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Systematic Review of the Current Literature on Structured Treatment Interruptions in HIV-infected Patients Receiving Antiretroviral Therapy – Implications for Future HIV Cure Trials

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Background

Structured treatment interruptions (STI) in patients on antiretroviral treatment (ART) for HIV-infection have been widely discussed, with development of viral resistance and increase of morbidity being of concern. However, current efforts for potential HIV cure strategies will require clinical trials that depend on analytical treatment interruptions (ATI) as an informative outcome parameter. We report on a systematic review of the current evidence on STIs and propose potential strategies for safe ATI as part of clinical trials on HIV cure.

Method

A systematic literature search on studies reporting on STIs was conducted using a defined search term. Therefore, Web of Science Core Collection, Korean Journal Database, Medline, and SciELO, covering the period from 1945 to 12/2015 were considered. All interventional and observational studies were reviewed and results extracted based on predefined criteria (Figure.1).

Results

We identified 847 potential studies investigating STI, published between 1999 and 2015. 34 studies including 19.238 patients, mostly enrolled into randomized controlled trials (RCTs) or interventional trials, met the inclusion criteria. Sample sizes varied from six to 5.472 patients among studies (median: 71). The duration of STI ranged from seven days to 49 months with overall follow-up durations varying from 24 weeks up to three years. Follow-up schedule during STI varied from two days up to six month (Table1). Patients experienced viral rebound (VL>50 copies/ml) for up to a median of 161 days after STI. Five large trials with a follow-up interval (up to six months) and 1.878 patients under STI reported the development of resistances in 196 patients. Adverse events and death were observed in 535 and 359 respectively. Disease progression to CDC stage B or C was reported in 548 patients. In comparison, ten small studies, with close follow-up intervals (up to 28 days) and 488 patients in total, reported viral rebound and adverse events in 13 and 1 patients respectively, but no deaths were observed (Figure 2).

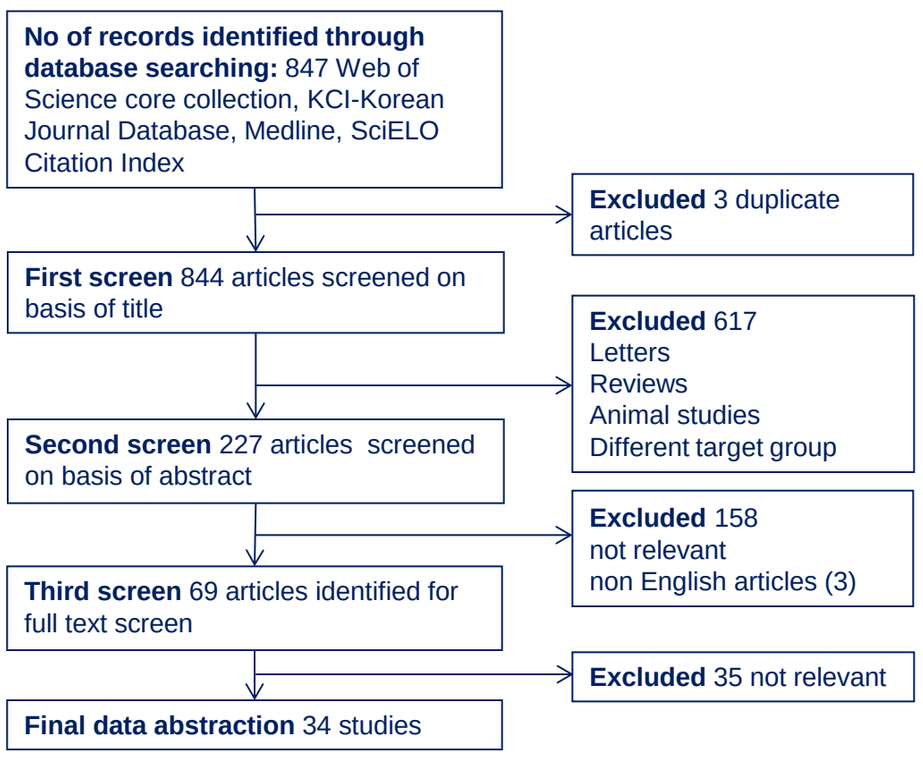

Figure 1: Search strategy and study selection through database searching in Web of Science.

Table 1: Comparing short –follow-up interval (≤ 28 days) with wide follow-up intervals (>28 days).

