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/mm^3?
  - 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

Guadalupe M, Sankaran S, et al. J Virol 2006

- 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

Pilcher C, Fiscus S, et al. NEJM 2005

- 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.

Simpson K, Biddle A, et al. CROI 2006

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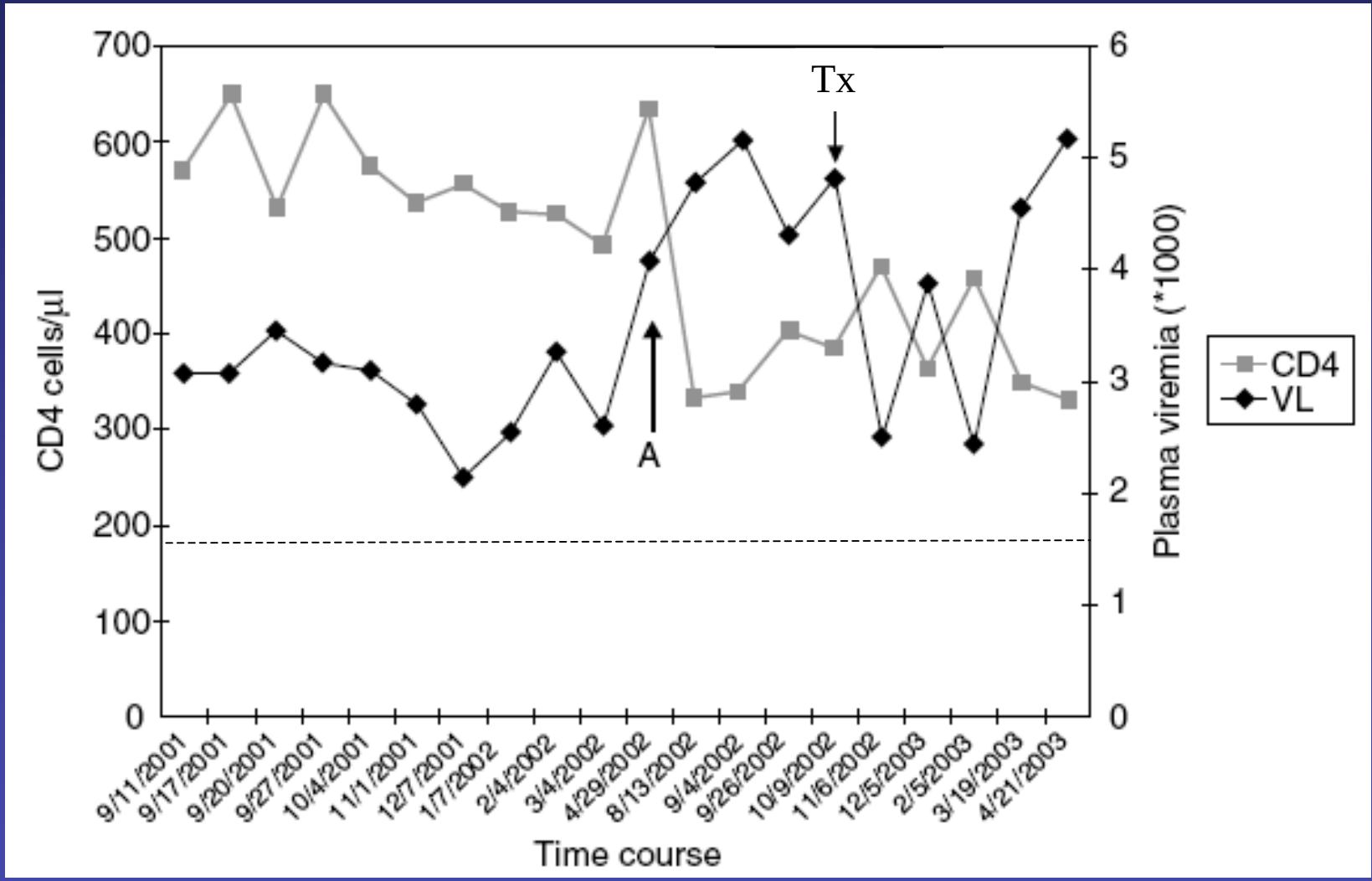
Superinfection After Primary HIV Infection



