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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 (Figure1).

Results

We identified 847 potential studies investigating STI. 34 studies including 46,637 patients, mostly enrolled into randomized controlled trials (RCTs) or interventional trials, met the inclusion criteria. Sample sizes varied from nine to 5,472 patients among studies (median: 70.5). 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 varied from weekly to every two months. Patients experienced viral rebound (VL>50 copies/ml) for up to 1,018 days after STI. Four large trials with a follow-up interval (up to six months) and 4,881 patients under STI reported the development of resistances in 18 patients. Adverse events and death were observed in 285 and 298 respectively. Disease progression to CDC stage B or C was reported in 548 patients. In comparison, ten small studies, with follow-up intervals (up to 30 days) and 527 patients in total, reported resistances in 17 patients, but no adverse events or deaths were observed.

Important findings

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

	Close follow-up	Wide follow-up
Number of drug resistances in individuals under TI	17 (n= 68)	193 (n= 1.161)
Adverse events	n= 12	n= 489
Cases of death	n= 0	n= 359
Median time to a virological rebound (>50 copies/ml)	14 days	46,5 days
Median time to baseline CD4 level after re-initiation of ART	NR	51,5 days
Median time to undetectable VL after re-initiation of ART	5,9 weeks	87,1 weeks

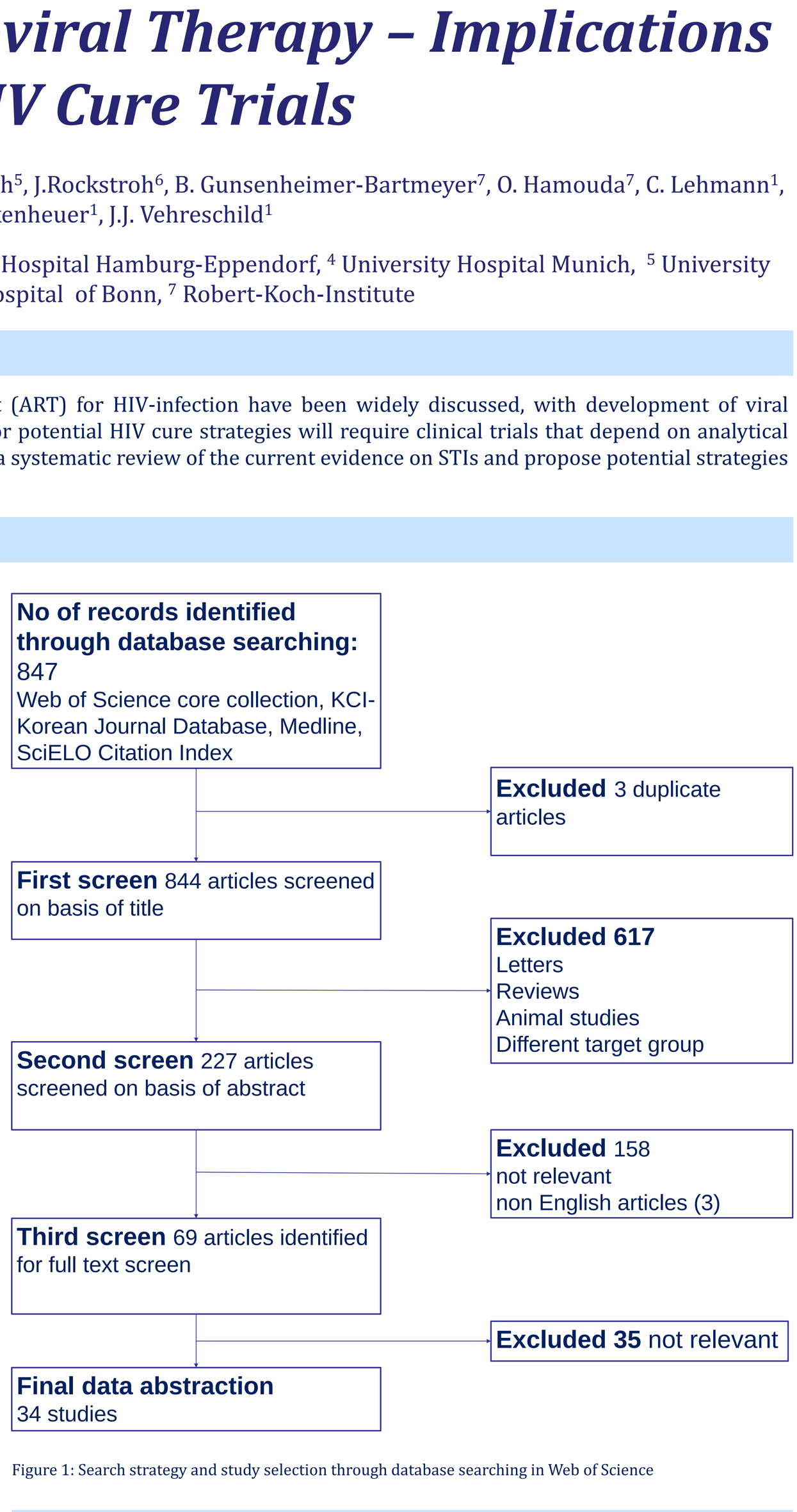

Figure 1: Search strategy and study selection through database searching in Web of Science

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. ATI may be a feasible strategy as part of HIV cure trials if patients undergo intense follow-up routines.

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