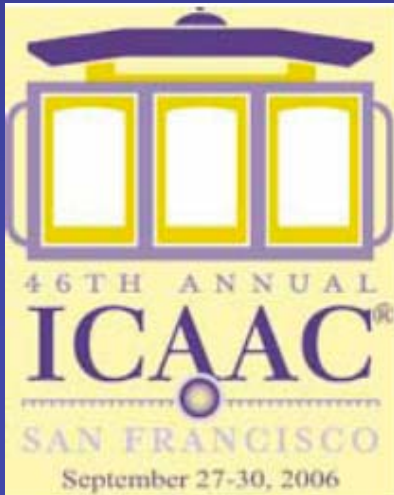


# Therapy of Acute HIV-1 Infection: An Update

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# Acute Infection: Treatment Issues

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- 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<sup>3</sup>?
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- What are the best measures of therapeutic efficacy?

# Primary HIV Infection: Acute + Early Infection

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## Transmitted HIV Infection (ARV Naïve)

- **Acutely** Infected: HIV RNA positive (VL  $\geq 5000$ ) or detectable serum p24 antigen, HIV EIA negative or WB indeterminate
- **Early** Infected: HIV EIA positive with simultaneous LS EIA O.D.  $\leq 1.0$  (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?

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- 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!!

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## 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

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## 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.

