

HIV infection in the elderly

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Abstract: In the US, an estimated 1 million people are infected with HIV, although one-third of this population are unaware of their diagnosis. While HIV infection is commonly thought to affect younger adults, there are an increasing number of patients over 50 years of age living with the condition. UNAIDS and WHO estimate that of the 40 million people living with HIV/AIDS in the world, approximately 2.8 million are 50 years and older. With the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, survival following HIV diagnosis has risen dramatically and HIV infection has evolved from an acute disease process to being managed as a chronic medical condition. As treated HIV-infected patients live longer and the number of new HIV diagnoses in older patients rise, clinicians need to be aware of these trends and become familiar with the management of HIV infection in the older patient. This article is intended for the general clinician, including geriatricians, and will review epidemiologic data and HIV treatment as well as provide a discussion on medical management issues affecting the older HIV-infected patient.

Keywords: HIV, epidemiology, treatment, aging, review

General HIV disease process

Human immunodeficiency virus type 1 (HIV-1) is an enveloped retrovirus belonging to the group of viruses known as lentiviruses. Transmission of HIV occurs when the virus enters the blood stream by direct contact or penetration of mucosal surfaces. Infection of human cells begins with the attachment of HIV to CD4 and other co-receptors such as CCR5 and CXCR4 on the surface of the cell. Once inside the cell, viral RNA is transcribed to DNA by the HIV reverse transcriptase. Viral DNA then integrates into the host cell genome and uses host cell mechanisms to produce viral progeny. HIV specifically targets and infects CD4⁺ cells, which includes T-helper lymphocytes and other mononuclear cells, ultimately leading to the destruction of these important mediators of the immune system.

Acute HIV infection can manifest as a nonspecific viral illness often described as flu- or mono-like symptoms which can include: fever, rash, lymphadenopathy, pharyngitis, myalgias, and malaise. Symptoms commonly persist for approximately 2 weeks, although they may last for several weeks in certain cases, and will resolve even without treatment. Development of HIV antibodies or seroconversion generally occurs between 3 to 6 weeks following initial infection. For the majority of the HIV-infected population, the intermediate period of chronic (or latent) HIV infection that follows the acute HIV syndrome can range from 10 to 15 years. Here, the individual remains generally asymptomatic, given that the immune system is still able to function and keep ongoing HIV replication under relative control. Over time, the continued destruction of CD4 cells by HIV progresses to the late stage of HIV infection known as acquired immunodeficiency syndrome or AIDS. AIDS is defined by a CD4 count <200 cell/mm³, CD4 percent <14%, or the presence of an opportunistic infection or HIV-associated malignancy (CDC 1992). Without HIV treatment, most HIV-infected persons with

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AIDS develop AIDS complications or death within 2–3 years, if not sooner.

Effects of aging and HIV infection on the immune system

The thymus is an important organ involved in the development of the human immune system and serves as the primary location for T lymphocyte maturation. T lymphocytes are genetically diverse, and function as naïve T cells responding to new antigenic exposures or as memory T cells responding to antigens the body has previously been exposed to. In particular, the activation of CD4⁺ T-helper cells triggers an immune response through T cell differentiation and proliferation; activation of B cells resulting in antibody development and secretion; stimulation of other effector cells, such as CD8⁺ cytotoxic T cells and macrophages, through cytokine release; and/or delayed-type hypersensitivity.

As a person ages, involution of the thymus occurs, and resultant thymic volumes are significantly lower in persons 45 years and older as compared to younger persons (Kalayjian et al 2003). Moreover, the production of naïve T cells declines with increasing age and thymic output is only minimal after age 55 (Naylor et al 2005). Increased age is further associated with diminished T cell functionality, reduced memory T cell populations, and fewer numbers of properly functioning CD8⁺ cytotoxic T cells (Effros 2004). These factors may explain why elderly persons are more prone to new infections, demonstrate less than optimal response to immunizations, or manifest anergy to skin tests such as with purified protein derivative (PPD).

