

To Start or *START*?

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DHHS Guidelines for Initiating ARV Tx in Asymptomatic Patients: 1998-2009

Year	CD4 Cell Count
June 1998	≤ 500
February 2001	≤ 350
April 2005	≤ 200
December 2007	≤ 350
December 2009	≤ 500

2009 Guidelines: A Closer Look

- ARV therapy should be initiated in all patients with a history of an AIDS-defining illness, or with CD4 count of < 350 cells
- ARV therapy at any CD4 count: pregnancy, HIV associated nephropathy and HBV coinfection when Tx is indicated
- ARV therapy is recommended for patients with CD4 counts between 350 and 500
 - Panel divided on the strength of this recommendation: 55% of Panel members voted for strong recommendation and 45% voted for moderate recommendation
- For patients with CD4 counts > 500 cells, 50% of Panel favored starting ARV therapy; other 50% view treatment as optional

Reasons for Shift

Year	CD4 Cell Count
June 1998	≤ 500
February 2001	≤ 350
April 2005	≤ 200
December 2007	≤ 350
December 2009	≤ 500

- No eradication
- Questionable efficacy
- Adherence struggles
- Side effects

Reasons for Shift

Year	CD4 Cell Count
June 1998	≤ 500
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- Improved efficacy
- Fewer side effects
- Better adherence
- Emerging data suggesting earlier treatment is better for personal health
- Treatment as prevention

Earlier Treatment: The Data

- North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)
- 22 research cohorts from the US and Canada (IeDEA Network); N=16,636 Tx-naïve patients
- <350 cells vs. 351- 500
 - 69% reduced risk of death (risk ratio: 1.69)
- <500 cells vs. >500 cells
 - 94% reduced risk of death (risk ratio: 1.94)

Earlier Treatment: The Data

- Antiretroviral Therapy Cohort Collaboration (ART-CC)
- 19 cohort studies from Europe and North America; N=24,444 Tx-naïve patients
- CD4s >350 vs. 200-349
 - declining risk of AIDS or death for up to 5 years
- 351–450 vs. 451–550 range
 - Similar rate of progression (risk ratio: 0.99)

Earlier Treatment: The Data

- Cohorts say untreated HIV infection associated with:
 - Higher risk of cardiovascular disease
 - Independent of CD4 count
 - Higher risk of malignancies
 - Higher risk when CD4s <500
 - Neurocognitive Decline
 - Lower risk when CD4s >350
 - T-cell activation, dysfunction and inflammation
 - Evident when CD4s <350

The Problem With Cohorts

- DHHS re: NA-ACCORD:

“Although large and generally representative of care in the United States, the study has several limitations, including the **small number of deaths** and the potential for **unmeasured confounders** that might have influenced outcomes independent of antiretroviral therapy.”

The Problem With Cohorts

- Early starters may be different in some unmeasured way that improves survival
 - What about depression? Greater empowerment? Access to care? Knowledge?
- Different levels of adherence as shown by viral suppression in NA-ACCORD
 - 81% in early start
 - 71% in deferred start
- Cause of death only known for 16% in NA-ACCORD
- No data on levels of resistance and toxicities of early treatment in these cohorts

The Problem With Cohorts

- Numerous cohort/observational studies demonstrated women on hormone replacement therapy (HRT) had *decrease* in risk of coronary heart disease (CHD)
 - HCPs recommend HRT as protection against CHD
- Randomized controlled trials demonstrated HRT caused small, but significant, *increase* in CHD risk
 - Women on HRT more likely to be from socio-economic groups with better than average diet and exercise
 - HRT use and decreased CHD risk were coincident effects of a common cause, rather than cause and effect

Treatment as Prevention

- Lower plasma viral loads are associated with decreases in the concentration of the virus in genital secretions
- Studies of HIV serodiscordant heterosexual couples have demonstrated a relationship between the level of plasma HIV RNA and transmission risk
 - When plasma HIV RNA levels are lower, transmission events are less common

Treatment as Prevention

- Other observational studies and models also suggest viral load suppression in treatment-adherent patients with no sexually transmitted infections substantially reduces the risk of HIV transmission

Treatment as Prevention

- Several lingering questions/concerns:
 - Public health benefit may not be as robust as advertised
 - Undetectable blood viral loads does not mean undetectable semen viral load
 - Most transmissions occur early in disease and we will still miss this window
 - Ethics of public health effort in absence of data confirming individual benefit of early treatment
 - Criminalization of those who choose to forgo treatment?
 - Benefit may be offset by risk

Early Therapy: What's the Balance?

- Potential Gains
 - Reduction in morbidity & mortality?
 - How much?
 - Reduction in HIV incidence?
 - Population specific?
- Potential Drawbacks
 - May treat LTNPs
 - Toxicities, known and unknown....
 - Adherence challenges
 - Resistance risk
 - Losing meds we may need later
 - Pipeline isn't robust
 - Cost of meds and labs

Early Therapy: Cost vs. Benefit?

For one year:

- Atripla: \$18,800
- 4 CD4 counts: \$800
- 4 viral loads: \$400

TOTAL: \$20,000

What Can't We Afford?

- Adherence counseling
- Prevention counseling
- Family planning
- Nutrition
- Stress reduction training
- Mental health
- Smoking cessation
- Substance abuse treatment

Early Therapy Rebuttals

- Time from CD4 500 to CD4 350 in untreated patients is ~3 years
 - Small additional period of risk when Tx goes on for decades
- Toxicities are preventable/reversible
- Treatment may further extend life
- Possibility of condom-free sex; incentive for medication adherence?

START Study

- Only way to know the benefits and risks of early treatment is to conduct a randomized, controlled study
- Strategic Timing of Antiretroviral Treatment (START) study
 - Being conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
 - Involving 90 sites in nearly 30 countries
 - Randomizing more than 4,000 Tx-naïve individuals with CD4s above 500 to either begin treatment immediately or defer treatment until their CD4s are less than 350 cells

START Study

- Primary objective: determine whether or not those who start therapy immediately are less likely to develop a serious AIDS illness, a serious non-AIDS illness or death from any cause
- Secondary objective: answer more specific questions about early treatment, including its effects on neurological, arterial, pulmonary and bone diseases.

The Big Question

- Should public policy, promoting individual and public health benefits of early treatment, be rolled out in the absence of randomized, controlled trial data?
 - Should we start or START?