Analytical treatment interruptions, their role in HIV cure research & ethical considerations

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Analytical treatment interruptions in HIV cure research Webinar
30.05.2024

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Disclosures

- Educational grant from Gilead Sciences
- Institution has received grant funding from Merck Sharpe & Dohme for the conduct of clinical trials
- Institution has received consulting fees from Viiv Healthcare and Gilead Sciences

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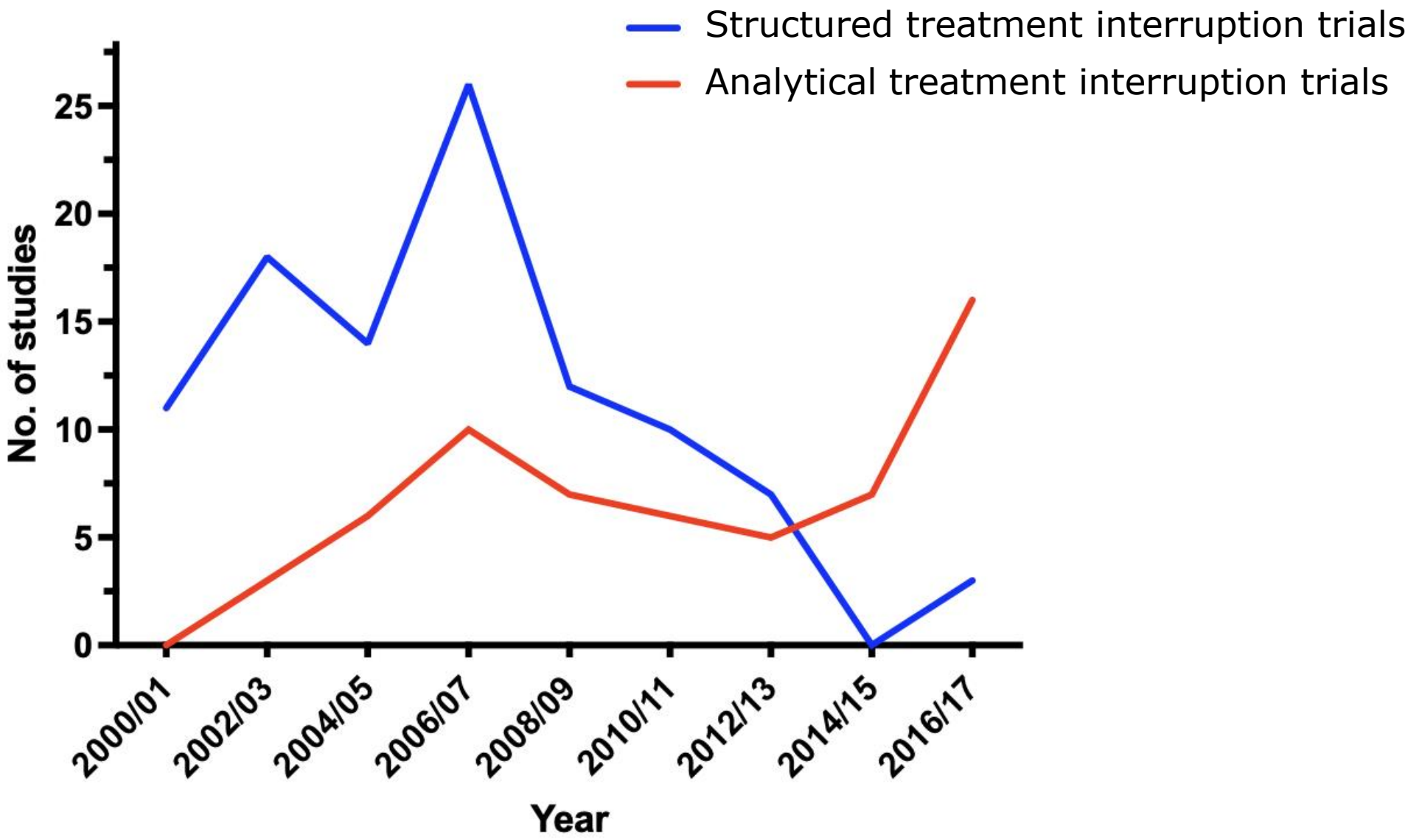
Outline

