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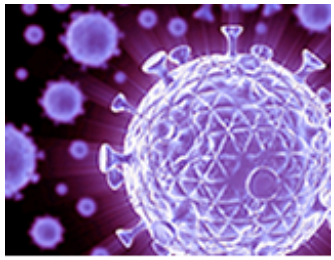

VOLUME 1, NUMBER 1

Screening and Management of Older Patients with HIV Infection

Editor's Note:

WELCOME…
… to this premier issue of eHIV Review, presented by the Johns Hopkins University School of Medicine. This CME–certified program has been developed to assist infectious disease specialists, primary care physicians, nurse practitioners, and other health care professionals involved in the treatment of HIV–infected patients.

Volume 1 of eHIV Review will comprise 6 newsletters, each reviewing the current literature on a single topic, authored by recognized experts in specific practice areas and peer–reviewed by the Johns Hopkins faculty. Each newsletter will be followed by a CME–certified audio interview with that issue's author, presented as a podcast and downloadable transcript, to help clinicians integrate the new data into current clinical practice.

In this Issue...

Over the past decade, the prevalence of HIV in older persons has increased. The higher prevalence of HIV infection in older individuals is related to both increased longevity from successful antiretroviral therapy (ART) and to the development of new HIV infections among older patients. Compared with younger patients infected with HIV (< 50 years of age), older persons infected with HIVs (≥ 50 years of age) exhibit better virologic response but worse immunologic recovery after initiation of ART. Older persons infected with HIV have more comorbidities that complicate the management of their disease than do their younger counterparts. Whether these comorbidities are developing at an earlier age than in the general population is currently unclear. Managing comorbid conditions in the setting of concomitant HIV infection can be associated with polypharmacy and significant drug–drug interactions.

In this issue, we review the epidemiology of HIV, patients' response to ART, and issues involved in managing polypharmacy among older persons infected with HIV.

LEARNING OBJECTIVES

After completing this activity, the participant will demonstrate the ability to:

- Describe the epidemiology of HIV infection in the older population
- Summarize treatment outcomes in older persons infected with HIV
- Discuss the issues of multimorbidity and polypharmacy among older persons infected with HIV.

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1.0 hour Physicians

Release Date

June 20, 2012

Expiration Date

June 19, 2014

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THIS ISSUE

Program Directors

Richard Moore, MD, MHS
Professor of Medicine
Director, Moore Clinic for HIV Care
Divisions of Infectious Diseases and Clinical Pharmacology
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Michael Melia, MD
Associate Professor of Medicine
Associate fellowship Program Director
Division of Infectious Diseases
The Johns Hopkins University School of Medicine
Baltimore, Maryland

GUEST AUTHOR OF THE MONTH

Commentary & Reviews:
Kelly A Gebo, MD, MPH
Associate Professor of Medicine, Epidemiology
The Johns Hopkins University School of Medicine
Baltimore, Maryland

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COMMENTARY

The prevalence of HIV in the older population is on the rise. This is related to the development of new HIV infections in the older population and to increased longevity of the population infected with HIV, attributable to successful treatment with antiretroviral therapy (ART). It is estimated that by 2015, 50% of patients infected with HIV will be ≥ 50 years of age.[1] As noted by Althoff and colleagues (reviewed in this issue), HIV in older patients is often diagnosed at lower CD4 cell counts and has concomitant AIDS–defining conditions compared with younger people. This may be partly related to the failure of health care providers to consider HIV as a possible diagnosis in older patients. Health care professionals must become comfortable discussing HIV risk behaviors with patients of all

ages, remain vigilant to the possible diagnosis of HIV in older persons, and test for HIV infection whenever appropriate.

In addition, once HIV has been diagnosed in an older patient, that person must be referred for initiation of ART as soon as possible. As reviewed by Althoff and associates in this issue, several studies have found that older patients infected with HIV have better rates of virologic suppression once they have begun ART, compared with younger patients, but their immune response is less robust than that of their younger counterparts. Older patients should begin ART as soon as possible to improve their long–term clinical outcomes.[2] Since adverse effects and toxicity associated with ART may be more common among older individuals compared with younger patients, health care providers must remain vigilant in monitoring for side effects and laboratory abnormalities once ART has been initiated.

