

Therapy for Early HIV Infection?

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Primary HIV Infection

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graph TD; A[Primary HIV Infection] --> B[ACUTE]; A --> C[EARLY]; B --- B1[Symptomatic days-weeks after infection]; B --- B2[Antibody negative]; B --- B3[HIV RNA or p24+]; C --- C1[Post-seroconversion]; C --- C2[Antibody +]; C --- C3[Variably defined as within 3-12 months];
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ACUTE

Symptomatic days-weeks after infection

Antibody negative

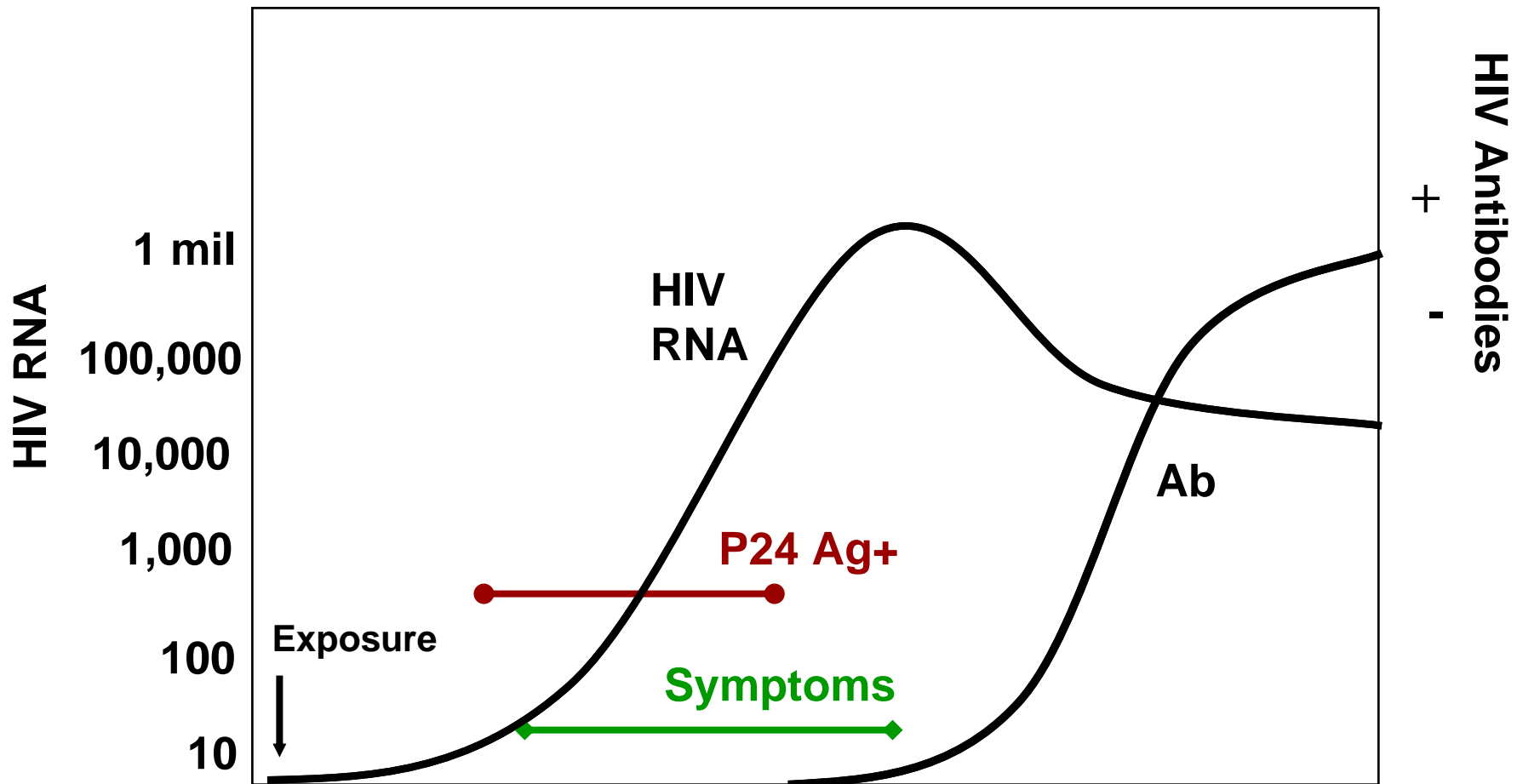
HIV RNA or p24+

EARLY

Post-seroconversion

Antibody +

Variably defined as within 3-12 months



PIC Longitudinal Study of Primary HIV Infection

- Total PIC cohort: acute+early=282
(150 in active follow-up)
- Enrollment focus since 10/2003:
 - Symptomatic with acute retroviral syndrome, EIA negative, RNA positive, at or immediately prior to enrollment
- 38 enrolled under these focused criteria in past 2 years
 - Includes 29 within the first 30 days after symptom onset (range 6-66 days)

