Acute/Primary HIV infection: Presentation, Diagnosis, and Therapeutic Options.

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Objectives

- Epidemiology
- Diagnosing acute HIV infection
- Public health testing initiatives
- Data on treatment of acute HIV infection
Estimated New HIV Infections, 2006, Overall and by Gender

- Total: 56,300
- Male: 41,400
- Female: 15,000

Note: Estimates from subgroups do not add to total due to rounding.

Source: Centers for Disease Control and Prevention
Awareness of Serostatus Among People with HIV and Estimates of Transmission

- ~25% Unaware of Infection
- ~75% Aware of Infection

People Living with HIV/AIDS: 1,039,000 - 1,185,000

New Sexual Infections Each Year: ~32,000

Marks, et al
*AIDS* 2006;20:1447-50

MMWR October 3, 2008
57(39);1073-1076

CDC

~54% of New Infections
~46% of New Infections

Revised 10/3/08
21% (233,000)

MMWR October 3, 2008
57(39);1073-1076
Natural Progression of HIV Infection: Acute + Recent = Primary HIV Infection (4-6 months)
Clinical Presentation of Acute HIV Infection

- Symptoms of acute HIV seroconversion after 2-3 week incubation period
  - Low-grade fever 80-90%
  - Fatigue 70-90%
  - Rash chest/ back 40-80%
    - Macular, blanching, faint
  - Adenopathy 40-70%
    - Cervical, axillary

More Symptoms...

- Headache: 32-70%
- Myalgias: 50-70%
- Night sweats: 50%
- Aseptic meningitis: 24%
- Oral or genital ulcers: 5-20%

Rash

Slide compliments of Dr. Neal Gregory
Days from Sexual Exposure to Onset of Symptoms in 12 Patients Who Could Identify the Exact Date & Time of the Sexual Exposure that Led to Acquisition of HIV

Questions to Ask to Determine Risk

- Sexual history, including use of barrier protection
- Use/sharing of injection drug tools
- Use of crack or other cocaine
- Sex for drugs
- Work history—occupational exposure?
Differential Diagnosis of Acute HIV

- Streptococcal throat infection
- Mononucleosis
- Acute cytomegalovirus
- Acute toxoplasmosis
- Mumps
- Other viral syndromes, including acute hepatitis
What is the earliest an HIV Ab test can detect HIV?

- Standard testing detects HIV about 2 weeks after symptoms, or 3-4 weeks after infection.

- 4th generation HIV test
  - Combines Ab with p24Ag detection
  - Moves the diagnosis up to about 2 weeks from time of infection
Exposure to HIV at mucosal surface (sex)

Virus collected by dendritic cells, carried to lymph node

HIV replicates in CD4 cells, released into blood

Virus spreads to other organs

Diagnosing Acute HIV

- HIV RNA PCR testing (viral load)
  - Detectable about 5 days after infection

- HIV antibody testing done concomitantly

- HIV antibody test repeated in 4 - 12 weeks, to document seroconversion
HIV-1 RNA Qualitative Assay

- FDA-approved in U.S in October, 2006 for the diagnosis of primary HIV-1 infection
  - Sensitivity similar to current VL assays
- Previously used to screen blood and plasma donors
- APTIMA HIV-1 RNA Qualitative assay
  - Gen-Probe Incorporated
Acute HIV in Prison

- Inmate-patient had unprotected, consensual, receptive anal intercourse with 2 male inmates at the Correctional Facility
  - One inmate with VL 53,000 c/mL
  - Second inmate with VL of 92 c/mL

Acute HIV in Prison

- Presented to medical unit on 12/31/03 with fever, sore throat, headache, nausea with vomiting, & developed urinary retention.
  - Jan. 6 & Jan. 13, 2004: HIV EIA negative
  - Jan 9 HIV RNA >750,000 c/mL
  - Jan.14 Genotype - pansensitive

Acute HIV in Prison

- January 20 CD4+ 338 cells/cmm and HIV RNA 234,000 c/mL
  - Patient started zidovudine, lamivudine, and efavirenz.
    - February 4 HIV EIA and Western Blot both positive
- March 19, 2004:
  - CD4+ 1,056 cells/cmm;
  - HIV RNA <50 c/mL

Sensitive-Less-Sensitive Assay

- Determines recent infection: surveillance
- Detuned assays
  - STARHS – Serological Testing Algorithm for Recent HIV Seroconversion
  - Takes advantage of lower Ab titer early in HIV
  - Uses a lower sensitivity assay (higher Ab cutoff)
- BED Capture ImmunoAssay
  - Branched peptide that includes gp41 sequences from HIV-1 subtypes B, E & D
  - Detects a gradual increase in the proportion of HIV-1-specific IgG in total IgG for 2 years after seroconversion
  - Extends seroconversion incidence period to 6 months
Recent HIV Infection?

