Analytical Treatment Interruptions in HIV Clinical Trials: A Systematic Review

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Background

- Treatment interruption (TI) has been studied in clinical trials since triple therapy ART has been available
  - Minimise toxicity
- SMART study: RCT continuous vs CD4 guided ART
  - Sig ↑ risk of death, OI, and non-AIDS events[1]

[1]SMART study Group, NEJM, 2006

Analytical Treatment Interruptions

- HIV cure clinical trials assess strategies and interventions aimed at achieving HIV remission or virological control off ART
- Analytical treatment interruption (ATI) is a structured, closely monitored, and temporary cessation of ART

Analytical Treatment Interruptions

- Immunological and virological dynamics during ATI are a critical outcome in cure trials
- Common feature of modern HIV cure trials
  - Poses potential risks
  - No standardised study protocols

Aim

Perform a systematic review of the literature around TI methodology in HIV clinical trials

- cure focused trials
- non-cure focused trials

Methods:

- Systematic review (PRISMA) of clinical studies where ART was interrupted by a clinician or investigator.
- Studies from 2000-2017
- Excluded case reports, TI shorter than 2 weeks
- Extracted data

- Descriptive analysis

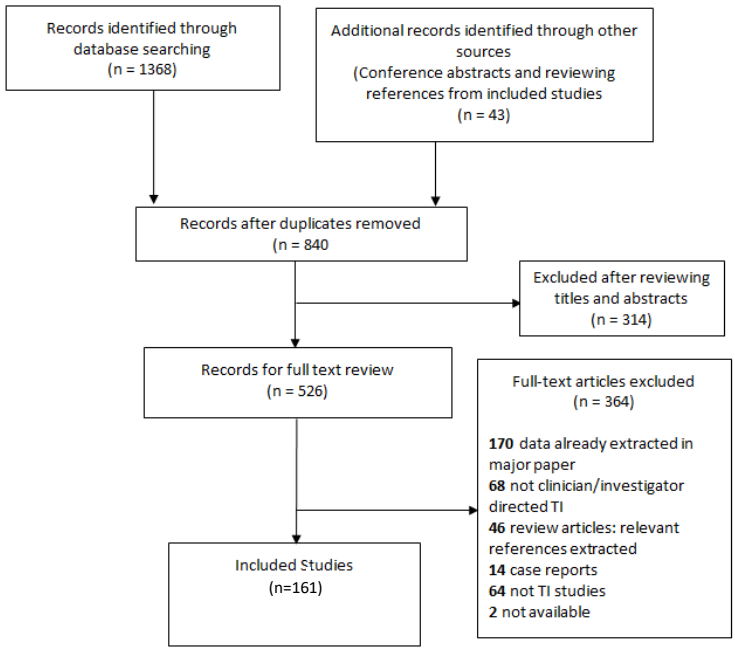
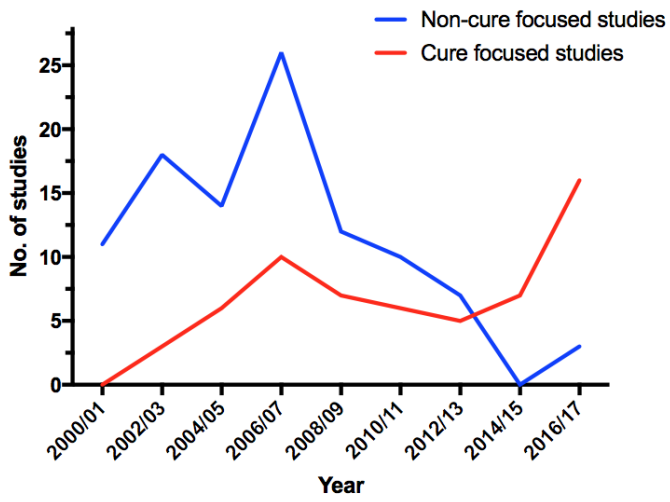


