

**A Phase I Randomized, Double-Blind, Placebo-Controlled Study of a Multi-Antigen DNA Vaccine Prime, rVSV Booster Vaccine in HIV-Infected Patients Who Began Antiretroviral Therapy During Acute/Early Infection (ClinicalTrials.gov Identifier: NCT01859325)**

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Laboratory of Immunoregulation/NIAID

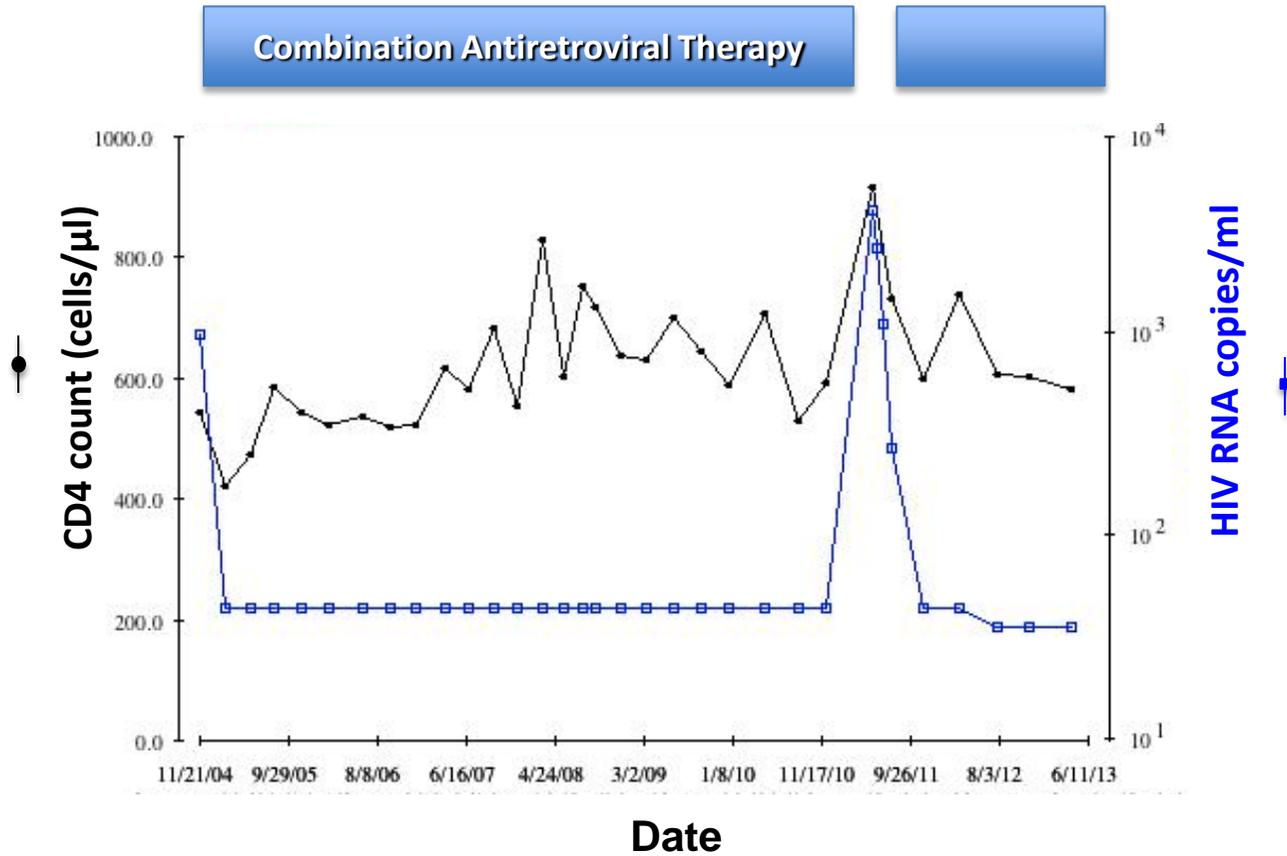
**Investigational New Drug (IND)#** 15459

**Study Sponsor:** NIAID

**Study Site:** NIH Clinical Center

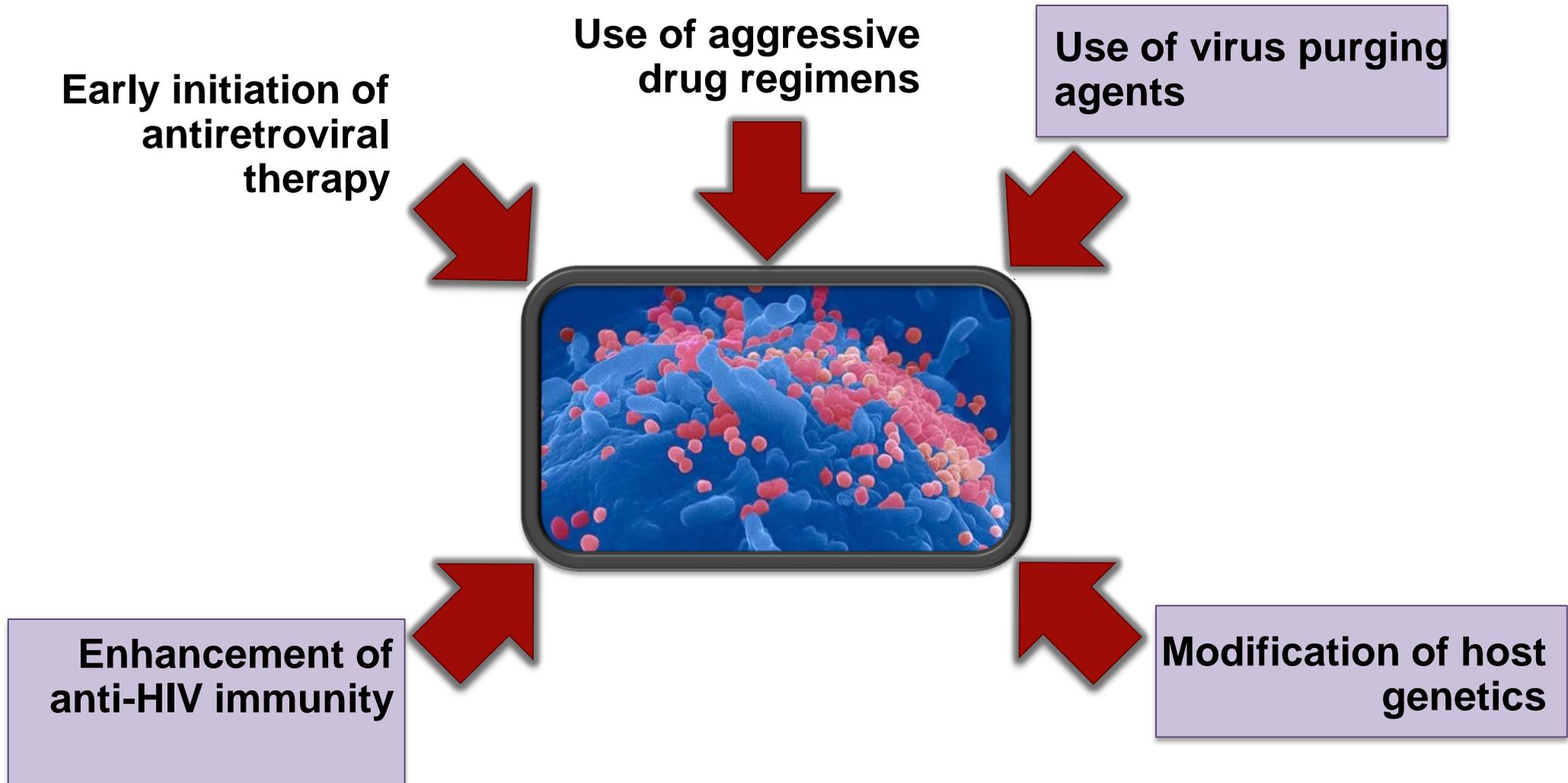
**Pharmaceutical Support :** Profectus Biosciences, Inc.  
Ichor Medical Systems