- Negative detuned assay
  - Recent infection

- Positive detuned assay
  - Infection occurred more than 4 - 6 months ago
Pooled HIV Nucleic Acid Testing
Pooling Schema

Individual specimens

Pool of 10
Pooling Schema

Individual specimens
N=100

Pools of 10
Pooling Schema

Individual specimens
N=100

Pools of 10

Master pool
Resolution Testing

Individual testing on 10 specimens

Pools of 10 screened

Master pools screened
Algorithm of the Procedures of the North Carolina Department of Health and Human Services for HIV Testing, Notification, and Surveillance

Flow Chart of Study Population
Acute HIV-1 Infections

- 2 of 25 were false positive NAATs
- Of the 23 acutely infected
  - 1 patient pregnant
  - 30% had symptoms of primary HIV
  - 26% developed symptoms later
  - Median VL 258,000 c/mL (2,609 – 5 million)
- PPV of combined Ab and NAAT algorithm was 0.997 (95% CI, 0.988 - >0.999)

Acute HIV-1 in New York City – February 11, 2009

- 17 cases of acute HIV from July – December 2008 from 4 STD clinics
- Pooled HIV PCR from 21,000 HIV Ab negative specimens
- 16 male, 1 female; Median age 28
- 11 (65%) were symptomatic
- Risk factors: unprotected anal intercourse with multiple/anonymous partners for men
  - Female had history of IDU and CSW

Health Advisory # 4: NYCDOHMH; 2/11/09.
Therapy for Acute HIV Infection
Prospective nonrandomized trial of ritonavir-boosted PI-based therapy in patients acutely (Ab negative within 14 days, n = 28) vs. recently infected with HIV (detuned EIA negative, n = 45)

If VL < 50 c/mL at 52 weeks, therapy interrupted
- Second course of therapy allowed if:
  - VL > 5,000 c/mL on 3 occasions or
  - VL > 50,000 c/mL on 2 occasions

Primary endpoint: HIV-1 RNA < 5000 copies/mL, 24 weeks after treatment interruption
- Acute arm 43% (95% CI: 24% to 63%)
- Recent arm 38% (95% CI: 24% to 53%;) \( p = 0.81 \)
ANRS Reservoir’s Study Group

- Patients enrolled within 10 weeks of acute HIV symptoms in observational study
  - Patients self-decided on HAART
  - N = 20 who were on HAART a median of 2.3 years and then stopped HAART
  - N = 18 who decided against HAART

- Follow-up at 144 weeks after stopping HAART
  - 31% of pts in treated group had VL < 400 copies/mL vs 0% in the untreated group (p<0.001)
    - 25% were < 50 copies/mL in the HAART group at 144 weeks
  - Monthly median CD4 cell loss was twice as high in the untreated group vs. the patients on HAART (-11.1 vs. -6 cells/mm³/month, respectively)

Thierry Prazuck*1, A Lafeuillade2, L Hocqueloux1, J P Viard3, V Avettand Fenoel4, and C Rouzioux4
1Ctr Hosp Regional Orleans La Source, France; 2Hosp Chalucet, Toulon, France; 3Ctr Hosp Univ Necker, Paris, France; and 4Ctr Hosp Univ Necker, Paris, France. CROI 2008, Abstract 695.
HIV-1 DNA Depletion and CD4 Restoration with HAART Initiated at the Time of Primary HIV Infection

- 161 patients
  - 22 started HAART within 10 weeks of symptomatic primary HIV infection (PHI)
  - 139 started HAART during chronic HIV (CHI)
- HIV DNA decrease was greater in the PHI group than the CHI group (median $-1.14 \log/1000$ PBMC vs $-0.51$, $p < 0.0001$).
- Median CD4+ T cell gain, final CD4+ count and CD4/CD8 ratio were significantly higher in the PHI group than in the CHI group
  - CD4+ cell gain: $+330/mm^3$ vs $+195/mm^3$, $p < 0.0005$
  - Final CD4+ count: $+1025/mm^3$ vs $+580/mm^3$, $p < 0.0005$
  - Ratio: $1.38$ vs $0.78$, $p < 0.0005$

