EXPERT COMMENTARY JULY 30, 2012

Recommendations for Initiating Antiretroviral Therapy Reflect Return to Earlier Treatment Methods

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The Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in Human Immunodeficiency Virus (HIV)-1-infected adults and adolescents, (1) updated at least once a year, provide the most current and comprehensive summary of the state of the evidence in this rapidly changing field.

Among the many updates provided with this DHHS guidance, perhaps the most carefully watched changes are those related to timing of the initiation of antiretroviral therapy (ART). For example, in this update, previously divided panelists united in favor of stronger recommendations regarding the initiation of ART in persons with 350 to 500 $CD4^+$ cells/μL or with over 500 $CD4^+$ cells/μL. The changes to the recommendations are summarized in Table 1 below (see Appendix A at the end of the Commentary for the recommendation rating scheme):

Table 1: Changes to Recommendations Ratings

CD4 count	March 2012 Recommendation Ratings	Prior Recommendation Ratings
350 to 500 $CD4^+$ cells/μL	AII	AII (55% of panelists) BII (45% of panelists)
> 500 $CD4^+$ cells/μL	BIII	BIII (50% of panelists) CIII (50% of panelists)

toward earlier treatment for HIV-infected persons. In the late 1990s recommendations regarding the use of highly active combination ART (referred to as HAART or sometimes cART) included persons with >500 $CD4^+$ cells/μL. (2) It soon became apparent, however, that available antiretroviral therapy was not curative, that therapy required a lifelong commitment, and that strict medication adherence was necessary to prevent the development of extensive antiretroviral resistance. Furthermore, medical disorders (e.g., lipodystrophy, metabolic syndrome, peripheral neuropathy, lactic acidosis, and cardiovascular disease) were frequent complications of therapy. The combination of relatively low rates of HIV-related complications in treatment-naïve persons with higher $CD4^+$ counts and these observations led to more conservative treatment guidelines, which limited antiretroviral therapy mostly to persons whose $CD4^+$ count had fallen to <200 to 350 cells/μL. (3)

The pendulum, however, has swung back in favor of earlier methods of treatment. Increased rates of disease due to comorbidities such as non-acquired immune deficiency syndrome (AIDS)-defining malignancies, vascular, kidney, and liver disease in HIV-infected persons with 350-500 $CD4^+$ cells/μL are now well-recognized. (4-9) Important recent studies indicate that rather than a result of adverse consequences of ART, AIDS comorbidities and mortality are largely a consequence of uncontrolled HIV replication, an effect that is associated with, and likely attributable to, increased T-cell activation and inflammation. (10-15) Compelling data also demonstrate that treating HIV-infected persons decreases transmission rates of HIV to uninfected sexual partners, (6) and support the premise that early treatment for all HIV-infected patients may halt the transmission of infection. (17)

When reviewing these guidelines, it is important to note that clinical evidence for treatment of HIV-infected patients with 350 to 500 $CD4^+$ cells/μL is inconsistent and at best supports a relatively modest 2% to 3% difference in AIDS-free survival after 3 to 5 years. (18, 19) Recommendations for treating a person with over 500 $CD4^+$ cells/μL remain based largely on expert opinion. A summary of the relevant studies is shown below in Table 2.

Table 2: Risk of Outcome in Persons Starting ART at Indicated Range rather than Deferring Therapy until $CD4^+$ Drops below Lower Threshold (Results Given as Mean and 95% Confidence Intervals)*

Study	Outcome	Measure	Mean (95% CI)	Notes
		Persons with >500 $CD4^\pm$ cells/μL		

ART-CC (20)	AIDS or death	Hazard ratio	1.01 (0.78-1.36)	A
CASCADE (18)	AIDS or death	Hazard ratio	1.10 (0.67-1.79)	B
ART-CC (20)	Death	Hazard ratio	1.07 (0.69-1.67)	A
CASCADE (18)	Death	Hazard ratio	1.02 (0.49-2.12)	B
NA-ACCORD (21)	Death	Relative risk	0.51 (0.36-0.73)	C
		Persons with 350–500 CD4± cells/μL		
Cohort analyses				
ART-CC (20)	AIDS or death	Hazard ratio	0.78 (0.64-0.96)	D
CASCADE (18)	AIDS or death	Hazard ratio	0.75 (0.49-1.14)	E
HIV-CAUSAL (19)	AIDS or death	Hazard ratio	0.72 (0.64-0.81)	F
ART-CC (20)	Death	Hazard ratio	0.88 (0.62-1.25)	D
CASCADE (18)	Death	Hazard ratio	0.51 (0.33-0.80)	E
HIV-CAUSAL (19)	Death	Hazard ratio	0.99 (0.82-1.19)	F
NA-ACCORD (21)	Death	Relative risk	0.59 (0.44-0.79)	G
Randomized clinical trials				
SMART (22)	AIDS or death	Hazard ratio	0.21 (0.045-1.0)	H

	death**		0.88)	
HPTN 052 (16)	Death	Hazard ratio	0.77 (0.34-1.76)	I

* All data taken directly from original publications; note that reciprocals of some data were used to provide consistency in the presentation.

