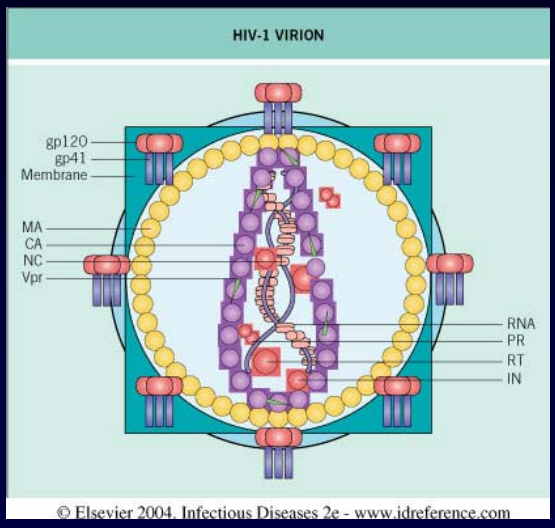
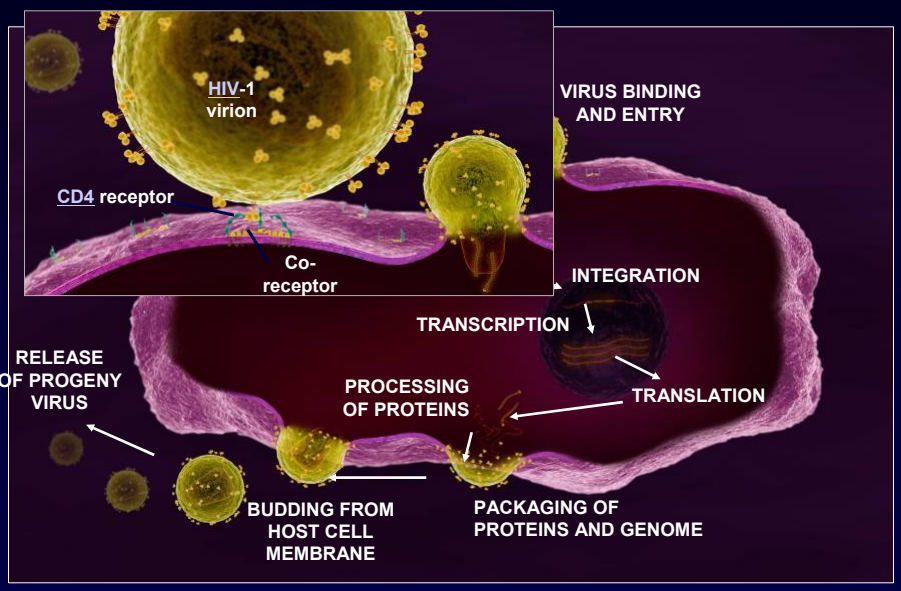
HIV Diagnosis and Pathogenesis

Scott M. Hammer, M.D.

