HIV Diagnosis and Pathogenesis

Scott M. Hammer, M.D.

HIV-1 Virion
Life Cycle of HIV

Virus Binding and Entry

Integration

Transcription

Translation

Processing of Proteins

Packaging of Proteins and Genome

Budding From Host Cell Membrane

Release of Progeny Virus

HIV Life Cycle
HIV Entry

CD4 Attachment

Co-receptor interaction

Anchorage

Fusion Complete

HR1-HR2 interaction
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
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

Typical Progressor

Viral Replication

CD4 Level

months

years

Primary HIV Infection

Clinical Latency

AIDS

Rapid Progressor

Viral Replication

CD4 Level

months

years

Primary HIV Infection

AIDS

Nonprogressor

Viral Replication

CD4 Level

months

years

Primary HIV Infection

Clinical Latency


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

- Early Opportunistic Infections
- Late Opportunistic Infections

Antiviral Agents for HIV

- Entry Inhibitors
- Reverse transcriptase inhibitors
- Protease inhibitors
**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 $10^9$ 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**
  - Depletion of CD4+ cells in lamina propria
  - Li et al.

- **HIV**
  - Absence of lymphoid cell aggregates in terminal ileum
  - Mehandru et al.
  - 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


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 Cw4
    » Associated with accelerated disease progression
  - Heterozygosity at all HLA class I loci
    » Appear to be protective
  - HLA-B57, HLA-B27, HLA-Bw4, 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

**Typical Progressor**
- Primary HIV Infection
- Clinical Latency
- AIDS

**Rapid Progressor**
- Primary HIV Infection
- AIDS

**Nonprogressor**
- Primary HIV Infection
- Clinical Latency

Phases of Decay Under the Influence of Potent Antiretroviral Therapy

- $T_{1/2} = 1$ d (productively infected CD4’s)
- $T_{1/2} = 2-4$ wks (macrophages, latently infected CD4’s, release of trapped virions)
- $T_{1/2} = 6-44$ mos (resting, memory CD4’s)
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

- $T_{1/2} = 1$ d (productively infected CD4’s)
- $T_{1/2} = 2-4$ wks (macrophages, latently infected CD4’s, release of trapped virions)
- $T_{1/2} = 6-44$ mos (resting, memory CD4’s)
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
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/mm³)
  - 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
  - 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

Progress in HIV Disease

HIV Pathogenesis

Monitoring ↔ Therapy