The Impact of HIV Cure-Related Study Drugs and Treatment Interruption on Viral Resuppression Rates

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Background

To assess the effectiveness of novel HIV curative strategies, “cure” trials require periods of closely monitored antiretroviral therapy (ART) analytical treatment interruptions (ATI).

We performed a systematic review and meta-analysis to identify the impact of ATI with or without novel therapeutics in cure-related studies on the time to viral resuppression following ART restart.

Methods

We searched Medline and Embase databases for clinical studies involving ATIs from 2015 onwards, with regular plasma HIV viral load (VL) measurements after restarting ART on completion of the ATI (Fig 1).

The primary outcome was the proportion of participants who experienced viral resuppression (VL <50 copies/mL) by 12 weeks post-ATI, stratified by receipt of interventional drug with ATI(IA) or ATI-only groups.

A random-effects meta-analysis and meta-regression were performed using R packages ‘meta’ and ‘metafor’. Bias was assessed using the Newcastle Ottawa Score, Cochrane Risk of Bias tool, funnel plots, and Eggers Test.

Of 1049 studies screened, 12 were relevant with available data and included in the analysis (n=180 participants)

Conclusions:

- 96% of study participants who underwent ATIs achieved viral suppression by 12 weeks after restarting ART.

- Receipt of an intervention drug did not impact viral suppression rates by week 12.

- When designing studies involving ATIs, time to viral resuppression after restarting ART should be reported, to assess the impact and safety of future trial interventions.

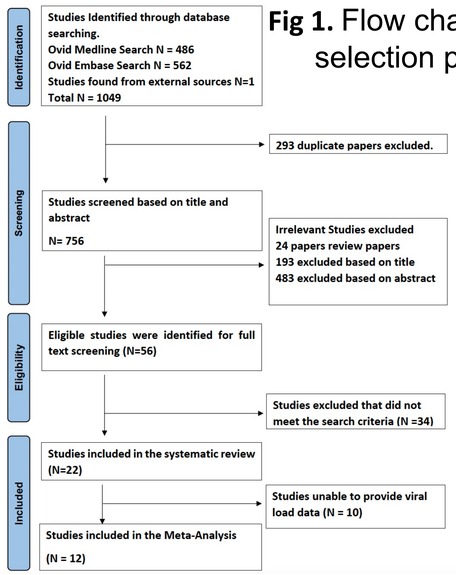


Fig 1. Flow chart of study selection process

Results

- 96% of participants achieved viral suppression within 12 weeks after restarting ART (95% CI: 83% - 99%)
- No difference was observed between ATI-only and IA subgroups (97% vs 96%, p=0·79). (Fig 2).

Fig 2. Forest plots of primary outcome events stratified by receipt of intervention with ATI or undergoing ATI-only protocols.

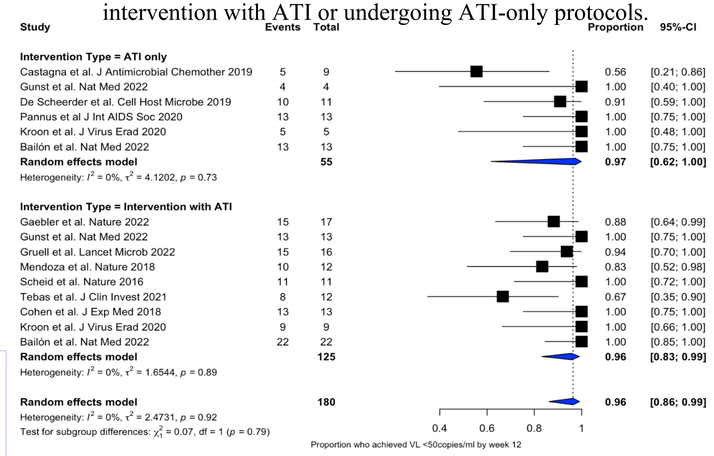
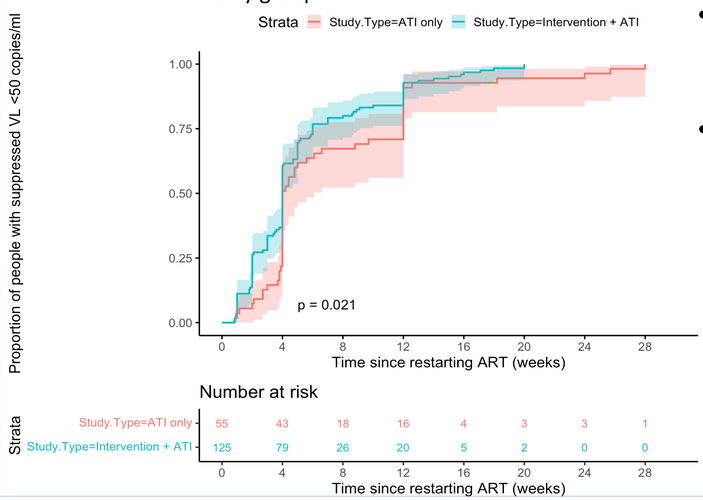


