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Effect of Age and HAART Regimen on Clinical Response in an Urban Cohort of HIV-Infected Individuals

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Background

As of 2004, 23% of those infected with HIV were older than 50 years of age. [1] The increase in prevalence among older adults is due to increased survival of those treated with HAART, as well as new HIV infections among older people. [2] Given the changing epidemiology of HIV, it is important to understand the effectiveness of antiretroviral treatment in older people.

Multiple studies have reported that older patients have worse HIV outcomes than younger patients. [3-6] However, most of these studies used data that preceded the availability of HAART. While several recent small studies have found differences in clinical responses to HAART between older and younger groups, the results have been conflicting. [7-13,13-22] Some studies have found similar rates of HIV-1 RNA suppression in different age groups [8-16], while others have found better virologic response in older adults. [17-22] Among studies which have shown similar viral response between older and younger groups, some have shown that older patients have slower rates of CD4 recovery and a lower magnitude of CD4 increase [9,11], while others have noted no difference in CD4 cell response between age groups. [10,12-14,16] Silverberg, et al. reported better virologic suppression but worse immunologic response in those over 50 years compared to younger patients. However, results were attenuated when adjusted for adherence levels and duration of follow up. [23]

Few studies have evaluated the role of antiretroviral regimen on clinical outcomes in different age groups. Therefore, we set out to compare the effectiveness of HAART in older versus younger adults in a large urban clinic. The goal of this study is to compare responses to HAART in HIV infected HAART-naïve adults <40 versus those ≥ 50 years of age overall and by type of HAART regimen (PI vs. NNRTI).

Methods

The Johns Hopkins University AIDS Service provides comprehensive primary and subspecialty medical care. At baseline, a comprehensive evaluation of medical and social histories, physical exam, and laboratory studies is recorded and is prospectively updated from the clinic-based medical record by trained data monitors every six months. Maintenance of the database and use of its contents for analysis are approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

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The results of this study were presented in part at the Infectious Diseases Society of America, San Diego CA, October 2007.

This study included 906 HAART-naïve patients who enrolled at the clinic between February 16, 1989 and January 26, 2006 and had HAART initiation dates between December 13, 1995 and February 9, 2006. Median follow-up time after HAART initiation was 46.1 months (range: 4.0 to 126.0 months). Patients who were on HAART for less than four months, or did not have a baseline CD4 count or HIV-1 RNA level were excluded from this analysis.

Definitions

Demographic variables included age at HAART initiation, race (African American, non-Hispanic Caucasian, and other), and sex. HIV transmission risk factors included a injection drug use (IDU), men who had sex with men (MSM), and heterosexual activity with an HIV-infected individual or with a partner at high risk for HIV (HET). Race was dichotomized as African-American versus all other races, and HIV risk factor as IDU versus those with non-IDU risk factors (MSM and/or HET). Clinical variables included CD4 counts (cells/ μ l) and HIV-1 RNA levels (copies/ml) at HAART initiation and throughout a patient's follow-up time at the clinic. Time-updated variables included CD4 counts and HIV-1 RNA levels within 60 days prior to viral suppression, CD4 count increase to 50 cells/ μ l, first opportunistic infection (OI), and death. HAART was defined as concomitant use of three drugs from two classes (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], or a fusion inhibitor) for more than 120 days. HAART initiation time periods were categorized as before 2003 or 2003 or after. Adherence data was collected using Audio Computer Assisted Self Interviews (ACASI). Adherent was defined as patients reporting 100% adherence with all HAART medication in the 24 hours before their interview. Opportunistic infections were defined by the 1993 Revised Classification System for HIV Infection by the Centers for Disease Control and Prevention. [24] Patients were considered eligible for PCP or MAC prophylaxis if they had one CD4 count <200 cells/ μ l or <50 cells/ μ l at any time during the study interval. Cause of death was dichotomized as AIDS related vs. non-AIDS related based on distinctions made by trained chart abstractors and expert physician review. AIDS-related deaths included those related to OIs, AIDS-associated malignancies, and failure to thrive as specified in the 1993 AIDS-defining illnesses. [24] Non-AIDS related deaths included causes not directly associated with HIV infection.

Outcomes

To evaluate virologic suppression we used HIV-1 RNA levels from all clinic visits since HAART initiation. Plasma HIV-1 RNA was categorized as undetectable ($\leq$ 400 copies/ml) or detectable ($>$ 400 copies/ml).

