

*When to Initiate Antiretroviral Therapy in HIV and Aging

- Antiretroviral therapy should be initiated in all patients over the age of 50, regardless of CD4 count
- Providers must be aware of possible increases in drug-drug interactions when prescribing ART to older patients

Multiple cohort studies involving untreated HIV-infected persons have established that older persons have a more rapid progression to AIDS and shortened survival when compared with younger persons (Phillips et al. 2008; Balslev et al. 1997; Rezza 1998; Egger et al. 2002). For HIV-infected persons older than 50, sparse data exist from randomized, controlled antiretroviral therapy clinical trials, as most randomized therapy trials have excluded persons older than 50 or 60. A retrospective analysis of 253 patients 50 years of age or older found antiretroviral therapy substantially improved survival rates (Perez & Moore 2003). Several large retrospective studies have clearly shown delayed and diminished CD4 cell recovery after starting antiretroviral therapy in older HIV-infected patients when compared with younger age groups (Khanna et al. 2008; Silverberg et al. 2007; Althoff et al. 2010; Cohere 2008). Studies have shown conflicting results with respect to virologic responses in older versus younger (Silverberg et al. 2007; Paredes et al. 2000; Manfredi et al. 2003; Lampe et al. 2006), with the most comprehensive study showing no significant difference in virologic responses based in older versus younger adults (Althoff et al. 2010).

The major antiretroviral therapy guidelines that most influences clinical practice in the United States—the Department of Health and Human Services

(DHHS) Panel guidelines (Panel DHHS - 2013)—now recommends initiating antiretroviral therapy in all persons infected with HIV. The recommendation to use antiretroviral therapy in all HIV-infected persons is based on reducing the risk of disease progression and decreasing the risk of HIV transmission. Data from several large cohort studies have strongly suggested a survival advantage with initiation of antiretroviral therapy earlier in the course of HIV disease (Kitahata et al. 2009; Sterne et al. 2009). In addition, growing evidence suggests that uncontrolled HIV infection produces a “chronic inflammatory state” associated with an increased risk of developing cardiovascular disease (Phillips et al. 2008) and non-AIDS malignancies (Bruyand et al. 2009), and CD4 counts below 500 are associated with higher cardiovascular risk (Lichtenstein et al. 2010), and risk for non-AIDS malignancies (Guiguet et al. 2009). The rationale for recommending antiretroviral therapy for the prevention of HIV transmission is based on several recent studies, most notably the landmark HPTN 052 trial that showed a greater than 95% reduction in HIV transmission in HIV serodiscordant couples when the HIV-infected partner received antiretroviral therapy (Cohen 2011).

The 2013 DHHS Antiretroviral Therapy guidelines specifically addressed the use of antiretroviral therapy for persons

50 and older, recommending initiating antiretroviral therapy in all persons older than 50 years of age regardless of CD4 cell count, primarily because, when compared with younger patients, these older HIV-infected individuals have increased risk for non-AIDS related complications and they have diminished CD4 cell count recovery in response to antiretroviral therapy (Panel DHHS - 2013). Further, the DHHS guidelines emphasized that older individuals potentially have increased risk for HIV transmission or acquisition, for several reasons, including (1) alterations reduced mucosal and immunologic defenses may occur with post-menopausal atrophic vaginitis, (2) older individuals have less incentive to use of condoms given the lack of need for pregnancy prevention, and (3) persons older than 50 have lower frequency of HIV screening given their perceived low risk for HIV infection (Adekeye OA 2012).

The use of antiretroviral therapy in older HIV-infected patients presents several challenges, predominantly due to the increased prevalence of non-HIV-related comorbid medical conditions, such as hyperlipidemia, hypertension, diabetes, and coronary artery disease (Skiest et al. 1996). In addition, older patients may have age-related changes in body composition that can alter medication volume of distribution and influence drug pharmacokinetics. Compared with younger patients, older patients are more likely to be taking multiple medications not related to HIV and thus increasing the likelihood for drug-drug interactions. Further, several studies have shown older HIV-infected patients have increased risk for developing drug-related toxicity, including hyperglycemia, elevated creatinine, and unfavorable alterations in lipid profile (Silverberg et al. 2007).