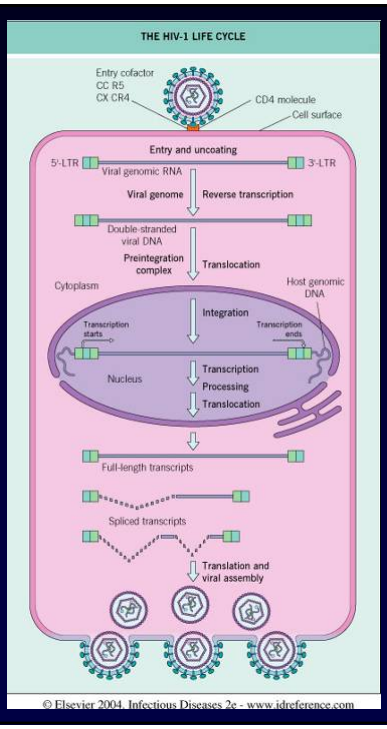
HIV-1 Virion



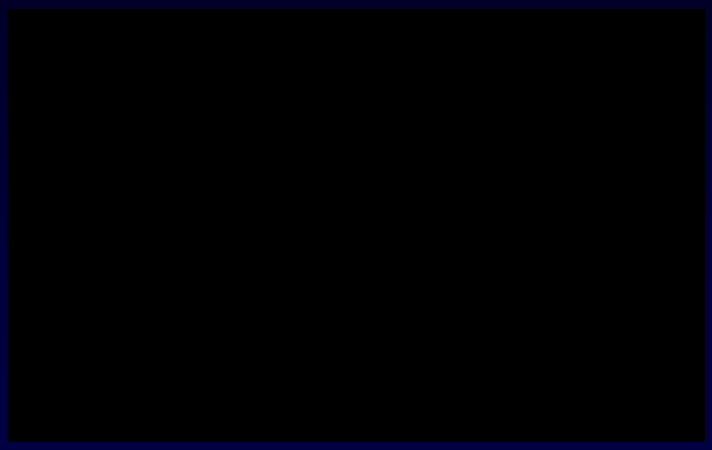
Life Cycle of HIV



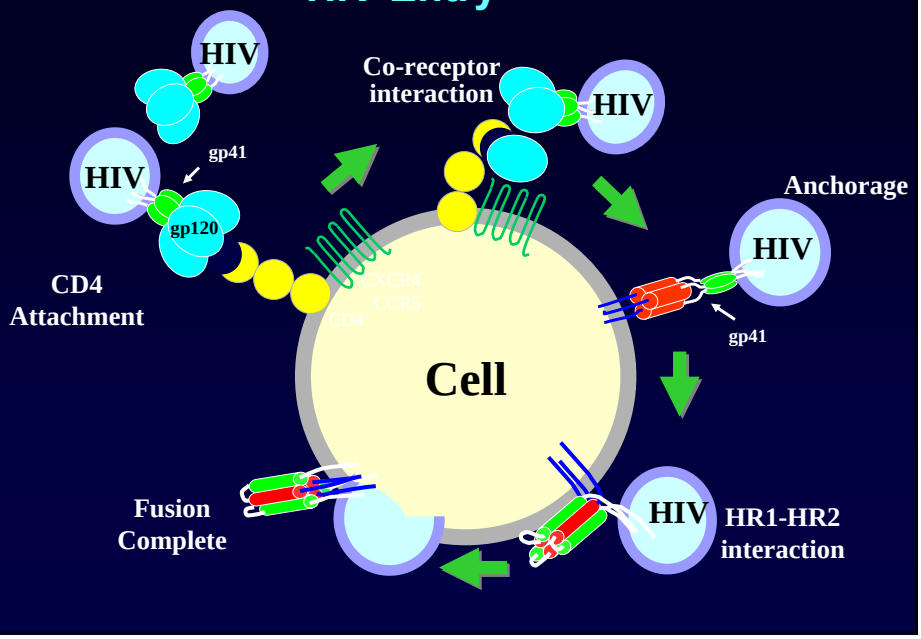
HIV Life Cycle



HIV Entry



HIV Entry

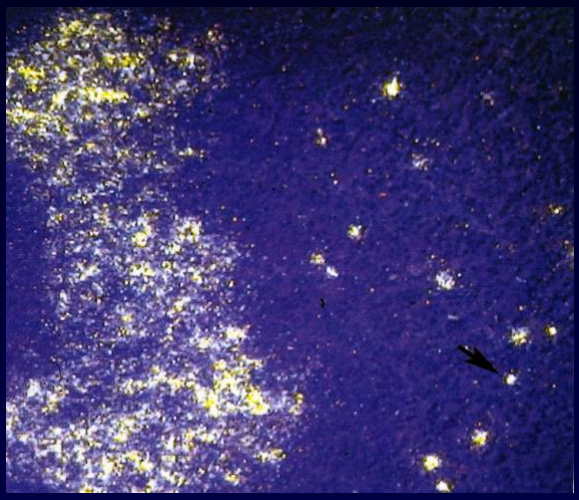


HIV Integration

Primary HIV Infection: Pathogenetic Steps

- Virus – dendritic cell interaction
  - Infection is typically with R5 (M-tropic) strains
  - Importance of DC-SIGN
- Delivery of virus to lymph nodes
- Active replication in lymphoid tissue
- High levels of viremia and dissemination
- Downregulation of virus replication by immune response
- Viral set point reached after approximately 6 months

