

Phase II Trial of Pharmacological HIV-1 Prevention

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Project Description: We propose to carry out an “accelerated” evaluation of chemoprophylaxis for the prevention of HIV-1 infection in Cambodia, a region that is suffering from the explosive spread of HIV-1. Current data show that the HIV-1 epidemic in Cambodia is the most serious in Southeast Asia. To address the extraordinary HIV-1 prevention needs in this country, we propose a novel prevention strategy based on chemoprophylaxis using an antiretroviral agent that has been recently approved for human use. Funds are requested in this application for a vanguard study of 200 sex workers to confirm the safety of the prevention treatment in HIV-1 uninfected Asian women, to determine the acceptability of a randomized placebo controlled trial, and to generate preliminary data on HIV-1 incidence, trial retention rates, and treatment efficacy.

The primary goal of this proposal is to conduct a Phase I/II trial evaluating the safety, tolerability and efficacy of chemoprophylactic therapy (once a day *Tenofovir*) to prevent HIV-1 acquisition in high-risk uninfected female sex workers. The evaluation will involve a series of carefully monitored randomized-placebo controlled studies in three phases: 1) a short term safety and acceptability phase involving the first 100 subjects randomized to each arm (50 in each group); 2) a one year extension of the study to determine estimates of incidence and retention in 200 women total (100 in each group); and 3) a phase III efficacy trial with HIV-1 incidence as the endpoint. In this proposal we request funds for to carry out the accelerated evaluation combining phases I and II.

Significance: Cambodia is ideal for this study at this time because of the recent explosive spread of HIV-1. The selected antiretroviral agent is FDA approved for human use, allows once-a-day dosing, is well tolerated for several years, and is active against most drug resistant HIV-1 strains. The study will also obtain preliminary information regarding HIV-1 incidence and drug efficacy that are required for planning a phase III trial. We estimate that 200 women treated for up to 24 months are sufficient to evaluate safety and acceptability, and may demonstrate efficacy if the prophylactic effect of the drug and the control group HIV-1 incidence prove to be comparable to estimates from non-human primate studies and Cambodian serosurveillance. This staged approach to prevention research is optimized to generate efficacy information in short time frames through use of pilot randomized studies in groups who suffer explosive HIV-1 spread before long term cohorts can be established. Pilot studies that confirm high incidence and acceptable interventions will be expanded into closely monitored efficacy trials. These studies ultimately aim to break the epidemic cycle of HIV-1 by protecting young women, which may also spare their future children and sexual partners.