	Close follow-up	Wide follow-up
Total number observed	n= 488	n= 18.750
Stage of HIV		
chronic (%)	7 (53.8%)	8 (38.1%)
acute (%)	4 (30.8%)	5 (23.8%)
not reported (%)	2 (15.4%)	13 (61.9%)
Previous time on ART in month (mean/ SD)	15 ± 9.64	12.8 ± 10.5
Duration of treatment interruption in days (mean/SD)	19.67 ± 11.60	144 ± 133.15
Baseline CD4 cell count (mean/ SD)	378.57 ± 90.63	403.13 ± 139.60
Baseline VL (mean/ SD)	155.38 ± 169.93	277.27 ± 578.09
Follow-up routine during TI in days (mean/ SD)	9.31 ± 9.25	67.48 ± 43.09
Time (weeks) to recover CD4 after reinitiating ART mean/SD)	NR*	51.50 ± 54.45
Time (weeks) to undetectable VL after reinitiating ART (mean/SD)	16.43 ± 21.20	93.67± 48.78

*Not reported

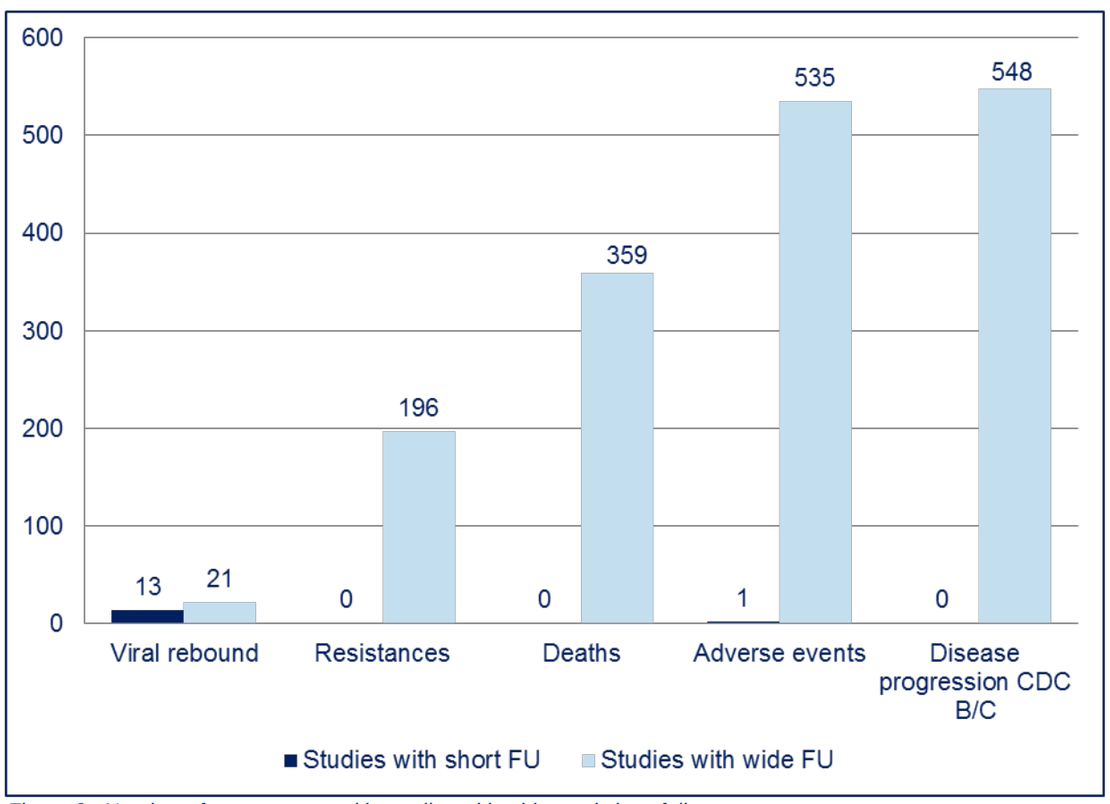

Figure 2: Number of cases reported in studies with wide- and close follow-up.

Conclusion

While large RCTs demonstrated detrimental effects of STIs on the health of HIV-infected patients, most had long follow-up intervals of up to six months. Small studies with short follow-up intervals and early treatment re-initiation did not show an increase of adverse effects. Resistances were only observed after repeated STI cycles or after 40 weeks of STI (Table 1). In summary, ATI may be a feasible strategy as part of HIV cure trials if patients undergo intense follow-up routines, including regular observation of CD4 and Viral load.

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