# Typical Course of Treated HIV Infection

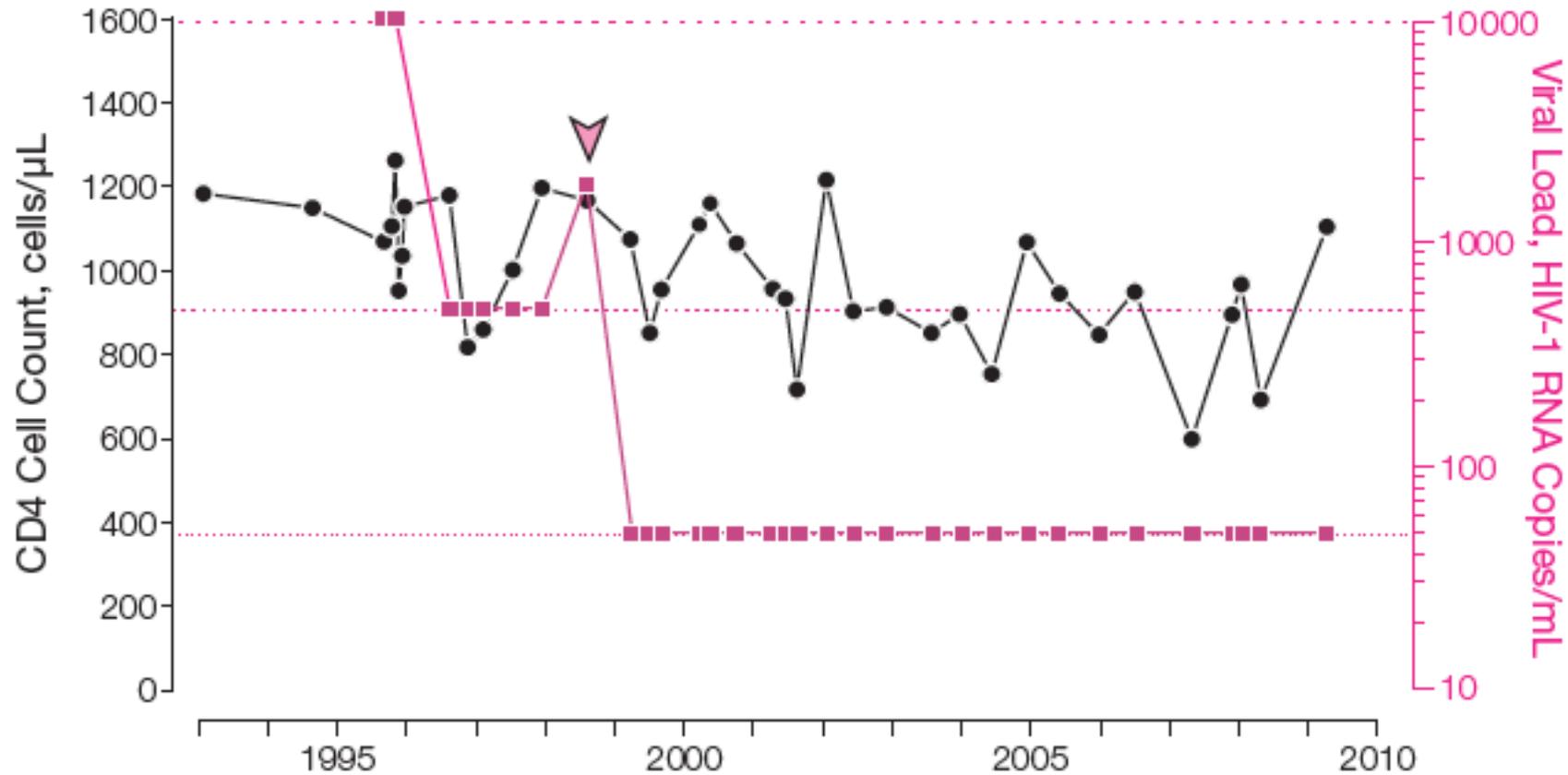


# Potential Strategies for Eradication or Functional Control of HIV

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# Immunologic Control of HIV Infection without cART (“Long-Term Non-progressor”)



# Therapeutic Vaccination as a Strategy for Achieving Immunologic Control of HIV Infection

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## ■ Target

HIV-infected CD4<sup>+</sup> T cells

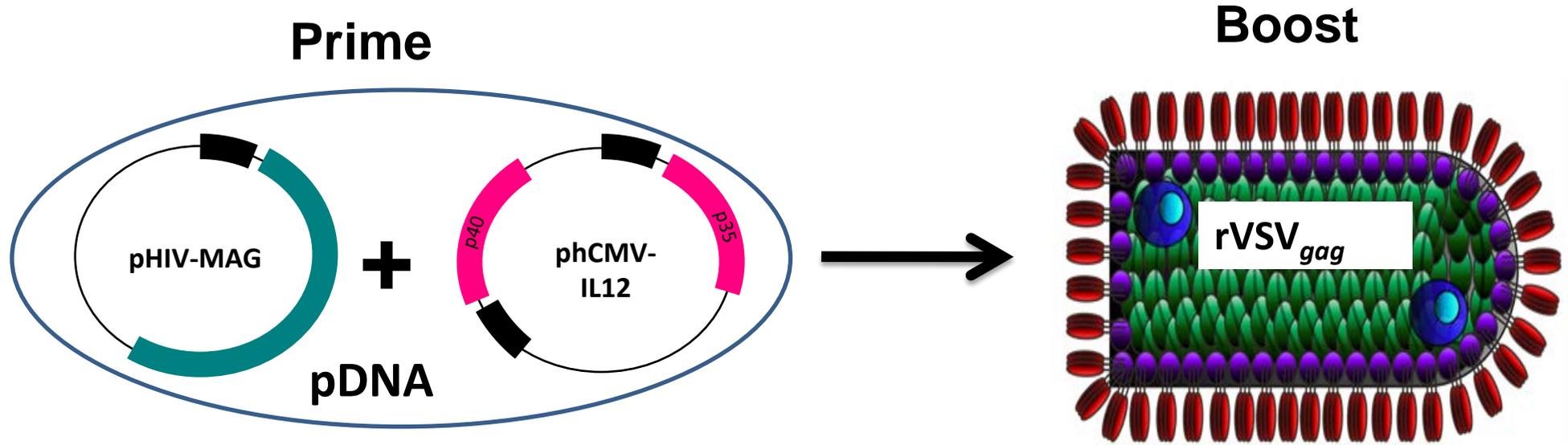
## ■ Mode of action

CTL-mediated killing of infected CD4<sup>+</sup> T cells upon recognition of viral antigen