We evaluated immunologic response by three methods: change in CD4 cell count from baseline and absolute increase in CD4 cell count from baseline. We measured change in CD4 count from baseline using CD4 count at HAART initiation and at clinic visits 6, 12, and 24 months after HAART initiation. CD4 counts at these intervals were calculated by averaging all CD4 counts recorded within 8 weeks before and after the 6, 12, and 24 month time periods. Given the fact this is an observational cohort, 23.7% of the population did not have a CD4 measurement at 6 months ($\pm$ 8 weeks) and 31.3% of the population did not have a CD4 measurement at 12 months ($\pm$ 8 weeks) after HAART initiation. For these patients, we estimated 6 month CD4 counts by averaging the CD4 count at HAART initiation and the 12 month CD4 value; estimates of the 12 month CD4, if not available, were done by averaging the 6 month and 18 month CD4 cell count. CD4 cell counts from all clinic visits since HAART initiation were included. Time to increase in CD4 cell count was days from HAART initiation to date of laboratory test where CD4 cell count had increased by 50 cells/ μ l or more. HIV disease progression was examined as time to new OI after HAART initiation. Survival was analyzed based on the clinic's death registry database.

Analysis

Differences in changes in HIV-1 RNA and CD4 count between older and younger groups were calculated using the Students t-test. Survival analysis included Kaplan-Meier estimates and Cox proportional hazards models using time to HIV-1 RNA suppression, CD4 increase by 50 cells/ μ l, new OIs, and all-cause mortality as the outcomes of interest. Estimated time to an event was calculated as time from HAART initiation to each outcome. Time to new OI and time to death are reported as time until the first 25% of patients were diagnosed with an OI or died (which is equivalent to a hazard of new OI of 0.75) with a 95% confidence interval for the hazard. Survival curves were statistically compared using log rank tests. Each outcome was analyzed using multivariate Cox proportional hazard models using clinical and demographic variables believed to be potential confounders. All multivariate regressions were adjusted for race, gender, HIV risk factor, history of OI before HAART initiation, CD4 count and HIV-1 RNA at HAART initiation, and time period of HAART initiation (before vs. after Jan. 1 2003). All reported p-values are two-sided and all statistical analysis were made using STATA 9.0 (College Station, TX). [25]

Analyses were repeated and stratified by treatment regimen, based on if regimens included at least one NNRTI or one PI.

Sensitivity Analysis

Individuals who were on both NNRTI and PI-based regimens (n=87) were included with those on NNRTI-only regimens in sensitivity analyses for each endpoint. As an additional sensitivity analysis for viral suppression, we constructed survival curves and regression models for time to sustained viral suppression, defined as at least two consecutive HIV-1 RNA levels $\leq$ 400 copies/ml. Models were also constructed in a sub-set of patients (n=439) who had recent adherence data from an ACASI interview. Additional models used time-updated HIV-1 RNA levels and CD4 counts for a subset of patients who had adequate data to calculate time-updated variables for each endpoint (viral suppression n=740, immune reconstitution n=734, first OI n=132, death n=208). All analyses were calculated in an "as treated" manner. For those patients who stopped HAART treatment while being followed at the clinic, the as treated analysis included only data collected while they were on HAART. An intention to treat sensitivity analyses was also performed for each endpoint.

Results

Demographics

Older patients were more likely to be male (76.5% vs. 65.5%, $p=0.01$) and less likely to report MSM as an HIV risk behavior (18.8% vs. 34.5%, $p<0.01$) than younger patients. (Table 1) Older patients were more likely to be started on an NNRTI-based regimen than younger patients (41.6% vs. 29.0%, $p<0.01$).

Clinical Outcomes

The median time from enrolment until HAART initiation (younger: 6.2 months vs. older: 6.0 months, $p=0.9$) and median duration on HAART did not differ by age group (younger: 48.1 vs. older: 36.5 months, $p=0.1$). (Table 2)

The median time to first undetectable HIV-1 RNA level was shorter in older vs. younger patients (3.2 vs. 4.4 months, $p=0.001$). (Figure 1a) When time to virologic suppression was stratified by treatment regimen, there was no difference by age in median time to suppression among those on NNRTI's (older: 2.8 months vs. younger: 3.0 months, $p=0.6$). (Figure 1b) However, among those on PI's, older patients suppressed more quickly than younger patients (3.7 vs. 5.4 months, $p<0.002$). (Figure 1c) Of note, younger patients on NNRTI's suppressed

more quickly than younger patients on PI's (3.0 vs. 5.4 months, $p<0.01$), but there was no difference in time to suppression by treatment regimen in older patients (NNRTI's: 2.8 months vs. PI's: 3.7 months, $p=0.6$).