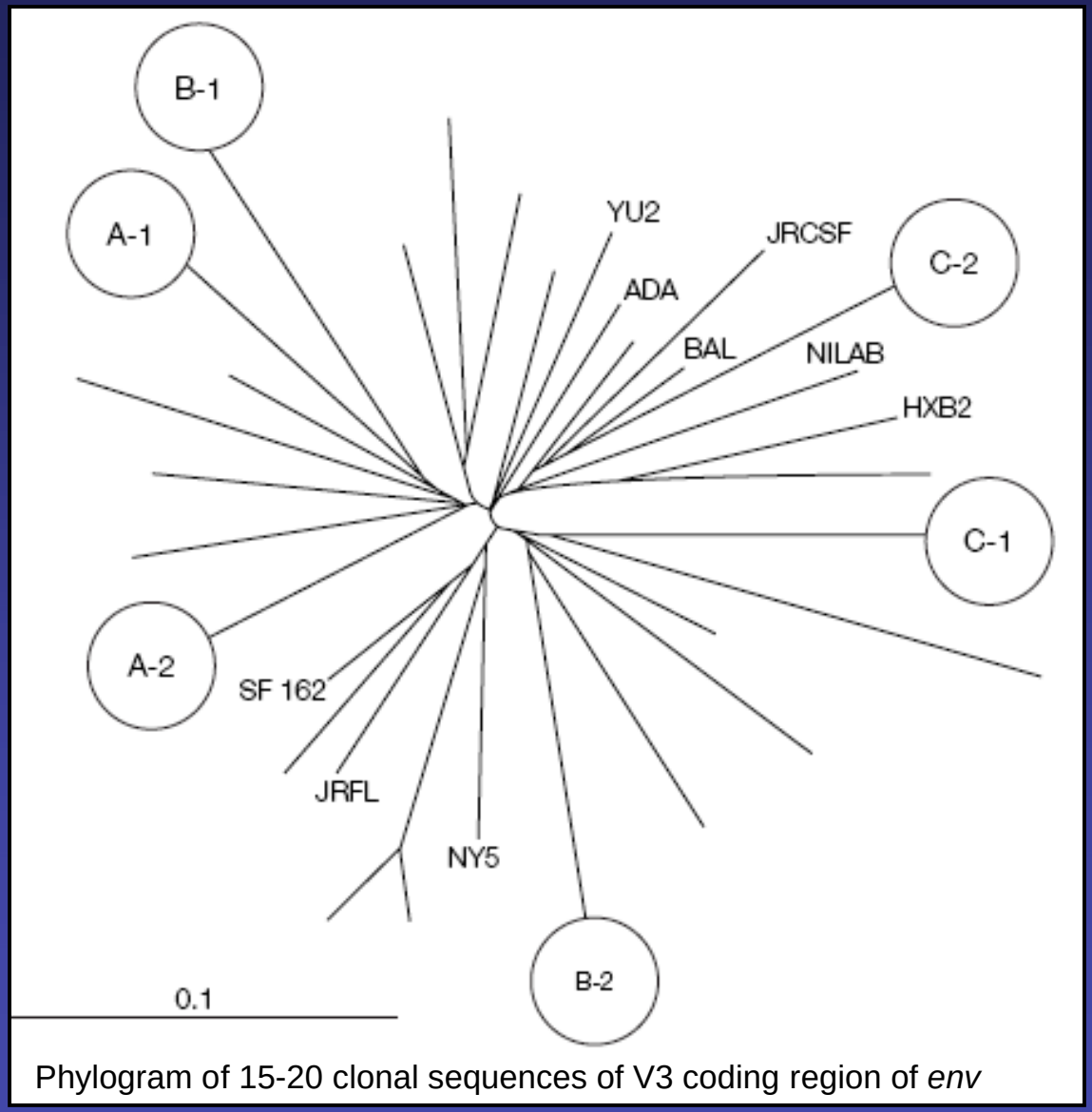
Smith DM, Wong JK, et al. AIDS 2005

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



Phylogram of 15-20 clonal sequences of V3 coding region of *env*

- 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 individuals' 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.

