HIV Diagnosis and Pathogenesis

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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

Laboratory Diagnosis of Established HIV Infection: Antibody Detection

- Screening
  - Serum ELISA
  - Rapid blood or salivary Ab tests
- Confirmation
  - Western blot
- Written consent for HIV Ab testing must be obtained and be accompanied by pre- and post-test counselling

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 indeterminant 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)

HIV-1 Virion

HIV Life Cycle

Tat = transcriptional activator
Rev = regulator of mRNA nuclear export
**Established HIV Infection: Pathogenesis**
- Active viral replication present throughout course of disease
- Major reservoirs of infection exist outside of blood compartment
  - Lymphoreticular tissues
  - 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

**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 varied subtypes to exhibit differential transmissibility and virulence
  - Potential for greater heterosexual spread of some subtypes

**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 Cu4
    » Associated with accelerated disease progression
  - Heterozygosity at all HLA class I loci
    » Appear to be protective
  - HLA-B57, HLA-B27, HLA-B8, HLA-B*5701
    » Associated with long-term non-progression
  - HLA-B14 and HLA-C8
    » Associated with long-term non-progression

Mechanisms of CD4+ Cell Death in HIV Infection

- HIV-infected cells
  - Direct cytopathic 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
- Rapid Progressor
- Nonprogressor

Phases of Decay Under the Influence of Potent Antiretroviral Therapy

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

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

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Initiation of Therapy in Established HIV Infection: Considerations

- Patient’s disease stage
  - Symptomatic status
  - CD4 cell count
  - Plasma HIV-1 RNA level

- 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 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;286:2986
- Sterling et al (JHU), AIDS 2001;15:2351-2357
- Palella et al (HOPS), Ann Intern Med 2003;138:620-626
- Sterling et al (JHU), J Infect Dis 2003;188:1660-1666

- No virologic or immunologic advantage to starting at CD4 >350 vs. 200-350; increased rate of virologic failure when starting at CD4 <200
- Cozzi-Lepri et al (ICONA), AIDS 2001;15:983-990

- Virologic responses comparable among groups with CD4 >200; slower decline to RNA <500 in those with RNA’s >100,000 at baseline

- 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

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

Prognosis According to CD4 and RNA: ART Cohort Collaboration

Natural History of Untreated HIV-1 Infection

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

MACS: CD4 Cell Decline by HIV RNA Stratum

HIV Resistance: Underlying Concepts

- Genetic variants are continuously produced as a result of high viral turnover and inherent error rate of RT
  - Mutations at each codon site occur daily
    » Survival depends on replication competence and presence of drug or immune selective pressure
  - Double mutations in same genome also occur but 3 or more mutations in same genome is a rare event
  - Numerous natural polymorphisms exist

Pre-existence of Resistant Mutants

- Viral replication cycles: $10^9$-$10^{10}$/day
- RT error rate: $10^{-4}$-$10^{-5}$/base/cycle
- HIV genome: $10^6$ bp
- Every point mutation occurs $10^4$-$10^5$ times/day
  - In drug naive individuals
    » Single and double mutants pre-exist
    » Triple and quadruple mutants would be predicted to be rare

Mellors et al: Ann Intern Med 1997;126:946-954
**HIV Resistance: Underlying Concepts**

- Implications
  - Resistance mutations may exist before drug exposure and may emerge quickly after it is introduced
  - Drugs which develop high level resistance with a single mutation are at greatest risk
    - e.g., 3TC, NNRTI's (nevirapine, efavirenz)
  - Resistance to agents which require multiple mutations will evolve more slowly
  - Partially suppressive regimens will inevitably lead to emergence of resistance
  - A high 'genetic barrier' needs to be set to prevent resistance
    - Potent, combination regimens

**HIV Drug Resistance: Definitions**

- Genotype
  - Determines phenotype
  - Major and minor mutations for PIs
- Phenotype
  - Drug susceptibility
- Virtual phenotype
  - Result of large relational genotype and phenotype database

**HIV Drug Resistance: Methodologies**

- Genotyping
  - Different platforms
    - Dideoxy sequencing
    - Gene chip
    - Point mutation assays
- Phenotyping
  - Recombinant virus assays
- Virtual phenotyping
  - Informatics
Nucleoside Analog Resistance

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Mutations Selected by PIs

Pyrophosphorolysis

Mutations in the GP41 Envelope Gene Associated With Resistance to Entry Inhibitors

Mutations Selected by NNRTIs

Progress in HIV Disease

HIV Pathogenesis

Monitoring       Therapy