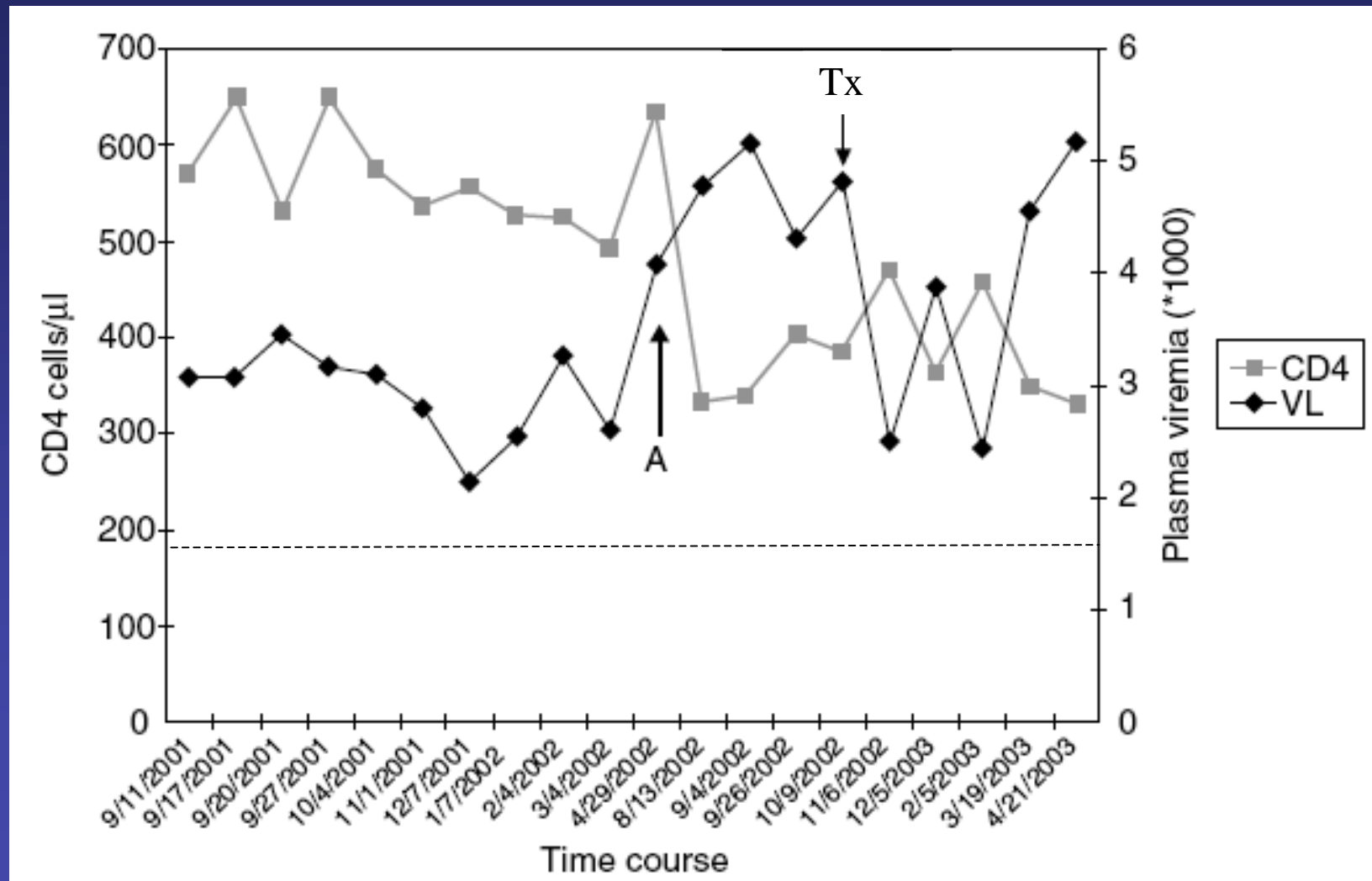
Simpson K, Biddle A, et al. CROI 2006

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# Superinfection After Primary HIV Infection

