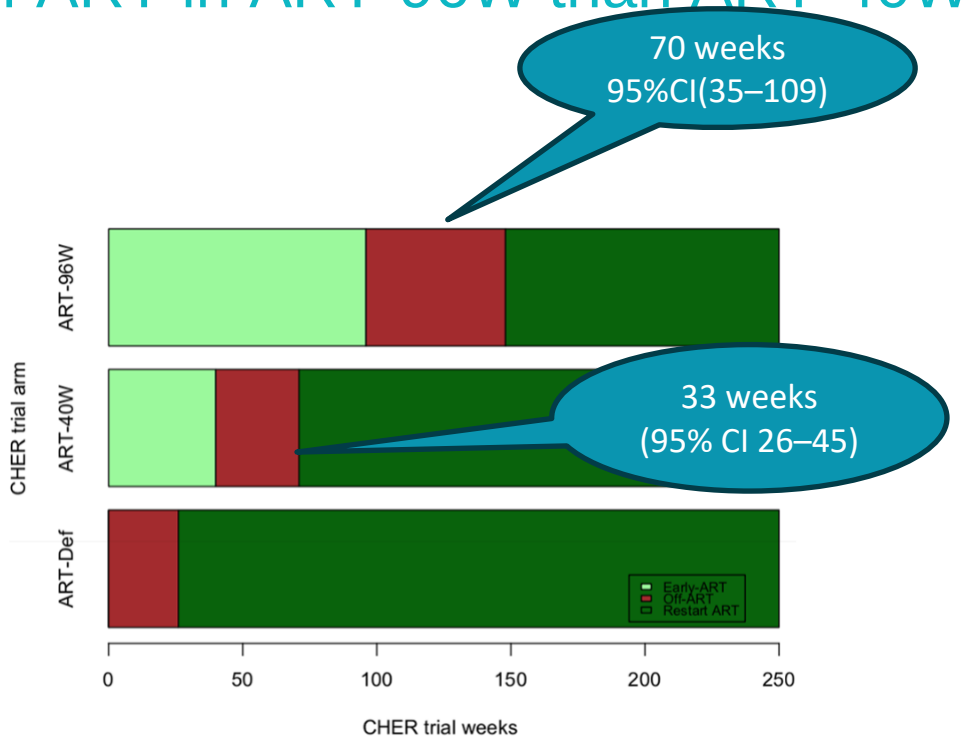


ART restart criteria

- CD4 <20%
- Clinical event

More time off ART in ART-96W than ART-40W

ART96W – ART46W = 37W
(−11 to 85)W; p=0·13



Cotton et al Lancet 2013; 382: 1555-63

CHER trial: Neurodevelopment more vulnerable in 1st year of life despite early ART,

- Early ART from 8.4 weeks much better than deferred ART (from 31.4 weeks)
- Locomotor with early ART worse than controls

Early antiretroviral therapy improves neurodevelopmental outcomes in infants

Barbara Laughton[a], Morna Cornell[b], Debbie Grove[c], Martin Kidd[d], Priscilla E. Springer[e], Els Dobbels[a], Anita Janse van Rensburg[a], Avy Violari[f], Abdel G. Babiker[g], Shabir A. Madhi[h], Patrick Jean-Philippe[i], Diana M. Gibb[g] and Mark F. Cotton[a]

Objectives: To evaluate the effect of early versus deferred antiretroviral therapy (ART) on neurodevelopment of infants from Cape Town participating in the CHER (Children with HIV Early Antiretroviral Therapy) trial.

Design: HIV-infected infants were randomised to early (<3 months) or deferred ART. HIV-uninfected infants (HIV-exposed and HIV-unexposed) provide background data.

Methods: Neurological examination and Griffiths Mental Development Scales (GMDS) were administered between 10–16 months of age, by testers blind to HIV status and randomised allocation. Mean quotients were compared using paired t-tests.