## ■ Challenges

1. Ineffectiveness on the persistent viral reservoir
2. Limited availability of immunogenic human-tested vaccines
3. Low efficacy in infected individuals with compromised immune system

# Profectus Vaccine Strategy



DNA Vaccine Delivery by  
*in vivo* Electroporation

- WT virus is a weak pathogen
- Replicates in the cytoplasm; does not integrate into host DNA
- Does not undergo re-assortment or recombination
- Extremely low seroprevalence in general population

# Profectus Clinical Trials



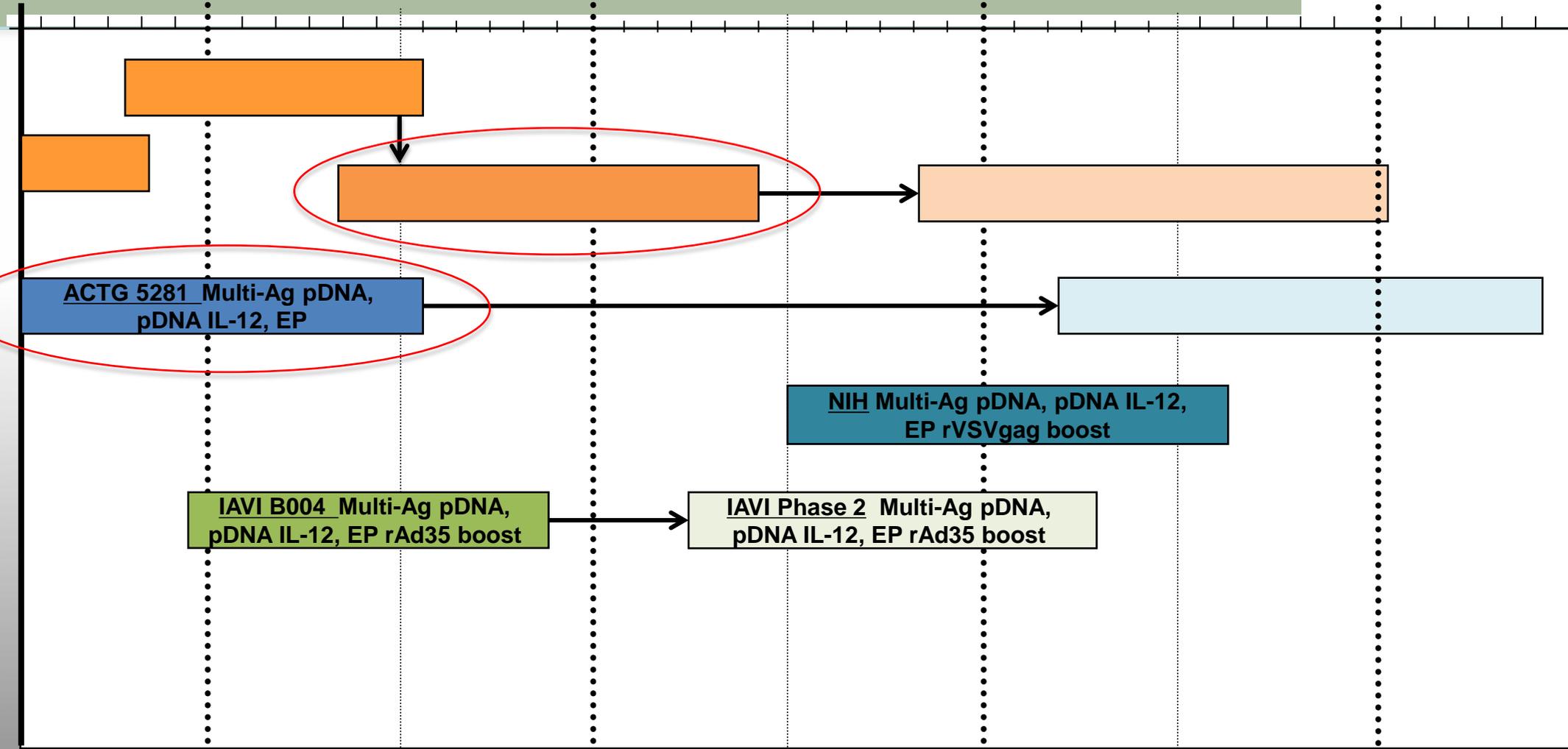
Profectus BioSciences, Inc.  
Jan 2015

Jan 2012

Jan 2013

Jan 2014

Jan 2015



ACTG Studies



HVTN Studies



IAVI Studies



NIH Intramural Study

# Therapeutic Vaccination as a Strategy for Achieving Immunologic Control of HIV Infection

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## ■ Target

HIV-infected CD4<sup>+</sup> T cells

## ■ Mode of action

CTL-mediated killing of infected CD4<sup>+</sup> T cells upon recognition of viral antigen

## ■ Challenges

1. Ineffectiveness on the latent viral reservoir
2. Limited availability of immunogenic human-tested vaccines
3. Low efficacy in infected individuals with compromised immune system

# Randomized, Double-Blind, Placebo-Controlled Study of a Multi-Antigen DNA Vaccine Prime, rVSV Booster Vaccine in HIV-Infected Patients Who Began Antiretroviral Therapy During Acute/Early Infection

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## Key Inclusion Criteria:

1. Institution of cART within 12 weeks of being diagnosed with acute or early HIV-1 infection.
2. Documentation of continuous cART treatment with suppression of plasma viremia for >1 year

## Key Exclusion Criteria

1. Co-infection with HBV or HCV
2. Changes in cART regimen due to virologic breakthrough

# Randomized, Double-Blind, Placebo-Controlled Study of a Multi-Antigen DNA Vaccine Prime, rVSV Booster Vaccine in HIV-Infected Patients Who Began Antiretroviral Therapy During Acute/Early Infection

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## **Primary Objective:**

To evaluate safety and tolerability of the study vaccines in subjects who began cART during acute or early HIV-1 infection.

## **Secondary Objective:**

To evaluate the efficacy of the study vaccines as determined by its effect on rebound viremia following analytical treatment interruption (ATI).