In addition, thymic function and production of naïve T cells may be inhibited by HIV infection (Douek et al 1998). Because these changes in the immune system are very similar to aging effects, progression of HIV infection in the elderly may be more pronounced. Not only are CD4 cell counts significantly lower in HIV-infected young and older adults when compared to their age-matched controls, but HIV-infected older subjects have the lowest counts (Kalayjian et al 2003). In both HIV-infected and non-HIV-infected older subjects, the proportion of functional CD8⁺ T cells was lower compared to the younger subjects, but HIV-infected older subjects appeared to be impacted most by having the lowest proportion among the four comparison groups. Since CD8⁺ cytotoxic T cells are important in the containment of HIV replication, reduction in their number and functionality associated with HIV infection and aging, coupled with loss of CD4 cells, may help explain the accelerated progression of HIV infection in older adults. Finally, changes in T-cell receptor expression

as a person ages, such as increased expression of the CCR5 co-receptor, is important in the pathogenesis of HIV infection and could also influence disease progression (Kalayjian et al 2003; Yung and Mo 2003). Thus, HIV infection can compound, or be synergistic with, the effects of aging on the human immune system.

Studies have demonstrated that age is an independent predictor of clinical progression in HIV. In a study evaluating the prognosis of HIV infection in treatment-naïve patients starting on HAART, Egger and colleagues (2002) identified age 50 years and older as an independent prognostic factor affecting clinical progression to AIDS or death. A retrospective case-control study conducted by Butt and colleagues (2001) revealed that age 60 years and older at time of HIV diagnosis was associated with shorter survival periods. Similarly, in their analysis of data from two large published HIV data sets, Babiker and colleagues (2001) determined that increasing age at time of seroconversion was associated with lower survival rates among HIV-infected patients, particularly in the years prior to the use of HAART. Adjusted for general aging effects on mortality, the median survival for those who were infected at ages 25 to 34 years old was 11 years, as compared to 6.6 years and 4.4 years in those who were infected at 55 to 64 years old and 65 years and older, respectively. The investigators also found that for every 10-year increase in age at time of HIV infection, the overall mortality rate increased by 43%. Aside from age at infection, the time since infection was positively correlated with increased mortality in older persons (ages 45 to 55 years old) who had the highest death rate as compared to younger persons less than 45 years old. Rapid progression to AIDS and decreased survival in older HIV-infected patients has also been confirmed in French and Spanish cohorts (Grabar et al 2004; Nogueras et al 2006).

Epidemiology

UNAIDS and WHO estimate that of the 40 million people living with HIV/AIDS in the world, approximately 2.8 million are 50 years and older. Data from industrialized countries and as reported by UNAIDS primarily reflects the HIV epidemic up to the age of 49 years. However, some data in the elderly have been reported. As of June 2006, 8% of HIV cases (12% of these are women) and 12% of AIDS patients were 50 years or older in Canada (Public Health Agency of Canada 2006). Of AIDS cases reported in 2006 in Australia, people over the age of 50 years accounted for 14% of AIDS cases (over 90% men) and 17% of deaths (National Centre in HIV Epidemiology and Clinical Research 2007). As of

2007 in the United Kingdom, 8.5% and 3.8% of HIV cases were diagnosed in men and women over the age of 50 years respectively (HPA Communicable Disease Surveillance Center 2007).

In the US, approximately one million people are infected with HIV, although an estimated one-quarter to one-third does not know of their HIV infection. It is also estimated that about 40,000 new HIV infections occur every year. Of new HIV/AIDS cases reported to the Centers for Disease Control and Prevention (CDC) in 2005, over 15% were in persons 50 years and older while nearly 2% of new diagnoses were in patients over 65 years of age (CDC 2006).

While 50 years of age is not generally used to identify "elderly" patients, this age cut-off is frequently used by the CDC in HIV/AIDS statistics, since this is much older than the average age (~30 years old) of the typical US HIV-infected person. Between 2001 and 2005, the estimated number of AIDS cases by age of diagnosis had risen by nearly 40% in persons 50 years and older (CDC 2006). During the same time period, the number of persons 50 years and older living with AIDS had doubled, and by the end of 2005, this age group represented close to 30% of the total US population living with AIDS.

The CDC HIV/AIDS Surveillance Report reveals other interesting trends among the older HIV population. Survival after HIV/AIDS diagnosis in older patients is reduced: only 60% versus 80% survival in HIV-infected adults aged 25 (CDC 2006). Survival beyond 12 months after an AIDS diagnosis also decreased as age at diagnosis increased among persons at least 35 years old, with the lowest survival rate among those over 65 years old. Between 2001 and 2005, the estimated number of deaths among persons with AIDS increased in those 45 years and older, with a 28% increase in persons 50 years and older and 18% increase in persons 60 years and older.