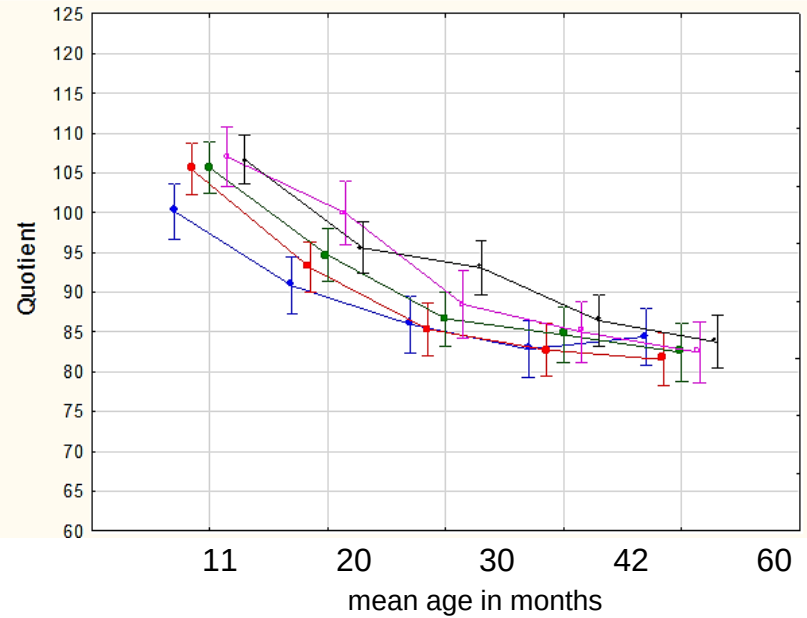
Results: 64 infants on early ART and 26 on deferred ART (of potential 77 and 38 respectively on CHER trial) were assessed at median age 11 months (range 10–16). On the GMDS, all scores were lower in the deferred arm and the General Griffiths and Locomotor Scores were significantly lower: mean (standard deviation): 100.1 (13.8) vs 106.3 (10.6) $p = 0.02$; and 88.9 (16.3) vs 97.7 (12.5), $p < 0.01$, respectively. Children with HIV who received early ART performed as well as children without HIV except on the locomotor subscale. Both infected and uninfected mean GMDS scores were within the average range.

Conclusions: Infants initiated on early ART have significantly better Locomotor and General Scores on the GMDS at median age 11 months compared to infants on deferred ART, despite careful monitoring and ready access to ART in the latter.

AIDS 2012, **26**:000–000

ART interruption: no effect on neurodevelopment in CHER Trial

Controls: HIV-exposed & unexposed
Age & community-matched



- ART-Def (n=28)
- ART-40W (n=35)
- ART-96W (n=33)
- HIV Exposed uninfected (n=34)
- HIV Unexposed (n=39)

Laughton JIAS 2018; 21: e25108

All HIV+ worse except visual perception

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Post-treatment control in children after early ART

- French adolescent (Visconti cohort) – 17y & ongoing
- Mississippi Baby – 17m & relapse
- CHER child – 16y & ongoing
- Ucwaningo cohort – 5/284 children off ART –ve plasma viral loads & loss of DNA for >30m

