Universal Voluntary Testing and Treatment: When to Start ART and Other Research Issues

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Evolution of Adult/Adolescent ART Treatment Guidelines

- **1987-1995**  Treat patients with AIDS-defining illnesses
  -- Various CD4 recommendations
- **1996-2001**  “Hit early, hit hard”
  -- offer ART at CD4 ≤500
- **2002-2007**  Weighing pros and cons
  -- Treat at CD4 ≤200; discuss/offer ART at CD4 200-350
- **2008**  Moving toward earlier ART
  -- Treat at CD4 ≤350; consider ART at CD4 >350 depending on comorbidities/patient scenarios
Improved Antiretroviral Regimens
More Effective, Better Tolerated, More Convenient
# Current Guidelines for Initiation of Antiretroviral Therapy in Adults and Adolescents

<table>
<thead>
<tr>
<th>Guideline</th>
<th>AIDS and/or Symptomatic HIV Disease</th>
<th>Asymptomatic by CD4 Cell Count</th>
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<tbody>
<tr>
<td>U.S. Department of Health and Human Services, 2008</td>
<td>Yes</td>
<td>Yes</td>
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<td>International AIDS Society–USA, 2008</td>
<td>Yes</td>
<td>Yes</td>
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<td>British HIV Association, 2008</td>
<td>Yes</td>
<td>Yes</td>
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<td>European AIDS Clinical Society, 2008</td>
<td>Yes</td>
<td>Yes</td>
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<td>Southern African Clinicians Society</td>
<td>Yes</td>
<td>Yes</td>
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<td>World Health Organization, 2006</td>
<td>Yes</td>
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Sources: Wilken & Gulick, CID 47:1580, 2008
Multiple Randomized, Controlled Trials and Observational Studies Strongly Support Initiation of ARV Therapy in Patients with CD4 Counts <200

A Controlled Trial of Two Nucleoside Analogues plus Indinavir in Persons with Human Immunodeficiency Virus Infection and CD4 Cell Counts of 200 per Cubic Millimeter or Less

SM Hammer et al. for the AIDS Clinical Trials Group 320 Study Team

Rates of Disease Progression by Baseline CD4 Cell Count and Viral Load after Initiating Triple-Drug Therapy

RS Hogg et al.
No randomized clinical trial definitively addresses the optimal time to initiate antiretroviral therapy in chronically infected patients with CD4 counts >200 cells/mm$^3$.

However, numerous observational studies assessing immunological parameters and HIV disease progression strongly support ARV therapy for patients with 200-350 cells/mm$^3$. 
Prognosis of HIV-1-Infected Patients up to 5 years after Initiation of HAART: Collaborative Analysis of Prospective Studies.

M May et al. for the Antiretroviral Therapy (ART) Cohort Collaboration

5-year Risk of AIDS or Death Following the Initiation of ART

- Risk Difference: 39%

CD4+ Cell Count at ART Initiation

- VL < 5 log10 copies/mL
- CDC stage A/B, age < 50 yrs
- no history of IDU
Growing Evidence from Developed Countries Suggests that ART Should be Initiated Earlier, at CD4 Counts >350
Patients Starting ART at CD4 Count >350 Significantly More Like to Achieve Normalized CD4 Counts Than Those Starting Later

CD4 Cell Counts of 800 Cells/mm³ or Greater after 7 years of Highly Active Antiretroviral Therapy are Feasible in Most Patients Starting with 350 Cells/mm³ or Greater

L Gras et al. and the AIDS Therapy Evaluation Project (ATHENA)

CD4+ Cell Count 6 years after Commencement of Highly Active Antiretroviral Therapy in Persons with Sustained Virologic Suppression

RD Moore & JC Keruly
Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival

Mari M. Kitahata et al.

- 69% higher risk of death for patients who deferred rather than initiated ART at a CD4 count between 351-500 (n=8,362)

- 94% higher risk of death for patients who deferred rather than initiated ART at a CD4 count >500 (n=9,155)
Timing of Initiation of Antiretroviral Therapy in AIDS-Free HIV-1-Infected Patients: a Collaborative Analysis of 18 HIV Cohort Studies

JAC Sterne and the When To Start Consortium

- 18 diverse observational cohorts in Europe and North America; total n = >45,000

- 28% higher risk of AIDS or death for patients who deferred ART until a CD4 count of 251-350, rather than starting therapy at CD4 count of 351-450; 13% higher risk of death
Cumulative Probability of AIDS or Death after Initiation of Combination ART, According to Range of CD4 Cell Count at Start of Treatment

Source: Sterne et al., Lancet, published online April 9, 2009
There is a Paucity of Data from Developing Countries on Early Initiation of ART (e.g. CD4 > 350)
NIH News
National Institutes of Health

June 8, 2009

Starting Antiretroviral Therapy Earlier Yields Better Clinical Outcomes

Interim Review Leads to Early End of Clinical Trial in Haiti

~4-fold increased risk of death for patients deferring ART until CD4 count dropped below 200 vs. initiating ART at CD4 count between 200-350 (n=816)
HPTN 052 –
Selected Research Goals

• Discordant couples study randomized to immediate or deferred therapy to determine:
  – Impact of early ART on HIV disease progression (between 550 and 250 CD4 cells)
  – Efficacy of ART in Preventing HIV Transmission
The START Study

START (INSIGHT I01): Strategic Timing of Antiretroviral Treatment

- Randomized study to determine whether immediate initiation of ART in patients with CD4 count > 500 is superior to deferral of ART until the CD4+ declines below 350.