The rise in overall number of persons 50 years and older newly diagnosed with HIV or living with HIV/AIDS may be a result of late diagnosis or due to the effectiveness of potent therapy currently available to treat HIV infection. These factors are further discussed in the next sections.

HIV risk behaviors

HIV is transmitted through sexual contact (commonly men-who-have-sex-with-men (MSM) or heterosexual), blood contact (eg, intravenous drug use (IDU), needle stick, or blood transfusion), and perinatally from mother-to-child. Risk factors for persons 50 years and older at time of HIV diagnosis have changed. Prior to blood supply screening,

blood transfusion was the primary route of transmission for this age group. Currently, MSM and IDU make up approximately 50% of risk factors associated with HIV infection in the older population. Among MSM in the US, from 2001 to 2004, HIV diagnosis increased in those 45 to 49 years old by 3.1% and by 6.2% in persons 50 to 54 years old (Hall 2007). Nevertheless, heterosexual contact (currently accounting for close to 10% of HIV infection in older adults) is also on the rise, predominately affecting women and minority groups. In older women, more than 50% of HIV infections are reported to be due to heterosexual transmission while IDU is much lower (nearly 15%). Among heterosexually-acquired HIV/AIDS cases reported to the CDC between 1999 and 2004, 19% and 12% were men and women 50 years and older respectively (Espinoza et al 2007). In addition, the estimated annual percentage change in heterosexually-acquired HIV/AIDS cases rose significantly among men 50–59 years old (+4.9%) and women 50–59 years old (+6.8%) and women 60 years and older (+4.1%). Concurrent diagnoses of HIV and AIDS was slightly higher in non-Hispanic White and Hispanics compared to non-Hispanic Blacks. However, this was increased for both genders, regardless of increasing age (Espinoza et al 2007).

Early in the US HIV epidemic, the National AIDS Behavior Survey found that in respondents 50 years and older who reported at least one HIV risk behavior there was a very low rate of condom use (>85% reported never using or had inconsistent use of condoms during sexual activity). In addition, more than 90% of respondents over 50 years old had never had an HIV test performed. In contrast, among the small subset of gay/bisexual men 50 years and older who reported at least one HIV risk behavior, 60% had been tested for HIV, and only 9% reported never using condoms while 52% reported always using condoms during sexual activity (Stall and Catania 1994). This data suggests that older adults who have at least one HIV risk factor are less likely to assume behaviors, such as condom use, that can prevent the transmission of HIV.

In a recent review of HIV risk factors in the elderly, older adults were found to engage in a variety of sexual activities, although older men reportedly were more sexually active than older women. A large majority of older women lacked knowledge of personal risk and/or had not engaged in protection behaviors. Although married older women were more sexually active than unmarried older women, women who had partners and minority women were less likely to use a barrier contraceptive method. Condom use among women appears to decrease with age, perhaps related

to not being concerned about pregnancy or the perception of not being at risk for sexually transmitted diseases (STDs). Some potential barriers to condom use include difficulties in communication between partners, concern for lack of trust, and feelings that the male partner controls condom use (Zablotsky and Kennedy 2003). Other factors which might increase the risk of HIV transmission among older women can include changing sexual relationships due to divorce or death and menopausal changes in vaginal mucosa increasing the likelihood for trauma and STDs (Shah and Mildvan 2006). Although drugs used to treat erectile dysfunction in older men have not been shown to result in increased HIV transmission in one study, this remains a possibility (Karlovsky et al 2004; Shah and Mildvan 2006).

An increased number of newly reported infections in the older adult may be due to late HIV testing. The majority of cases are not acute infection, but rather chronic, long standing HIV infection. Factors associated with late or missed diagnosis of HIV infection in older people include: routine HIV screening being uncommon in this age group; poor awareness of HIV risk factors (including safe sex practices); failure of health care providers to consider HIV infection in this patient population; and confusion about HIV-specific or opportunistic infection (OI) symptoms with symptoms of other diseases frequently associated with older age (eg, Alzheimer's, dementia) (CDC 1998; Mack and Ory 2003; Grabar et al 2006). Thus, HIV should be considered in sexually active older persons, even if they report being monogamous.

