A010: Phase I, dose-escalation clinical trial to evaluate the safety and immunogenicity of a replication-defective HIV-1 vaccine (HIVAX) in HIV-1 infected subjects receiving highly active antiretroviral therapy

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Overview

- Background
  - Over 50 million worldwide will be infected with HIV by 2010
  - Highly active antiretroviral therapy (HAART) results in substantial declines in mortality and morbidity and currently is a life long treatment
  - HAART can be associated with long-term toxicities including liver dysfunction and metabolic abnormities
  - Viral resistance continues to be a challenge
- Need for novel effective alternative therapies remains
- An important avenue of investigation has been immune based therapy such as therapeutic HIV vaccines in order to improve immune control of viral replication

Immunologic Strategy

- Importance of CD8 cytotoxic T lymphocytes (CTL) & CD4 T cell responses in containing HIV replication is well appreciated.
- In contrast to robust CD8 CTL responses, HIV specific CD4 T cell responses are weak to absent
- HAART in acute HIV infection can preserve HIV-1 specific CD4 response and a subset have maintained virologic control following therapy
- SIV models have reported STI augmentation of immune responses and improved viral control following treatment
- Vaccine strategies to maintain a large T cell memory pool for long lasting immunity remains.

Proposed vaccine: HIVAX

- Replication-defective HIV-1 pseudotyped with VSV-G to present HIV antigens endogenously in vaccine recipients
- A unique property is that the proposed vaccine can only initiate single cycle infections, allowing prolonged antigen presentation
- Preclinical studies were evaluated in rhesus monkeys and strong cellular and humoral immune responses were seen

Rhesus Monkey Model Summary

- No RCL in vaccinated monkeys.
- Replication defective vaccine is safe.
- Vaccine elicits long-lasting immune responses.
- Protective immunity after one year vaccination.
- Immune responses can be boosted with same vaccine.
- Protection is associated with magnitude of T cell response after heterologous challenge.

Study Schema

- Study design: Randomized, double-blind placebo-controlled dose escalation study evaluating two doses of HIVAX followed by a 12 week antiretroviral treatment interruption among vaccine recipients
- Population: chronic HIV infection on stable HAART with a CD4 cell count > 500 and HIV RNA <50
- Duration: 24 week vaccination phase followed by 12 wk antiretroviral therapy interruption and 12 wk follow up
- Sample size: 30 subjects (15 per dose cohort)
- Regimen: Vaccination at weeks 0, 8 and 16 with brief pause before and after vaccination. Sequential dosing cohorts of 10^8 and 10^9 transduction units

Study Evaluations

- Vaccination Phase:
  - Clinical assessment and laboratory evaluation at screening, entry and wks 0, 4, 8, 12, 16, 20 and 24
- Antiretroviral treatment interruption Phase:
  - Clinical assessment and laboratory evaluation monthly through week 48

Study Hypothesis

- Replication-defective HIV-1 vaccine (HIVAX) attenuated by multiple deletions of the *pol*, *env*, *vif* and *nef* genes is safe and
- immonogenetic in subjects with chronic HIV infection and sustained viral suppression on HAART

- preliminary proof of concept that vaccination with HIVAX will improve immune control of viral replication following a 12 week antiretroviral treatment interruption

Study Objectives

- Primary Objective:
  - To determine the safety of two doses (10^8 and 10^9) of the study vaccine (HIVAX)
  - Identify early indication of immunogenicity
    - Magnitude of ELISpot INF-γ response to HIV-gag and tat/rev peptide pools
- Secondary Objectives:
  - To further evaluate immunogenicity
    - CD4/CD8 T cell proliferative cell responses
    - HIV-1 specific responses (polyfunctional CD4 and CD8 cells)
  - To gain insight into virologic control following a brief antiretroviral therapy treatment interruptions
    - Change in viral setpoint from nadir value

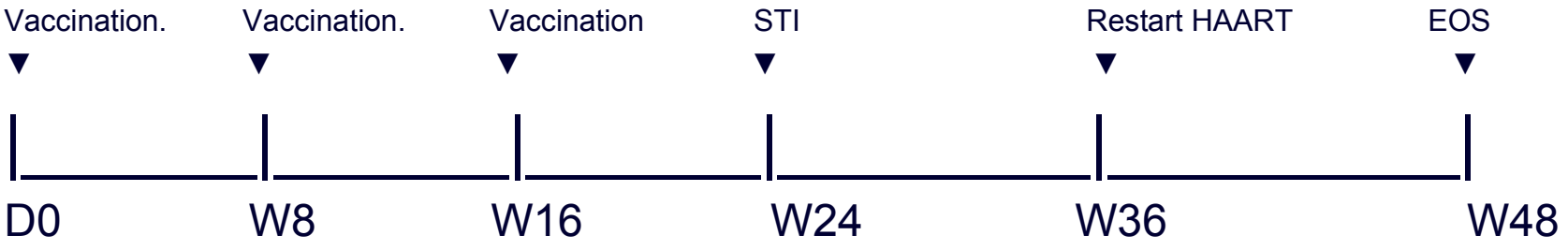
Dose escalation study design

- Two dose levels (10^8 and 10^9)
- Dose cohort 1 (lower dose, 10^8)
  - 10 vaccine/5 placebo subjects
  - dose limiting toxicity (one ≥ grade 3 toxicity)
  - dose escalation if no ≥ grade 3 toxicity occurs
- Dose cohort 2 (higher dose, 10^9)
  - 10 vaccine/5 placebo subjects
  - dose limiting toxicity will result in termination of further dosing and enrollments
- Maximum Tolerated Dose may not be defined if no grade 3 or greater toxicity seen
  - Dose selection with dependent on immune response
- Over site: CFAR Safety Monitoring Committee

Overview of study

Vaccination Phase
Placebo-Controlled

Antiretroviral treatment interruption Phase
Vaccine recipients



ART Restart guidelines

- CD4 cell count <400 or 50% decrease from baseline on two consecutive occasions within one week
- RNA > 2.5 fold increase above nadir value on two consecutive occasion within one week
- Development of any HIV/AIDS-defining illness.

Study Inclusion Criteria

- Chronic HIV infection on stable HAART for ≥ 12 months
- CD4 > 500 cells and HIV RNA < 50 copies/ml for 6 months
- Stable hematologic/chemistry laboratory tests
- Men and women ≥ 18 years of age

Study Exclusion Criteria

- Prior AIDS defining illness
- Nadir CD4 cell < 250
- Prior documented virologic failure on HAART
- HBsAg+, HCV, RPR+,
- No prior chemotherapy and no immunosuppressive or investigational agents with 90 days of entry
- Vaccination within 30 days of entry
  - Flu vaccination within 2 weeks of entry
- Any prior HIV vaccine
- Pregnancy and breastfeeding

Conclusions

- Rhesus monkey studies demonstrate that this replication defective lentivirus vaccine is safe and immunogenic.
- Phase I study is designed in as a rapid proof of concept model to assess safety as well as immunogenicity and impact on viral replication