** World Health Organization (WHO) stage 4 event, or a severe bacterial infection or pulmonary tuberculosis

Notes:

A Outcome starting ART with 451 to 550 $CD4^+$ cells/μL vs deferring until 350 to 450 $CD4^+$ cells/μL

B Outcome starting ART with 500 to 799 $CD4^+$ cells/μL vs deferring therapy

C Outcome starting ART with >500 $CD4^+$ cells/μL vs deferring until $CD4^+$ count <500 cells/μL

D Outcome starting ART with 350 to 450 $CD4^+$ cells/μL vs deferring until 250 to 350 $CD4^+$ cells/μL

E Outcome starting ART with >350 $CD4^+$ cells/μL vs deferring therapy

F Outcome starting ART within 6 months of having 500 $CD4^+$ cells/μL vs deferring until within 6 months of having 350 $CD4^+$ cells/μL

G Outcome starting ART with >350 $CD4^+$ cells/μL vs deferring until $CD4^+$ count <350 cells/μL

H Outcome starting ART with >350 $CD4^+$ cells/μL vs deferring until $CD4^+$ count <250 cells/μL

I Outcome starting ART with >350 to 500 $CD4^+$ cells/μL vs deferring until $CD4^+$ count <250 cells/μL

Source: This table was created by the author for this commentary.

As illustrated in Table 2 above, the NA-ACCORD study revealed a lower rate of mortality in persons who started therapy before the $CD4^+$ count was <500 cells/μL. (21) However, the CASCADE or ART-CC studies did not reflect any improvement in mortality rates, and neither of these latter studies uncovered any difference in the aggregate rates of AIDS and death. (18, 20) For persons with 350 to 500 $CD4^+$ cells/μL who started on ART rather than deferring therapy the NA-ACCORD and CASCADE investigators demonstrated a mortality benefit. (18, 21) Similarly, the ART-CC (18, 20) and HIV-CAUSAL (19) groups, as well as two randomized controlled clinical trials, (16, 22) displayed decreased aggregate rates of AIDS and death. However, there was no difference in aggregate rates of AIDS and death in the CASCADE study, and no mortality benefit in the ART-CC and HIV-CAUSAL studies. To quote the guidelines, "these studies suggest that initiating ART in patients with $CD4^+$ counts between

Each cohort analysis differs in strength due to variations in the mode of statistical analysis, the selection of control group, the duration for which ART was deferred in the control group, and the amount of missing data. As with all non-randomized trials, differences in rates of access to medical care, pre-existent medical and psychiatric comorbidities, patient behaviors related to health-seeking activities, alcohol consumption/abuse, injection-drug and other substance use, smoking, and adherence to therapy may bias the outcomes of the cohort studies. (20, 21, 23) It is also worth noting that the results from one of the clinical trials were driven mainly by the incidence of extrapulmonary tuberculosis, thus potentially decreasing the relevance of these results in areas with low rates of this disease, (16) and that the results of the other trial were derived from a secondary subgroup analysis. (22)

In summary, although randomized clinical trials clearly demonstrate benefit for persons with <350 $CD4^+$ cells/μL starting ART, (24) a weak evidentiary basis exists to recommend initiation of ART at higher $CD4^+$ cell counts, especially in persons with over 500 $CD4^+$ cells/μL. As stated in the guideline, "When discussing starting antiretrovirals at higher $CD4^+$ cell counts (>500 cells/mm^3), clinicians should inform patients that data on the clinical benefit of starting treatment at such levels is not conclusive, especially for patients with very high $CD4^+$ counts." The guideline also acknowledges that "...concerns remain over the unknown overall benefit, long-term risks, and cumulative additional costs associated with earlier treatment." Moreover, despite the substantial public health benefits of ART, decisions about when to initiate ART should be based primarily on the potential benefit and harms to the HIV-infected individual for whom therapy is being considered.

Readers should understand that these guidelines reflect the evidence available at the time of development. As stated in the document, "Further ongoing research (both randomized clinical trials and cohort studies) to assess the short- and long-term clinical and public health benefits and cost effectiveness of starting therapy at higher $CD4^+$ counts is needed." A prospective, randomized trial that seeks to determine the benefits of initiating antiretroviral therapy at a $CD4^+$ cell count >500 cells/μL versus deferring therapy until the $CD4^+$ declines to <350 cells/μL is currently underway and has enrolled over 60% of the target population. (25) Upon successful completion, this study will provide tremendous insight to healthcare providers regarding the benefits of early antiretroviral therapy. Meanwhile, in the absence of more conclusive evidence, clinicians and patients must continue to carefully consider the strengths and weaknesses of the available data regarding the initiation of ART when $CD4^+$ cell counts are greater than 350 to 500 cells/μL.

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Potential Conflicts of Interest

Dr. Goetz is a member of the HIV Technical Advisory Group, Veterans Healthcare Administration. He states no financial or personal conflicts of interest with respect to this commentary.

Appendix A

Rating Scheme for Recommendations

Strength of Recommendation

A. Strong recommendation for the statement
B. Moderate recommendation for the statement
C. Optional recommendation for the statement

Quality of Evidence for Recommendation

I. One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II. One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
III. Expert opinion

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