Although CD4 counts and HIV–1 RNA levels are strong predictors of mortality, other biomarkers, including hemoglobin, creatinine, transaminases, and hepatitis B or C coinfection, as well as alcohol use and substance abuse and dependence, have been shown to be associated with an increased risk for mortality (described by Justice and associates in this issue). Therefore, HIV providers must be aware not only of a patient's CD4 count and HIV–1 RNA level, but also of the possible need for treatment of substance use and alcohol dependency, anemia, renal insufficiency, and hepatitis coinfection, to reduce a patient's risk for mortality.

Older patients infected with HIV also have more comorbid conditions than do their younger counterparts (see Haase and coworkers, reviewed in this issue), with many of these conditions increasing in prevalence with advanced age (e.g., hypertension, diabetes, malignancies, cerebrovascular and cardiovascular events). As the incidence of comorbidities rises, older patients with HIV are often treated with multiple medications in addition to ART. Drug–drug interactions are common and must be assessed each time a new medication is added to a patient's treatment regimen. Further, health care providers must be cognizant of contraindicated medications or dosing adjustments that must be made when using boosted protease inhibitors and other common medications such as benzodiazepines, erectile dysfunction drugs, and lipid–lowering agents.

Although premature aging among patients infected with HIV continues to be debatable, new information from the study by Shiels and collaborators (reviewed herein) provides additional insight into the issue by demonstrating that for most malignancies, there is no difference in age at diagnosis between the AIDS and the general populations. Future studies will have to be conducted that adjust appropriately for age to determine whether other comorbid conditions are occurring at younger ages in the setting of HIV infection. At this point, our findings would suggest that age–appropriate screening for cancer should be continued in the older HIV–infected population.

HIV in the older patient is a relatively new field that is growing in importance. Although significant progress has been made in evaluating the response to ART by age–group, numerous issues remain unknown and need to be examined. For example, how do we prioritize the treatment of comorbid disease in persons living with HIV? Should we screen for and treat comorbid conditions in these people more aggressively than we do among those without HIV infection? Increased interest has been generated among investigators and funding agencies in these areas of research, and that will hopefully lead to enhancing our understanding of the optimal management of HIV and concomitant comorbid conditions in the older population within the next five years.

Commentary References

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CD4 COUNT AT INITIAL PRESENTATION FOR HIV CARE, STRATIFIED BY AGE

Althoff KN, Gebo KA, Gange SJ, et al; North American AIDS Cohort Collaboration on Research and Design. **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 Res Ther.* 2010;7:45.

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Althoff and colleagues evaluated CD4 count at initial presentation for HIV care among patients followed in the North American AIDS Cohort Collaboration on Research and Design (NA–ACCORD)—an initiative of 13 US and Canadian clinical cohorts. The results of their study were stratified by age–group (≥ 50 years of age vs. < 50 years of age). The authors assessed all patients who presented for care to any of the cohorts in NA–ACCORD between 1997 and 2007. Patients' initial CD4 count and any AIDS diagnosis within 3 months of presentation for HIV care were the outcomes of interest. Statistical comparisons were made among different demographic and clinical characteristics to investigate trends across time.

This study revealed 3 important findings: First, during the study interval, the proportion of patients who presented for care and were >50 years of age increased from 21% to 27%. Older patients had lower median CD4 counts at presentation compared with younger patients at all time points. Although the median CD4 count increased from 208 cells/mm^3 in 1997 to 266 cells/mm^3 in 2007 in the older age–group, the median CD4 count increased similarly in the younger age–group—from 269 cells/mm^3 in 1997 to 336 cells/mm^3 in 2007. In addition, a greater proportion of older patients (13% in 1997 and 9% in 2007) had an AIDS–defining diagnosis at or within 3 months prior to initial presentation for HIV care compared with younger patients (10% in 1997 and 8% in 2007).