PHI: Early Seeding of Lymphoid Tissue

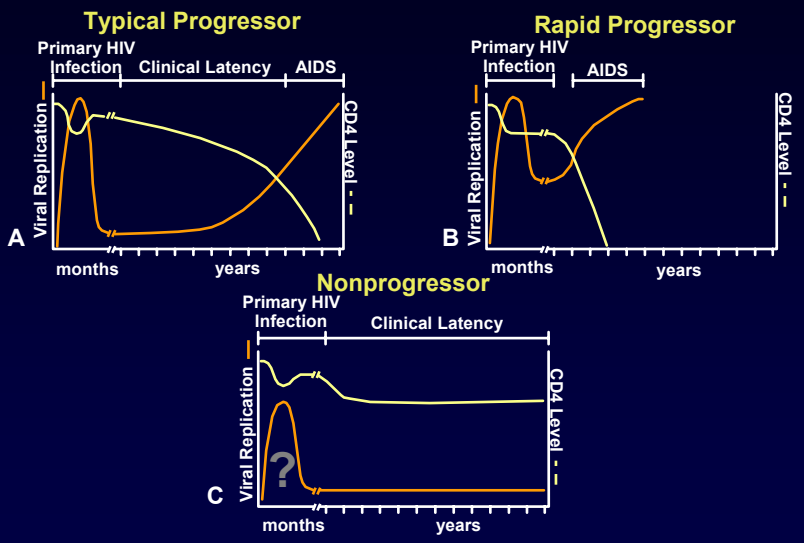


Schacker T et al: J Infect Dis 2000;181:354-357

Primary HIV Infection: Clinical Characteristics

- 50-90% of infections are symptomatic
- Symptoms generally occur 5-30 days after exposure
- Symptoms and signs
  - Fever, fatigue, myalgias, arthralgias, headache, nausea, vomiting, diarrhea
  - Adenopathy, pharyngitis, rash, weight loss, mucocutaneous ulcerations, aseptic meningitis, occas. oral/vaginal candidiasis
  - Leukopenia, thrombocytopenia, elevated liver enzymes
- Median duration of symptoms: 14 days

The Variable Course of HIV-1 Infection



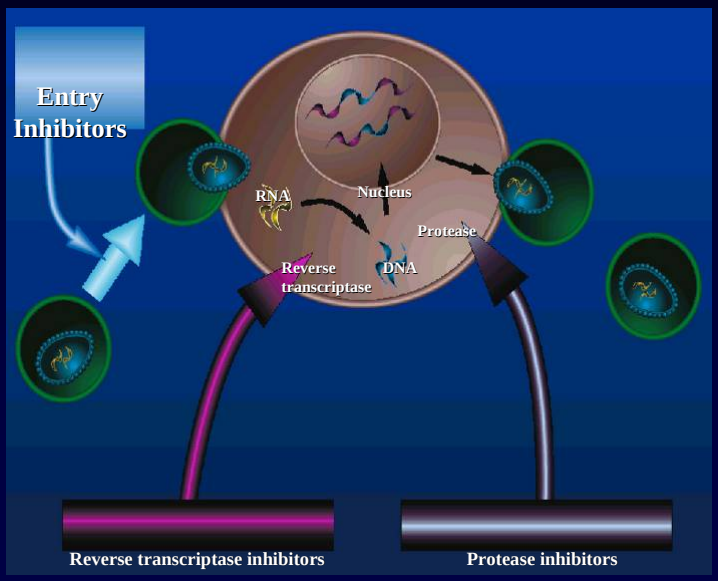
Reprinted with permission from Haynes. In: DeVita et al, eds. *AIDS: Etiology, Treatment and Prevention*. 4th ed. Lippincott-Raven Publishers; 1997:89-99.

Primary HIV Infection: Determinants of Outcome

- Severity of symptoms
- Viral strain
  - SI (X4) vs. NSI (R5) viruses
- Importance of GI tract associated lymphoid tissue (GALT)
- Immune response
  - CTL response
  - Non-CTL CD8 responses
  - Humoral responses?
- Viral set point at 6-24 months post-infection
- Other host factors
  - Chemokine receptor and HLA genotype
- Gender and differences in viral diversity?
- Antiviral therapy
  - Near vs. long-term benefit?