Laurent Hocqueloux*1, V Avettand-Fènoël2, S Jacquot3, T Prazuck1, A Mélard2, J-P Viard2, G Le Moal4, C Rouzioux2, and ANRS Reservoir Study Group. 2009 CROI, Abstract 515.
The Prospective, Randomized Primo-SHM Study

- Randomized, open-label triple arm study for pts with primary HIV infection
- Temporary HAART:
  - 24 weeks (n=19) or
  - 60 weeks (n=18) vs
  - No therapy (n=11)
- HAART: Zidovudine/lamivudine + efavirenz + lopinavir/r
- Objective: Plasma viral load 36 weeks after seroconversion in no-therapy arm, or 36 weeks after therapy interruption in the treatment arm

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1Ctr for Infection and Immunity Amsterdam, The Netherlands; 2Academic Med Ctr, Amsterdam, The Netherlands; 3Intl Antiviral Therapy Evaluation Ctr, Amsterdam, The Netherlands; 4Univ Med Ctr, Utrecht, The Netherlands; 5Academic Hosp Maastricht, The Netherlands; and 6Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands. CROI 2008, Abstract 698b.
Results: treated vs. untreated

**Plasma HIV-1 RNA**

- **p**<0.005
- Log VL treated vs. untreated
- Log VL treated vs. baseline

**CD4+ T cells**

- **p**<0.005
- CD4 treated vs. untreated
Conclusions: Primo-SHM Study

“Both 24 and 60 weeks of HAART during PHI lower the plasma HIV-RNA set point after treatment interruption compared to no early treatment.”
Dutch Primo-SHM Cohort: Time Off HAART

- 102 pts evaluable with primary HIV from 2003 - 2008
  - 47 untreated; 55 in treated group
  - 32 patients in original cohort still on HAART, so not evaluated
- Median duration of early HAART: 28 weeks
  - 23 pts in untreated arm started HAART due to low CD4 count or symptomatic disease
  - 10 pts in early HAART group restarted HAART after planned interruption
- Untreated pts: Initiated HAART at mean of 126 weeks (95% CI 104 – 150 weeks)
- Treated Pts: Re-initiated HAART at mean of 181 weeks (161-201) p = 0.001
  - This was true even when corrected for time already spent on HAART during primary HIV infection

Steingrover R et al. CROI 2009, Abstract 70bLB.
Dutch Primo-SHM Cohort: Time Off HAART

KM plot of total time off HAART, p = 0.001.

Steingrover R et al. CROI 2009, Abstract 70bLB.
Effect of ART of Different Durations in Primary HIV Infection

- ARVs initiated within first 6 months of HIV seroconversion
- 348 early treated patients; 675 deferred therapy
  - 147 received ART of limited duration

Duration of HAART:
- < 6 months: n = 38
- 6 – 12 months: n = 40
- > 12 months: n = 69

N Pantazis1, Giota Touloumi*1, P Vanhems2, J Gill3, K Porter4, and CASCADE Collaboration
1Athens Univ Med Sch, Greece; 2CNRS UMR 5558, Univ Lyon 1, France; 3Southern Alberta HIV Clin, Calgary, Canada; and 4Med Res Council Clinical Trials Unit, London, UK. CROI 2008, Abstract 697.
The effect of antiretroviral treatment of different durations in primary HIV infection

Nikos Pantazis¹, Giota Touloumi¹, Philippe Vanhems², John Gill³, Kholoud Porter⁴ and the CASCADE collaboration

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Figure 4. Viral load “set-point” (average of all viral load measurements/individual taken >1 year after SC and while both groups were off ART and “Early treatment” individuals had stopped HAART for at >6 months) and duration of “early” HAART.

Effect of ART of Different Durations in Primary HIV Infection

“No difference in HIV RNA set-points between the early and deferred groups ($p = 0.43$).”

“AIDS rates were similar but death rates were higher in the deferred group ($p = 0.05$), mainly due to an increased number of non-AIDS deaths in this group.”

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1Athens Univ Med Sch, Greece; 2CNRS UMR 5558, Univ Lyon 1, France; 3Southern Alberta HIV Clin, Calgary, Canada; and 4Med Res Council Clinical Trials Unit, London, UK. CROI 2008, Abstract 697.
Summary

- Be alert for acute HIV infection
- HIV viral RNA assay is the diagnostic test of choice
- Results on treatment inconclusive
  - Refer for clinical trial if available
Gracias!

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