There was no difference in immunologic response by age group for mean change in CD4 count or time to CD4 count increase by 50 cells/ μ l. (Figure 2) At 24 months, younger patients had on average an increase of 160 cells/ μ l (SD=199), and older patients had an increase of 171 cells/ μ l (SD=174, $p=0.8$). (Figure 2a) There was no difference in change in CD4 count by age when results were stratified by CD4 count and HIV-1 RNA at HAART initiation. Similarly, there was no difference by age in time to an absolute increase in CD4 count of 50 cells/ μ l (younger: 3.3 months vs. older: 3.4 months, $p=0.6$). (Figure 2b) Stratification by treatment regimen yielded similar results by age for both mean change in CD4 cell count and time to absolute increase by 50 cells/ μ l. Younger patients on NNRTI's had an earlier immune response than younger patients on PI's (3.0 vs. 3.7 months, $p=0.04$), but there was no difference in immune response by treatment regimen in older patients. There was no difference between age groups, race, sex, HIV risk factor, or HAART regimen between those who had estimated CD4 cell counts and those who did not.

Given the interrelationship between viral suppression and CD4 cell recovery, we examined CD4 cell recovery stratified by time to viral suppression. Time to absolute CD4 count of 50 cells/ μ l was associated with decreased time to viral suppression. CD4 increase occurred more quickly among those who suppressed in less than 3.9 months (median time to suppression for the entire population) compared to those who suppressed after 3.9 months (time to absolute CD4 increase to 50 cells/ μ l, 2.3 vs. 5.4 months, $p<0.01$).

After HAART initiation younger patients had a higher incidence of at least one new OI (30.5% vs. 21.5%, $p<0.01$) than older patients. (Table 2) A higher percentage of younger patients were diagnosed with esophageal *Candidiasis* (15.2% vs. 8.0%, $p=0.02$), and cerebral toxoplasmosis (2.5% vs. 0.0%, $p=0.05$) as first OI after HAART initiation. There were no differences by age in rate of diagnosis of the other OIs. The most commonly diagnosed first OIs after HAART initiation in both older and younger patients were *Candidiasis*, *Herpes* encephalitis (6.7% of older patients, 6.6% of younger patients), and PCP (6.0% of older patients, 10.5% of younger patients). There was no difference by age in MAC or PCP prophylaxis. Time to new OI after HAART initiation was shorter in younger patients vs. older patients (25% of younger patients diagnosed with OI at 39.7 months [95% CI of 25th percentile survivor function 0.71-0.78] vs. 88.8 months [95% CI 0.62-0.83], $p=0.1$). (Figure 3a)

Older patients had shorter survival time than younger patients (25% of younger patients died by 58.8 months [95% CI if the 25th percentile survivor function 0.71-0.78] vs. 36.2 months [95% CI 0.67-0.82], $p=0.02$) (Figure 3b), and also had higher overall mortality compared to younger patients (35.6% vs. 27.3%, $p=0.04$). (Table 2) When stratified by treatment regimen, survival was similar by age for patients on PI's (25% of younger patients died at 57.9 months [95% CI of 25th percentile survivor function 0.70-0.79] vs. 52.0 months for older patients [95% CI 0.64-0.84], $p=0.2$), whereas among those on NNRTI's, survival was significantly longer for younger patients compared to older patients (25% of younger patients died at 59.3 months [95% CI 0.65-0.82] vs. 34 months for older patients [95% CI 0.58-0.83], $p=0.02$). There was no difference in survival between treatment regimens when stratified by age. A similar percentage of younger and older patients died of AIDS-related causes (66.9% vs. 61.7%, $p=0.5$). (Table 2) Among younger patients these included MAC (1.9%) and PCP (1.9%) and among older patients these included advanced AIDS (3.7%), failure to thrive (3.7%), and HIV dementia (3.7%). The most common non-AIDS related causes of death among younger patients were pneumonia (23%), chronic renal failure (11%), stroke (6%) and hepatitis (6%) and among

older patients were hypertension/hypertensive urgency (17%), and cardiovascular disease (17%).

