Methods: A total of 161 HIV-infected asymptomatic patients with CD4 cell count $> 500 \times 10^6$ cells/l and viral load $> 10 \,000$ copies/ml were randomly assigned to one of five treatment groups: no treatment, twice daily zidovudine and thrice daily zalcitabine (ZDV-ddC), twice daily zidovudine and didanosine (ZDV-ddI), twice daily stavudine and didanosine (D4T-ddI), or a twice daily three-drug regimen with stavudine and lamivudine and ritonavir. The endpoints were progression to $< 350 \times 10^6$ cells/l CD4 cells, to $< 500 \times 10^6$ cells/l with either two Centers for Disease Control class B symptoms or an increase of viral load $> 0.5 \log_{10}$ copies/ml above baseline, or to AIDS or death. In various substudies, the lymphoid tissue and cerebrospinal fluid viral load, development of genotypic resistance, proliferative responses to mitogens and cytomegalovirus, and HIV-1 specific antigens and other immunophenotypic markers were also analysed.

Results: Progression rates to study endpoints within 1 year were greater in the control group (31%) than in all groups receiving antiretroviral therapy pooled together (5%; estimated hazard ratio 7.41; 95% confidence interval 5.72-74.55; $P < 0.001$). The peak mean viral load decrease was greater in the three-drug group when compared with any of the three groups with a two-drug regimen (2.32, 1.65, 1.72 and 1.84, respectively; $P \leq 0.001$). At 1 year, viral load remained below 20 copies/ml in 30 out of 33 patients in the three-drug group (91%) and in only eight out of 94 patients (9%) in two-drug groups ($P = 0.001$). The peak mean increase in CD4 cells was also greater in the three-drug group than in the double treatment arms (259 versus 85, 144 and 145 $\times 10^6$ cells/l, respectively; $P = 0.001$). By comparison, 36% of patients in the three-drug group regimen had to change the therapy as a result of adverse events. Substudies were performed in 60 patients recruited at two sites. Tonsillar tissue HIV RNA was measured in seven patients (two in the two-drug groups and five in the three-drug group) in whom plasma HIV RNA was $< 20$ copies/ml at 1 year. It was 15 151 and 133 333 copies/mg tissue in the two patients from the two-drug group, $< 40$ copies/mg tissue in four patients in the three-drug group, and 485 copies/mg in one patient in the three-drug group. At 1 year there was a mean increase of 4.21 $\pm 2.94$% in CD8+CD38+ cells in the control group and a decrease of 9.48 $\pm 3.36$% in the two-drug groups ($P = 0.01$), and 19.87 $\pm 3.64$ in the three-drug group ($P = 0.001$ and $P = 0.05$, for comparisons with control group and two-drug groups, respectively). Although proliferative responses to cytomegalovirus antigens were significantly greater in those receiving antiretroviral therapy, response to HIV-1 p24 antigen was not detected in any patient in either treatment group.

Conclusions: This study supports the recommendation to start antiretroviral therapy with a three-drug combination during very early stages of HIV-1 disease, at least if viral load is above a cut-off point (10,000 copies/ml in our study). The risk of progression was sevenfold higher in non-treated patients at 8 months of follow-up. Some immune system parameters improved toward normal values after 1 year of antiretroviral therapy, but the proliferative response of CD4 T lymphocytes against the p24 HIV-1 antigen was not recovered. Therapeutic approaches with more potent, better-tolerated and more convenient regimens will increasingly favour early intervention with antiretroviral therapy.

HIV-1 specific cytolytic T-lymphocyte activity correlates with lower viral load, higher CD4 count, and CD8+CD38-DR-phenotype: comparison of statistical methods for measurement

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ABSTRACT

Objectives: The objective of this study was to use novel statistical methods to determine the correlation between HIV-1-specific cytolytic T-lymphocyte (CTL) activity and HIV-1 plasma viral load, in a blinded study of HIV-infected patients at various stages of clinical disease.

Methods: Peripheral blood mononuclear cells (PBMC) were collected and stored at enrollment and 2 weeks later, from 15 HIV-infected individuals who were receiving stable antiretroviral therapy for the previous 6 weeks and during the study period. HIV-1-specific CTL activity was measured using an antigen-specific PBMC in vitro stimulation method. Measurements of plasma viral load, as well as CD4+ and CD8+ T