## **Exploratory Objectives:**

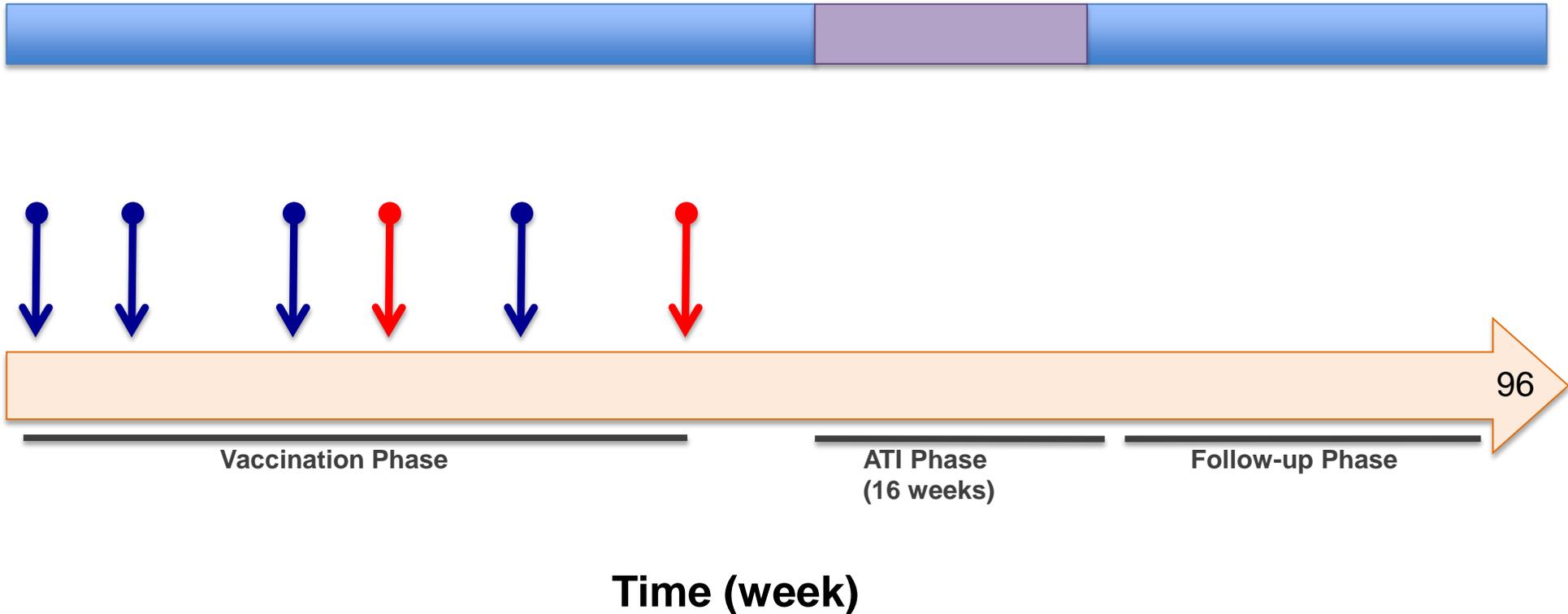
1. To assess the effect of the study vaccines on the rate of decay of the HIV-infected, CD4+ T cell reservoir.
2. To determine the immunogenicity of the study vaccines.