This study demonstrated that between 1997 and 2007, an increasing proportion of patients who initially presented for HIV care in North America were >50 years of age. Although the median CD4 count increased across time for patients in both age–groups (>50 years of age and >50 years of age) and the proportion of patients who presented for initial HIV care with a CD4 count >350 cells/mm^3 increased in both age–groups, the authors suggested that older patients were presenting with advanced disease, as measured by low CD4 counts and a significant proportion having an AIDS diagnosis within 3 months of HIV diagnosis (10%). This implies that older patients are not being tested and linked to care as efficiently as are their younger counterparts, thus reinforcing the importance of HIV testing and improved linkage to care among this population. Health care providers should assess HIV risk behaviors in all patients, regardless of age, testing those at risk and linking HIV–infected individuals to appropriate HIV care as quickly as possible.

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RESPONSE TO HAART, STRATIFIED BY AGE AND REGIMEN CLASS

Althoff KN, Justice AC, Gange SJ, et al; North American AIDS Cohorts Collaboration on Research and Design (NA-ACCORD). **Virologic and immunologic response to HAART, by age and regimen class.** *AIDS.* 2010; 24(16):2469-2479.

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In this second 2010 report, Althoff and coworkers evaluated the short–term (24–month) virologic and immunologic response to highly active antiretroviral therapy (HAART) by age and initial regimen class in patients followed in NA–ACCORD. Virologic response was defined as HIV–1 RNA levels < 500 copies/mL and immunologic response was defined as

a rise of ≥ 100 CD4 cells/mm^3 following initiation of HAART. The results were stratified by age–group (< 50 years of age vs. ≥ 50 years of age) and by regimen type (nonnucleoside reverse transcriptase inhibitor–based regimen vs. boosted protease inhibitor–based regimen).

This study evaluated 12,196 patients, with a mean age of 42 years (range, 18 to 83 years) who initiated HAART between 1998 and 2008. The majority of the subjects were male and white and had a sexual HIV risk factor (men who have sex with men or heterosexual). Half of the patients discontinued their initial HAART regimen within 24 months. Approximately half of those patients stopped ART entirely, while the other half switched their regimen class, suggesting either resistance or potential adverse effects or toxicity. Those who initiated ART at the oldest ages represented the smallest proportion of patients who switched regimen class or discontinued treatment (51% in those 18 to < 30 years of age vs. 44% in those ≥ 60 years of age). The occurrence of HIV–1 RNA suppression increased with increasing age, although this was not statistically significant. In contrast, the prevalence of an immunologic response decreased with increasing age. Specifically, the adjusted hazard odds ratio for increase in CD4 count of ≥ 100 cells was 0.74 in the ≥ 60–year–old age–group, compared with 1.0 in the 18– to < 30–year–old age–group. When analyzed according to regimen type, the interaction of age and initial HAART regimen class was not statistically significant for either virologic or immunologic outcomes.

This study has several important implications. Notably, half of the patients who were evaluated discontinued their HAART regimen within 24 months. Although there may be lower rates of treatment discontinuation with an initial HAART regimen because of the use of newer ART medications that are easier to tolerate, this should remain an important area of study. For patients infected with HIV who require lifelong therapy, optimizing the initial HAART regimen is an important consideration. In addition, although prior studies have demonstrated that older patients experience improved virologic response compared with younger patients, in this study, the differences between older and younger patients were not significant. However, the results of this study were similar to those of other studies that have demonstrated decreased immune recovery in older patients. Interestingly, the authors found no benefit to either regimen type by age–group for immune recovery, suggesting that either regimen type may be equally as effective in older patients. Of note, this study did not evaluate the impact of toxicity and non–AIDS–related comorbidities on virologic and immunologic outcomes. Future studies are warranted to examine the reasons for discontinuation of an initial HAART regimen. An important take–away message from this study is that initiating ART at higher CD4 counts in older persons may improve their long–term immunologic and clinical outcomes, since these patients appear less likely to be able to reconstitute their immune systems once ART has been initiated.

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BIOMARKERS BEYOND CD4 COUNT AND VIRAL LOAD FOR PREDICTING MORTALITY IN HIV–INFECTED PERSONS

Justice AC, McGinnis KA, Skanderson M, et al; VACS Project Team. **Towards a combined prognostic index for survival in HIV infection: the role of 'non–HIV' biomarkers.** *HIV Med.* 2010;11(2):143-151.