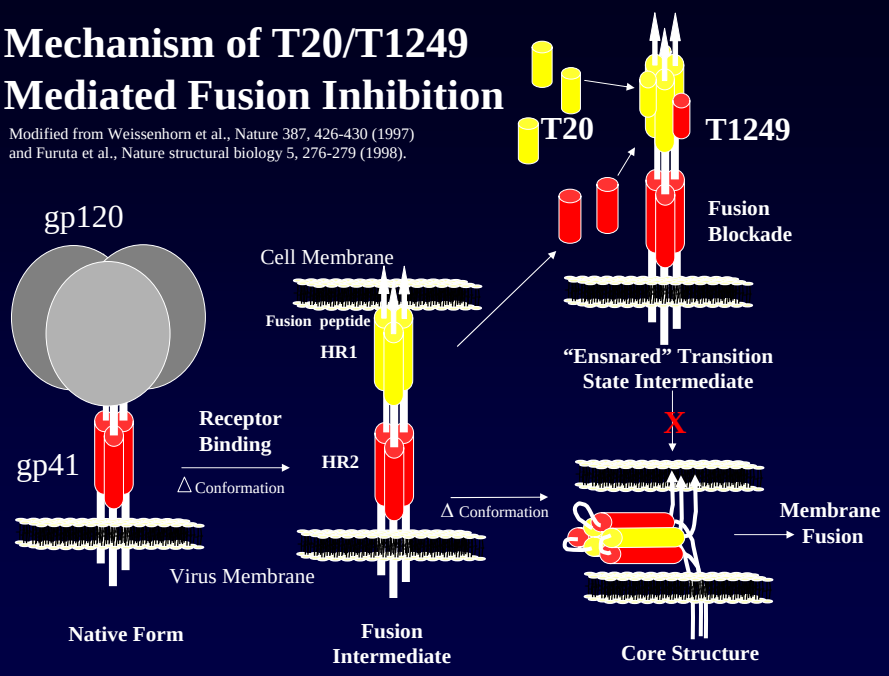
Natural History of Untreated HIV-1 Infection

Antiviral Agents for HIV



Mechanism of T20/T1249 Mediated Fusion Inhibition

Modified from Weissenhorn et al., Nature 387, 426-430 (1997) and Furuta et al., Nature structural biology 5, 276-279 (1998).



HIV Diagnosis

- Consider in anyone presenting with symptoms and signs compatible with an HIV-related syndrome or in an asymptomatic person with a risk factor for acquisition
- Full sexual and behavioral history should be taken in all patients
  - Assumptions of risk (or lack thereof) by clinicians are unreliable
- CDC urging that HIV testing be part of routine medical care

Laboratory Diagnosis of Established HIV Infection: Antibody Detection

- Screening
  - Serum ELISA
  - Rapid blood or salivary Ab tests
- Confirmation
  - Western blot
  - In some settings, confirmation of one rapid test is done by performing a second, different rapid test
- Written consent for HIV Ab testing must be obtained and be accompanied by pre- and post-test counselling
  - Consent process may change to make it simpler and easier but proper counselling remains crucial

Laboratory Diagnosis of Acute HIV-1 Infection

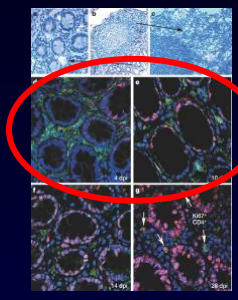
- Patients with acute HIV infection may present to a health care facility before full antibody seroconversion
  - ELISA may be negative
  - ELISA may be positive with negative or indeterminate Western blot
- Plasma HIV-1 RNA level should be done if acute HIV infection is suspected
- Follow-up antibody testing should be performed to document full seroconversion (positive ELISA and WB)

Established HIV Infection: Pathogenesis

- Active viral replication present throughout course of disease
- Major reservoirs of infection exist outside of blood compartment
  - Lymphoreticular tissues
    - » Gastrointestinal tract (GALT)
  - Central nervous system
  - Genital tract
- Virus exists as multiple quasispecies
  - Mixtures of viruses with differential phenotypic and genotypic characteristics may coexist
- At least 10 X 10^9 virions produced and destroyed each day
- $T_{1/2}$ of HIV in plasma is <6 h and may be as short as 30 minutes
- Immune response, chemokine receptor status and HLA type are important codeterminants of outcome

GI Associated Lymphoid Tissue Following Acute Infection

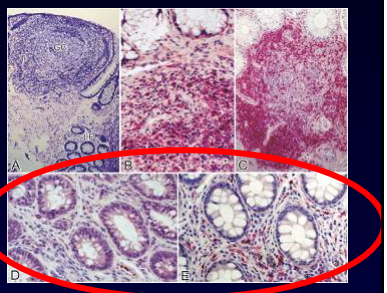
SIV



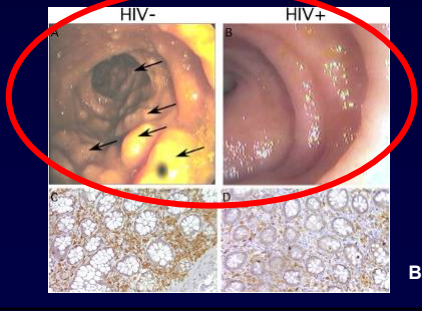
Li et al.