# Vaccination Regimen

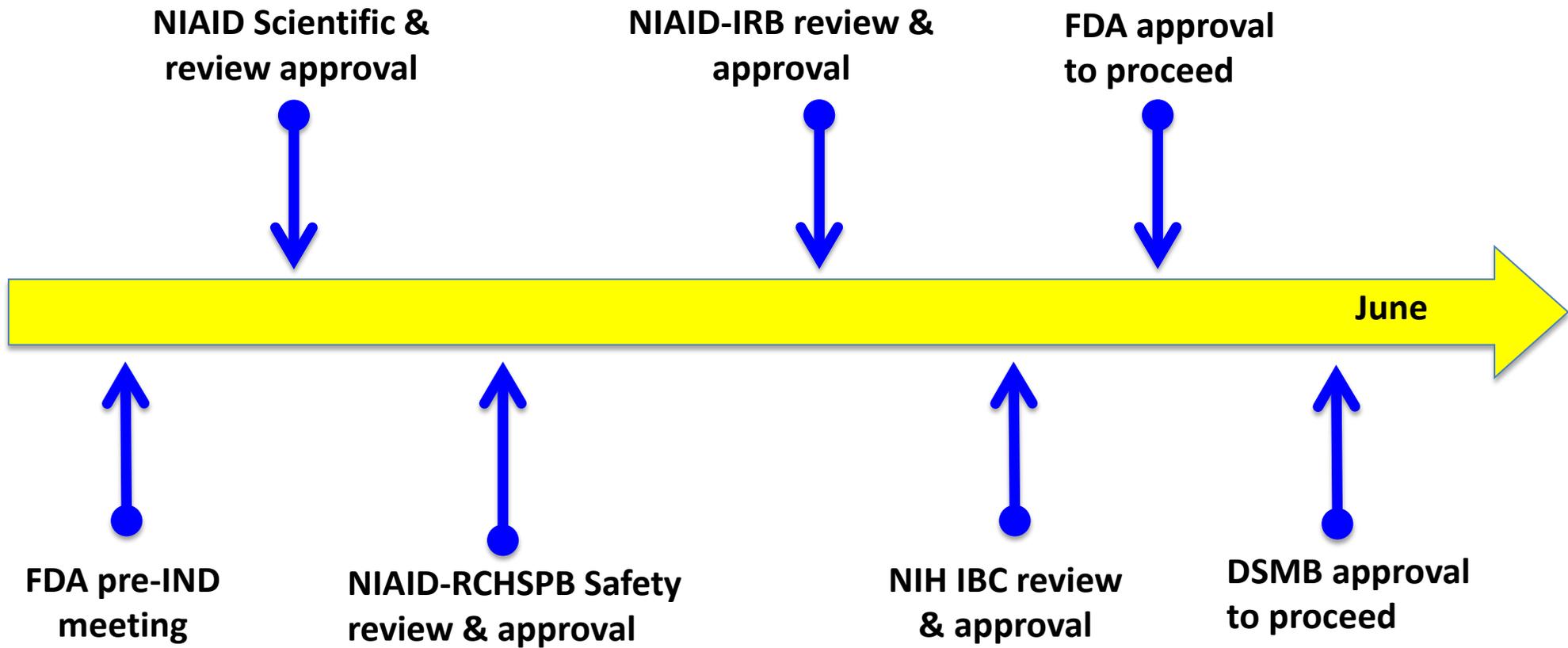
N=30

Initiated ART during acute/early phase of infection

Randomized 1:1 Vaccine or placebo



# NIAID HIV-MAG pDNA/ rVSV Therapeutic Vaccine Trial: Regulatory Review Time Line

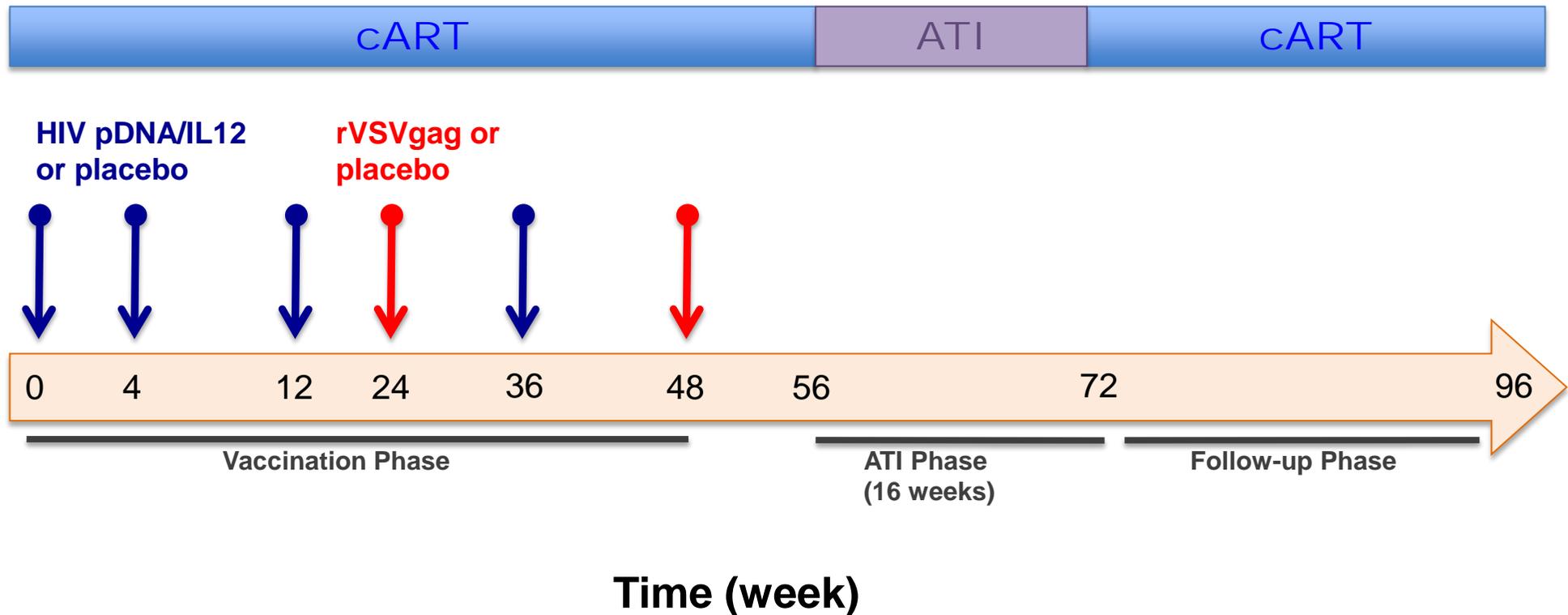


# Vaccination Regimen

N=30

Initiated ART during acute/early phase of infection

Randomized 1:1 Vaccine or placebo



# Analytical Treatment Interruption (ATI)

## Potential Risks

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### ■ Development of drug resistance

- SPARTAC trial (*N Engl J Med*, 2013)
  - no difference between standard of care and treatment interruption arms in either the rate of resistance mutations (1.6% in both arms) or virologic failure after starting/restarting cART

### ■ Development of AIDS-defining conditions

# Development of AIDS-Defining Conditions in Randomized Trials of ATI in Subjects Treated During Early HIV Infection

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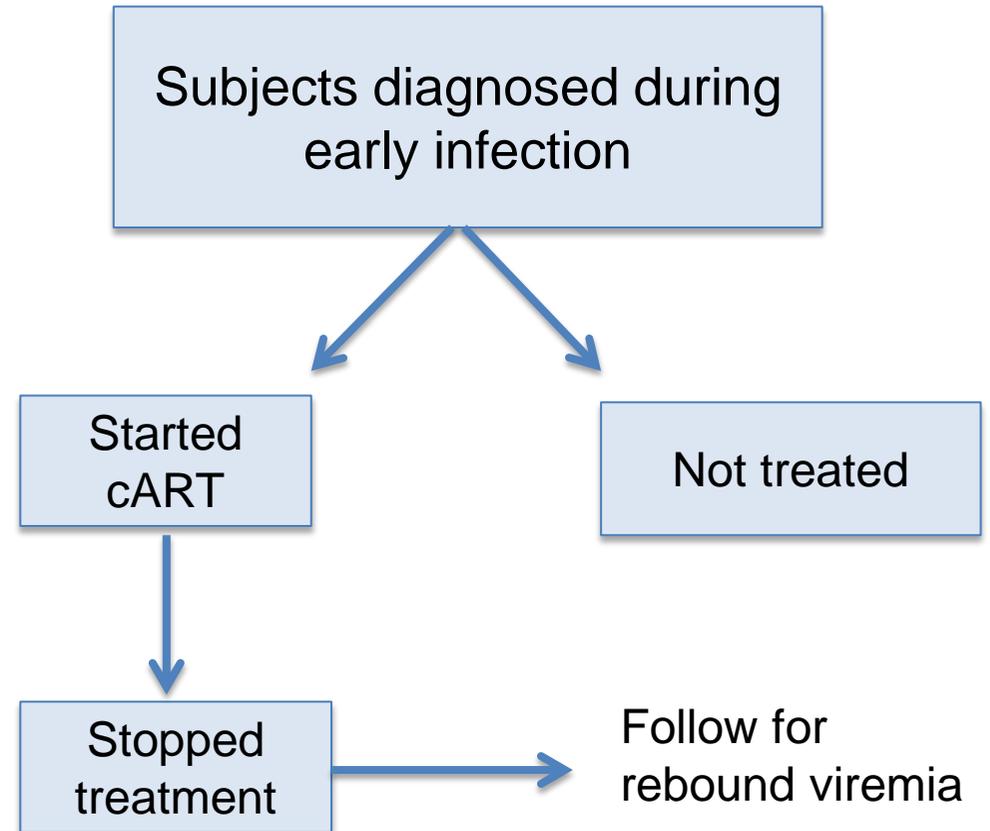
Trial	N with ATI	ATI Duration (median)	Progression to AIDS	Monitoring Frequency (CD4 counts)
ACTG 371	73	24 weeks	0	Every 4 weeks
<b>ACTG 5187</b>	20	40 weeks	0	Every 2 weeks
ACTG 5217	39	60 weeks	0	Every 4 weeks
<b>ANRS 095</b>	39	Serial 12 week	0	Not stated
Primo-SHM	78	3 years	4 (5%)*	monthly
SPARTAC	243	4 years	13 (5%)	Every 2-3 months

\* Occurred > 16 weeks into ATI at CD4 counts <350 cells/ $\mu$ l

# Control of Plasma Viremia After Treatment Interruption in Two Observational Cohorts Starting cART During Early HIV Infection “Post-treatment controllers”

