Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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HIV and the Older Patient (Last updated January 28, 2016; last reviewed January 28, 2016)

Key Considerations When Caring for Older HIV-Infected Patients Receiving Antiretroviral Therapy (ART)
• Antiretroviral therapy (ART) is recommended for all patients regardless of CD4 T lymphocyte cell count **(AI)**. ART is especially important for older patients because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART. • Adverse drug events from ART and concomitant drugs may occur more frequently in older HIV-infected patients than in younger HIV-infected patients. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older HIV-infected patients should be monitored closely. • Polypharmacy is common in older HIV patients; therefore, there is a greater risk of drug-drug interactions between antiretroviral drugs and concomitant medications. Potential for drug-drug interactions should be assessed regularly, especially when starting or switching ART and concomitant medications. • HIV experts, primary care providers, and other specialists should work together to optimize the medical care of older HIV-infected patients with complex comorbidities. • Early diagnosis of HIV and counseling to prevent secondary transmission of HIV remains an important aspect of the care of the older HIV-infected patient.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Effective antiretroviral therapy (ART) has increased survival in HIV-infected individuals, resulting in an increasing number of older individuals living with HIV infection. In the United States, among persons living with HIV infection at year-end 2013, 42% were age 50 years or older, 6% were age 65 or older, and trends suggest that these proportions will increase steadily.[1] Care of HIV-infected patients increasingly will involve adults 60 to 80 years of age, a population for which data from clinical trials or pharmacokinetic (PK) studies are very limited.

There are several distinct areas of concern regarding the association between age and HIV disease.[2] First, older HIV-infected patients may suffer from aging-related comorbid illnesses that can complicate the management of HIV infection. Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of clinical syndromes generally associated with advanced age. Third, reduced mucosal and immunologic defenses (such as post-menopausal atrophic vaginitis) and changes in risk related-behaviors (e.g., decrease in condom use because of less concern about pregnancy or more high-risk sexual activity with increased use of erectile dysfunction drugs) in older adults could lead to increased risk of acquisition and transmission of HIV.[3,4] Finally, because older adults are generally perceived to be at low risk of HIV infection, screening for this population remains low.

HIV Diagnosis and Prevention in the Older Adult

In older adults, failure to consider a diagnosis of HIV likely contributes to later initiation of ART.[5] The Centers for Disease Control and Prevention (CDC) estimates that in 2013, 37% of adults aged 55 years or older at the time of HIV diagnosis met the case definition for AIDS. The comparable CDC estimates are 18% for adults aged 25 to 34 years and 30% for adults aged 35 to 44 years.[6] In one observational cohort, older patients (defined as those ≥35 years of age) appeared to have lower CD4 T lymphocyte (CD4) cell counts at seroconversion, steeper CD4 count decline over time,[7] and tended to present to care with significantly lower CD4 counts.[8] When individuals >50 years of age present with severe illnesses, AIDS-related opportunistic infections (OIs) need to be considered in the differential diagnosis of the illness.

Although many older individuals engage in risk behaviors associated with acquisition of HIV, they may see

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themselves or be perceived by providers as at low risk of infection and, as a result, they are less likely to be tested for HIV infection than younger persons.[9,10] Despite CDC guidelines recommending HIV testing at least once in individuals aged 13 to 64, and more frequently for those at risk,[11] HIV testing prevalence remains low (<5%) among adults aged 50 to 64, and decreases with increasing age.[12] Clinicians must be attuned to the possibility of HIV infection in older adults, including those older than 64 years of age and especially in those who may engage in high-risk behaviors. Sexual history taking is therefore an important component of general health care for HIV-uninfected older adults, together with risk-reduction counseling, and screening for HIV and sexually transmitted infections (STIs), if indicated.

Impact of Age on HIV Disease Progression

HIV infection presents unique challenges in aging adults and these challenges may be compounded by ART:

- HIV infection itself is thought to induce immune-phenotypic changes akin to accelerated aging,[13] but recent laboratory and clinical data provide a more nuanced view of these changes. Some studies have shown that HIV-infected patients may exhibit chromosomal and immunologic features similar to those induced by aging.[14,15] However, other studies show the immunologic changes to be distinct from age-related changes.[16] In addition, although data on the increased incidence and prevalence of age-associated comorbidities in HIV patients are accumulating,[17,18] the age of diagnosis for myocardial infection and non-AIDS cancers in HIV-infected and HIV-uninfected patients is the same.[18,19]
- Older HIV patients have a greater incidence of complications and co-morbidities than HIV-uninfected adults of similar age, and may exhibit a frailty phenotype—defined clinically as a decrease in muscle mass, weight, physical strength, energy, and physical activity,[20] although the phenotype is still incompletely characterized in the HIV population.