- Types of analytical treatment interruptions
- ATI trials, past and present
- Risks of ATI
- Community perspectives
- Minimising risk of ATI



Lau AIDS Res Human Retro 2019

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Structured Treatment Interruption	Analytical Treatment Interruption
• Pre-SMART and START era • "drug holiday" • Minimise toxicities • Therapeutic option for multi-resistant virus or treatment failure • Lack of pregnancy data	• Pause of ART during HIV cure trial • Closely monitored • Pre-set threshold to restart • Increasingly common in HIV cure trials

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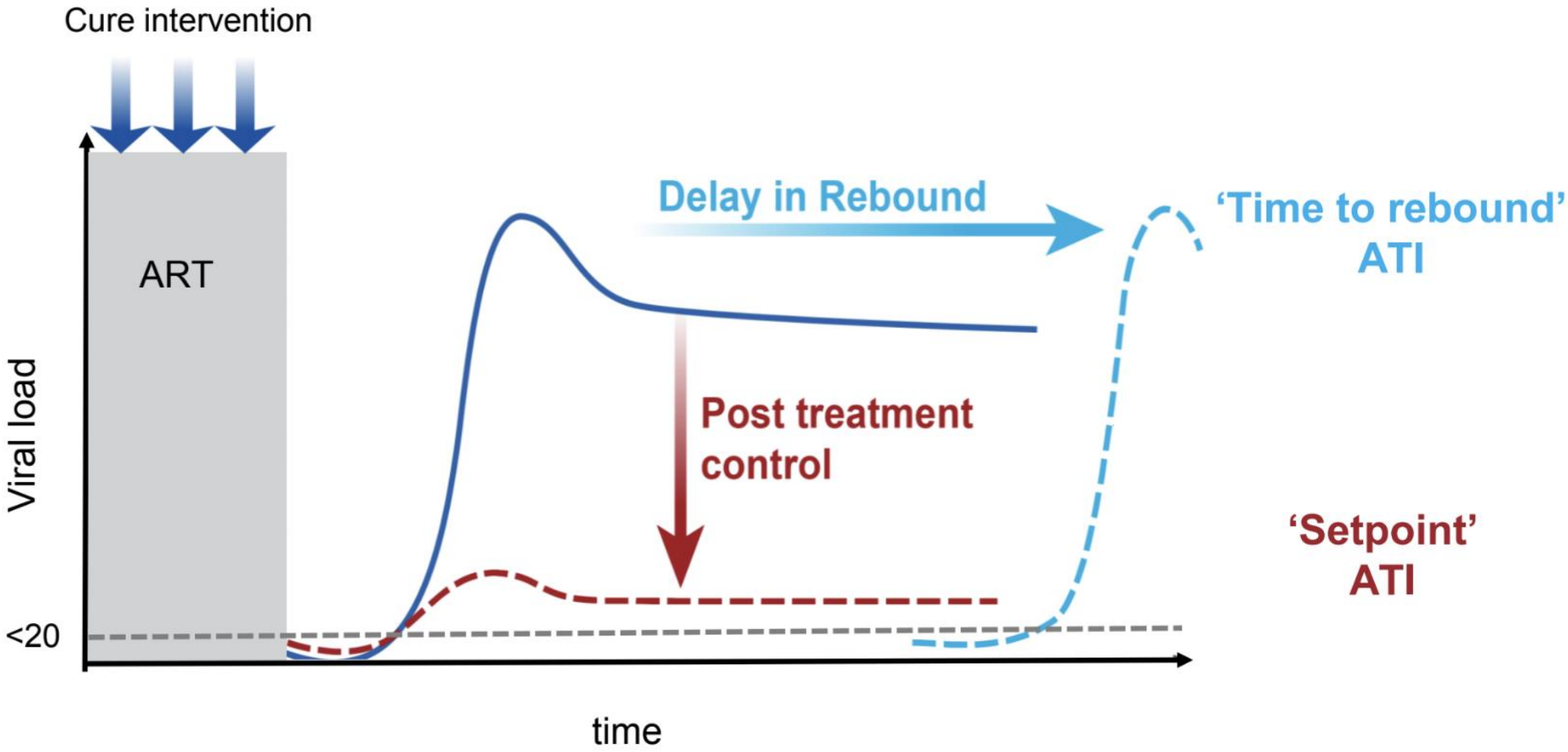
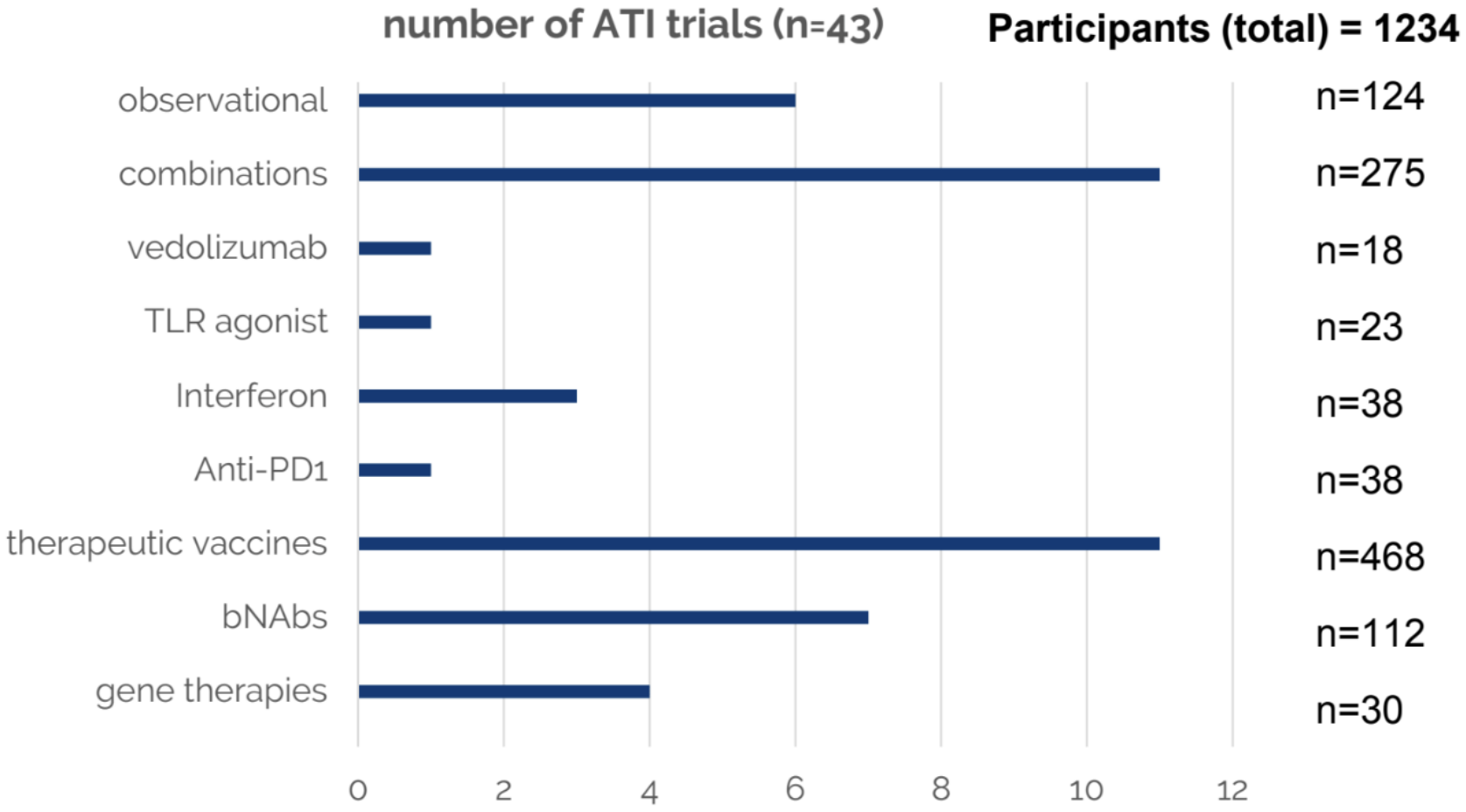
Two types of ATI



Current ATI cure trials



Primarily sites in USA
1 paediatric study
Majority set point

ATI in LMIC

- Botswana
- Puerto Rico
- Thailand

Date extracted from summary provided by Richard Jeffreys, TAG

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Short ATI are safe

7 trial cohorts[1-3], n=31

No:

- adverse events during TI
- expansion of reservoir
- new resistance
- long-term immunological abnormalities
- virological failure post ART resumption
- HIV transmission

1) Clarridge, PLoS Pathog 2018; 2) Salantes, J Clin Invest. 2018; 3) Strongin, J Virol. 2018;

Set-point ATI have risks

1 death during ATI[1]
- Vaccine study w48 into ATI with acute myocardial infarction

2 cases of HIV transmission[2,3]

Long term clinical events[4]
- 10 trials
- 181 participants
- ATI 4x higher risk non-AIDS events

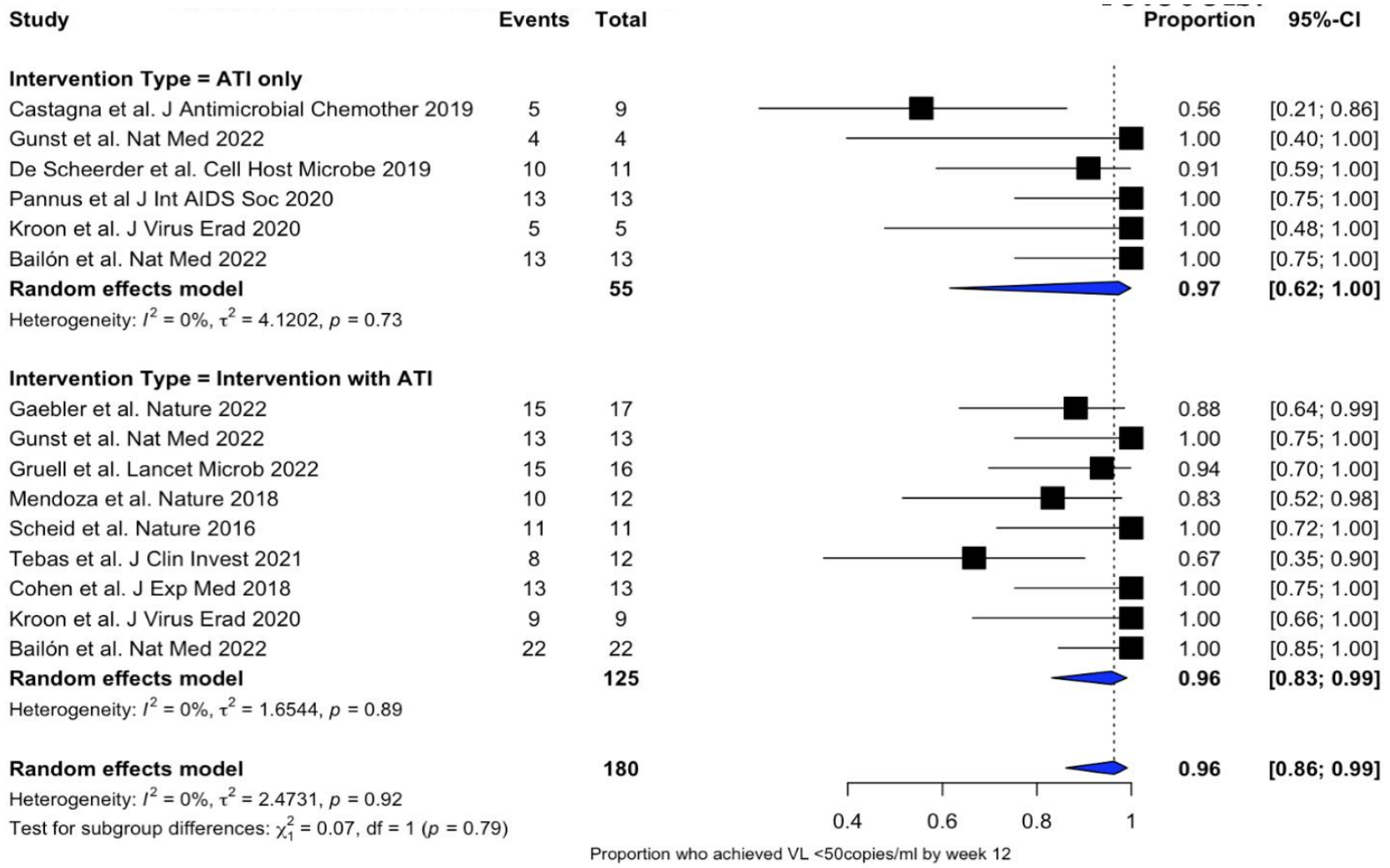
Long term impact on reservoir[6,7]
- IPDA remained elevated 52w post ART restart in chronic treated