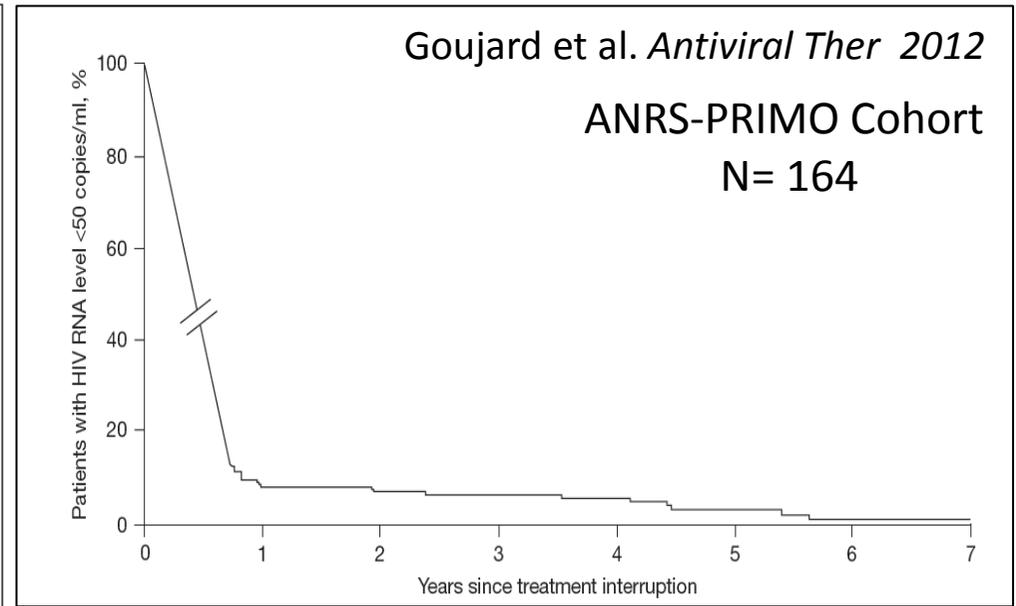
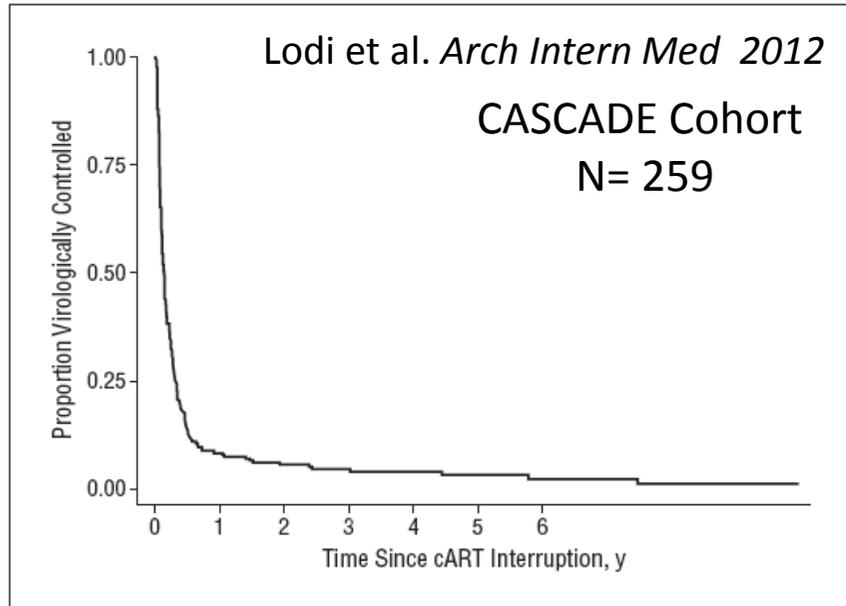
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- CASCADE Cohort  
N= 259  
Lodi et al. *Arch Intern Med* 2012
- ANRS-PRIMO Cohort  
N= 164  
Goujard et al. *Antiviral Ther* 2012



# Control of Plasma Viremia After Treatment Interruption in Two Observational Cohorts Starting cART During Early HIV Infection “Post-treatment controllers”

% with virologic suppression



Time since treatment interruption (years)

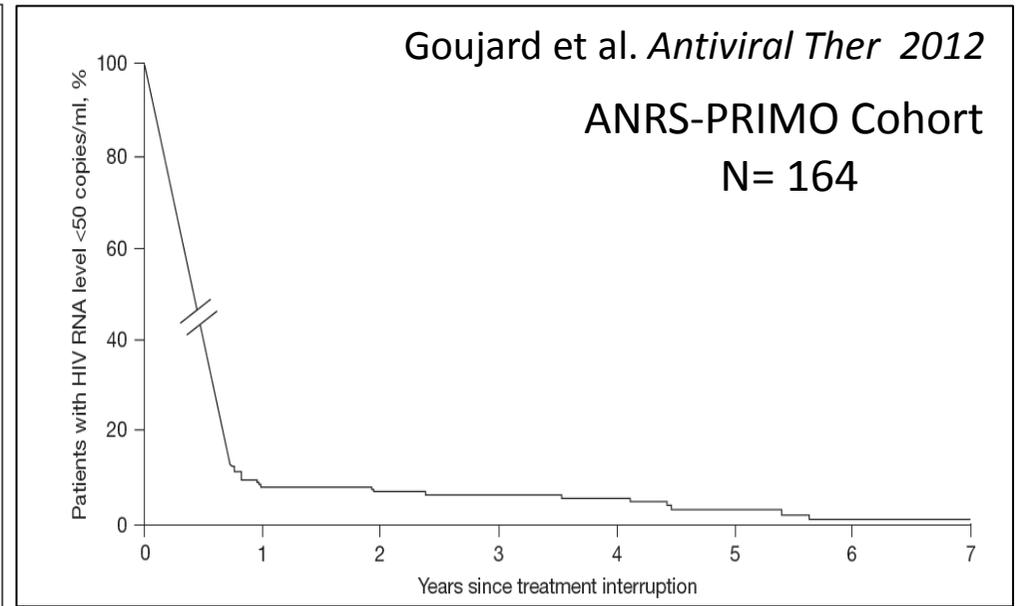
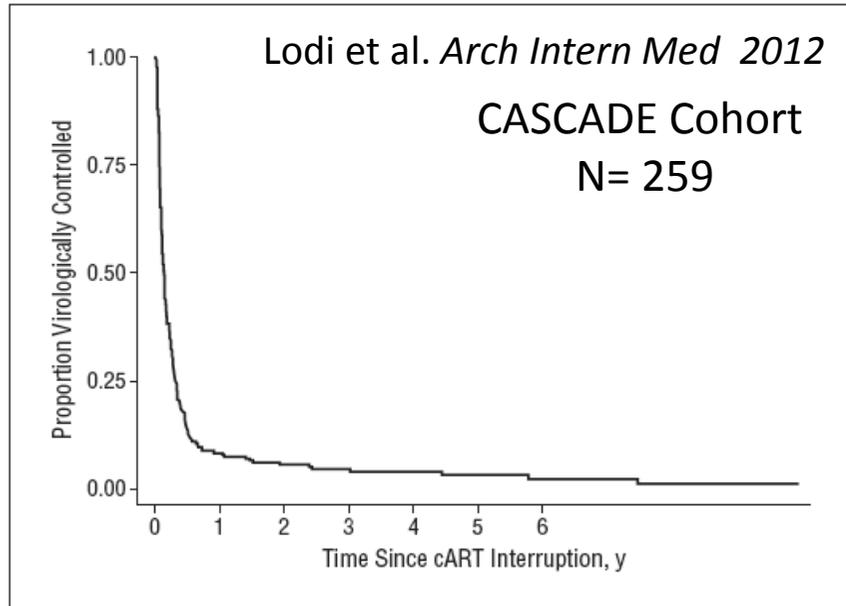
# Possible Long-Term Consequences of 16 week ATI in Individuals Who Started cART During Early Infection

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- Possibly impair “post-treatment control” of viremia by interrupting treatment too soon.
  - Only a risk if there is a correlation between the duration of cART prior to treatment interruption and post-treatment control

# Control of Plasma Viremia After Treatment Interruption in Two Observational Cohorts Starting cART During Early HIV Infection “Post-treatment controllers”