PIC Longitudinal Follow-up

- Observational study
- Participants are followed with the same frequency of visits and the same evaluations regardless of decision to initiate therapy or not
- Treatment is not provided at the PIC
- Visit schedule is weekly x 4 wks, then q4wks x 3m, then q8wks x 4m, then q6m

Primary Infection Clinic Study Objectives

- Clinical
 - Compare the impact of early versus deferred HAART on clinical, immunological and virological parameters.
 - Determine if the course of acute and early HIV-1 infection differs in patients acquiring drug-resistant strains.
- Immunology
 - Determine the natural history of HIV-1 and the impact of early versus delayed HAART on
 - the earliest T cell responses in acute HIV-1 infection
 - evolution of T cell responses at viral set point
 - long-term changes in HIV-1 specific epitope recognition, viral escape, lineage differentiation and antiviral function

Primary Infection Clinic Study Objectives

- Virology
 - Determine the relationship between various factors (incl duration of infection, plasma levels of HIV-1 RNA) on the number, fitness, and expression activity of virus in latently infected resting CD4+ lymphocytes and macrophages/monocytes.
 - Identify and quantify the tissue distribution of HIV-1 in acute and early HIV-1 infection, and how this changes as a function of clinical response and duration of therapy.
 - Determine the relationships between plasma HIV-1 RNA titers and quantity of HIV-1 in tissue sites, and the impact of HAART.

Treatment in Primary Infection

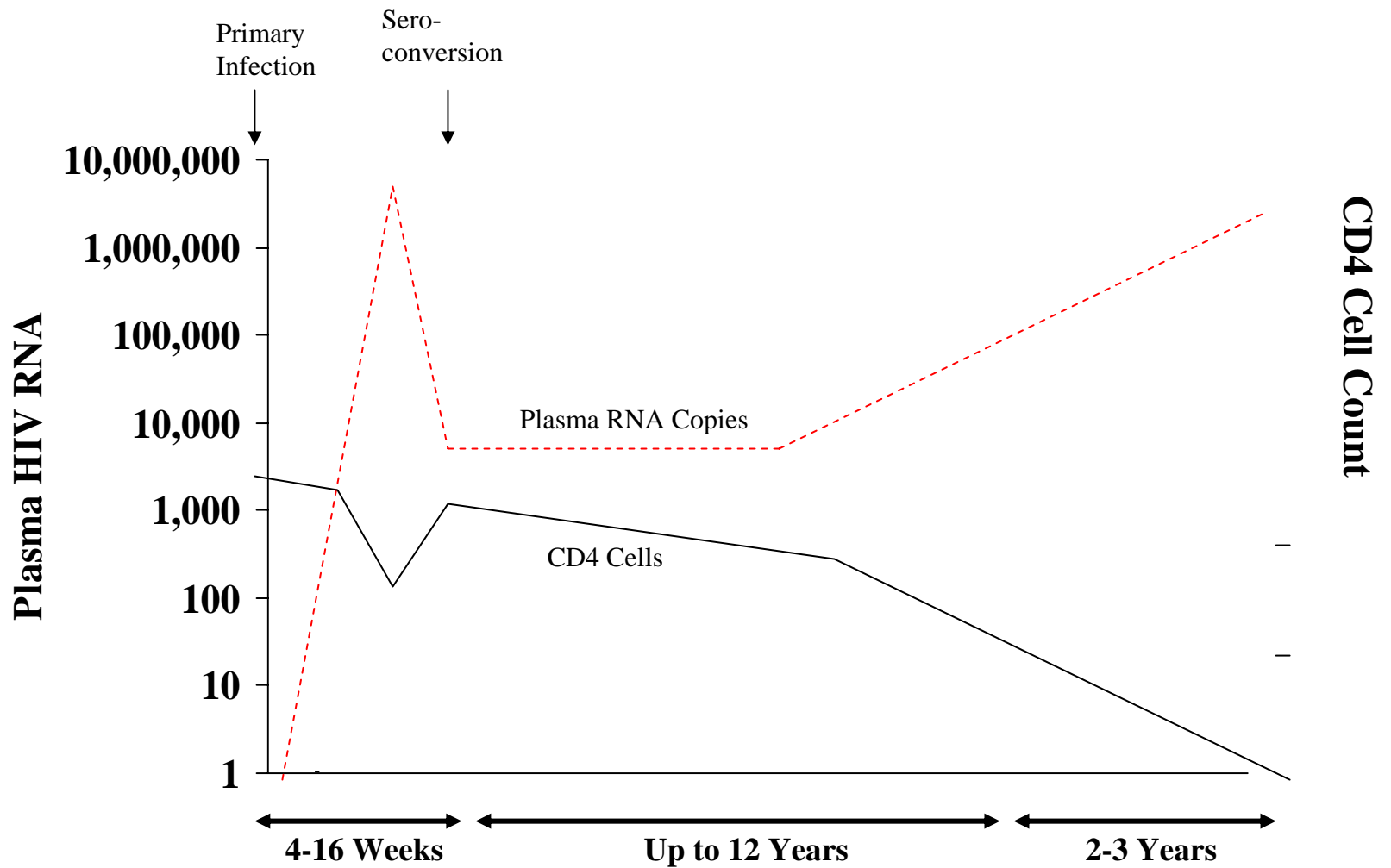
- No randomized trials of HAART
- Some data show immune control with HAART followed by STI in pts tx'd during acute infection (Rosenberg, Nature, 2000)
- Tx within 2 wks of seroconversion led to CD4/VL benefits 18 months after stopping treatment (Hecht, 12th CROI, 2005)
- Improved HIV-specific immune responses