Currently, complete sexual histories may not be routinely obtained from older patients by practitioners as a result of discomfort regarding their own sexuality, the sexual orientation of the patient, or the lack of recognition that continued sexual activity is important in overall wellness of patients. In addition, older patients may not be comfortable with disclosing information that they feel they should be discrete about.

HIV testing

HIV testing in the older adult usually includes an enzyme immunoassay (EIA) screening test to detect HIV antibodies followed by a confirmatory test such as a Western blot or immunofluorescence assay (IFA) if the screening test is positive. Rapid tests, utilizing blood samples or oral secretions, can yield results in as little as 30 minutes and can be performed in the clinic or office with minimal equipment or training. Positive rapid test results should still be confirmed with a confirmatory test. HIV viral load tests (which detect HIV RNA in blood plasma) are not usually recommended for the diagnosis of HIV infection because of lower specificity

and therefore higher chance for false positive results, although the test may be useful in detecting acute HIV infection in the right clinical context when seroconversion has not yet occurred.

In a study of hospitalized patients who were 60 years and older at time of death and had no history of HIV or AIDS, 6.2% of men and 8.9% of women were found to be HIV-seropositive, and more than 60% of those patients who tested HIV-positive had no documented or identifiable risk factors for HIV (el-Sadr and Gettler 1995). In the CDC 2006 National Health Interview Survey, adults 65 years and older had the lowest HIV testing rates (only 11.4% had ever had an HIV test) compared to other age groups (the highest rate being 53.5% among adults 25 to 34 years old) (CDC 2007). Factors which might hinder older adults from seeking an HIV test include misconceptions about HIV infection and who it affects, denial of risk factors, sense of hopelessness even if HIV-positive status was known, and active drug use (Lekas et al 2005).

The CDC has recently revised their guidelines for routine testing for HIV infection. Written informed consent, as well as pre- and post-test counseling is required in most jurisdictions. Current CDC HIV testing guidelines suggest routine, voluntary HIV screening in all persons age 13–64 yrs old in health care settings, regardless of risk; repeat HIV screening at least annually in persons with known risk factors; and opt-out HIV screening with the opportunity to ask questions and the option to decline testing (Branson et al 2006).

Since many patients over the age of 65 years are sexually active they should be tested at least once. Our group has also recently determined that one time HIV testing is cost-effective in those people over the age of 65, particularly if they are sexually active (Sanders et al in press). It is also important to consider periodic testing in persons with continued risk. If a person is found to be HIV-positive, they should be counseled to notify their sexual partner (or injecting partner, if applicable) and to encourage the partner to be tested for HIV. Requirements for partner notification when HIV infection is diagnosed varies by state law, and in some jurisdictions, health care providers may be able to notify partners regarding possible exposure to HIV even without the HIV-infected person's consent. Once HIV infection has been established, it is important for providers to continually encourage and discuss risk and harm reduction as well as safe sex practices with their patients.

HIV treatment

Antiretroviral (ARV) therapy in HIV treatment is made up of a combination regimen, usually including a minimum of

3 different ARV agents, preferably from at least two different classes. Currently, there are 6 classes of antiretroviral agents available (Table 1): nucleoside reverse transcriptase inhibitors (NRTIs) block the viral RNA to DNA transcription process by substituting in chain-terminating nucleosides (or nucleotides) in the DNA chain; nonnucleoside reverse transcriptase inhibitors (NNRTIs) change the conformation of the reverse transcriptase enzyme, rendering the enzyme dysfunctional; protease inhibitors (PIs) inhibit the protease enzyme which cleaves viral proteins into functional components prior to packaging into new HIV particles; fusion inhibitors which block the fusion of HIV with the host cell at the initial point of contact preventing HIV infection; entry inhibitors which block the entry of HIV into the host cell by blocking the cell-surface co-receptor CCR5; and integrase inhibitors prevent the integration of the viral DNA into the host genome. At this

time, available data regarding fusion, entry, and integrase inhibitors have reserved usage of these agents to “salvage therapy”, where HIV-infected patients have limited treatment options available due to significant viral resistance.