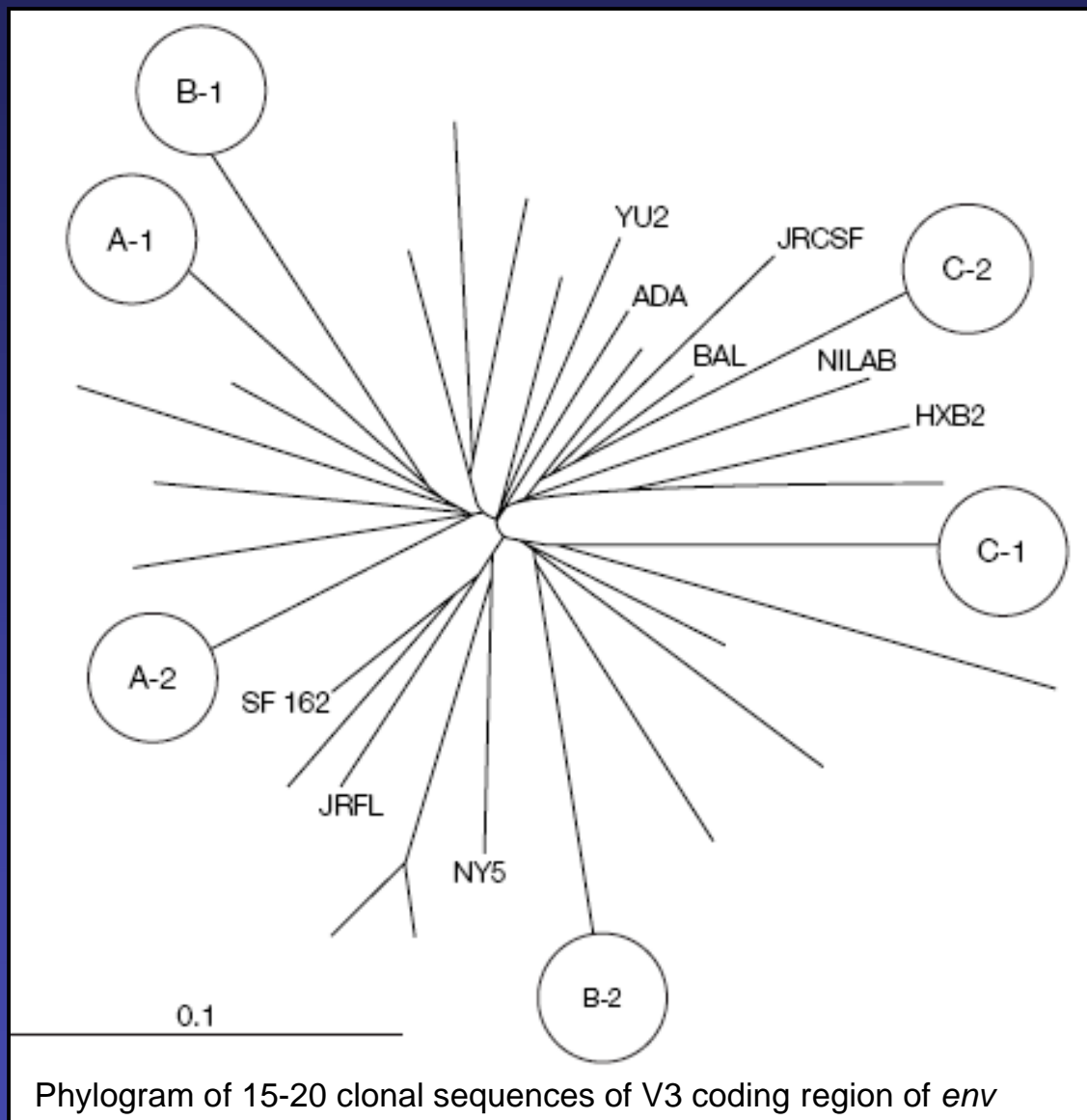


# Superinfection Study Design

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- 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.

# RESULTS

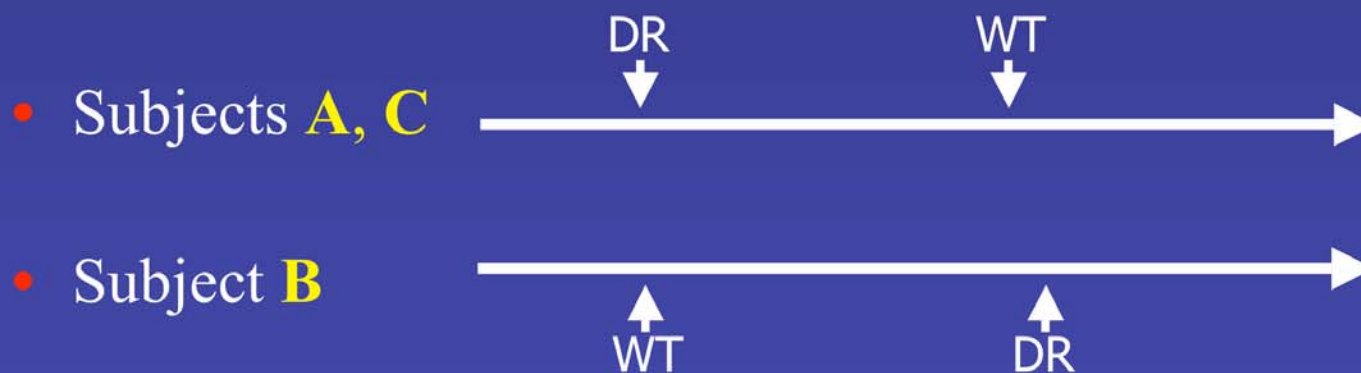


- Three cases of intraclade B superinfection were identified representing a rate of **5% per year**
- Superinfection occurred 5-13 months after the estimated date of initial infection.
- All three individuals were male and had homosexual exposures as their only HIV risk factor.

# Clinical Implications

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- 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.



# HIV Superinfection

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- 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

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- 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?

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- 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?

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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<sub>10</sub> copies/milliliter) between treated and untreated subjects at follow-up time points.**

Follow-up time point	Acute treatment <sup>a</sup> group minus untreated group		Early treatment <sup>b</sup> group minus untreated group	
	Unadjusted	Adjusted	Unadjusted	Adjusted
24 weeks	-0.48 <sup>c</sup> (-0.82 to -0.13)	-0.69 <sup>c</sup> (-1.01 to -0.38)	-0.49 <sup>c</sup> (-0.66 to -0.32)	-0.51 <sup>c</sup> (-0.68 to -0.35)
48 weeks	-0.29 (-0.17 to 0.13)	-0.59 <sup>c</sup> (-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 <sup>c</sup> (-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.

<sup>a</sup> Subjects who started receiving HAART within 2 weeks of antibody seroconversion.

<sup>b</sup> Subjects who started receiving HAART between 2 weeks and 6 months after antibody seroconversion.

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

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# CONCLUSIONS

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- 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

# HOWEVER

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- 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 log<sub>10</sub> copies/ml; 95% CI, 0.58 to 0.25)

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# Treatment of Acute Infection: Assessment of Efficacy

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- 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!

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- 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

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## 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

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- 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

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- 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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