Initiating Antiretroviral Therapy in the Older HIV Patient

ART is recommended for all HIV-infected individuals (**AI**; see Initiation of Antiretroviral Therapy section). Early treatment may be particularly important in older adults in part because of decreased immune recovery and increased risk of serious non-AIDS events in this population. In a modeling study based on data from an observational cohort, the beneficial effects of early ART were projected to be greatest in the oldest age group (patients between ages 45 and 65 years).[21] No data support a preference for any one of the Panel's recommended initial ART regimens (see What to Start) on the basis of patient age. The choice of regimen should instead be informed by a comprehensive review of the patient's other medical conditions and medications. The What to Start section (Table 7) of these guidelines provides guidance on selecting an antiretroviral regimen based on an older patient's characteristics and specific clinical conditions (e.g., kidney disease, elevated risk for cardiovascular disease, osteoporosis). In older patients with reduced renal function, dosage adjustment of nucleoside reverse transcriptase inhibitors (NRTIs) may be necessary (see Appendix Table 7). In addition, ARV regimen selection may be influenced by potential interaction of antiretroviral medications with drugs used concomitantly to manage co-morbidities (see Tables 18-20b). Adults age >50 years should be monitored for ART effectiveness and safety similarly to other HIV-infected populations [see Table 3]; however, in older patients, special attention should be paid to the greater potential for adverse effects of ART on renal, liver, cardiovascular, metabolic, and bone health (see Table 14).

HIV, Aging, and Antiretroviral Therapy

The efficacy, PKs, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically. There is no evidence that the virologic response to ART differs in older and younger patients. In a recent observational study, a higher rate of viral suppression was seen in patients >55 years old than in younger patients.[22] However, ART-associated CD4 cell recovery in older patients is generally slower and lower in magnitude than in younger patients.[8,23-25] This observation suggests that starting ART at a younger age may result in better immunologic response and possibly clinical outcomes.

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Hepatic metabolism and renal elimination are the major routes of drug clearance, including the clearance of ARV drugs. Both liver and kidney functions decrease with age and may result in impaired drug elimination and increased drug exposure.[26] Most clinical trials have included only a small proportion of participants over 50 years of age, and current ARV dosing recommendations are based on PK and pharmacodynamic data derived from participants with normal organ function. Whether drug accumulation in the older patient may lead to greater incidence and severity of adverse effects than seen in younger patients is unknown.

HIV-infected patients with aging-associated comorbidities may require additional pharmacologic interventions that can complicate therapeutic management. In addition to taking medications to manage HIV infection and comorbid conditions, many older HIV-infected patients also are taking medications to relieve discomfort (e.g., pain medications, sedatives) or to manage adverse effects of medications (e.g., anti-emetics). They also may self-medicate with over-the-counter medicines or supplements. In HIV-negative older patients, polypharmacy is a major cause of iatrogenic complications.[27] Some of these complications may be caused by medication errors (by prescribers or patients), medication non-adherence, additive drug toxicities, and drug-drug interactions. Older HIV-infected patients are probably at an even greater risk of polypharmacy-related adverse consequences than younger HIV-infected or similarly aged HIV-uninfected patients. When evaluating any new clinical complaint or laboratory abnormality in HIV-infected patients, especially in older patients, clinicians should always consider the possible role of adverse drug reactions from both ARV drugs and other concomitantly administered medications.

Drug-drug interactions are common with ART and can be easily overlooked by prescribers.[28] The available drug interaction information on ARV agents is derived primarily from PK studies performed in small numbers of relatively young, HIV-uninfected participants with normal organ function (see Tables 18-20b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of the interaction may be greater in older HIV-infected patients than in younger HIV-infected patients.