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This study by Justice and coworkers was designed to develop and validate an index for predicting mortality in patients infected with HIV using both classic HIV markers (AIDS–defining illnesses, CD4 count, and HIV–1 RNA level) and "non–HIV markers." The non–HIV markers that were evaluated in this study included hemoglobin, transaminases, platelets, creatinine, hepatitis B and C serologies, substance abuse or dependence (alcohol or drug), and age. The overall study outcome was all–cause mortality. The authors used discrimination statistics for each biomarker group alone and in combination in the development and validation of the model. This study was performed in the Veterans Aging Cohort Study (VACS)—a sample of > 13,500 veterans initiating combination ART within the Veterans Affairs Healthcare System.

Close to 10,000 patients had complete data—the majority were male (98%) and black (51%). The median age of the study population was 45 years. More than one–third of subjects had CD4 counts < 200 cells/μL, and 18% had HIV–1 RNA levels > 10,000 copies/ml. Nearly one–third of patients had a diagnosis of alcohol or drug use/dependence. During the study interval, 2566 patients died.

Although highly associated with death from HIV disease progression, CD4 cell count, HIV–1 RNA level, and AIDS–defining conditions failed to capture all of the important effects of HIV on mortality. After adjusting for CD4 count and viral load, several biomarkers, particularly anemia (hemoglobin < 12 g/dL), Fibrosis Index (FIB–4) > 3.25, estimated glomerular filtration rate (eGFR) < 30 mL/min, and hepatitis virus infection, were strongly associated with death when analyzed as a group and when analyzed with CD4 counts and HIV–1 RNA levels in a combined model of HIV and non–HIV biomarkers.

The authors identified a number of important, potentially modifiable factors beyond CD4 count and HIV–1 RNA levels that were highly correlated with death in veterans infected with HIV. Although this analysis focused on veterans, the results of the study have now been validated in other populations in Europe and North America. This model currently predicts mortality in patients infected with HIV, as well as two established prognostic indices—the Acute Physiology and Chronic Health Evaluation (APACHE) III and the Charlson Comorbidity Index—in intensive care unit (ICU) patients. The significance of this model is its ability to identify patients at high risk for an adverse event and then modify such important contributing factors as alcohol and tobacco use, hepatitis C virus therapy, treatment of anemia, and renal insufficiency, to reduce a patient's risk for death. This model has since been shown to be associated with other adverse events, including ICUuse, hospitalization, and HIV disease progression within the Veterans Affairs Healthcare System. This suggests that this combination of clinical factors, while not exhaustive, significantly improves the prediction of adverse outcomes among persons infected with HIV.

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AGE AT CANCER DIAGNOSIS AMONG INDIVIDUALS WITH AIDS

Shiels MS, Pfeiffer RM, Engels EA. **Age at cancer diagnosis among persons with AIDS in the United States.** *Ann Intern Med.* 2011;153(7):452-460.

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This study by Shiels and associates was designed to compare age at diagnosis of non—AIDS–defining malignances in both the AIDS and the general populations, after adjustment for differences in age and other demographic characteristics. The authors conducted a registry linkage study of 15 HIV/AIDS and cancer registry databases in the

United States. They examined 212,055 persons with AIDS enrolled in the US HIV/AIDS Cancer Match Study between 1996 and 2007 and compared age–at–diagnosis distributions for various types of cancer in both the AIDS and the general populations, after adjustment for other demographic factors.

In this study, the proportion of time contributed by older persons (≥ 65 years of age) was far smaller in the AIDS population compared with the general population (1.5% vs. 12.5%, respectively). The most common cancer diagnoses were lung cancer (605 cases), anal cancer (282 cases), and Hodgkin's lymphoma (226 cases). The age at diagnosis for most cancer types was approximately 20 years younger among persons with AIDS compared with those in the general population; however, after adjustment for differences in the populations at risk, the median age at diagnosis did not differ between the AIDS population and the general population for most types of cancer, including colon (52 vs. 52 years, respectively), breast (44.5 vs. 46 years, respectively), and prostate (58.5 vs. 58 years, respectively). For two types of cancer, lung (50 vs. 54 years, respectively) and anal (42 vs. 45 years, respectively), age at diagnosis was younger in the AIDS population compared with the general population, whereas the median age at diagnosis for Hodgkin's lymphoma was older in AIDS patients compared with the general population (42 vs. 40 years, respectively).

