HIV-1 is grouped phylogenetically into clades, which may impact rates of HIV-1 disease progression. Clade D infection in particular has been shown to be more pathogenic. Here we confirm in a Nairobi-based prospective female sex worker cohort (1985–2004) that Clade D (n = 54) is associated with a more rapid CD4 decline than clade A1 (n = 150, 20.6% vs 13.4% decline per year, 1.53-fold increase, p = 0.015). This was independent of "protective" HLA and country of origin (p = 0.053), which in turn were also independent predictors of the rate of CD4 decline (p = 0.026 and 0.005, respectively). These data confirm that clade D is more pathogenic than clade A1. The precise reason for this difference is currently unclear, and requires further study. This is first study to demonstrate difference in HIV-1 disease progression between clades while controlling for protective HLA alleles.