Depletion of CD4+ cells in lamina propria

HIV



Mehandru et al.



Absence of lymphoid cell aggregates in terminal Ileum.

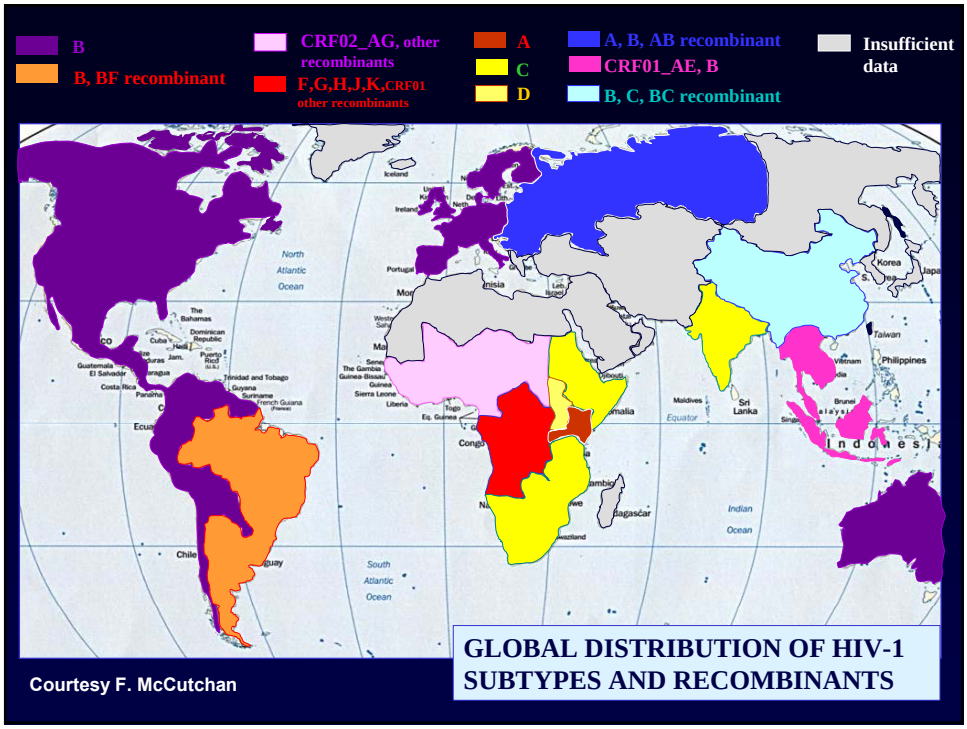
Benchley et al.

Determinants of Outcome: Selected Viral Factors

- Escape from immune response
  - Under immune selective pressure (cellular and humoral), mutations in *gag*, *pol* and *env* may arise
- Attenuation
  - *nef* deleted viruses associated with slow or long-term nonprogression in case reports and small cohorts
- Tropism
  - R5 to X4 virus conversion associated with increased viral pathogenicity and disease progression
- Subtypes
  - Potential for differential risks of heterosexual spread or rates of disease progression

HIV Nomenclature

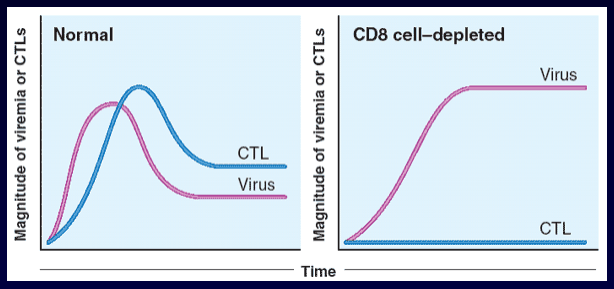
- Groups
  - M, N, O
- Subtypes
  - At least 9
- Sub-subtypes
- Circulating recombinant forms
  - At least 15



Host Factors in HIV Infection (I)