CNS impacts[8]
- 4 ATI studies
- n=30
- Viral RNA detected in CSF of 6% of participants

1) Pollard Lancet ID 2014; 2) Lelièvre JID, 2019; 3) Ugarte JID, 2019; 4) Richart AIDS 2021;5) Manning CROI 2024; 6) Hellmuth CID 2021

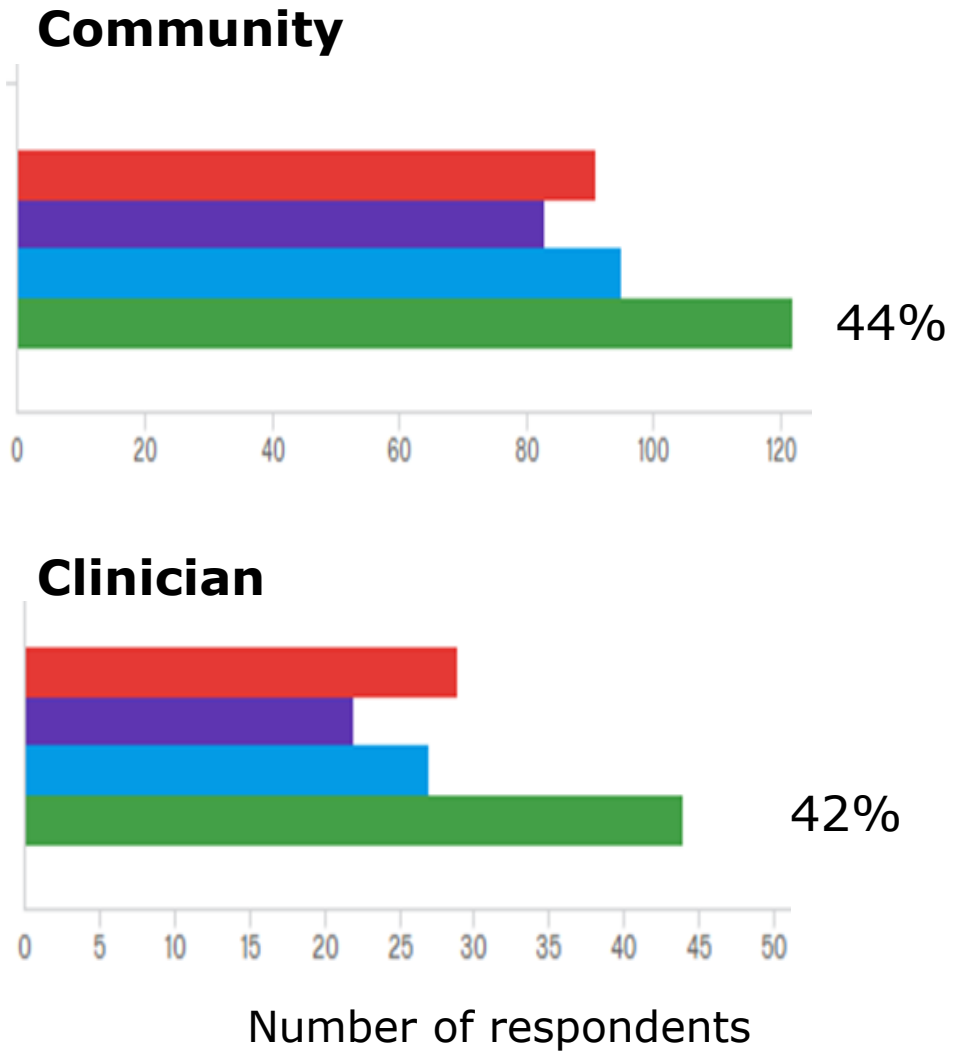
Viral re-suppression post ATI

- Systematic review and meta-analysis
- 12 studies, n=180
- 96% viral suppression by 12 weeks
- Not impacted by receipt of interventional drug