Cox proportional hazard regressions were used to identify factors associated with time to each outcome: a) virologic suppression, b) increase in CD4 by 50 cells/ μ l, c) new opportunistic illness, d) death. (Table 3) In the adjusted analysis, older age was associated with increased likelihood of virologic suppression (Adjusted Hazard Ratio (AHR) 1.26 95% CI [1.03-1.55]) and death (1.44 [1.04-2.01]). Older age was not associated with change in CD4 count or time to new OI after HAART initiation. NNRTI-based regimens significantly increased the likelihood of virologic suppression (1.28 [1.09-1.51]), but were not associated with other outcomes. Initiating HAART after 2003 vs. before 2003 was associated with shorter time to virologic suppression (1.68 [1.34-2.12]) and earlier CD4 count increase (1.38 [1.10-1.72]), but not increased survival.

Sensitivity Analyses

Sensitivity analyses performed as an ITT analysis showed similar results for all endpoints. The median time to first undetectable viral load was shorter in older than younger patients (3.2 vs. 4.6 months, $p < 0.01$). As in the as treated analysis, there was no difference by age in mean change of CD4 counts, time until CD4 increase in 50 cells/ μ l (older: 3.4 vs. younger: 3.5 months, $p = 0.5$), nor time until new OI. Overall trends in survival in the ITT analysis were similar to those in the as treated analysis. Survival was greater in the as treated analysis compared to the ITT analysis. Less than half of younger patients died in the as treated analysis, whereas younger patients had a median survival of 122 months in the ITT analysis. Survival was also greater for older patients in the as treated analysis compared to the ITT analysis (101 vs. 90 months).

Several other sensitivity analyses were performed. Consistent with time to first undetectable viral load, the median time to the second consecutive undetectable HIV-1 RNA was also shorter in older vs. younger patients (7.4 vs. 12.6 months, $p < 0.01$). Including those on both NNRTI and PI-based regimens with those on NNRTI-only regimens did not affect the results. In a sub-set analysis, after adjusting for other factors, sub-optimal adherence to HAART was not associated with decreased time to suppression (AHR 0.91 [0.73-1.13]), immunologic response (0.89 [0.72-1.10], new OI (0.91 [0.64-1.30]) nor survival (0.79 [0.52-1.23]). In a sub-set analysis using time-updated CD4 counts and HIV RNA-1 levels, older age was no longer associated with decreased time to suppression (1.06 [0.82-1.30]), nor survival (1.80 [0.79-4.10]). NNRTI-based regimens were associated with decreased time to suppression (1.24 [1.05-1.48]) as in our primary analysis, but were also associated with earlier CD4 count increase (1.22 [1.03-1.44]) in this sensitivity analysis. Initiating HAART after 2003 was associated with shorter time to virologic suppression (1.62 [1.28-2.04]), earlier CD4 count increase (1.27 [1.00-1.68]), and longer time to new OI (6.03 [2.52-14.42]).

Discussion

In this study, older HIV infected HAART-naïve adults started on HAART achieved virologic suppression faster than younger HIV infected individuals. Also, time to increase in CD4 cells did not differ by age group. Finally, mortality was higher in older patients, despite slower HIV disease progression.

Hinkin and colleagues found that improved virologic response among older adults was due to better adherence to HAART, and Silverberg, et al. found that controlling for adherence mitigated the differences in virologic responses between age groups. [23,26] In this cohort, there was no difference in adherence reported by patients in each age category. Although sample size limits our ability to adjust for adherence when determining factors associated with

virologic suppression, subset analysis of those for whom adherence data was available implies adherence was not a factor in virologic suppression. This suggests that adherence was not a confounder in this population.

Despite increased virologic suppression in older compared to younger patients, there was no difference in immune response between age groups. Although others have shown similar results regarding virologic suppression, previous longitudinal analyses showed depressed immunologic response in older patients. [20-22] CD4 cell recovery has been shown to be inversely associated with age, and one hypothesis is that decreased immunologic responses among older patients may be due to thymic suppression. [9,11,27,28] Differences between study populations, including comorbidities such as hepatitis viruses and frailty, are potential variables we could not account for and could affect immunologic reconstitution. [29] Individual variability in CD4 cell counts and accuracy of measurement techniques could attenuate differences between populations. We also did not measure duration of HIV infection, which has been shown to influence CD4 cell count.[30]

Although older patients had fewer new OIs than younger patients, not surprisingly, older patients had worse survival than younger patients. The percentage of AIDS-related deaths are similar between older and younger groups. This suggests that younger patients have more non-fatal OI's than older patients. Comorbid medical conditions, which will need to be evaluated in future studies, could also contribute to decreased survival in older patients.