- Cell-mediated immunity
  - Cytotoxic T cells
    - » Eliminate virus infected cells
    - » Play prominent role in control of viremia, slowing of disease progression and perhaps prevention of infection
  - T-helper response
    - » Vital for preservation of CTL response
- Humoral immunity
  - Role in prevention of transmission and disease progression unclear

Role of CTL's in Control of Viremia



Letvin N & Walker B: Nature Med 2003;9:861-866

Host Factors in HIV Infection (II)

- Chemokine receptors
  - CCR5-Δ32 deletion
    - » Homozygosity associated with decreased susceptibility to R5 virus infection
    - » Heterozygosity associated with delayed disease progression
  - CCR2-V64I mutation
    - » Heterozygosity associated with delayed disease progression
  - CCR5 promoter polymorphisms
    - » 59029-G homozygosity associated with slower disease progression
    - » 59356-T homozygosity associated with increased perinatal transmission

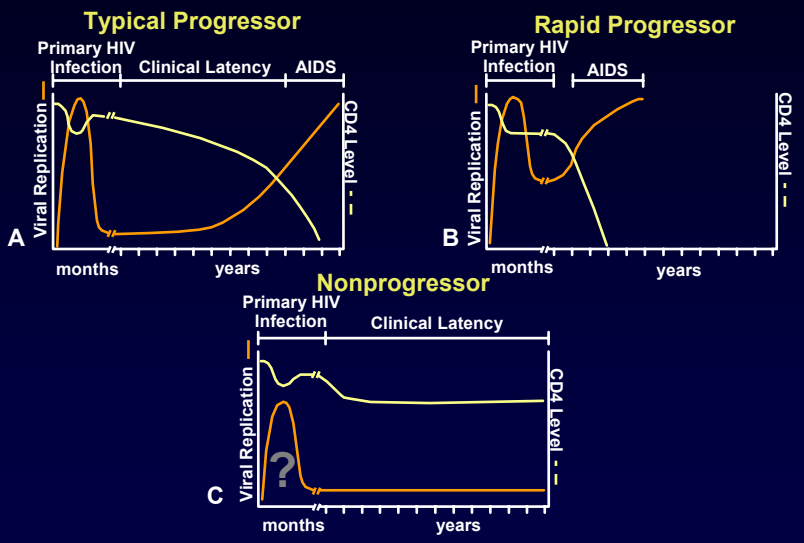
Host Factors in HIV Infection (III)

- Other genetic factors
  - Class I alleles B35 and Cω4
    - » Associated with accelerated disease progression
  - Heterozygosity at all HLA class I loci
    - » Appear to be protective
  - HLA-B57, HLA-B27, HLA-Bω4, HLA-B*5701
    - » Associated with long-term non-progression
  - HLA-B14 and HLA-C8
    - » ?Associated with long-term nonprogression

Mechanisms of CD4+ Cell Death in HIV Infection

- HIV-infected cells
  - Direct cytotoxic effect of HIV
  - Lysis by CTL's
  - Apoptosis
    - » Potentiated by viral gp120, Tat, Nef, Vpu
- HIV-uninfected cells
  - Apoptosis
    - » Release of gp120, Tat, Nef, Vpu by neighboring, infected cells
  - Activation induced cell death