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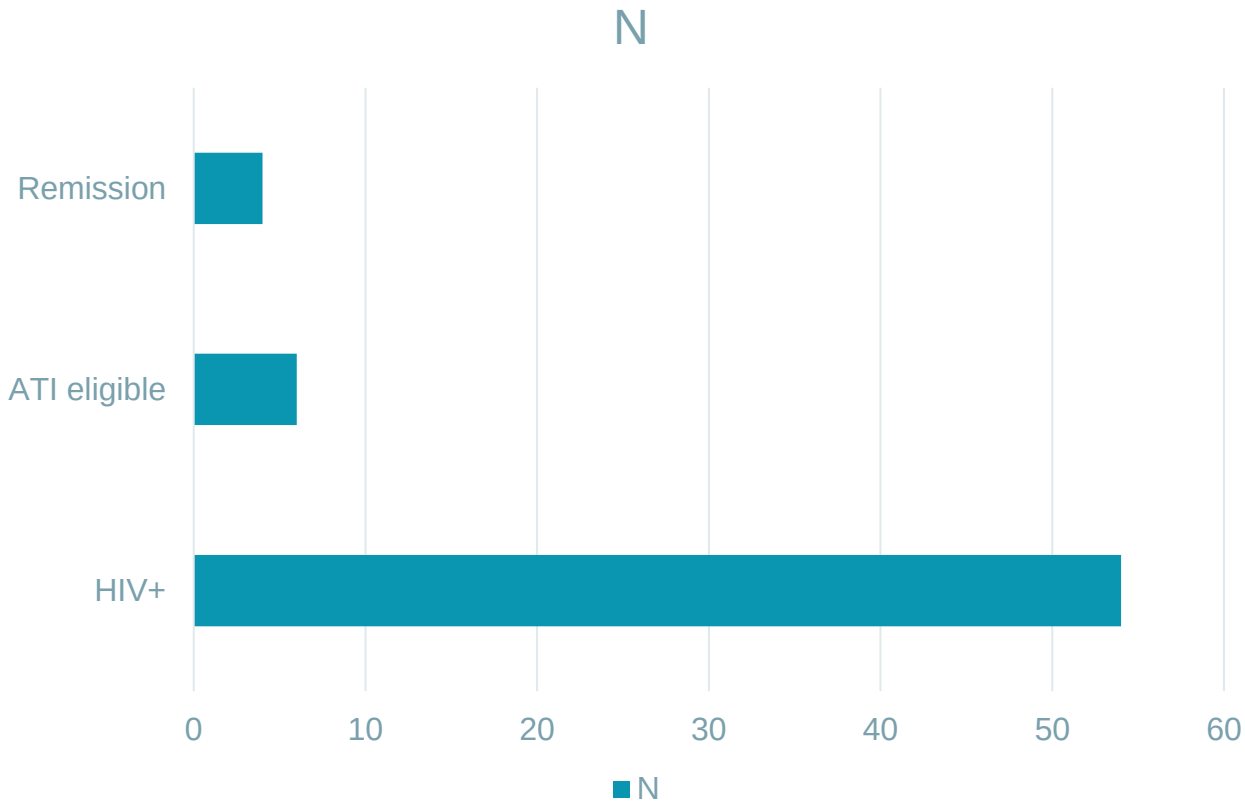
P1115: ART-free HIV-1 remission in very early treated children



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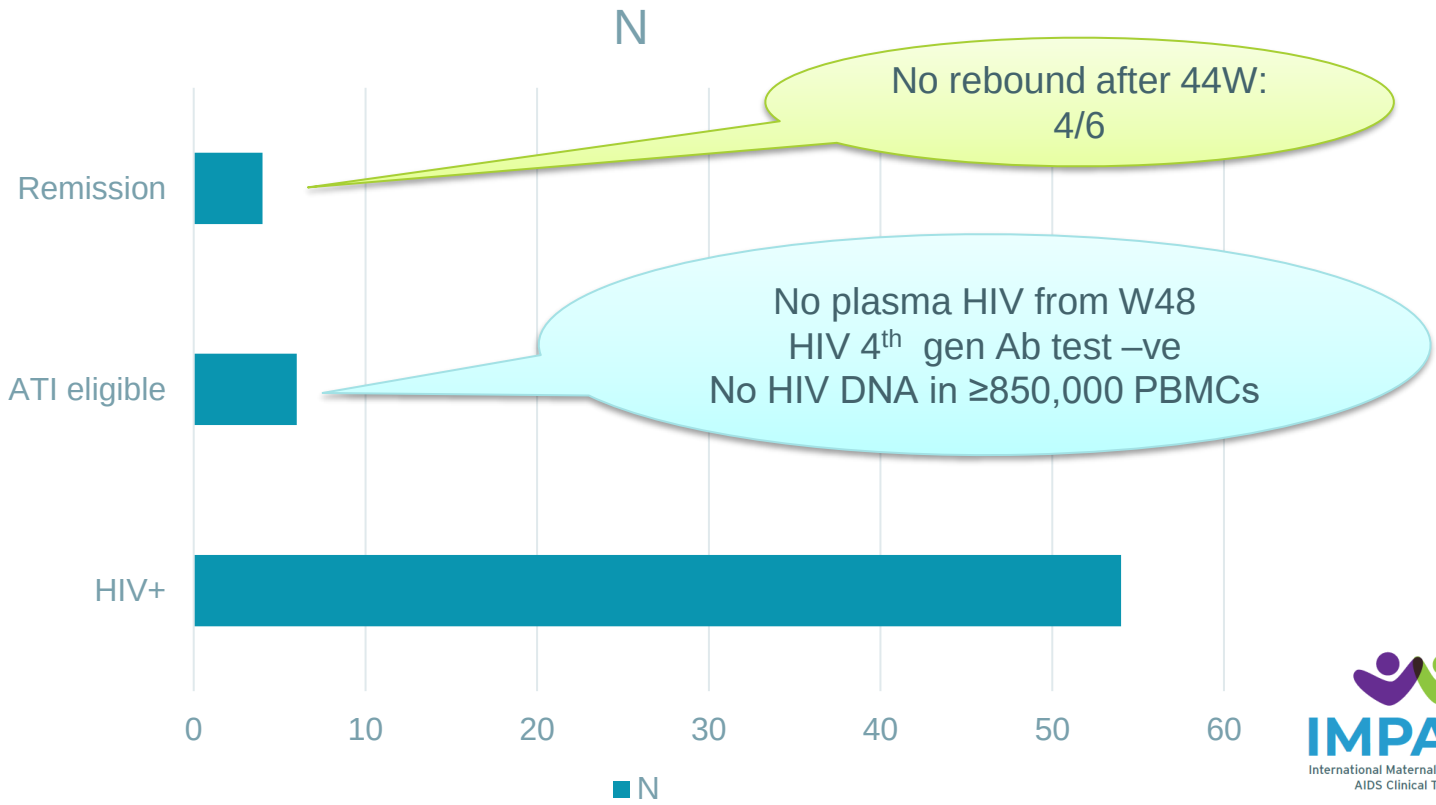

