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T-cell receptor excision circles (TREC) and maintenance of long-term non-progression status in HIV-1 infection

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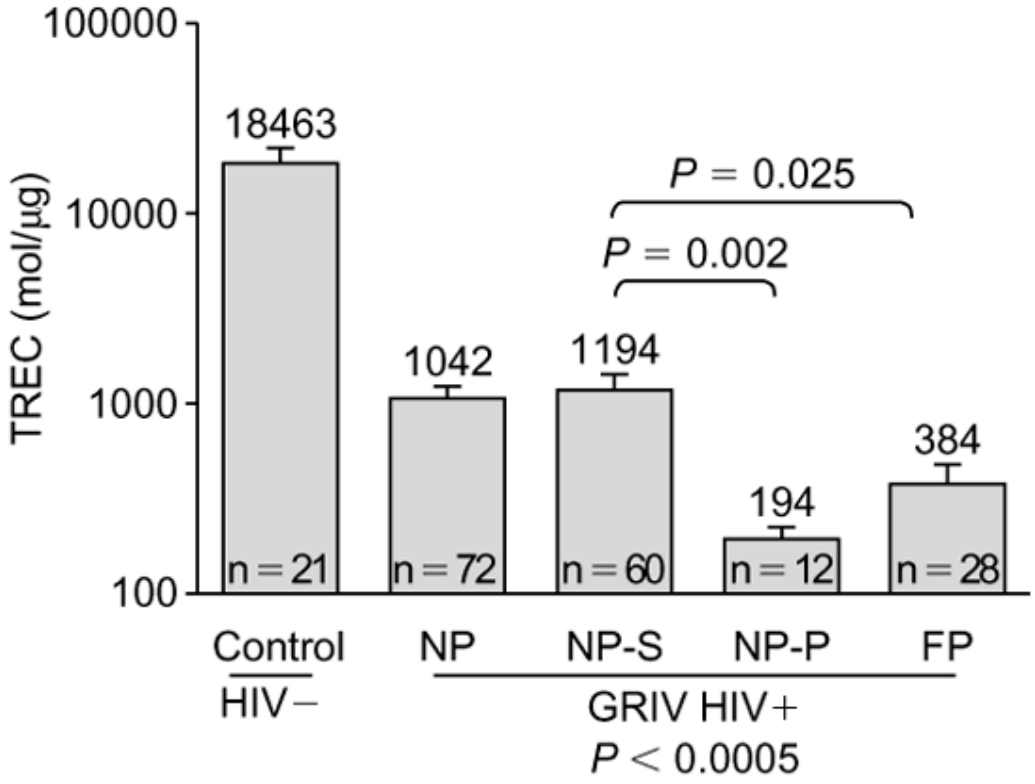
T-cell receptor excision circles (TREC) in peripheral blood mononuclear cells (PBMC) were evaluated in the Genetic Resistance to Human Immunodeficiency Virus cohort of HIV-1-seropositive non-progressors (NP). After a short follow-up, NP were sub-grouped as stable (NP-S), or with signs of disease progression (NP-P). Initial TREC were higher in NP-S compared to NP-P (*P* = 0.002), even after adjusting for CD4 and CD8 T-cell counts and viral load (*P* = 0.048), but not p24 antigenemia (*P* = 0.076). Higher initial TREC were 100% predictive of the maintenance of non-progression status during follow-up.

The development of quantitative competitive polymerase chain reaction (QC-PCR) assays to detect episomes from T-cell receptor (TCR) gene rearrangement [1] was originally described as a means of quantitating recent thymic emigrants [2]. Reduced T-cell receptor excision circles (TREC) in HIV-1 infection and their rebound with highly active antiretroviral therapy [2], however, reflect a balance between the production, proliferation, redistribution and elimination of circulating T cells that have recently undergone TCR rearrangement or few cell divisions since TCR rearrangement [2,3]. The decrease in TREC in HIV-1-infected adults is now thought largely to reflect cellular proliferation and death caused by viral immune activation [3]. It is also possible that reduced thymic output and increased proliferation are not mutually exclusive causes of the TREC decline in HIV infection [4,5].

Despite debate concerning the mechanism underlying the decrease in TREC in HIV-1 infection, the potential utility of TREC as a surrogate marker for evaluating the risk of disease progression and AIDS in HIV-1-infected individuals has been suggested [6,7]. In the studies described here, we measured TREC by QC-PCR [2] in the Genetic Resistance to Human Immunodeficiency Virus (GRIV) cohort, comprised solely of serum and peripheral blood mononuclear cell (PBMC) DNA samples from HIV-1-seropositive long-term non-progressors (NP) naive to antiretroviral therapy, and fast progressors (FP) [8]. On the basis of information obtained during a brief follow-up period (median 20 months), NP were sub-grouped into those maintaining non-progressor status and therefore stable (NP-S), and those showing signs of disease progression (NP-P). Initial TREC (prior to follow-up) were compared between the NP sub-groups and FP by analysis of variance (ANOVA) and by covariance (ANCOVA) with CD4 and CD8 T-cell counts, p24 antigenemia and viral load as covariates. *P* values are reported on an adjusted scale with significance set at α = 0.05 after Bonferroni's correction for multiple comparisons (SPSS 10.0; SPSS Inc., Chicago, IL, USA).