The Variable Course of HIV-1 Infection



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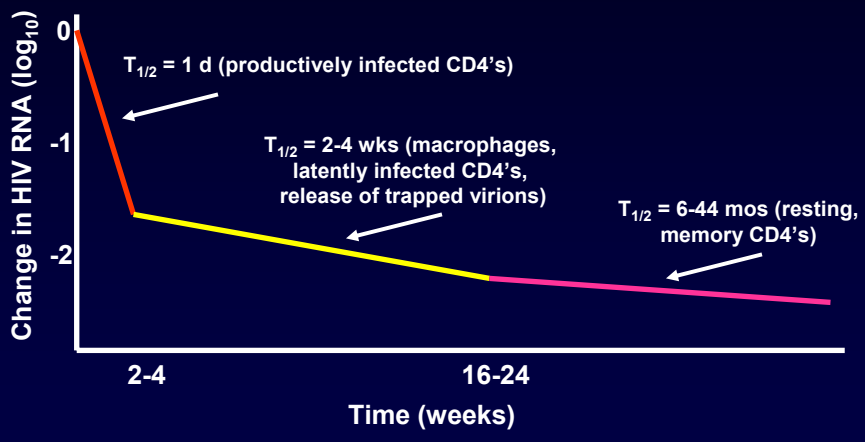
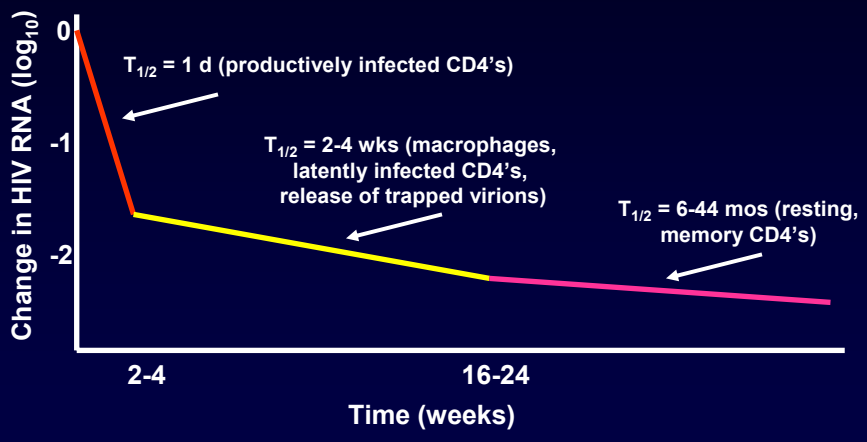
Phases of Decay Under the Influence of Potent Antiretroviral Therapy



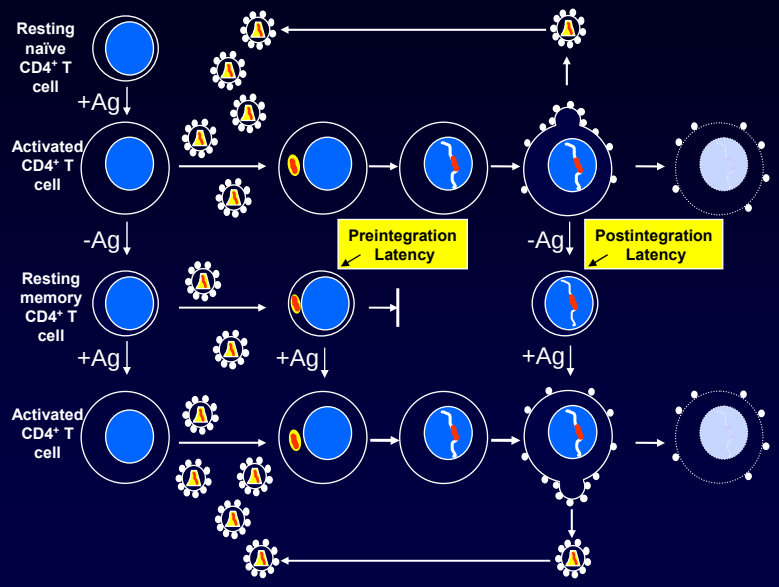
Therapeutic Implications of First and Second Phase HIV RNA Declines

- Antiviral potency can be assessed in first 7-14 days
  - Should see 1-2 log declines after initiation of therapy in persons with drug susceptible virus who are adherent
- HIV RNA trajectory in first 1-8 weeks can be predictive of subsequent response
  - Durability of response translates into clinical benefit