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

  Pao D, Andrady U, et al. J AIDS 2004

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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

  – Rosenberg ES, et al. Nature: 2000; Girard PM, et al. AIDS: 2001

  – 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.

  Kaufmann DE, et al. Plos Med: 2004

- Two open-label studies of potent ARV therapy in subjects initiating treatment after HIV seroconversion did not influence subsequent viral set point

  Markowitz M, et al. JID: 2002; Fidler S, et al. AIDS: 2002

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

Hecht FM, Wang L, et al. JID 2006

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.

Follow-up time point	Acute treatment[a] group minus untreated group		Early treatment[b] group minus untreated group	
	Unadjusted	Adjusted	Unadjusted	Adjusted
24 weeks	−0.48[c] (−0.82 to −0.13)	−0.69[c] (−1.01 to −0.38)	−0.49[c] (−0.66 to −0.32)	−0.51[c] (−0.68 to −0.35)
48 weeks	−0.29 (−0.17 to 0.13)	−0.59[c] (−1.02 to −0.16)	−0.05 (−0.29 to 0.19)	−0.10 (−0.35 to 0.15)
72 weeks	−0.35 (−0.91 to 0.21)	−0.68[c] (−1.30 to −0.07)	0.13 (−0.21 to 0.48)	0.10 (−0.27 to 0.47)

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

Hecht FM, Wang L, et al. JID 2006

HOWEVER

- 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

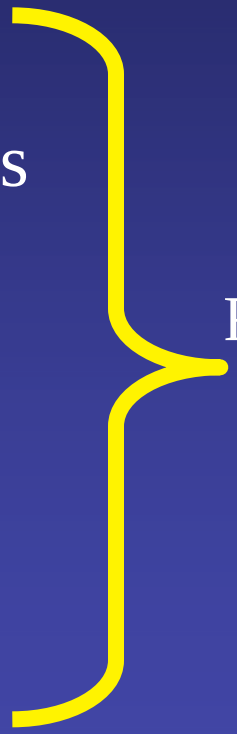
Smith DE, Walker BD, et al. AIDS: 2004

- 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)
  - SPARTAC: comparison of 3 strategies of intervention: long course [48 wk] ARV, short course [12 wk] ARV, no ARV (N=360)

CRITICAL QUESTIONS REMAIN

Recruitment Opportunities:

- Microbicide trials
- Pre-exposure prophylaxis trials
- Vaccine trials (HVTN)
- Behavioral trial networks
- CHAVI network
- AIEDRP network
- Other detection studies



Randomized Treatment Intervention Trials

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

ACKNOWLEDGMENT

University of California, San Francisco - Jay Levy, Rick Hecht
University of Washington, Seattle - Ann Collier
University of Colorado Health Sciences Center - Elizabeth Connick
CREAIDS, Salvador, Brazil - Eduardo Netto
University of Zimbabwe-Clinical Research Centre - James Gita Hakim
Aaron Diamond AIDS Research Center - Marty Markowitz
SUNY Downstate - Jack DeHovitz
Columbia University - Scott Hammer, Christine Hogan
University of California, San Diego - Douglas Richman, Susan Little
Harbor - University of California, Los Angeles - Eric Daar
Cedars-Sinai Medical Center - Eric Daar
Johns Hopkins University - Joseph Margolick
University of British Columbia - Brian Conway
McGill University - Raffick-Pierre Sékaly, Jean-Pierre Routy
University of Alabama at Birmingham - Michael Kilby
Vanderbilt University - David Haas
Duke University - Charles Hicks
UNC - Chapel Hill - Christopher Pilcher
Massachusetts General Hospital - Bruce Walker, Eric Rosenberg
Fenway Community Health - Daniel Cohen
University of New South Wales - David Cooper
Brigham and Women's Hospital - Paul Sax