Nonadherence is the most common cause of treatment failure. Complex dosing requirements, high pill burden, inability to access medications because of cost or availability, limited health literacy including misunderstanding of instructions, depression, and neurocognitive impairment are among the key reasons for nonadherence.[32] Although many of these factors associated with non-adherence may be more prevalent in older patients, some studies have shown that older HIV-infected patients may actually be more adherent to ART than younger patients.[29-31] Clinicians should regularly assess older patients to identify any factors, such as neurocognitive deficits, that may decrease adherence. To facilitate medication adherence, it may be useful to discontinue unnecessary medications, simplify regimens, and recommend evidence-based behavioral approaches including the use of adherence aids such as pillboxes or daily calendars, and support from family members (see Adherence to Antiretroviral Therapy).

Non-AIDS HIV-Related Complications and Other Comorbidities

Among persons treated effectively with ART, as AIDS-related morbidity and mortality have decreased, non-AIDS conditions constitute an increasing proportion of serious illnesses.[33-35] Neurocognitive impairment, already a major health problem in aging adults, may be exacerbated by the effect of HIV infection on the brain.[36] In a prospective observational study, neurocognitive impairment was predictive of lower retention in care among older persons.[37] Neurocognitive impairment probably also affects adherence to therapy. Social isolation and depression are also particularly common among older HIV-infected adults and, in addition to their direct effects on morbidity and mortality, may contribute to poor medication adherence and retention in care.[38,39] Heart disease and cancer are the leading causes of death in older Americans.[40] Similarly, non-AIDS events such as heart disease, liver disease, and cancer have emerged as major causes of morbidity and mortality in HIV-infected patients receiving effective ART. The presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection may add to the disease burden of aging

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HIV-infected adults.[41-43] HIV-specific primary care guidelines have been updated with recommendations for lipid and glucose monitoring, evaluation and management of bone health, and management of kidney disease, and are available for clinicians caring for HIV-infected older patients.[44-48]

Switching, Interrupting, and Discontinuing Antiretroviral Therapy in Older Patients

Given the greater incidence of co-morbidities, non-AIDS complications and frailty among older HIV-infected patients, switching one or more ARVs in an HIV regimen may be necessary to minimize toxicities and drug-drug interactions. For example, expert guidance now recommends bone density monitoring in men aged ≥50 years and postmenopausal women, and suggests switching from tenofovir disoproxil fumarate or boosted protease inhibitors to other ARVs in older patients at high risk for fragility fractures.[45]

Few data exist on the use of ART in severely debilitated patients with chronic, severe, or non-AIDS terminal conditions.[49,50] Withdrawal of ART usually results in rebound viremia and a decline in CD4 cell count. Acute retroviral syndrome after abrupt discontinuation of ART has been reported. In severely debilitated patients, if there are no significant adverse reactions to ART, most clinicians would continue therapy. In cases where ART negatively affects quality of life, the decision to continue therapy should be made together with the patient and/or family members after a discussion on the risks and benefits of continuing or withdrawing ART.

Healthcare Utilization, Cost Sharing, and End-of-Life Issues

Important issues to discuss with aging HIV-infected patients are living wills, advance directives, and long-term care planning, including related financial concerns. Out-of-pocket health care expenses (e.g., copayments, deductibles), loss of employment, and other financial-related factors can cause temporary interruptions in treatment, including ART, which should be avoided whenever possible. The increased life expectancy and the higher prevalence of chronic complications in aging HIV populations can place greater demands upon HIV services.[51] Facilitating a patient's continued access to insurance can minimize treatment interruptions and reduce the need for other services to manage concomitant chronic disorders.

Conclusion

HIV disease can be overlooked in aging adults who tend to present with more advanced disease and experience accelerated CD4 loss. HIV induces immune-phenotypic changes that have been compared to accelerated aging. Effective ART has prolonged the life expectancy of HIV infected patients, increasing the number of patients >50 years of age living with HIV. However, unique challenges in this population include greater incidence of complications and co-morbidities, and some of these complications may be exacerbated or accelerated by long term use of some ARV drugs. Providing comprehensive multidisciplinary medical and psychosocial support to patients and their families (the "Medical Home" concept) is of paramount importance in the aging population. Continued involvement of HIV experts, geriatricians, and other specialists in the care of older HIV-infected patients is warranted.

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