Phases of Decay Under the Influence of Potent Antiretroviral Therapy



Model of Post-Integration Latency



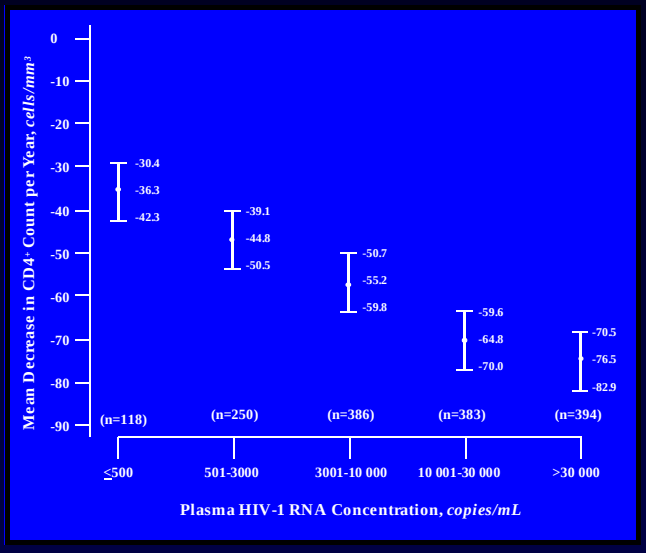
Siliciano R et al

Therapeutic Implications of Third Phase of HIV RNA Decay: Latent Cell Reservoir

- Viral eradication not possible with current drugs
- Archive of replication competent virus history is established
  - Drug susceptible and resistant
- Despite the presence of reservoir(s), minimal degree of viral evolution observed in patients with plasma HIV RNA levels <50 c/ml suggests that current approach designed to achieve maximum virus suppression is appropriate

Natural History of Untreated HIV-1 Infection

MACS: CD4 Cell Decline by HIV RNA Stratum



Mellors et al: Ann Intern Med 1997;126:946-954

CD4 and HIV-1 RNA (I)

- Independent predictors of outcome in most studies
- Near-term risk defined by CD4
- Longer-term risk defined by both CD4 and HIV-1 RNA
- Rate of CD4 decline linked to HIV RNA level in untreated persons

CD4 and HIV-1 RNA (II)

- Good but incomplete surrogate markers
  - For both natural history and treatment effect
- Thresholds are arbitrary
  - Disease process is a biologic continuum
  - Gender specificity of HIV RNA in early-mid stage disease needs to be considered
- Treatment decisions should be individualized
  - Baseline should be established
  - Trajectory determined

"Non-AIDS" Conditions

- Since 2006, a number of "non-AIDS" conditions have been described to be associated with uncontrolled HIV-1 viremia, even in persons with relatively well preserved CD4 cell counts (e.g., >350/mm^3)
  - Cardiovascular events
  - Hepatic disease
  - Renal disease
  - Malignancies
- Direct effect of HIV-1 on organ systems, associated immune activation and/or other mechanisms may be involved
- Active area of investigation
- Redefining HIV-related disease progression and influencing decision of when to start ART

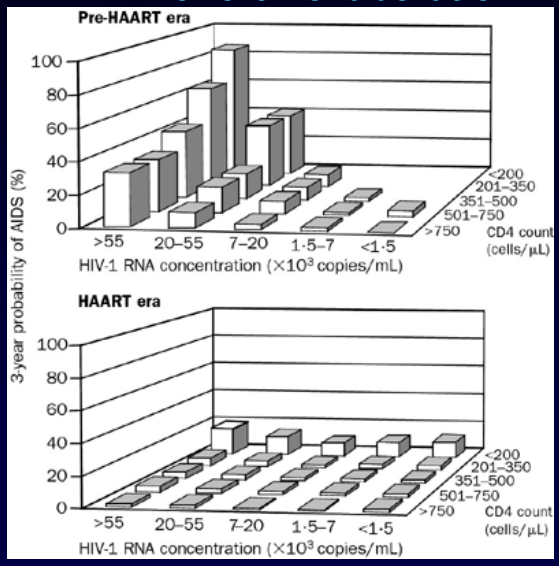
Initiation of Therapy in Established HIV Infection: Considerations

- Patient's disease stage
  - Symptomatic status
  - CD4 cell count
  - Plasma HIV-1 RNA level
  - Presence of, or risk factors for, "non-AIDS" conditions
    - » Cardiovascular, hepatic and renal disease
- Patient's commitment to therapy
- Philosophy of treatment
  - Pros and cons of 'early' intervention

Initiation of Therapy in Asymptomatic Persons: Population Based Studies

- Clinical outcome clearly compromised if Rx begun when CD4 <200
  - Miller et al (EuroSIDA), Ann Intern Med 1999;130:570-577
  - Hogg et al (British Columbia), JAMA 2001;286:2568
  - Sterling et al (JHU), AIDS 2001;15:2251-2257
  - Pallela et al (HOPS), Ann Intern Med 2003;138:620-626
  - Sterling et al (JHU), J Infect Dis 2003;188:1659-1665
- Clinical outcome compromised if Rx begun when CD4 <200 or RNA >100,000
  - Egger et al (13 cohorts, >12,000 persons), Lancet 2002;360:119-129

Prognosis According to CD4 and RNA: ART Cohort Collaboration



Egger M et al: Lancet 2002;360:119-129

Progress in HIV Disease