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Problems with ATI studies

- Frequent visits for viral load & health
  - Weekly for 8 weeks, then 2 weekly for 10 weeks etc.
  - Many blood draws & large volumes
  - School issues
- Disappointment if viral load rebounds
  - Child, family, team

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Potential problems with ATI

- Acute retroviral syndrome – (2/6 in P115.
  - Fever, sore throat & rash when virus rebounds
  - Restarting ART should solve
- Increased reservoir size – unlikely
- Fall-off in coping at school due to the virus
  - Possible, but unlikely

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Are there international ATI guidelines?

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

Lancet HIV 2019; 6 (4) e259-68

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

171 citations

- 41 experts: adult & pediatric (n = 3) clinicians, virologists, immunologists, bioethicists, patient advocates, statisticians, social scientists, Regulatory authorities & Funders (FDA, NIH, AmfAR) & industry
- Countries: US, Denmark, South Africa, Spain, Switzerland, Thailand & UK
- Participation by invitation

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Mainly adult-focused

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Guidance-for children

- No ATI <2y of age

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Since 1st workshop

- Much learnt
- Need more participants with experience and perspectives from LMICs
- Pediatric & adolescent populations – more input needed

2024 (ATI) Consensus Workshop, Nairobi, 8-10 May 2024

SANTHE
SUB-SAHARAN AFRICAN NETWORK FOR TB/HIV RESEARCH EXCELLENCE
Advancing African Science, Fighting HIV/AIDS and TB