Fig 3. Kaplan Meier survival plot of proportion of people with suppressed plasma viral load <50 copies/ml against time in weeks stratified by IA vs ATI-only groups



- All participants achieved viral suppression over time (Fig 3).

- Although there appeared to be a difference between IA vs ATI-only over time to achieving viral suppression (Fig 3) in the survival analysis, this was not significant once other variables were adjusted for (Table 1).

- Longer time to viral suppression was associated with: (Table 1)
  - Plasma HIV viral load at ART restart
  - Use of Protease Inhibitors compared with other ART regimes (primarily Integrase Inhibitors-based)
  - Longer intervals for HIV VL monitoring
  - Older age
  - Duration of ATI

Table 1. Multivariable Cox proportional-hazards analysis

		N (%) / Mean (SD)	Univariable HR	Univariable 95% CI	Univariable p-value	Multivariable HR	Multivariable 95% CI	Multivariable p-value
Patient characteristics								
Age (years)*		40.7 (10.7)	0.98	0.97 – 1.00	0.011	0.97	0.96 – 0.99	**<0.001**
Gender*+	Female (Ref)	14 (8.4%)						
	Male	152 (91.6%)	0.67	0.39 – 1.18	0.164	0.97	0.54 – 1.73	0.914
HIV-related characteristics								
Plasma HIV viral load at ART restart (Log copies/ml)		4.3 (0.9)	0.56	0.46 – 0.67	<0.001	0.47	0.38 – 0.59	**<0.001**
Nadir CD4 (per 100 cells/μl increase)		571.2 (425.2)	1.00	0.94 - 1.06	0.914			
CD4 at study enrolment (per 100 cells/μl increase)		764.9 (294.6)	0.97	0.97 - 1.02	0.267			
Duration since HIV diagnosis (years)		6.6 (7.1)	0.99	0.97 – 1.01	0.314			
ART regimen containing Protease Inhibitors	No (Ref)	166 (92.2%)						
	Yes	14 (7.8%)	0.48	0.28 – 0.84	0.010	0.37	0.19 – 0.73	**0.004**
ART regimen containing Integrase Inhibitors	No (Ref)	46 (25.6%)						
	Yes	134 (74.4%)	1.34	0.94 – 1.91	0.103	1.56	0.99 – 2.44	0.053
Study characteristics								
Duration of ATI (weeks)*		9.7 (8.3)	1.01	0.99 – 1.02	0.625	0.96	0.94 – 0.98	**<0.001**
Mean interval of HIV VL monitoring between ART restart and viral suppression (weeks)		3.4 (2.1)	0.73	0.67 – 0.79	<0.001	0.66	0.59 – 0.74	**<0.001**
Study type	ATI only (Ref)	55 (30.6)						
	IA	125 (69.4)	1.41	1.02 – 1.95	0.039	0.89	0.57 - 1.40	0.612

* Fixed variables for multivariable model + A transgender participant was not included in the multivariable analysis due to n <5.

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