Figure 1: PRISMA search strategy flow chart

Results

- 161 TI studies (Jan 2000-July 2017)
- 101 non-cure focused
- 60 cure focused

Number of studies without an intervention have declined



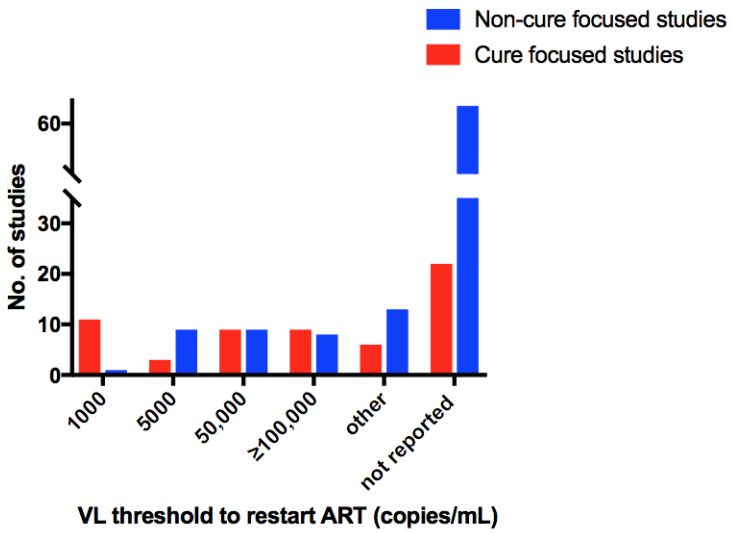
Cure interventions

- Therapeutic vaccines (31)
- IL-2 (4)
- Interferon (3)
- Antibodies (4)
- Gene editing (2)
- Hydroxyurea (2)
- Early ART (3)
- Combination (5)
- Other (6)

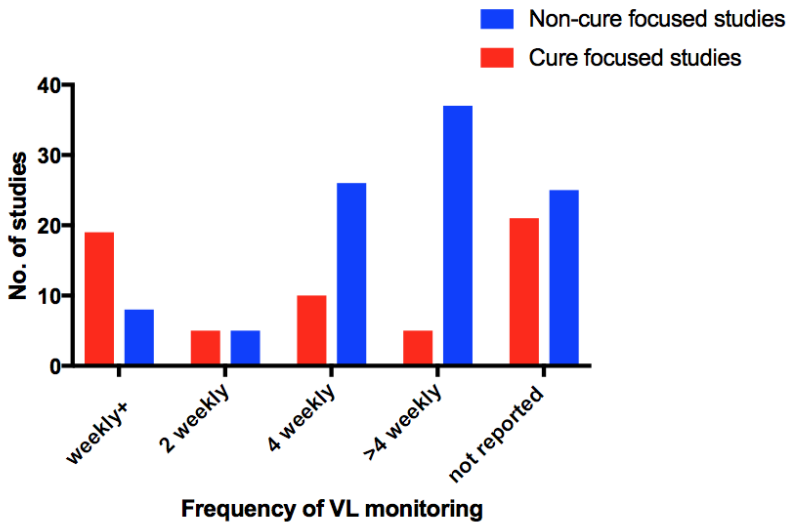
TI studies

	Non-cure focused (n=101)	Cure focused (n=60)
Study design	39 (39%) RCT	37 (62%) RCT
Median n (IQR)	27 (13-27)	29 (25-74)
Median age (IQR) yrs	39 (35-42) 7 paeds studies	40 (38-44) 1 paeds studies
Majority male	64/72 (89%) 4 studies - all male participants	44/45 (98%) 12 studies - all male participants

Lower VL threshold to restart ART in cure focused trials



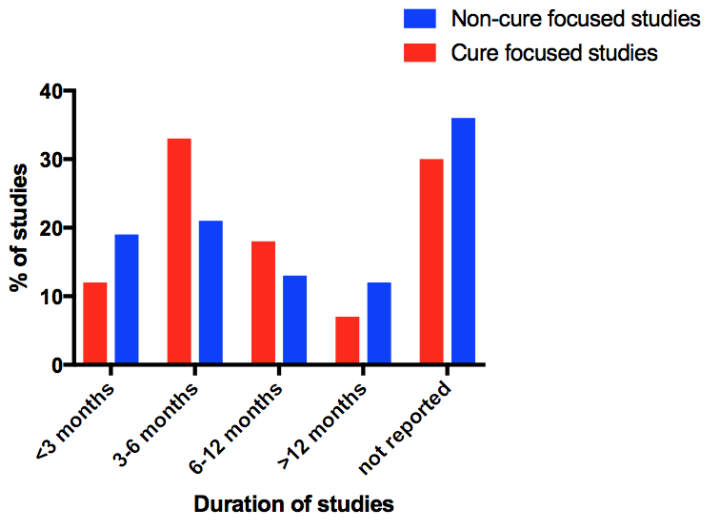
Cure focused studies monitor VL more frequently



Variation in reported duration of TI

- Set duration (38)
- Opened ended (5)
- Multiple sequential (9)
- Minimum (5)
- Maximum (17)
- Mean (5)
- Median (30)

Cure focused studies did not have shorter TI



Set point vs time to viral rebound

- BNAb studies (3)
  - Time to viral rebound
  - 200-1000c/mL
- Therapeutic vaccine studies (31)
  - Set point
  - 3000c/mL-300,000 c/mL

Adverse Events

- 31/101 (31%) non-cure focused studies reported AEs
- 15/60 (25%) cure focused studies reported AEs
- 1 death in cure focused studies
  - out of 2148 participants
  - Myocardial infarction 15 weeks into ATI