Combination therapy for HIV infection is required as the virus can develop resistance quickly to one agent if given as monotherapy. HIV replicates at high levels producing billions of copies per day. Since the HIV reverse transcriptase does not necessarily produce copies that are completely the same as the parent strain, mutations are created, some of which can result in ARV drug resistance. In the presence of less potent ARV therapy, viral replication continues unabated in the presence of ARV drugs, allowing viral strains containing drug-associated mutations to outcompete parent strains without these mutations. With combination regimens, it takes the virus much longer to develop resistance to the entire regimen, if at all.

Table 1 Antiretroviral agents for treatment of HIV infection

Drug class	Available agents generic (common abbreviation) – alphabetic order
Nucleoside reverse transcriptase inhibitor (NRTI)	Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Tenofovir (TDF) Zidovudine (AZT or ZVD)
Nonnucleoside reverse transcriptase inhibitor (NNRTI)	Delavirdine (DLV) Efavirenz (EFV) Etravirine (ETR) Nevirapine (NVP)
Protease inhibitor (PI)	Atazanavir (ATV) Darunavir (DRV) Fosamprenavir (FPV) Indinavir (IDV) Nelfinavir (NFV) Ritonavir (RTV) Saquinavir (SQV) Tipranavir (TPV)
Fusion inhibitor	Enfuvirtide (T-20)
Entry inhibitor	Maraviroc (MVC; Selzentry™; Pfizer Inc., New York, NY, USA)
Integrase inhibitor	Raltegravir (RAL; Isentress™; Merck and Co., Inc., Whitehouse Station, NJ, USA)
Combination agents – NRTIs	
Lamivudine/Zidovudine (Combivir®; GlaxoSmithKline, Research Triangle Park, NC, USA)	
Abacavir/Lamivudine (Epzicom®; GlaxoSmithKline, Research Triangle Park, NC, USA)	
Tenofovir/Emtricitabine (Truvada®; Gilead Sciences, Inc., Foster City, CA, USA)	
Abacavir/ Lamivudine/Zidovudine (Trizivir®; GlaxoSmithKline, Research Triangle Park, NC, USA)	
Combination agents – NNRTI + 2 NRTIs	
Efavirenz/Emtricitabine/Tenofovir (Atripla®; Bristol-Myers Squibb and Gilead Sciences, LLC, Foster City, CA, USA)	
Combination agents – PIs	
Lopinavir/Ritonavir (common abbreviation: LPV/r) (Kaletra®; Abbott Laboratories, North Chicago, IL, USA)	

Treatment guidelines are available for the management of ARV therapy naïve patients from the US Department of Human and Health Services (DHHS 2008) and the International AIDS Society-USA (IAS-USA) collaborative (Hammer et al 2006) (Table 2), as well as other expert panels from Europe and Australia. Based on evidence from clinical trials and expert opinion, current treatment guidelines have established preferred recommended regimens that include 1 NNRTI + 2 NRTIs or 1 PI + 2 NRTIs. Alternate regimens are also provided in the guidelines for select cases where certain ARV drug classes are contraindicated because of drug interactions, ARV resistance, or severe intolerance to preferred regimens.

The decision to start ARV treatment requires the assessment of several factors including medical necessity, psychological readiness, sociologic stability, and cultural factors. Guidelines have been established as to when ARV treatment should be initiated based on the CD4 count. In general, ARV treatment should be recommended to anyone with an AIDS-defining illness, HIV-associated nephropathy, or a CD4 count <350 cells/mm³ regardless of viral load level. In those with a CD4 count >350 cells/mm³, ARV treatment can be considered based on an assessment of potential risks (eg, drug toxicities) and benefits (eg, slow down disease progression) of therapy.

Because of the development of ARV resistance, poor medication adherence, and medication toxicities, antiretroviral regimens do fail. In treatment-experienced patients, other combination ARV regimens to which their viral strain is not resistant as determined by resistance testing are then prescribed. When viral resistance is present, it is important to utilize at least 2 new active antiretrovirals, since the addition of a single active antiretroviral to a failing regimen can quickly result in viral resistance to the newly added agent. Ultimately, multi-drug resistance limits treatment options significantly. Although the current US DHHS (2008) guidelines address management of drug-resistant HIV in treatment-experienced patients, the guidelines panel acknowledges that there is no consensus on specific treatment strategies and that treatment of these patients are often complex. Therefore, HIV treatment of such patients is usually undertaken by experienced HIV practitioners based on emerging data and clinical HIV expertise and is still evolving.