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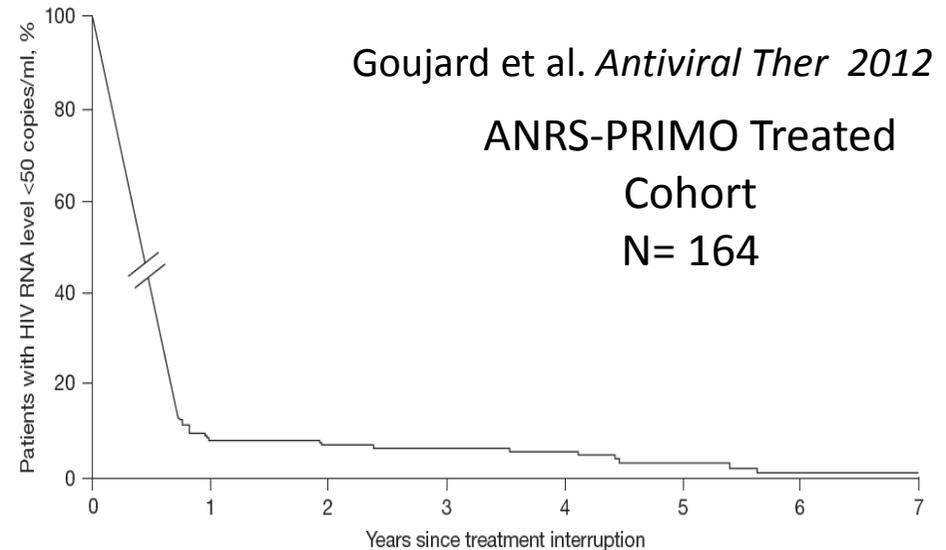
## Spontaneous Control of Viral Replication during Primary HIV Infection: When Is “HIV Controller” Status Established?

*Clin Infect Dis*, 49:982, 2009

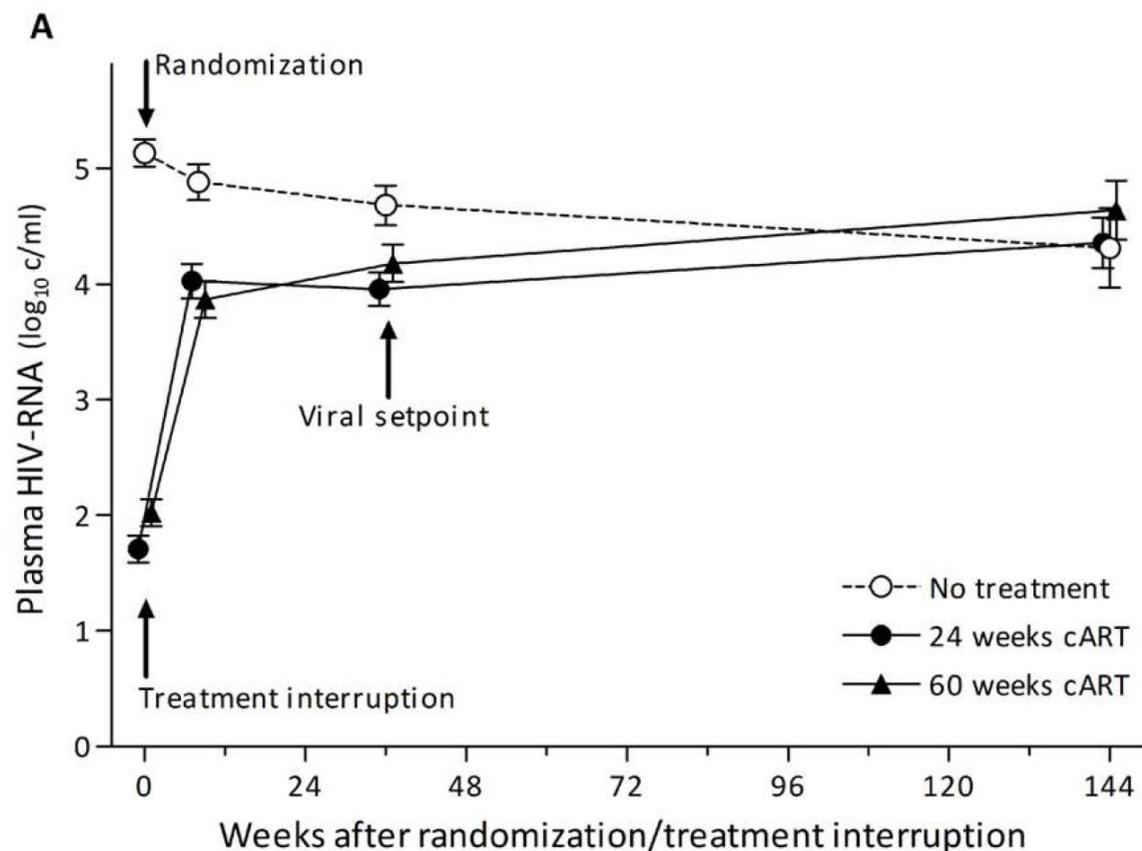
Cécile Goujard,<sup>1,2</sup> Marie-Laure Chaix,<sup>3</sup> Olivier Lambotte,<sup>1,2</sup>  
Christiane Deveau,<sup>4</sup> Martine Sinet,<sup>2</sup> Julien Guergnon,<sup>5</sup>  
Valérie Courgnaud,<sup>6</sup> Christine Rouzioux,<sup>3</sup> Jean-François Delfraissy,<sup>1,2</sup>  
Alain Venet,<sup>2</sup> Laurence Meyer,<sup>4</sup> and the Agence Nationale  
de Recherche sur le Sida (ANRS) PRIMO Study Group

### ANRS-PRIMO COHORT (untreated)

4% of 211 untreated subjects followed after primary HIV infection maintained suppression of viremia for median of 4.1 years



# Duration of cART Treatment Is Not Correlated with Viral Set-Point Following Treatment Interruption in Subjects Treated During Early Infection: The Primo-SHM Trial



No cART	36	33	28	22	18	17	16	13	7	6	5	3	2
24 weeks	38	38	27	37	29	33	29	26	25	20	17	13	13
60 weeks	38	38	37	34	34	23	30	30	25	16	9	17	10