- Clinical cites in 23 countries in N. America, S. America, Europe, Africa, Middle East, Asia

- Enrollment opened in March, 2009
Benefits and Risks of Initiating Antiretroviral Therapy in Asymptomatic Patients with CD4 T-Cell Counts >350
# Pros and Cons of Early ART

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<th>Pros</th>
<th>Deferred ART</th>
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<tr>
<td><strong>Early ART</strong></td>
<td><strong>Preserve drugs for use</strong></td>
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<tr>
<td>Reduce risk of death/AIDS/serious non-AIDS events</td>
<td>when needed</td>
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<tr>
<td>Reduce HIV transmission?</td>
<td>Reduce costs</td>
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<table>
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<tr>
<th>Cons</th>
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<tr>
<td>Increased side effects</td>
<td>Higher risk of AIDS/ non-AIDS events/death</td>
</tr>
<tr>
<td>Limit future options</td>
<td>Increased HIV transmission?</td>
</tr>
<tr>
<td>Increased costs</td>
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Source: International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
Selected Parameters to be Assessed, Prospectively and Retrospectively

- Benefit of early HIV treatment on serious clinical events (both AIDS & non-AIDS)
- Effect of early HIV treatment on:
  - Cost
  - Adverse events
  - Resistance
  - Adherence & regimen use
  - Metabolic abnormalities
  - Body composition
Opportunities for Preventing HIV Infection

Unexposed (precoital/coital) - Behavioral, structural
Male circumcision, condoms

Exposed (postcoital) - Vaccine, topical microbicides, PrEP

Exposed (postcoital) - Vaccine, Pep

Infected - Treatment of HIV, reduced infectivity

Years -> Hours -> 72h - 28d -> Years

Opportunities for Preventing HIV Infection

Unexposed

- Behavioral, structural
  - Male circumcision, condoms

Exposed (precoital/coital)

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Exposed (postcoital)

- Vaccine, Pep

Infected

- Treatment of HIV, reduced infectivity

 Expanded HIV Treatment to Slow Transmission: Selected Studies

**THE LANCET** Infectious Diseases

*Could Widespread Use of Combination Antiretroviral Therapy Eradicate HIV Epidemics?*

JX Velasco-Hernandez, HB Gershengorn & SM Blower

**The Journal of Infectious Diseases**

*Expanded Access to Highly Active Antiretroviral Therapy: a Potentially Powerful Strategy to Curb the Growth of the HIV Epidemic*

VD Lima, JD Montaner et al.
Universal, Voluntary “Test and Treat” Concept

Universal Voluntary HIV Testing with Immediate Antiretroviral Therapy as a Strategy for Elimination of HIV Transmission: a Mathematical Model

RM Granich et al.

“This approach merits further mathematical modelling, research, and broad consultation.”
As with all mathematical models, the voluntary test and treat model is based on a number of assumptions that require validation with research.

Universal Voluntary Testing and Treatment for Prevention of HIV Transmission

CW Dieffenbach and AS Fauci
Selected Research Issues Related to the Voluntary “Test and Treat” Approach

- Universal testing
- Relationship of the stage of HIV infection to efficiency of transmission
- Efficacy of ART in preventing HIV transmission
- Drug resistance
- Behavioral “disinhibition”
- Benefit to the individual
- Cost-effectiveness for society
A Policy Cocktail for Fighting HIV

By Anthony S. Fauci

Three-pronged approach to curbing HIV/AIDS pandemic:

- Pre-exposure prophylaxis of high-risk individuals with antiretroviral therapy (PrEP)
- Universal, voluntary testing/immediate antiretroviral therapy ("test and treat" approach)
- Cure/functional cure research
CD4+ Count-Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group

- n=5472; >95% ARV-experienced
- For patients receiving episodic ART guided by CD4 counts versus continuous ART at CD4>350
  - 80% higher risk of death
  - 70% higher risk of major cardiovascular, renal and hepatic disease
477 patients who were either ART-naive or who had not received ART for 6 months were analyzed.

For patients receiving episodic ART guided by CD4 counts versus continuous ART at CD4 >350:

- 3.5-fold increased risk of OI or death (15 vs. 5 events)
- 7-fold risk increased risk of serious non-AIDS events (cardiovascular, renal and hepatic disease) or non-OI death (12 vs. 2 events)
Time to Major Clinical Event Among Patients who were ART-Naive or Who had Discontinued ART for 6 Months When They Entered the SMART Study

Hazard Ratio = 4.19 (95% CI: 1.69-10.4)
P = 0.002