Therapy of Acute HIV-1 Infection: An Update

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Acute Infection: Treatment Issues

• Can ARV treatment restore the massive depletion of mucosal CD4+ T cells associated with acute HIV infection?

• Is drug resistance testing at presentation with primary infection sufficient to guide therapy initiated months or years later?

• What are the relative merits of treating acute/early infection vs. waiting until CD4+ T cells drop below 350 cells/mm³?
  – Does transient therapy during primary infection alter the viral set-point or long term disease progression?

• What are the best measures of therapeutic efficacy?
Primary HIV Infection: Acute + Early Infection

Transmitted HIV Infection (ARV Naïve)

- **Acutely** Infected: HIV RNA positive (VL ≥5000) or detectable serum p24 antigen, HIV EIA negative or WB indeterminate

- **Early** Infected: HIV EIA positive with simultaneous LS EIA O.D. ≤ 1.0 (Vironostika-LS EIA; bioMerieux, Raleigh, NC) or documented seroconversion w/i last 6 months
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Reconstitution of Mucosal CD4+ T cell Depletion?

• ARV Treatment associated with delayed and biphasic restoration of mucosal CD4+ T cells
  – Rate of restoration significantly higher than seen in chronically infected patients

• ARV Treatment was not associated with reconstitution of the mucosal CD4+ T cell depletion despite sustained viral suppression throughout treatment.
  Mahandru S, Poles M, et al. JEM 2004
Studies of ACUTE Treatment Needed!!

What are the endpoints?

- Potent therapy during acute/early infection associated with increased CD4+ T cell numbers in peripheral blood.

BUT….

- T lymphocytes in peripheral blood represent only 2-5% of total lymphocytes
- GI tract harbors the majority of the body’s lymphocytes
- Acute HIV infection results in significant destruction of memory CD4+ T cells that express CCR5
- Unclear if therapy restores this reservoir and whether this response may be dependent upon rapid initiation of treatment
- Assessment: jejunal vs. rectosigmoid biopsies?
Feasibility of Identifying Acutely Infected Study Volunteers

Subjects Needed:

- Nucleic Acid Amplification Testing (NAAT) makes identification of acutely HIV infected individuals feasible.
- NAAT testing is cost effective when applied in North Carolina to all public health HIV test sites. NAAT added:
  - $3.63 per specimen
  - $17,515 per additional index case identified
  - 3.3% increase over annual budget


- At a cost per QALY of $4,345, the program appears to be well below the cost-effectiveness threshold of $50,000,
  - Interventions that cost less than $50,000 are generally considered good public health investment opportunities in the United States.

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Superinfection After Primary HIV Infection


Graph showing the time course of CD4 cells and plasma viremia following treatment (Tx)
Superinfection Study Design

• Objective: to identify the rate of HIV superinfection among newly infected subjects.
• Study Population: 78 treatment naïve subjects from San Diego and Los Angeles AIEDRP Cohorts were enrolled.
• Comparison of genetic diversity between two blood samples collected at least 6 months apart (mean 283 days).
• Methods: clonal sequencing of env, length polymorphism of env, and dye-primer RT sequencing.

Smith, D, Wong J K, et al., JAMA 2004
RESULTS

• Three cases of intraclade B superinfection were identified representing a rate of 5% per year.

• Superinfection occurred 5-13 months after the estimated date of initial infection.

• All three individuals were male and had homosexual exposures as their only HIV risk factor.

Smith, D, Wong J K, et al., JAMA 2004
Clinical Implications

• Superinfection negatively impacted each individual’s clinical course.
  – Six months after acquiring the superinfecting strain, viral loads increased and CD4 counts decreased more than the rest of the cohort (p<.05).
  – Each case had a change in ARV susceptibility.

• Subjects A, C

• Subject B

Smith, D, Wong J K, et al., JAMA 2004
HIV Superinfection

- Infection with HIV does not necessarily provide protection against superinfection with the same or divergent HIV subtype.
- ARV Treatment in the 1-2 years following HIV infection should consider a potential superinfection risk of 5% among at-risk individuals.
  - Incidence density of 2.1/100 person years (95% CI: 0.6% to 5.2%) in similar cohort.
  
  Grant, R. et al., Abstract 59: CROI, 2005

- Cost of drug resistance re-screening of high risk individuals who meet selected criteria has not yet been determined
Treatment of Transmitted Drug Resistance

- Drug resistance testing is recommended for the initial selection and management of ARV therapy in patients with acute HIV infection
  
  DHHS Guidelines for ARV Use in Adults: 2005

- Transmission of drug resistant virus to recently infected subjects is associated with:
  - Fewer initial treatment options
  - Delayed treatment responses
  - More frequent virological failure

  Little S, et al. NEJM 2002

- Archival persistence of transmitted resistant variants will occur and later tests may fail to detect resistant virus and lead to suboptimal management

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Does transient therapy alter outcome?

• Two non-randomized studies of ARV therapy (one potent, one triple NRTI) initiated during acute HIV infection suggest that transient therapy (1-3 yrs) results in prolonged virologic suppression in a subset of patients who discontinue treatment
  - Though virologic control was not sustained in the former study: only 6 of 14 (43%) patients achieved control for up to 360 days, 3 of 14 (21%) suppression >720 days.