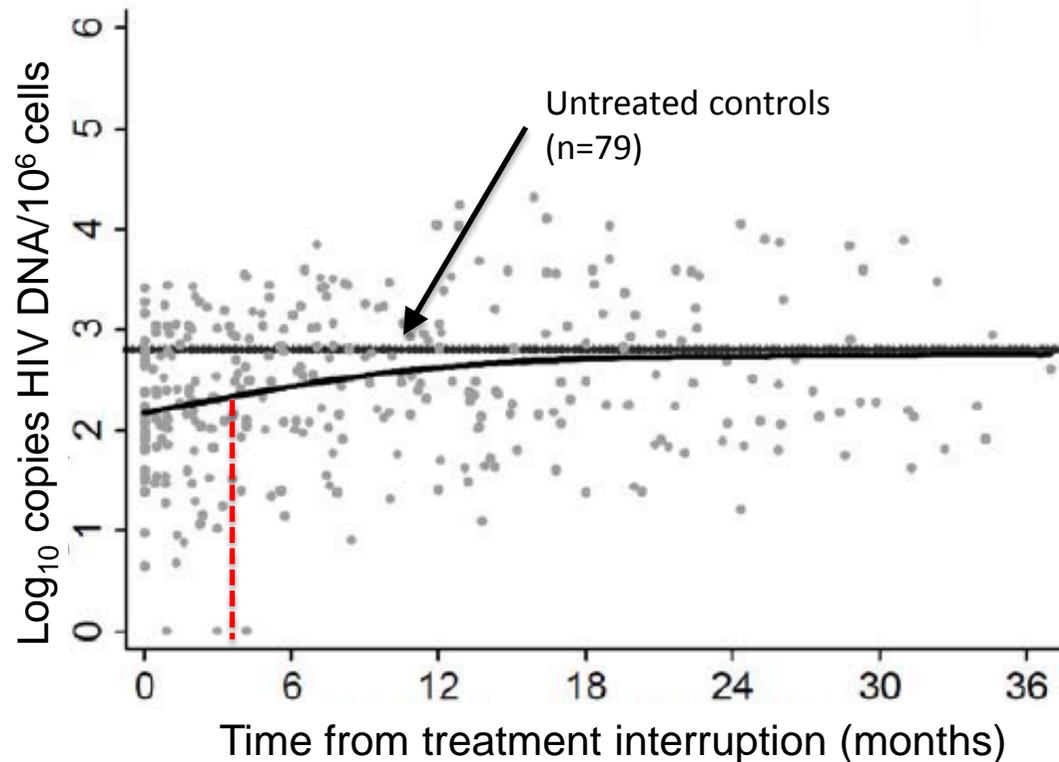
# Possible Long-Term Consequences of 16 week ATI in Individuals Who Started cART During Early Infection

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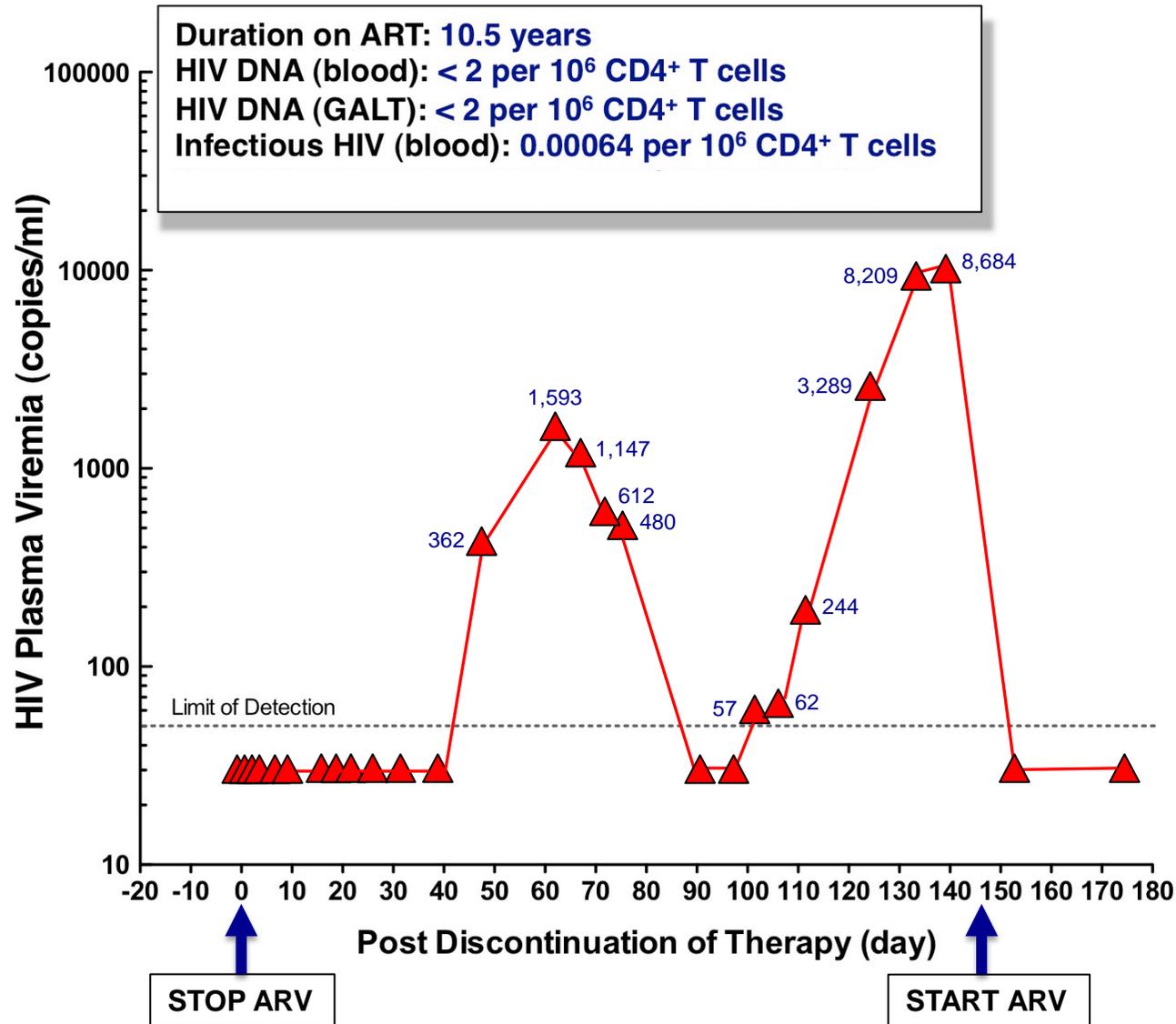
- Possibly impair “post-treatment control” of viremia by interrupting treatment too soon.
  - Only a risk if there is a correlation between the duration of cART prior to treatment interruption and the post-treatment control
- Increasing the size of the latent reservoir
  1. Does 16 weeks of treatment interruption significantly increase the size of the infected CD4 reservoir?
  2. How well does the size of the infected CD4 reservoir correlate with immunologic control of HIV?

# Stability of Cell-Associated HIV DNA Levels After Treatment Interruption in 33 Subjects Treated During Primary HIV Infection

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# Rebound of HIV Viremia Following Discontinuation of Antiretroviral Therapy in a Patient Treated Early In the Course of Infection



# Possible Long-Term Consequences of 16 week ATI in Individuals Who Started cART During Early Infection

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## Summary

- Available evidence does not support a correlation between duration of antiretroviral therapy and “post-treatment control”
- Available evidence indicates that only small changes in the size of the latent CD4 reservoir are likely to occur during a 16 week treatment interruption
- Absolute size of the CD4 latent reservoir has not been shown to predict virologic outcome

# Response to Reviewer Comment Regarding Need for Placebo (Control) Group

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## ■ Assess tolerance of the vaccine regimen

- Reactogenicity symptoms
- Interpretation of clinical and laboratory abnormalities-relation to vaccine vs. other confounding factors (e.g. toxicity from concomitant medications, other medical comorbidities).

## ■ Problems with using historical controls

- Historical studies differ in:
  - Definition of early infection and timing of cART initiation in relation to time of infection
  - cART regimens used
  - Frequency of monitoring, duration of ATI, and duration of follow-up