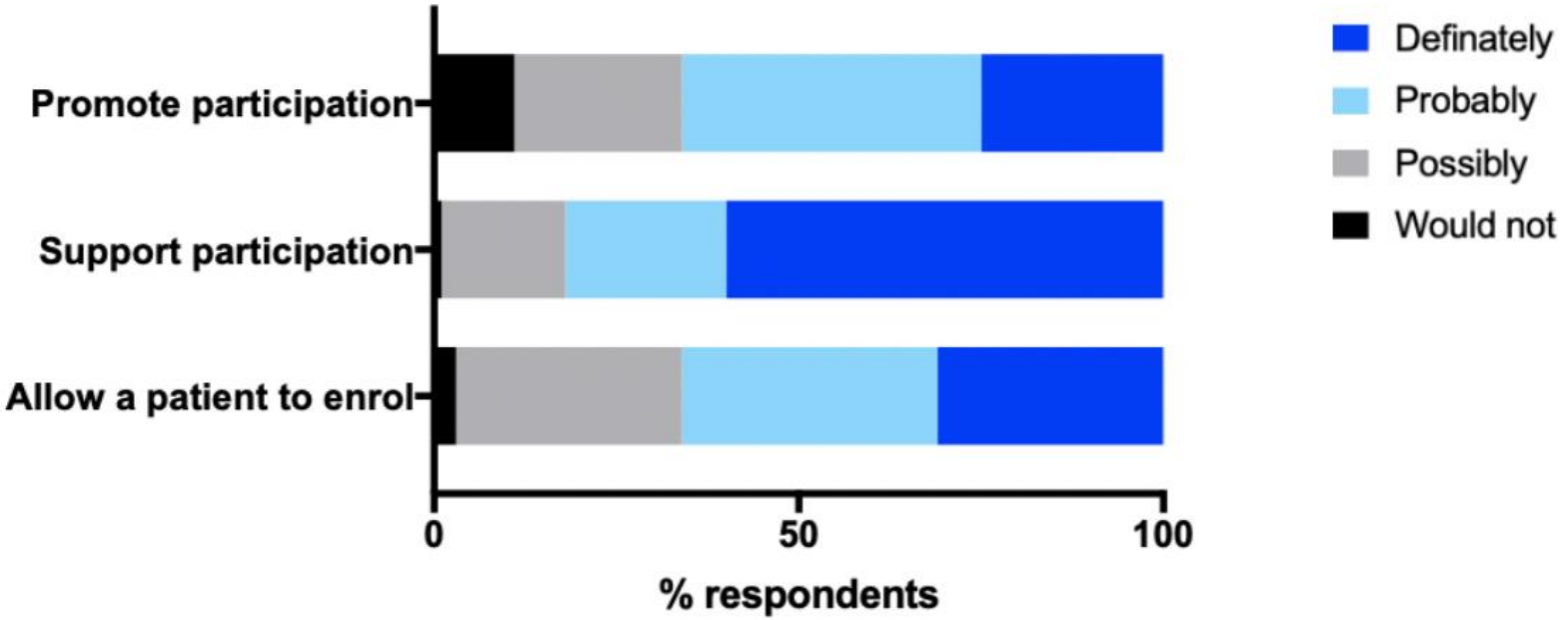
Community Perspectives

Concerns about risks of ATI



Lau AIDS Res Human Res

Providers on patient trial enrolment



Lau, AIDS Res Ther, 2020

Clinicians

- Effectiveness of contemporary ART regimens
- Lack of concrete benefit to participation
- Trial study duration and follow-up
  - Impact on fertility
  - Language barriers
- Work, care obligations and social commitments
- Time needed to explain research in clinic

Chong, Missing Voices, unpublished

Risk Mitigation during an ATI

Reduce adverse events for the participant

- Exclude those with low CD4 nadir, history of cancer/CAD
- High baseline CD4+ count
- Age limit
- Strict restart criteria

Reduce risk of transmission to others (Partner Protections)

- Education of participant and adapt approach over time
- PrEP for partners
- Community engagement and CAB

Considerations for special populations

- Paediatrics and adolescents
- Co-infections (COVID, TB)

Slide courtesy of Sharon Lewin

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INTERRUPTING HIV TREATMENT IN A CLINICAL STUDY

You have enrolled in an HIV Cure study at Alfred Health. This study include an Analytical Treatment Interruption (ATI). This factsheet gives you more information about the role of ATI in HIV cure research.

WHY IS ATI NECCESSARY?