• Two open-label studies of potent ARV therapy in subjects initiating treatment after HIV seroconversion did not influence subsequent viral set point
Does Transient Therapy Alter Natural History?

Comparative retrospective study design using AIEDRP cohort:

- Patients (13 acute, 45 early) who initiated treatment w/i 2 wks-6 mo of seroconversion and continued for at least 12 weeks.
  - Followed by Tx interruption (median duration of ARV in both treatment groups was ~1.5 years)
- Untreated acute and early participants (n=337) censored at time of ARV initiation
- Compared HIV RNA and CD4 outcome at 24, 48, and 72 weeks

RESULTS

Table 2. Differences in mean HIV-1 RNA levels (expressed as log_{10} copies/milliliter) between treated and untreated subjects at follow-up time points.

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**NOTE.** Data in parentheses are 95% confidence intervals.

\(^a\) Subjects who started receiving HAART within 2 weeks of antibody seroconversion.

\(^b\) Subjects who started receiving HAART between 2 weeks and 6 months after antibody seroconversion.

\(^c\) \(P<.05\).

Adjusted analysis: controls for differences in VL and CD4 counts at baseline

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CONCLUSIONS

- Comparable CD4 increases were seen in both acute and early treated groups (CD4 benefit not lost until wk 72 in the early treated group)
- Results suggest that treatment given during acute HIV infection may modify the long-term course of disease
- In previous treatment studies, 0.6 log decrease in VL corresponded to an ~50% reduction in the risk of disease progression over 6 years
- Subjects who initiated HAART later but within 6 months of seroconversion appeared to receive more transient benefits

Limitations: Tx not randomized, Tx regimens heterogeneous, reasons for stopping not assessed, unmeasured differences in study groups possible

• Similar French study compared 58 patients (7 acute, 51 early) from the PRIMO cohort who initiated treatment <3.5 months after HIV infection
  – Sustained virologic response for 17.3 months
  – Followed by Tx interruption
• Natural history cohort (1988-1996) who met same PRIMO eligibility criteria were used for controls (n=116)
• Compared HIV RNA and CD4 outcome at 12 months after treatment interruption
• The estimated VL in the Tx’d group was slightly lower than the value reached at the same point during the natural history (0.16 log10 copies/ml; 95% CI, 0.58 to 0.25)

Desquilbet L, et al. AIDS 2004
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Treatment of Acute Infection: Assessment of Efficacy

• Increases in CD4+ T cell numbers in peripheral blood?
• Magnitude and breadth of HIV-specific CD4+ and CD8+ T-cell responses?
• Total cell-associated infectivity?
• The rate of clearance of HIV-1 DNA?
• The durability of plasma RNA suppression?
• Rate or magnitude of reconstitution of memory CD4+ T cell depletion in the GI mucosa?
• Alteration of natural history outcomes following transient courses of treatment?
RANDOMIZED CLINICAL TRIALS NEEDED!

• 31 studies reviewed in Medline review:
  – Only 4 were randomized clinical trials
  – Only 4 included >50 subjects


• Currently 4 RCT ongoing to assess several treatment issues
  – ACTG 371: Initially randomized, induction treatment for acute and early infection followed by STI (N=121)
  – AIN501/A5216: HAART +/- CsA in acute HIV infection (N=50)
  – AIN503/A5217: Treatment vs. no treatment for early HIV (N=150)
  – AIN504/A5218: Therapeutic immunization and treatment interruption for acute and early treated subjects (N=120)
CRITICAL QUESTIONS REMAIN

Recruitment Opportunities:

- Microbicide trials
- Pre-exposure prophylaxis trials
- Vaccine trials (HVTN)
- Behavioral trial networks
- CHAVI network
- AIEDRP network
- Other detection studies
ARV Therapy for ACUTE Infection: Summary

• Available data suggests treatment of Acute HIV may:
  – Normalize CD4+ T-cell numbers in the peripheral blood
  – Prolong virologic control in a subset of patients who discontinue treatment after 1-2 years
  – Preserve functional HIV-specific T-cell clones (in vitro cell proliferation, cytokine production, cytotoxic responses)
  – Reduce the risk of HIV transmission
  – Reduce the risk of HIV superinfection
  – Permit durable suppression a 13% virologic failure rate in the first 3 years of therapy
  – Insufficient data to know the effect on reconstitution of depleted mucosal memory CD4+ T cells

• Potential Risks:
  – Select for drug resistant variants in poorly compliant patients
  – Expose individuals who might otherwise “control” their virus to unnecessary ARV toxicity
ARV Therapy for EARLY Infection: Summary

- Available data suggests treatment of Early HIV may:
  - Reduce the risk of HIV transmission (less potential risk compared to acute HIV)
  - Reduce the risk of superinfection (unclear how long this risk persists)
  - Permit durable suppression with very low rates of AE and virologic failure
  - Insufficient data to demonstrate improved disease outcomes, though time to CD4<350 may improved with treatment
  - Unlikely to have profound effect on reconstitution of depleted mucosal memory CD4+ T cells

- Potential Risks:
  - Select for drug resistant variants in poorly compliant patients
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