WRAIR
Walter Reed Army Institute of Research
MILITARY HIV RESEARCH PROGRAM

2024 Analytical Treatment Interruption (ATI) Consensus Workshop

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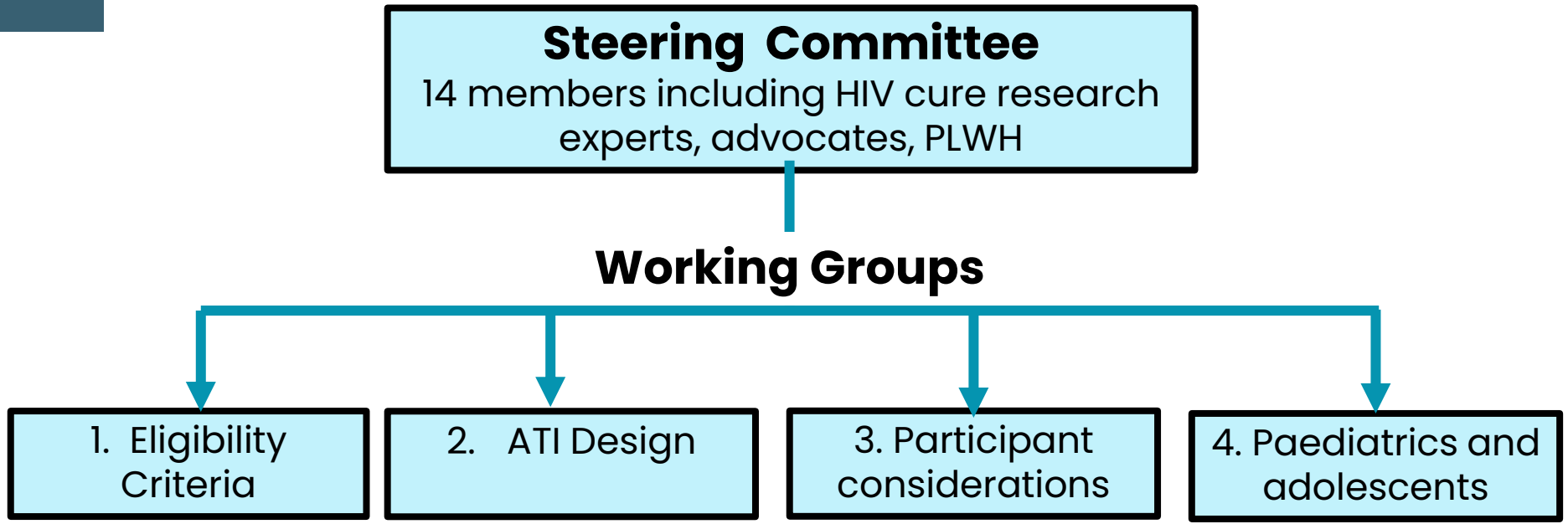
Planning for 2024 ATI Consensus Workshop



Working groups met regularly to gather evidence, consult beyond the Steering Committee, & to formulate key issues for consensus voting

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Pediatric / Adolescent (perinatally acquired) working group

6th February 2024: invitation to Philip Goulder & join organizing committee

- Co-chairs: Philip Goulder & Mark Cotton
- Moderator: Gareth Tudor-Williams
- Members:
  - In-person: Mutsa Bakwura-Dangarembizi, Adeodata Kekitiinwa, Louise Kuhn, Deborah Persaud, Roger Shapiro, Gabi Cromhout, Nomonde Bengu
  - On-line: Mo Archary, Paolo Palma, Nicola Cotugno, Violet Korutaro

Do we want to combine with adult group or observe & develop guidance in a separate event?

Drafting updated international recommendations for ATI trials

AIDS 2024

~100 Participants from 5 continents (half from Africa): scientists, clinicians, community advocates, persons living with HIV & representatives of funding, regulatory, and industry organizations

Which children qualify for ATI?

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Which children qualify

Must be very healthy
Doing well & suppressed on ART
Excellent CD4 levels

2 main ATI study designs

Time to rebound	Set point
Resume ART immediately once viral load detectable	Resume ART if an agreed set point is not achieved

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2 main ATI study designs

Time to rebound	Set point
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P1115

IMPAACT 2039 Immunological interventions

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Pediatric ATI Trials

Placebo arm: ATI trials in infants, children & adolescents could include placebo arm if reasonable chance of success in any arm

Adolescents

Can participate

If behaviorally acquired HIV, with appropriate resources in research team, considered in adult ATI trials

Extensive psychosocial support for ATI study participants & families should be provided by personnel within the study team who have training in ATI studies

Pediatric ATI Trials

	2019	2024
Age <2yo exclusion criterion for ATI studies	Yes	Yes
Support for HIV disclosure	N/A	Recommended
Specific entry criteria	N/A	Listed
Specific ART restart criteria	N/A	Listed

IAS 2024

Cure symposium

2 youth from CHER cohort on ART with 3 people cured of HIV (City of Hope, Dusseldorf & London patients)

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THANKS!

Any questions?

You can find me at

- mcot@sun.ac.za

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Acknowledgments

Debbie Persaud, P1115 team, CHER team (Avy Violari, Barbara Laughton, Kennedy Otwombe, Sam Fry, Shaun Barnabas) Santhé (Thumbi Ndung'u) Henry M Jackson Foundation (Lydie Trautmann)

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