To really understand if the drug we are testing is able to control HIV without antiviral medications, we have to interrupt your usual HIV treatment. There is currently no test that can tell us if HIV has been eliminated from your body.

DO I HAVE TO STOP MY HIV TREATMENT?

Participation in this study is voluntary, and you do not have to stop your HIV treament if you are not comfortable with this. Please talk to your study doctor if you have any concerns about ATI in this study.

IS ATI SAFE?

Yes. Several studies have shown that short, closely monitored ATI are safe. This ATI will not have any longterm impacts on your immune system, your CD4 count or your ability to have undetectable HIV levels when you restart treatment.

WHAT WILL HAPPEN DURING THE ATI?

The study team will arrange for very close follow up and frequent blood tests to monitor your health and HIV viral load. If your viral load goes above a certain level, your treatment will be restarted.
You can ask to restart treatment at anytime during ATI.

COULD I TRANSMIT HIV TO MY PARTNER?

There have been 2 reports of HIV transmission during ATI, but we will take precautions to minimise the risks of this. The study team can also arrange for your partner to be linked to a PrEP provider.
What is PrEP?

Please speak to our study team if you have any questions or concerns about ATI in this trial.
Phone: 90766908 or email: gaclinresearch@alfred.org.au

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KEEPING YOU SAFE DURING THE COVID-19 PANDEMIC

You have enrolled in an HIV Cure trial at Alfred Health. Here's what we've changed about the way we do research to minimise risks during the COVID-19 pandemic.

COVID-19 VACCINES

We encourage you to get the COVID-19 vaccine when is is offered to you.

Read more about COVID-19 vaccines here

TRANSPORT

We will provide taxi vouchers or free parking tickets to avoid using public transportation.

FLEXIBLE STUDY VISITS

Where possible, study visits will be conducted remotely.

If needed, we will provide you with equipment or visit you at home.

COVID-19 TESTING

Regular asymptomatic testing will be performed during the study

Please contact us if you have symptoms, or if you have been diagnosed with COVID-19. We can arrange for urgent testing to be done and support your recovery at home or in hospital.

WHAT CAN I DO?

Wear a mask inside the hospital

Wash your hands regularly

Remember to keep your distance from others

Summary slide for community

Key points:

- ATI an integral part of HIV cure research, with strong scientific rationale for "set point" ATI
- Over 1200 participants have completed an ATI with very few adverse events

What does this mean to the field of research?

- Standardised methods to report ATI outcomes and adverse events are needed
- All possible events need active mitigation strategies

What does this mean for community?

- ATIs are here to stay… for now
- Risk mitigation, including partner protections, and **community engagement** is an essential part of ATI trial design

Acknowledgements

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Barbara Scher
Jennifer Audsley

ICASO
Brent Allan

Positive Women Victoria
Kirsty Machon

People with HIV who have volunteered for the studies presented in this talk

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Cipriano Martinez
Brent Clifton
John Rule

Swinburne University
Gordon Campbell

UCSD
Karine Dube

International Community Advocacy
Richard Jeffries
A. Toni Young
Michael Louella

ATI participant perspectives

"Initially when you start they're taking a copious amount of bloods, they're closely monitoring you, letting you know viral loads, CD4 counts each week, blood pressure, heart rate, all those sorts of things every week. So I feel very comfortable with the staff…"

At some point, I looked at their plan … And, like, the virus had just come back. And they're like, okay, we skip to every other week for blood. I'm like, okay, could I actually ask y'all that we go every week for blood? Because it's a little weird that, all of a sudden, y'all are—at the heart of it, as the virus rebounding, you're saying, go every other week, or—you know, like, that makes no sense to me … I need it to know whether the virus is spiking; what's my body doing? Knowledge—that information is my medicine. Don't deny me my medicine. – Participant #06

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ATI participant perspectives

this … I had this feeling of a lot of responsibility for all of these people. And to have to post that the experiment didn't work … I felt like a failure … It took me a couple of days.

because my viral load started going up again. So, I'm back on my HIV medication now … I kind of feel like I let our community down. I mean, I'm not depressed about it, but I don't know. I was hoping I make it through the whole three-month area and then I could stay off my medications, but I don't know. I'm not saying I feel like a failure, but I just feel like I'd let the whole HIV community down.

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