

# Initiation of Potent Combination Antiretroviral Therapy Among HIV-infected Patients at All CD4 Cell Count Levels Within Six Months of First Clinic Visit is Associated with Better Outcomes

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## Introduction

- Optimal timing for initiation of potent combination antiretroviral treatment is not known
- Risks associated with antiretroviral therapy including long-term toxicities and the development of drug resistance must be weighed against the benefits of treatment
- No prospective studies comparing the outcomes of early versus delayed initiation of potent combination antiretroviral therapy
- In the absence of long-term clinical outcomes data, the decision to initiate antiretroviral therapy is guided by an individual's virologic, immunologic, clinical status, and risk of disease progression

## Background

•Previous studies reported an increased risk of disease progression among patients with CD4 cell count<200/mm<sup>3</sup> at the time of initiating antiretroviral therapy

•8th Conference on Retroviruses and Opportunistic Infections, Chicago, IL February 4-8, 2001

•Kaplan J, Hanson D, Karon J, et al. Late Initiation of Antiretroviral Therapy (at CD4+Lymphocyte Count <200 Cells/ml) Is Associated with Increased Risk of Death [Abstract #520]

•Hogg R, Yip B, Wood E, et al. Diminished Effectiveness of Antiretroviral Therapy among Patients Initiating Therapy with CD4+Cell Counts Below 200/mm<sup>3</sup> [Abstract #342]

•Chen R, Westfall A, Cloud G, et al. Long-Term Survival After Initiation of Antiretroviral Therapy [Abstract #341]

•Sterling T, Chaisson R, Bartlett J, Moore R. CD4+Lymphocyte Level Is Better than HIV-1 Plasma Viral Load in Determining When To Initiate HAART [Abstract #519]

•Findings confounded by increased risk of progression associated with underlying severity of HIV disease among patients with CD4 cell count<200/mm<sup>3</sup> (independent of antiretroviral treatment)

•Risk of progression at higher CD4 cell counts unclear due to limited number of clinical endpoints among these patients

## Background

•The risk of progression of HIV disease associated with initiating treatment at various CD4 cell count levels cannot be defined in the absence of a comparison group of untreated patients at the same stage of disease

•One study (using a nested case control design) compared the adjusted risk of disease progression among patients starting potent antiretroviral treatment at a CD4>350/mm<sup>3</sup> with those at the same disease stage who were **not** treated and found a significant increase in risk of progression among untreated patients with a CD4>350/mm<sup>3</sup>

•Opravil M, Ledergerber B, Furrer H, et al. Clinical benefit of early initiation of HAART in patients with asymptomatic HIV infection and CD4 counts >350/mm<sup>3</sup> [Abstract #LB6]

## Specific Aims

•We conducted this study to examine the effect of initiating antiretroviral treatment at all CD4 cell count levels on disease progression and death

•After controlling for patients' underlying disease stage as defined by CD4 cell count level and baseline HIV-1 RNA level

## Methods

- Setting
  - Retrospective cohort study of HIV-infected patients cared for in a University-based HIV specialty clinic
- Study cohort
  - HIV-infected individuals whose first clinic visit occurred after the availability of PIs (1995 and 2001)
  - No HIV-related clinical conditions (asymptomatic) prior to or during the 6 months following the initial clinic visit (initial observation period)
  - Thus, all patients in the study cohort had the same potential to experience any clinical endpoint
- Source of data
  - University of Washington HIV Information System (UWHIS)

## Statistical Analysis

•We used Cox proportional hazards survival analysis to determine the adjusted hazard ratio (HR) of disease progression or death

•According to whether a patient received PI or NNRTI-based combination antiretroviral treatment, dual NRTI therapy, or no antiretroviral treatment within the initial observation period

•Controlling for CD4 cell count level within 6 months of the initial visit, baseline HIV-1 RNA level, and demographic characteristics

•Clinical endpoints included symptomatic HIV-related conditions, opportunistic infections, and death

**Table 1. Populations Characteristics**

Characteristics	Number of Patients (%)
<b>Age</b>	
< 30	48 (23.0)
30-39	114 (54.5)
40-49	36 (17.2)
50+	11 ( 5.3)
<b>Gender</b>	
Female	19 ( 9.1)
Male	190 (90.9)
<b>Race</b>	
Black	29 (13.9)
Caucasian	139 (66.5)
Hispanic	18 ( 9.6)
Other	23 (11.0)
<b>Risk Factor</b>	
MSM	132 (63.2)
IDU	32 (15.3)
Heterosexual	26 (12.4)
Other/Unknown	19 ( 9.1)
<b>Insurance</b>	
Medicaid	20 ( 9.6)
Medicare	15 ( 7.2)
Other Public	128 (61.2)
Private	46 (22.0)

