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The prospective significance of HIV-specific cytotoxic T lymphocyte (CTL) responses in highly exposed, persistently seronegative populations is unknown. In 1996-1997 we screened for CTL responses against HIV clade B Env in 39 recently enrolled Kenyan female sex workers, and followed these women prospectively. Annual HIV incidence was 5.8%. CTL were independently associated with age and recent HIV-1 exposure, but were not prospectively associated with protection in a multivariable model that included HIV-1 exposure and duration of sex work.