Antiretroviral treatment interruptions in HIV clinical trials: A systematic review

Lau JSY[1], Smith MZ[2], Lewin SR[1,2], McMahon JH[1]
[1] Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia
[2] The Peter Doherty Institute for Infection and Immunity, University of Melbourne and Royal Melbourne Hospital, Melbourne, Australia
jillian.lau@monash.edu
Jillian Lau MBBS BMedSc, FRACP

Background

- An important clinical endpoint in HIV cure trials is whether an intervention can lead to virological control, or a delay to viral rebound off antiretroviral therapy (ART).
- Treatment interruption (TI) has been associated with harm to trial participants and there are currently no standardized TI protocols.
- We reviewed TI practices in HIV clinical trials, describing: criteria to restart ART, monitoring and duration of TI, and adverse outcomes associated with these studies.

Methods

- Systematic review of TI methodology in HIV clinical studies from 2000-2017 identified via Ovid MEDLINE, EMBASE and recent HIV conference abstracts (IAS and CROI).
- Extracted data included: participant demographics, frequency of HIV viral load (VL) monitoring, criteria to restart ART (CD4 T cell count/mm^3, and HIV VL copies/mL single or repeated) TI duration (median, mean or mode), and adverse events associated with TI.
- Cure focused (CF) studies explored interventions aiming to achieve virological control off ART or identify potential cure interventions. Non-cure focused (NCF) studies examined TI to optimize clinical outcomes such as minimizing the adverse effects of ART.
- A descriptive analysis was performed.

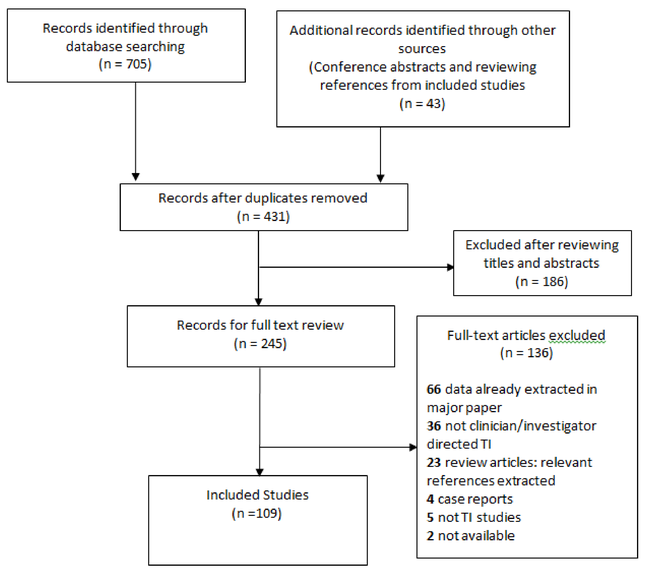

Fig. 1: PRISMA search strategy flow chart

Results

- 109 studies: 42 (39%) CF and 67 (61%) NCF (Fig. 1)
- Median (IQR) participant age was 40 years (36-44) for CF and 39 (34-42) for NCF studies.
- Median (IQR) number of participants was 21 (13-52) for CF and 26 (15-99) in NCF.
- 31/32 (97%) of CF and 42/52 (81%) of NCF studies, where reported, had a majority of male participants.

Frequency of Viral load monitoring

- HIV VL monitoring frequency ranged from every 2 days to every 16 weeks. The most common reported VL monitoring frequency was monthly for 21/46 (46%) NCF studies and weekly or more frequently for 20/30 (67%) CF studies (Fig.2 and 3)