This is one of the first studies to look at effect of HAART regimen type on clinical response by age group. In multivariate analysis, NNRTI use was associated with more rapid virologic suppression and longer time to new OI, but not with improved immunologic response or survival. Younger patients on NNRTI-based regimens suppressed more quickly and had slightly faster immunologic response than younger patients on PI-based regimens. However, there were not differences by treatment regimen in older patients in any of the clinical outcomes. Patterson, et al. found immune reconstitution and viral suppression did not vary by treatment regimen when stratified by age. [16] Consistent with literature that demonstrates increased effectiveness of current regimens, those who started on HAART regimens after 2003 suppressed faster with shorter time to increased CD4 count; however, starting HAART after 2003 was not a significantly associated with survival.

There are several potential limitations to this study. First, this study includes patients at only one site that has a relatively high proportion of minority race and injection drug users, and therefore may not generalize to all HIV clinics. Second, a small sample size limits our ability to comment on the significance of stratifications involving smaller subsets of the population, especially those addressing older patients on different treatment regimens. In addition, given the limited number of patients for whom adherence data is available, it is difficult to draw conclusions regarding the impact of adherence on clinical endpoints.

We did not control for informative censoring of older patients, who, due to shorter life expectancy are less likely to reach the clinical endpoints than younger patients. Also, we were not able to determine time of seroconversion or length of HIV infection. As with other studies, the older group of patients includes both those who were infected recently as well as those who have aged with HIV. As the HIV infected population ages, future studies may need to evaluate differences in these two groups of patients, especially those relating to differences in immunological response.

Non-AIDS-defining comorbid medical conditions may be especially relevant in treating HIV in older people. The pathophysiology associated with comorbid medical conditions as well as pharmaceutical regimens associated with treating them could affect the progression of HIV as well as antiretroviral metabolism. [31,32] Future studies will need to examine long term

outcomes of HAART therapy including the impact of comorbidities on HIV disease progression, potential drug-drug interactions, and potential differences in drug toxicity profiles in older adults.

The shift in the paradigm of HIV to a chronic disease has several implications for treatment. Age-specific treatment guidelines that have different recommendations for older vs. younger patients may be warranted, with initiation of HAART at higher CD4 cell count for older compared to younger patients. Given adequate immunologic response but decreased survival, additional study is needed to determine appropriate initiation of HAART therapy in older HIV infected adults.

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References

- [1]. Centers for Disease Control and Prevention (CDC). HIV/AIDS Surveillance Report, 2005. 2006.
- [2]. Mack KA, Ory MG. AIDS and older Americans at the end of the Twentieth Century. *J Acquir Immune Defic Syndr* 2003;33(Suppl 2):S68–75. [PubMed: 12853855]
- [3]. Operskalski EA, Stram DO, Lee H, Zhou Y, Donegan E, Busch MP, et al. Human immunodeficiency virus type 1 infection: relationship of risk group and age to rate of progression to AIDS. Transfusion Safety Study Group. *J Infect Dis* 1995;172:648–655. [PubMed: 7658055]
- [4]. Belanger F, Meyer L, Carre N, Coutellier A, Deveau C. Influence of age at infection on human immunodeficiency virus disease progression to different clinical endpoints: the SEROCO cohort (1988–1994). The Seroeco Study Group. *Int J Epidemiol* 1997;26:1340–1345. [PubMed: 9447415]
- [5]. Ferro S, Salit IE. HIV infection in patients over 55 years of age. *J Acquir Immune Defic Syndr* 1992;5:348–353. [PubMed: 1548571]
- [6]. Rezza G. Determinants of progression to AIDS in HIV-infected individuals: an update from the Italian Seroconversion Study. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17(Suppl 1):S13–6. [PubMed: 9586645]
- [7]. Goetz MB, Boscardin WJ, Wiley D, Alkasspoles S. Decreased recovery of CD4 lymphocytes in older HIV-infected patients beginning highly active antiretroviral therapy. *AIDS* 2001;15:1576–1579. [PubMed: 11504992]
- [8]. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med* 1999;131:81–87. [PubMed: 10419445]
- [9]. Manfredi R, Chiodo F. A case-control study of virological and immunological effects of highly active antiretroviral therapy in HIV-infected patients with advanced age. *AIDS* 2000;14:1475–1477. [PubMed: 10930176]
- [10]. Knobel H, Guelar A, Valdecillo G, Carmona A, Gonzalez A, Lopez-Colomes JL, et al. Response to highly active antiretroviral therapy in HIV-infected patients aged 60 years or older after 24 months follow-up. *AIDS* 2001;15:1591–1593. [PubMed: 11505000]
- [11]. Viard JP, Mocroft A, Chiesi A, Kirk O, Roge B, Panos G, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis* 2001;183:1290–1294. [PubMed: 11262215]
- [12]. Yamashita TE, Phair JP, Munoz A, Margolick JB, Detels R, O'Brien SJ, et al. Immunologic and virologic response to highly active antiretroviral therapy in the Multicenter AIDS Cohort Study. *AIDS* 2001;15:735–746. [PubMed: 11371688]
- [13]. Tumbarello M, Rabagliati R, Donati K de Gaetano, Bertagnolio S, Montuori E, Tamburrini E, et al. Older age does not influence CD4 cell recovery in HIV-1 infected patients receiving highly active antiretroviral therapy. *BMC Infect Dis* 2004;4:46. [PubMed: 15530169]

