Differential Genotypic Evolution of HIV-1 Quasispecies in Cerebrospinal Fluid and Plasma: A Systematic Review

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**Supplementary methodology**

**Search strategy and inclusion**

We performed a systematic search in the PubMed database in January 2013 (Fig. 1) to investigate to what extent the CNS constitutes a distinct virological compartment by comparing host cell tropism and resistance associated mutations in relation to HIV RNA levels and neurological symptoms.

The first search included: HIV; ‘human immunodeficiency virus’ and aids. The second search: CSF; ‘cerebrospinal fluid’; CNS and ‘central nervous system’. The third search included: resistance, resistant, tropism, CXCR4 and CCR5. In the final search we combined these three searches to create an output of papers that overlapped in these three searches.

We included original research papers or abstracts of studies that compare resistance mutations or HIV-1 tropism in CSF with plasma or blood. The clinical studies could be cross-sectional studies, cohort studies, patient-control studies, or (non-) randomized controlled trials. We excluded studies not published in English. Hereafter, we used a systematic procedure to identify potentially relevant reports. At first, all titles that clearly were about topics other than comparing HIV-1 mutations or env characteristics in CSF and plasma were excluded (exclusion step 1). Secondly, we excluded the reports or abstracts if they described in vitro or postmortem studies only, or if only HIV RNA levels were compared and not mutations or envelop characteristics, unless they were relevant for background information (exclusion step 2). Subsequently, full-length papers were retrieved if they did not consist of abstracts only and screened for relevance (exclusion step 3). For all studies we evaluated the methods, number of patients included in the studies, and the number of patients with discordant resistance patterns. If only the numbers of mutations were included, but not the exact type, the study was not included for evaluation of discordant mutations. Additionally, we evaluated the patient population and drug characteristics. Only studies that used paired plasma and CSF samples were included and analyzed. If a report stated that the samples were taken more than seven days apart, pairs were excluded from our analysis. References of the included articles were screened to ensure all relevant reports for analysis or background information were included.

**Analysis**

All data was pooled and descriptive statistics were performed. Viral loads between CSF and plasma pairs were not normally distributed and as such compared with the nonparametric Wilcoxon matched-pairs signed-rank test. The Mann-Whitney U test was used to compare continuous variables between subjects assigned to certain categories (e.g. neurologically symptomatic) and categorical data by a Chi-square test. Correlations were determined with the Spearman’s rank correlation. A correlation coefficient (r) < 0.4 was considered low, between 0.4 and 0.7 moderate, and > 0.7 high. The search yielded 671 titles. After critical appraisal, 35 studies describing a total of 671 samples from 555 subjects could be included in this review (Fig. 1). Depending on the analysis, different numbers of paired samples and subjects were compared.