References

- Adekeye, O.A. et al. The new invincibles: HIV screening among older adults in the U.S. *PLoS One*. 2012;7(8):e43618.
- Althoff, K.N. et al. 2010. CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation? *AIDS research and therapy*, 7(1), p.45.
- Balslev, U. et al. 1997. Influence of age on rates of new AIDS-defining diseases and survival in 6546 AIDS patients. *Scandinavian journal of infectious diseases*, 29(4), pp.337-43.
- Bruyand, M. et al. 2009. Role of uncontrolled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 49(7), pp.1109-16.
- Cohen, M.S. et al. 2011. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 365(6), pp.493-505.
- Cohere, 2008. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group. Response to combination antiretroviral therapy: variation by age. *AIDS*, pp.1463-73.
- Egger, M. et al. 2002. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*, 360(9327), pp.119-29.
- Guiguet, M. et al. 2009. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *The lancet oncology*, 10(12), pp.1152-9.
- Khanna, N. et al. 2008. CD4+ T cell count recovery in HIV type 1 - infected patients is independent of class of antiretroviral therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 47(8), pp.1093-101.
- Kitahata, M.M. et al. 2009. Effect of early versus deferred antiretroviral therapy for HIV on survival. *The New England Journal of medicine*, 360(18), pp.1815-26.
- Lampe, F.C. et al. 2006. Changes over time in risk of initial virological failure of combination antiretroviral therapy: a multicohort analysis, 1996 to 2002. *Archives of internal medicine*, 166(5), pp.521-8.
- Lichtenstein, K.A. et al. 2010. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 51(4), pp.435-47.
- Manfredi, R. et al. 2003. Antiretroviral treatment and advanced age: epidemiologic, laboratory, and clinical features in the elderly. *Journal of acquired immune deficiency syndromes (1999)*, 33(1), pp.112-4.
- Mothe, B. et al. 2009. HIV-1 Infection in Subjects Older than 70: A Multicenter Cross-Sectional Assessment in Catalonia, Spain. *Current HIV Research*, 7(6), pp.597-600.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services.

February 12, 2013. AIDSInfo
<http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/0>

Paredes, R et al. 2000. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. *Archives of internal medicine*, 160(8), pp.1123-32.

Perez, J.L. & Moore, R.D., Greater Effect of Highly Active Antiretroviral Therapy on Survival in People Aged ≥ 50 Years Compared with Younger People in an Urban Observational Cohort. Phillips, A N et al. 1991. More rapid progression to AIDS in older HIV-infected people: the role of CD4+ T-cell counts. *Journal of acquired immune deficiency syndromes*, 4(10), pp.970-5.

Phillips, Andrew N et al. 2008. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antiviral therapy*, 13(2), pp.177-87.

Rezza, G., 1998. Determinants of progression to AIDS in HIV-infected individuals: an update from the Italian Seroconversion Study. *Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association*, 17 Suppl 1, pp.S13-6.

Silverberg, M.J., Leyden, W., et al. 2007. Older age and the response to and tolerability of antiretroviral therapy. *Archives of internal medicine*, 167(7), pp.684-91.

Silverberg, M.J., Neuhaus, Jacqueline, et al. 2007. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS (London, England)*, 21(14), pp.1957-63.

Skiest, D.J. et al. 1996. The importance of comorbidity in HIV-infected patients over 55: a retrospective case-control study. *The American journal of medicine*, 101(6), pp.605-11.

Sterne, J.A.C. et al. 2009. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*, 373(9672), pp.1352-63.

Thompson, M.A. et al. 2010. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA : the Journal of the American Medical Association*