Is there a clinical benefit?

- Randomized study of ZDV-monotx showed fewer minor OIs in tx'd pts (Niu JID 1998)
- Non-randomized HAART for 78 wks during primary infection led to fewer minor OIs, mucocutaneous diagnoses, respiratory infections (Berrey, JID, 2001)

Treatment in Early Infection

- How early is early?
- Why consider treatment in early infection?



Defining Early HIV Infection

- After seroconversion
- ? Relate to setpoint at ~ 120 days
- ? Relate to time to set up reservoirs by ~ 6m

Early Treatment

Pros and Cons

- Easier control of viral replication
- Prevention of CD4 decline
- Decreased transmission risk
- ARTx side effects
- Med related decrease in QOL
- Earlier development of resistance

Treatment in Early Infection

Possible Benefits

- Limit the development of latent reservoir of non-replicating HIV
- Preserve HIV-specific immune responses
- Greater likelihood of response to ARTx given a ? more homogeneous viral population in early infection

Why consider early treatment?

- Although there are virologic and immunologic data that suggest a benefit to early therapy, there is no evidence of long-term clinical benefit
- Virologic setpoint has been shown to correlate with clinical course
- Does early treatment alter virologic setpoint?

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents

The healthcare provider and the patient should be fully aware that therapy for primary HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. Certain authorities endorse treatment of acute HIV infection on the basis of the theoretical rationale and limited but supportive clinical trial data. Apart from patients with acute primary HIV infection, experienced clinicians also recommend consideration of therapy for patients among whom seroconversion has occurred within the previous 6 months.

ACTG 5217

- A Randomized Study of Treatment with Emtricitabine/Tenofovir DF and Lopinavir/Ritonavir versus no Therapy in Newly Infected HIV-1 Subjects to Determine Whether Potent Antiretroviral Therapy Alters the Virologic Setpoint