- [14]. Orlando G, Meraviglia P, Cordier L, Meroni L, Landonio S, Giorgi R, et al. Antiretroviral treatment and age-related comorbidities in a cohort of older HIV-infected patients. *HIV Med* 2006;7:549–557. [PubMed: 17105515]
- [15]. Cuzin L, Delpierre C, Gerard S, Massip P, Marchou B. Immunologic and clinical responses to highly active antiretroviral therapy in patients with HIV infection aged >50 years. *Clin Infect Dis* 2007;45:654–657. [PubMed: 17683004]
- [16]. Patterson K, Napravnik S, Eron J, Keruly J, Moore R. Effects of age and sex on immunological and virological responses to initial highly active antiretroviral therapy. *HIV Med* 2007;8:406–410. [PubMed: 17661850]
- [17]. Paredes R, Mocroft A, Kirk O, Lazzarin A, Barton SE, van Lunzen J, et al. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. *Arch Intern Med* 2000;160:1123–1132. [PubMed: 10789605]
- [18]. Le Moing V, Chene G, Carrieri MP, Alioum A, Brun-Vezinet F, Piroth L, et al. Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. *AIDS* 2002;16:21–29. [PubMed: 11741159]
- [19]. Goodkin K, Shapshak P, Asthana D, Zheng W, Concha M, Wilkie FL, et al. Older age and plasma viral load in HIV-1 infection. *AIDS* 2004;18(Suppl 1):S87–98. [PubMed: 15075503]
- [20]. Grabar S, Kousignian I, Sobel A, Le Bras P, Gasnault J, Enel P, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. *AIDS* 2004;18:2029–2038. [PubMed: 15577624]
- [21]. Nogueras M, Navarro G, Anton E, Sala M, Cervantes M, Amengual M, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis* 2006;6:159. [PubMed: 17087819]
- [22]. Bosch RJ, Bennett K, Collier AC, Zackin R, Benson CA. Pretreatment factors associated with 3-year (144-week) virologic and immunologic responses to potent antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007;44:268–277. [PubMed: 17146370]
- [23]. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry CP Jr. Older age and the response to and tolerability of antiretroviral therapy. *Arch Intern Med* 2007;167:684–691. [PubMed: 17420427]
- [24]. Centers for Disease Control (CDC). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* 1992;41:1–19.
- [25]. Stata Corp.. Stata Statistical Software: Release 9.0. 2005.
- [26]. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS* 2004;18(Suppl 1):S19–25. [PubMed: 15075494]
- [27]. Mackall CL, Fleisher TA, Brown MR, Andrich MP, Chen CC, Feuerstein IM, et al. Age, thymopoiesis, and CD4+ T-lymphocyte regeneration after intensive chemotherapy. *N Engl J Med* 1995;332:143–149. [PubMed: 7800006]
- [28]. Douek DC, Vescio RA, Betts MR, Brenchley JM, Hill BJ, Zhang L, et al. Assessment of thymic output in adults after haematopoietic stem-cell transplantation and prediction of T-cell reconstitution. *Lancet* 2000;355:1875–1881. [PubMed: 10866444]
- [29]. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 2006;54:991–1001. [PubMed: 16776798]
- [30]. Soriano V, Castilla J, Gomez-Cano M, Holguin A, Villalba N, Mas A, et al. The decline in CD4+ T lymphocytes as a function of the duration of HIV infection, age at seroconversion, and viral load. *J Infect* 1998;36:307–311. [PubMed: 9661942]
- [31]. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther* 1997;61:331–339. [PubMed: 9091249]

- [32]. Gebo KA. HIV and aging: implications for patient management. *Drugs Aging* 2006;23:897–913.
[PubMed: 17109568]