Whether on or off antiretroviral therapy, as CD4 cell counts decline, patients become more prone to opportunistic infections such as Pneumocystis pneumonia (PCP) and malignancies such as non-Hodgkin's lymphoma. Opportunistic infections (OI) in HIV/AIDS account for significant morbidity and mortality in this patient population. Although

Table 2 Preferred initial treatment regimens recommended for HIV-treatment-naïve adult patients based on adult HIV treatment guidelines from US DHHS^a and IAS-USA^b

Preferred base	US DHHS	IAS-USA
NNRTI-Based	Efavirenz	Efavirenz OR Nevirapine
	PLUS	PLUS
	Tenofovir/Emtricitabine OR	Tenofovir/Emtricitabine OR
	Abacavir/Lamivudine	Zidovudine/Lamivudine OR Abacavir/Lamivudine
PI-Based, Ritonavir boosted	Lopinavir/Ritonavir OR	Lopinavir/Ritonavir OR
	Atazanavir/Ritonavir OR	Atazanavir/Ritonavir OR
	Fosamprenavir/Ritonavir	Fosamprenavir/Ritonavir
	PLUS	PLUS
	Tenofovir/Emtricitabine OR	Tenofovir/Emtricitabine OR
	Abacavir/Lamivudine	Zidovudine/Lamivudine OR Abacavir/Lamivudine

Abbreviations: DHHS, Department of Health and Human Services; IAS, International AIDS Society; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

^aDepartment of Health and Human Services: Panel on Antiretroviral Guidelines for Adults and Adolescents 2008; ^bHammer et al 2006.

antiretroviral therapy has significantly reduced the incidence of OIs and improved survival in HIV infection, just receiving ARV therapy does not preclude the need for OI prophylaxis in patients with continued severe immunosuppression (eg, CD4 count $<200/\text{mm}^3$). Even without ARV therapy, OI prophylaxis can delay presentation of first AIDS-related illness. Patients who develop an OI and have continued immunosuppression below a CD4 count of $200/\text{mm}^3$ after successful treatment still require secondary prophylaxis to prevent recurrence. In those patients in whom ARV treatment has resulted in significant increases in CD4 count above $200/\text{mm}^3$, most OI prophylaxis can be safely discontinued in the majority of patients. Guidelines jointly developed by the US Public Health Service and the Infectious Diseases Society of America are available to assist with identifying when certain OI prophylaxis are indicated, based primarily on CD4 cell count and are summarized in Table 3a and Table 3b (CDC 2002).

HIV treatment in older patients

There are no specific treatment guidelines currently available that focus on management in the older HIV-infected adult. Additionally, there is limited information on the efficacy and safety of selected antiretroviral regimens for older patients. Even with the initiation of antiretroviral therapy,

CD4 cell recovery may be limited in elderly HIV-infected patients. In one study of 3,015 HIV-infected patients, of whom 13% were 50 years and older, the mean CD4 cell counts rose significantly within the first six months of ARV therapy; however, mean CD4 cell count increases were significantly higher in younger patients as compared to older patients when stratified by baseline HIV viral load and CD4 cell counts (Grabar et al 2004). Prior to this study, Manfredi and Chiodo (2000) had demonstrated similar results where patients 55 years and older showed a significantly blunted CD4 cell count response compared to the response seen in patients 35 years and younger. A more recent study showed that initial CD4 cell count response in older patients was slower during the initial phase of HAART therapy, but after 3 years of ARV therapy, the CD4 cell counts were not significantly different from that of younger patients (Silverberg et al 2007).

Limited CD4 cell recovery in elderly HIV-infected patients may be due to age-associated decrease in thymic function and therefore slower response (Douek et al 1998), or possibly as a result of having lower CD4 cell counts at baseline (Grabar et al 2004; Nogueras et al 2006). In contrast, there are some studies suggesting that CD4 cell count rises and virologic responses are not dissimilar between older and younger HIV-infected patients (Wellons et al 2002; Tumbarello et al 2004).

