OBJECTIVES: To determine the efficacy of isoniazid 300 mg daily for 6 months in the prevention of tuberculosis in HIV-1-infected adults and to determine whether tuberculosis preventive therapy prolongs survival in HIV-1-infected adults. DESIGN AND SETTING: Randomized, double-blind, placebo-controlled trial in Nairobi, Kenya. SUBJECTS: Six hundred and eighty-four HIV-1-infected adults. MAIN OUTCOME MEASURES: Development of tuberculosis and death. RESULTS: Three hundred and forty-two subjects received isoniazid and 342 received placebo. The median CD4 lymphocyte counts at enrolment were 322 and 346 x 10(6)/l in the isoniazid and placebo groups, respectively. The overall median follow-up from enrolment was 1.83 years (range, 0-3.4 years). The incidence of tuberculosis in the isoniazid group was 4.29 per 100 person-years (PY) of observation [95% confidence interval (CI) 2.78-6.33] and 3.86 per 100 PY of observation (95% CI, 2.45-5.79) in the placebo group, giving an adjusted rate ratio for isoniazid versus placebo of 0.92 (95% CI, 0.49-1.71). The adjusted rate ratio for tuberculosis for isoniazid versus placebo for tuberculin skin test (TST)-positive subjects was 0.60 (95% CI, 0.23-1.60) and for the TST-negative subjects, 1.23 (95% CI, 0.55-2.76). The overall adjusted mortality rate ratio for isoniazid versus placebo was 1.18 (95% CI, 0.79-1.75). Stratifying by TST reactivity gave an adjusted mortality rate ratio in those who were TST-positive of 0.33 (95% CI, 0.09-1.23) and for TST-negative subjects, 1.39 (95% CI, 0.90-2.12). CONCLUSIONS: Overall there was no statistically significant protective effect of daily isoniazid for 6 months in the prevention of tuberculosis. In the TST-positive subjects, where reactivation is likely to be the more important pathogenetic mechanism, there was some protection and some reduction in mortality, although this was not statistically significant. The small number of individuals in this subgroup made the power to detect a statistically significant difference in this subgroup low. Other influences that may have diluted the efficacy of isoniazid include a high rate of transmission of new infection and rapid progression to disease or insufficient duration of isoniazid in subjects with relatively advanced immunosuppression. The rate of drug resistance observed in subjects who received isoniazid and subsequently developed tuberculosis was low.