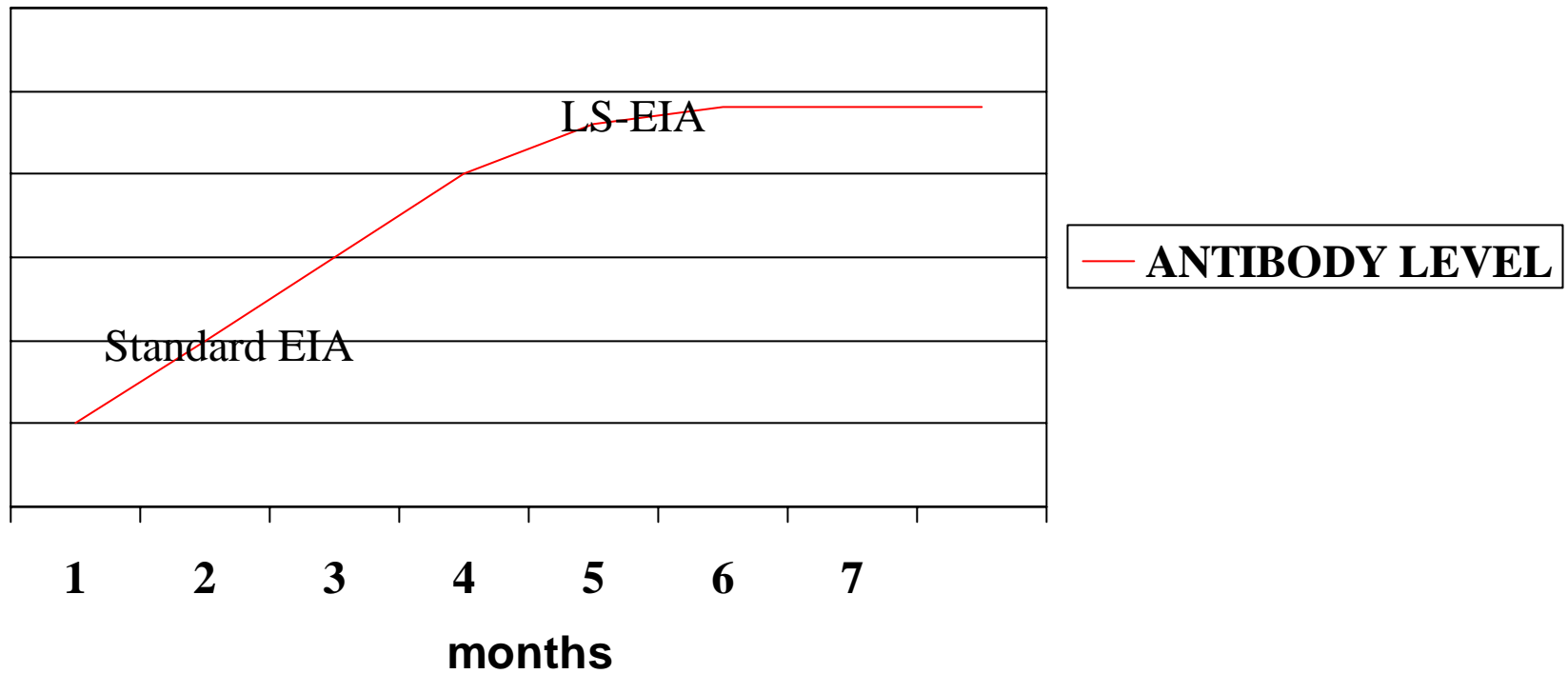
Hypothesis

- 36 weeks of HAART given to subjects within six months of HIV acquisition will alter the virologic setpoint as compared to subjects who do not receive antiretroviral therapy
- Plasma HIV-1 RNA levels at 72 weeks will be lower in the treated group

Early Infection Criteria

- Positive EIA and a positive Western Blot
- And either:
 - Negative detuned EIA ($OD \leq .75$)
 - Negative EIA within prior 6m
 - Negative or indeterminate WB within prior 6m

LS-EIA



Other inclusion/exclusion criteria

- No prior ARTx (PEP > 1yr ago ok)
- CD4 \geq 350
- RNA \geq 500
- No class B or C conditions (unless part of seroconversion illness)
- No prior receipt of an investigational HIV vaccine

Study Design

- 96-week randomized open-label study
- 150 recently HIV-infected subjects
- Randomized 1:1 to therapy vs no therapy for 36 weeks
- HAART = Truvada/Kaletra
- Primary endpoint: plasma \log_{10} HIV-1 RNA averaged at 72 and 76 weeks

Resistance

- Genotype is done at screening
- Treatment may be started before results are known
- If resistance to one component: substitution allowed, subject may continue in study
- If resistance to > 2 components: study regimen discontinued, subject withdrawn from study

On-study management

- Any subject not on treatment who meets clinical, virologic, or immunologic criteria for treatment initiation will be offered protocol therapy.
- This includes subjects who were treated and have stopped therapy as designated at wk 36, as well as subjects in the no-therapy arm.

Treatment (Re)Initiation

- CD4 < 350 (x2) after 12 weeks
- HIV-1 RNA > 750,000 (x2) after 4 weeks
- HIV-1 RNA > 200,000 (x2) after 12 weeks
- Clinical progression to class B or C condition
- CD4 < 200 at any time

Study Objectives

- To compare the virologic setpoint 72 weeks after study entry in subjects with early HIV infection who are randomized to HAART with individuals who are randomized to receive no therapy
- In addition, to compare the virologic setpoint 36 weeks after treatment discontinuation in subjects randomized to treatment (72 weeks into the study) with virologic setpoint 36 weeks after study entry in subjects randomized to no treatment

- If no treatment benefit shown by comparing HIV-1 RNA at 72 weeks: no treatment benefit.
- If treatment benefit shown at 72 weeks, but not by comparing 36 weeks of tx (week 72) to week 36 in untreated group: it may be that only time delay is accounting for the difference.
- If treatment benefit is shown in both comparisons: this demonstrates a positive benefit of treatment.