This study refutes the findings of a number of earlier studies[1-7] that suggested malignancies developed at an earlier age in patients with HIV compared with the general population. The authors have used age adjustment techniques to demonstrate that age at diagnosis for most malignancies does not differ between those with and without AIDS. This has implications for other studies of comorbid disease, as many of those investigations did not use the same types of age adjustment. The authors noted a younger–than–expected age at diagnosis for lung and anal cancer among those with AIDS. This could be related to higher–risk behaviors in the AIDS population, such as smoking and human papillomavirus infection from anal intercourse; however, these data were not collected as part of the registry data. Future studies are warranted to explore whether this reflects the acceleration of carcinogenesis by HIV or potentially earlier exposure to cancer risk factors. For the moment, this study suggests that current cancer screening guidelines should be followed and that older patients should continue to undergo routine evaluation for cancer with mammograms and colonoscopy at age–appropriate intervals.

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MULTIMORBIDITY AND POLYPHARMACY IN HIV-INFECTED PERSONS

Haase B, Ledergerber B, Furrer H, et al; Swiss HIV Cohort Study **Morbidity and aging in HIV-infected persons: the Swiss HIV Cohort Study.** *Clin Infect Dis.* 2011;53(11):1130-1139.

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Haase and colleagues examined the influence of aging on the epidemiology of non–AIDS diseases in the Swiss HIV Cohort Study between 2008 and 2010. The authors abstracted data from all patients >16 years of age followed at seven sites during this study interval to assess for the presence of numerous comorbid conditions, including osteoporosis, diabetes, malignancy, hypertension, hepatitis, lipoatrophy, and cardiovascular disease. The investigators also abstracted data on non–HIV medications taken by these patients during this time period. They conducted multivariate modeling to assess for associations of comorbid condition or use of non–HIV medication with age.

The authors evaluated 8444 patients who had nearly 41,000 visits during the study interval. Although the median age of the cohort was 45 years, 26% of the participants were 50 to 64 years of age and 5% were ≥ 65 years of age. Overall, 2% of the patients died, with the most common reasons for death including malignancies (23%), infectious diseases (15%), and cardiovascular events (12%). A total of 994 incident non–AIDS clinical events were reported during the study period, which outnumbered AIDS events. Five percent of participants 50 to 64 years of age and 5% of those ≥ 65 years of age had ≥ 4 comorbidities. The most common comorbid conditions were hypertension (56%), hepatitis C coinfection (23%), depression (15%), fat accumulation (18%), and fat loss (17%). Other than depression, all of these conditions were more common with increasing age. Among the 115 non—AIDS–related malignancies that were diagnosed, those that occurred most often included liver (13%), lung (10%), prostate (7%), breast (6%), and skin (6%). In multivariate analysis, the hazard ratios for bacterial pneumonia, stroke, myocardial infarction, bone fractures, osteoporosis, diabetes, and non—AIDS–defining malignancies were higher in the 50– to 64–year–old and ≥ 65 years age–groups compared with those < 50 years of age. After adjustment for other important factors, including CD4 cell count, viral load, gender, intravenous drug use, tobacco, and duration of HIV infection, the associations of malignancies with age remained strong.

Of the non–ART medications, utilization of antihypertensive agents was quite high (12% in those < 50 years of age, 36% in those 50 to 64 years of age, and 64% in those ≥ 65 years of age). The next most common category was lipid–lowering agents (13% overall), followed by antidepressants (10%). Not surprisingly, lipid–lowering agents, oral antidiabetic agents, insulin, and antiplatelet drugs were all more commonly used in older patients than in those < 50 years of age.

This study has several important findings. Comorbidity and multimorbidity from non—AIDS–related diseases is an increasing issue among patients infected with HIV, particularly those = 65 years of age. In addition, these conditions require numerous other medications, which can complicate disease management in older patients infected with HIV. Drug–drug interactions, food restrictions, and complicated dosing schedules all render adherence to multiple treatment regimens difficult. As the HIV population continues to age, health care providers must be vigilant in screening and treating concomitant comorbid conditions; however, they must remain attentive to the difficulties involved in adhering to multiple medications and the costs to the patient associated with polypharmacy.

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