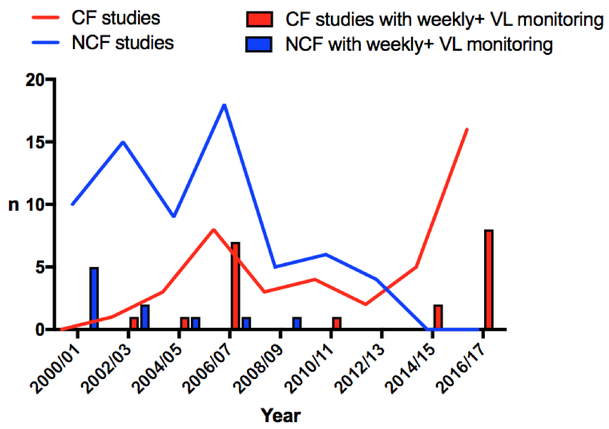

Fig. 2 Monitoring HIV VL weekly or more frequently

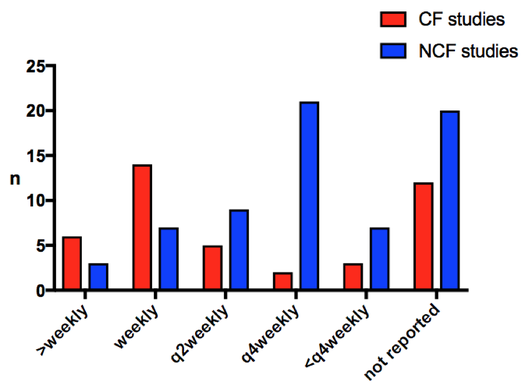

Fig. 3: Frequency of VL monitoring in CF studies

Threshold to restart therapy

- 24/42 CF, and 38/67 NCF studies reported CD4 threshold to restart therapy, <350 cells/mm^3 was the most common reported threshold in 15 (63%) of CF and 15 (39%) NCF studies.
- For CF studies, the most common HIV VL thresholds were >1000c/mL and >50,000c/mL in 7/28 (25%) each.
- For NCF studies the most common reported VL threshold was 5000 c/mL in 7 studies, but only 25/42 (60%) reported a VL threshold to re-initiate ART.

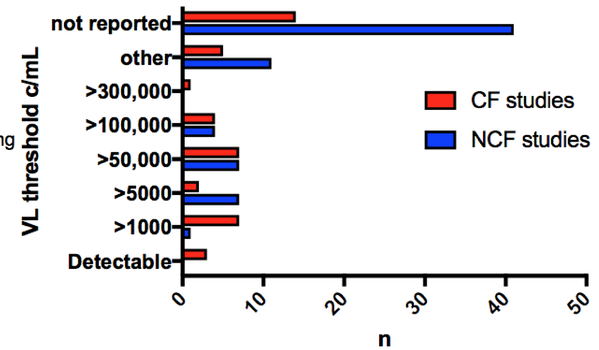

Fig. 4: VL Thresholds to restart ART

Duration

- Studies reported duration in different ways including pre-determined TI duration (set TI), median or mean duration off ART.
- Median TI duration ranged from 7 days to 22 months in NCF, and 14 days to 24 months in CF studies.
- 9/49 (18%) NCF studies interrupted treatment for >12 months and 3/29 (10%) CF studies had TI for this long. 25/49 (51%) NCF interrupted ART for <3 months, compared with 13/29 (45%) CF studies.

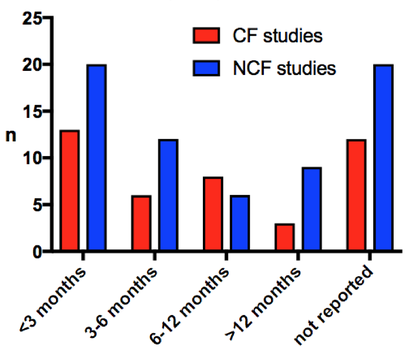

Fig.5: Duration of TI studies

Adverse events

- Adverse events possibly or probably related to TI were reported in 25/67 (37%) NCF studies (Table).
- 6/42 (14%) of CF studies reported adverse events, with one death from myocardial infarction during TI, out of a total of 1597 participants.

	Adverse event reported
NCF studies	Development of HIV resistance Acute retroviral syndrome Thrombocytopenia Lymphadenopathy Severe AIDS defining conditions/death HIV related event/symptoms Major CVS/renal/liver disease AIDS defining event not otherwise specified
CF studies	Development of HIV resistance Acute retroviral syndrome Thrombocytopenia AIDS defining events HIV related event/symptoms Death (MI)

Table: Clinically significant adverse events reported in TI studies, possibly or probably related to TI

Prevention of HIV transmission

- 5 NCF, and 1 CF study reported counseling participants about possible transmission risk and advised safe sexual practices. No studies reported offering HIV pre-exposure prophylaxis to partners of participants.

Conclusions

- Great heterogeneity was noted in frequency of virological monitoring, criteria to re-initiate ART and duration of TI.
- CF studies with TI are more common in the last 5 years likely related to recommendations for universal ART.
- TI in the CF studies were managed with more conservative parameters than NCF as reflected in number of studies monitoring weekly or more frequently and shorter TI duration, compared to NCF TI studies.
- Virological thresholds to re-initiate ART varied widely and were often not reported, particularly in NCF studies.
- CF studies were more likely to re-initiate ART based on VL monitoring.
- This research will assist the design of future trials involving TI and to potentially standardize an approach to this intervention.