Table 3a Recommendations for primary prophylaxis of opportunistic infections in HIV-infected individuals based on CD4 cell count (CDC 2002)

CD4 cell count (cells/mm ³)	Opportunistic infection	Recommended primary prophylactic therapy	When primary prophylaxis can be discontinued
<200	Pneumocystis pneumonia (PCP)	DOC: TMP/SMX Alternatives: • Dapsone • Dapsone + Pyrimethamine (+ Leucovorin) • Pentamidine, aerosolized • Atovaquone	CD4 > 200 cells/mm ³ for at least 3 consecutive months
<100	Toxoplasmosis ^a	DOC: TMP/SMX Alternatives: • Dapsone + Pyrimethamine (+ Leucovorin) • Atovaquone (+/- Pyrimethamine, + Leucovorin)	CD4 > 200 cells/mm ³ for at least 3 consecutive months
<50	Mycobacterium avium complex (MAC)	DOC: Azithromycin or Clarithromycin Alternatives: • Rifabutin • Azithromycin + Rifabutin	CD4 > 100 cells/mm ³ for at least 3 consecutive months

Abbreviations: DOC, drug of choice; TMP/SMX, trimethoprim/sulfamethoxazole.

Notes: ^aPrimary prophylaxis for toxoplasmosis is indicated when CD4 cell count is less than 100 cells/mm³ and patient is toxoplasmosis immunoglobulin G (IgG) antibody positive.

Table 3b Opportunistic infections for which secondary prophylaxis is recommended (CDC 2002)

Opportunistic infection	Recommended secondary prophylactic therapy	When secondary prophylaxis can be discontinued
Pneumocystis pneumonia (PCP)	DOC: TMP/SMX Alternatives: • Dapsone • Dapsone + Pyrimethamine (+ Leucovorin) • Pentamidine, aerosolized • Atovaquone	CD4 >200 cells/mm ³ for at least 3 consecutive months
Toxoplasmosis	DOC: Sulfadiazine + Pyrimethamine + Leucovorin Alternatives: • Clindamycin + Pyrimethamine + Leucovorin • Atovaquone + Pyrimethamine + Leucovorin	CD4 >200 cells/mm ³ for at least 6 consecutive months, completed initial therapy, and asymptomatic
Disseminated Mycobacterium avium complex (MAC)	DOC: Clarithromycin + Ethambutol (± Rifabutin) Alternatives: • Azithromycin + Ethambutol (± Rifabutin)	CD4 > 100 cells/mm ³ for at least 6 consecutive months, completed 12 months of treatment, and asymptomatic
Cytomegalovirus (CMV) infection	DOC: Ganciclovir Alternatives: • Valganciclovir • Foscarnet • Cidofovir	CD4 > 100–150 cells/mm ³ for at least 6 consecutive months and no active disease
Cryptococcosis	DOC: Fluconazole Alternatives: • Itraconazole	CD4 > 100–200 cells/mm ³ for at least 6 consecutive months, complete initial treatment, and asymptomatic

In yet other studies, older patients tended to achieve better virologic control compared to younger patients, possibly due to better medication adherence (Paredes et al 2000; Grabar et al 2004; Silverberg et al 2007).

Whether the HIV-infected elderly are at higher risk for adverse side effects from antiretroviral therapy is less well documented. Medication side effects in general tend to be higher in older patients (Bowman et al 1996), and may be related to age-associated declines in hepatic and renal function. Hepatic mass, blood flow, and metabolism (via Cytochrome P450 enzyme amount and function) are decreased with age (Sotaniemi et al 1997). In addition, aging-related decrease in renal mass, blood flow, tubular secretion, and glomerular filtration (Ramsay and Tucker 1981) can lead to drug accumulation and result in drug toxicity. Other factors such as polypharmacy can further contribute to increased adverse events (Bowman et al 1996). HIV can decrease renal function by specifically infecting the kidney

leading to a condition known as HIV-associated nephropathy (HIVAN) (Herman and Klotman 2003). HIVAN is more likely to occur in those who are Black, have AIDS, and are not on ARV treatment (Lucas et al 2004).