TREC were reduced in HIV-1-seropositive NP and FP compared to seronegative individuals (Fig. 1; $P < 0.0005$) as reported by others [2-4,9]. By ANOVA, initial TREC (before follow-up) were higher in NP-S (stable during subsequent follow-up) compared to both unstable NP-P ($P = 0.02$) and FP ($P = 0.025$), in agreement with a previous report correlating higher TREC with a decreased risk of progression [6]. TREC in PBMC have previously been demonstrated to correlate with CD4 and CD8 T-cell subsets, including naive subsets [10,11], and to correlate inversely with activation status [3,11]. To determine if the difference in TREC between NP-S and NP-P was secondary to differences in lymphocyte counts, TREC were compared after adjusting for CD4 and CD8 T-cell counts by ANCOVA. Adjusted TREC remained higher in NP-S relative to NP-P ($P = 0.023$); in contrast, TREC were no longer significantly different in FP. Presumably, reduced TREC in FP largely reflects lower CD4 T-cell counts, although this does not appear to be the main explanation for lower TREC in NP-P. Other confounding factors of TREC in FP include the effect of antiretroviral therapy [2,3] in some FP (but not NP), and the much shorter duration of infection compared with NP (< 3 versus > 8 years; NP median = 11 years) [8]. After including p24 antigenemia as a covariate in ANCOVA, the difference in TREC between NP-S and NP-P was no longer significant, although a trend was present ($P = 0.076$). However, the difference in TREC between NP-S and NP-P was significant using viral load as a covariate in ANCOVA ($P = 0.048$) instead of p24 antigenemia. The difference in TREC between NP-S and NP-P may be due to immune activation status [3], although other mechanisms may also contribute [4,5]. Several previously identified correlates of TREC were observed in NP-S, such as the duration of infection and CD4 T-cell counts [2,3]. TREC was inversely related to p24 antigenemia across the GRIV cohort as a whole. Median ages were similar for all groups.



NP sub-groups	High TREC	Low TREC	Total
NP-S	25*	35	60
NP-P	0	12	12
Total	25	47	72

Fig. 1. T-cell receptor excision circles in peripheral blood mononuclear cells from seronegative individuals and HIV-1-seropositive Genetic Resistance to Human Immunodeficiency Virus cohort non-progressors and fast progressors, and stable and unstable non-progressor sub-groups. T-cell receptor excision circles (TREC) were lower in all Genetic Resistance to Human Immunodeficiency Virus (GRIV) groups compared to seronegative controls. TREC were higher in stable non-progressors (NP-S) compared to non-progressors (NP) showing signs of disease progression (NP-P) and fast progressors (FP) by analysis of variance (ANOVA). *The predictive value of a higher initial TREC for the maintenance of non-progression status during subsequent follow-up was 100%.

Because higher TREC were associated with stable long-term non-progression in HIV-1 infection, the predictive value of initial TREC in the maintenance of non-progression status during subsequent follow-up was estimated. TREC above the lower 95% confidence limit for the mean of the NP group (634 mol/μg) were designated high, and those below were considered low (Fig. 1). High TREC in NP-S were treated as true positives; low TREC in NP-P were true negatives. The predictive value of higher TREC for the maintenance of long-term non-progression status during subsequent follow-up (median 20 months) was 100% (Fig. 1), comparable to higher CD4 T-cell count (89.2%), lower p24 antigenemia (89.5%) and viral load (90.5%). In contrast, the predictive value of lower TREC for progression was only 25.5%, comparable to CD4 T-cell count (26.4%), p24 antigenemia (22.7%) and viral load (21.7%). Although lower TREC did not rule out continued non-progression in NP, at least during the short follow-up period, longer prospective studies do appear to support the prognostic value of lower TREC for the risk of disease progression [6,7]; it is possible that more NP with lower TREC would be re-classified as unstable (NP-P) with a longer follow-up. A broad range of CD4 cell counts was observed for both higher TREC (460-1570 cells/μl) and lower TREC (510-1940 cells/μl) groups.

The GRIV cohort is a collection of serum and PBMC DNA samples established to identify immune responses and genetic polymorphisms associated with long-term non-progression in HIV-1 infection [8,12,13]. Unfortunately, because of the nature of the GRIV cohort, it is not possible to evaluate TREC in T-cell subsets or to adjust for differences in immune activation or proliferation using markers such as HLA-DR/CD38 or Ki67, respectively [10]. TREC in PBMC may not be as accurate a marker as TREC in T-cell subsets, as a result of the presence of varying percentages of non-T cells. Similarly, TREC are substantially influenced by immune activation and proliferation [3]. We were able, however, to adjust for CD4 and CD8 T-cell counts, p24 antigenemia and viral load by ANCOVA. The difference in TREC between stable NP-S and unstable NP-P is not solely caused by differences in CD4 and CD8 T-cell counts, although it may primarily reflect differences in immune activation status and proliferation. Regardless of the mechanism(s) responsible for the decline of TREC in HIV-1 infection, TREC in PBMC may be a useful surrogate marker for

predicting the likelihood of continued clinical stability.

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