Prevention of HIV transmission

- 9/101 (9%) non-cure focused studies, 1/60 (2%) cure focused studies reported counselling participants about possible transmission risk and advised safe sexual practices.
- No studies reported offering PrEP to partners of participants

- Cure studies: more frequent monitoring, restart ART based on VL, lower VL threshold → less adverse events reported
- Set point vs time to viral rebound TI
- PrEP not offered to seronegative partners of participants

Limitations

- Heterogeneity of studies
- Missing data
- Unpublished conference abstracts

Conclusions

- ATI increasingly being used
- Heterogeneity in TI methodology, evolved over time
- Different aims to achieve HIV cure/remission reflect different TI methods
- PrEP and counseling re: transmission risk reduction should be included in study protocols for ATI trials

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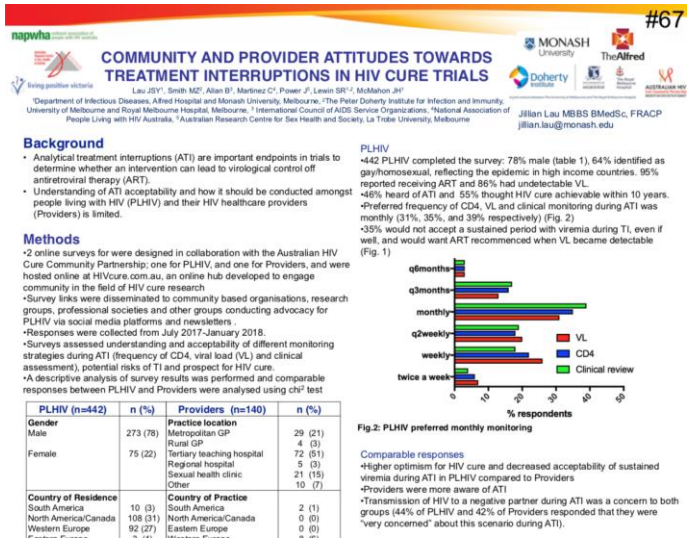

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COMMUNITY AND PROVIDER ATTITUDES TOWARDS TREATMENT INTERRUPTIONS IN HIV CURE TRIALS

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Background

- Analytical treatment interruptions (ATI) are important endpoints in trials to determine whether an intervention can lead to virological control off antiretroviral therapy (ART).
- Understanding of ATI acceptability and how it should be conducted amongst people living with HIV (PLHIV) and their HIV healthcare providers (Providers) is limited.

Methods

•2 online surveys for were designed in collaboration with the Australian HIV Cure Community Partnership; one for PLHIV, and one for Providers, and were hosted online at HIVcure.com.au, an online hub developed to engage community in the field of HIV cure research
•Survey links were disseminated to community based organisations, research groups, professional societies and other groups conducting advocacy for PLHIV via social media platforms and newsletters .
•Responses were collected from July 2017-January 2018.
•Surveys assessed understanding and acceptability of different monitoring strategies during ATI (frequency of CD4, viral load (VL) and clinical assessment), potential risks of TI and prospect for HIV cure.
•A descriptive analysis of survey results was performed and comparable responses between PLHIV and Providers were analysed using chi^2 test

PLHIV (n=442)	n (%)	Providers (n=140)	n (%)
Gender		**Practice location**	
Male	273 (78)	Metropolitan GP	29 (21)
		Rural GP	4 (3)
Female	75 (22)	Tertiary teaching hospital	72 (51)
		Regional hospital	5 (3)
		Sexual health clinic	21 (15)
		Other	10 (7)
Country of Residence		**Country of Practice**	
South America	10 (3)	South America	2 (1)
North America/Canada	108 (31)	North America/Canada	0 (0)
Western Europe	92 (27)	Eastern Europe	0 (0)

PLHIV

•442 PLHIV completed the survey: 78% male (table 1), 64% identified as gay/homosexual, reflecting the epidemic in high income countries. 95% reported receiving ART and 86% had undetectable VL.
•46% heard of ATI and 55% thought HIV cure achievable within 10 years.
•Preferred frequency of CD4, VL and clinical monitoring during ATI was monthly (31%, 35%, and 39% respectively) (Fig. 2)
•35% would not accept a sustained period with viremia during TI, even if well, and would want ART recommenced when VL became detectable (Fig. 1)

Fig.2: PLHIV preferred monthly monitoring

Comparable responses

•Higher optimism for HIV cure and decreased acceptability of sustained viremia during ATI in PLHIV compared to Providers
•Providers were more aware of ATI
•Transmission of HIV to a negative partner during ATI was a concern to both groups (44% of PLHIV and 42% of Providers responded that they were "very concerned" about this scenario during ATI).

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