**Table 2. First Visit Information**

Characteristics	Number of Patients (%)
<b>PI-Based Regimen</b>	<b>58 (27.8)</b>
Indinavir	19 (32.8)
Nelfinavir	24 (41.4)
Ritonavir	12 (20.7)
Saquinavir	3 ( 5.2)
<b>NNRTI-Based Regimen</b>	<b>31 (14.8)</b>
Efavirenz	20 (64.5)
Nevirapine	11 (35.5)
<b>NRTI (only) Regimen</b>	<b>39 (18.7)</b>
<b>No Antiretroviral Therapy</b>	<b>81 (38.8)</b>
<b>CD4 cell count/mm<sup>3</sup></b>	
> 500	54 (25.8)
351-500	51 (24.4)
201-350	63 (30.1)
≤ 200	41 (14.8)
<b>HIV-1 RNA copies/ml</b>	
> 50,000	64 (30.6)
10,000 - 49,999	56 (26.8)
3,000 - 9,999	21 (10.0)
50 - 2,999	39 (18.7)
BLQ < 10,000	17 ( 8.1)
BLQ < 500	12 ( 5.7)

## Results

•209 patients were observed for a median of 29.2 months (range 6.5 to 80.0 months)

•73 patients had a clinical event and 5 patients died following the initial observation period

•AIDS-defining conditions observed included candidiasis (esophageal), cryptosporidiosis (chronic intestinal), encephalopathy (HIV), herpes simplex (chronic), Kaposi's sarcoma, *Mycobacterium tuberculosis*, cytomegalovirus (encephalitis), recurrent pneumonia, wasting syndrome

•Symptomatic conditions included bacterial endocarditis, candidiasis (oral, persistent vulvovaginal), cervical dysplasia (carcinoma in situ), herpes zoster (multidermatomal), peripheral neuropathy

•90% of patients with CD4 cell count<200/mm<sup>3</sup> received potent combination antiretroviral treatment during the study period

**Table 3. Antiretroviral Treatment During Initial Observation Period by Year**

	No Antiretroviral Therapy	NRTI (Only) Regimen	PI/NNRTI-Based Regimen	No. (%)
1995-1996	29 (37.2)	34 (43.6)	15 (19.2)	78 (37.3)
1997-1998	24 (40.7)	2 ( 3.4)	33 (55.9)	59 (28.2)
1999-2001	28 (38.9)	3 ( 4.2)	41 (56.9)	72 (34.4)
	81 (38.8)	39 (18.7)	89 (42.5)	209

## Results

•Patients initiating PI or NNRTI-based combination antiretroviral treatment at all CD4 cell count levels within 6 months of their initial clinic visit had less than half the rate of disease progression (HR=0.44; P<0.01) compared with patients who did not receive treatment

•Disease progression or death occurred in 28% of patients receiving PI or NNRTI-based vs. 46% of patients receiving NRTIs, and 43% of patients who did not receive antiretroviral treatment during the initial observation period

•As expected, after controlling for the effect of antiretroviral treatment, patients whose CD4 cell count was ≤200 cells/mm<sup>3</sup> or 201-350 cells/mm<sup>3</sup> at the initial clinic visit had higher rates of disease progression (HR=2.42; P<0.01; HR=1.73, P=0.10) than patients with a CD4 cell count >350 cells/mm<sup>3</sup>

**Table 4. Relative Hazard of Disease Progression or Death According to Selected Variables (N=209)**

Variable	N	Hazard Ratio (95% CI)	p-value
<b>Age</b>			
<30	48	0.95 (0.49-1.85)	>0.2
30-39	114	1 (Ref)	
40+	47	1.07 (0.79-1.47)	>0.2
<b>Gender</b>			
Female	19	1 (Ref)	
Male	190	0.80 (0.32-2.02)	>0.2
<b>Race</b>			
Black	29	0.79 (0.35-1.81)	>0.2
Caucasian	139	1 (Ref)	
Hispanic	18	0.36 (0.1-1.23)	0.10
Other	23	0.69 (0.32-1.50)	>0.2
<b>Risk Factor</b>			
MSM	132	1 (Ref)	
IDU	32	1.99 (1.08-3.67)	0.03
Heterosexual	26	1.06 (0.43-2.60)	>0.2
Other/Unknown	19	2.31 (0.93-5.76)	0.07
<b>CD4 cell count/mm<sup>3</sup></b>			
>350	105	1 (Ref)	
201-350	63	1.73 (0.90-3.33)	0.10
< 200	41	2.42 (1.32-4.41)	<0.01
<b>HIV-1 RNA copies/ml</b>			
< 10,000	89	1 (Ref)	
10,000-49,999	56	1.17 (0.6-2.28)	>0.2
> 50,000	64	1.74 (0.97-3.13)	0.07
<b>Treatment within 6 months</b>			
No Treatment	81	1 (Ref)	
NRTI Based Regimen	39	0.79 (0.43-1.46)	>0.2
PI/NNRTI Based Regimen	89	0.44 (0.25-0.77)	<0.01

## Discussion

•Our results demonstrate a significant clinical benefit of antiretroviral treatment for patients at **all** CD4 cell count levels

•Longer-term follow up enables better assessment of the clinical benefit of antiretroviral treatment

•Sample size limits generalizability of results

## Conclusion

•Clinical benefit of antiretroviral treatment must be balanced with the long-term risks associated with antiretroviral medications when making decisions about when to initiate therapy