Age-related changes in body composition can also influence drug pharmacokinetics by altering drug volume of distribution (Ramsay and Tucker 1981; Bressler and Bahl 2003). Decreases in body weight and in total body water can lead to more concentrated drug levels in blood and tissues, and can result in enhanced drug effects and toxicity. On the other hand, increases in body fat, which acts as a depot for lipid soluble drugs, can result in decreased serum drug concentrations and may initially lower drug effects. With repeated dosing and time, accumulation of lipid-soluble drugs in body fat can lead to toxicity. Slower gastrointestinal absorption rate may lead to delayed onset of drug effects. Drugs that are highly-protein bound may produce

enhanced effects as a person ages and protein concentrations decline. Receptor and drug transporter genotype (eg, P-glycoprotein, P-gp or MDR1) can also profoundly affect drug concentrations and resultant ARV responses (Evans and McLeod 2003). Alteration in P-gp or cytochrome production or function in the elderly could possibly lead to altered responses to drugs (Bressler and Bahl 2003; Kinirons and O'Mahony 2004).

Common and notable adverse effects of ARVs are listed in Table 4 and are also reviewed in detail elsewhere (Carr and Cooper 2000; Manfredi 2002; DHHS 2008). Gastrointestinal side effects, such as nausea and vomiting as well as diarrhea, are common with nearly all of the antiretroviral therapies currently available. Since Efavirenz frequently exerts central nervous system effects, caution is advised when used in elderly patients who have dementia or other underlying psychiatric or cognitive disorder. Tenofovir is associated with renal toxicity and should be used with caution in patients with reduced renal function. Additionally, all ARV agents can potentially cause hepatotoxicity, especially NNRTIs and PIs, and may have increased risk for adverse hepatic effects in patients with underlying liver disease or hepatic insufficiency. To further limit toxicity, all NRTIs (with the exception of Abacavir) must be dose adjusted in renal insufficiency. It must be noted that limited data are available to provide guidance on specific dosage adjustments of other antiretrovirals when used specifically in elderly patients with renal and/or hepatic insufficiency.

Compared to noninfected persons, HIV-infected patients appear to have a higher prevalence of metabolic syndrome (Bonfanti et al 2007). HAART therapy has also been implicated in causing a metabolic syndrome characterized by decreased glucose tolerance and increased insulin resistance, dyslipidemias, elevated blood pressure, and abdominal obesity, conditions which appear to be primarily associated with long-term use of HIV protease inhibitors (Carr et al 1999; Mulligan et al 2000; Palacios and Santos 2007). These drug-induced metabolic changes, along with older age, have been associated with increased risk for cardiovascular disease and myocardial infarction (Friis-Moller et al 2003; Iloeje et al 2005; Friis-Moller et al 2007).

Limited data to date suggests that older HIV-infected patients experience more adverse events (Knobel et al 2001) and are at higher risk for lab abnormalities (Silverberg et al 2007) than younger HIV-infected patients receiving ARV therapy. Drug-related adverse events could also be related to medication nonadherence. Medication adherence issues in HIV-infected elderly will be discussed below.

Drug-drug interaction issues

A number of non-HIV related medications can be affected by, or directly affect, HIV medications through drug-drug interactions, leading to either significant toxicity or decreased efficacy of the target medications. In general, NNRTIs and PIs are metabolized in the liver and can induce or inhibit hepatic Cytochrome P450 enzymes such as CYP 3A4. Therefore, practitioners should keep in mind potential interactions between ARVs and medications that are predominately substrates of 3A4 when prescribing drug therapy. Examples of interacting medications include: Warfarin, calcium channel blockers, azole antifungals, benzodiazepines, and anticonvulsants. Conversely, drugs that strongly induce CYP 3A4 (eg, Rifampin), can significantly lower levels of most NNRTIs and PIs, and thus concurrent administration is contraindicated. Additionally, acid suppressants can alter the absorption of certain ARVs (eg, Atazanavir) and result in subtherapeutic levels of the ARVs and ultimately regimen failure. Table 5 provides a summary of drugs where concomitant administration with ARVs is contraindicated (DHHS 2008). In contrast, the addition of low-dose Ritonavir to another protease inhibitor (a practice commonly referred to as "boosting") provides a favorable pharmacokinetic interaction resulting in increased efficacy of the target protease inhibitor. Current HIV treatment guidelines recommend Ritonavir boosting as part of the protease inhibitor-based therapies for treatment-naïve patients (DHHS 2008; Hammer et al 2006).

Co-morbid disease states

Between 1996 and 2000, rates of hospitalization among HIV-infected patients 50 years and over increased while hospitalization rates for those 18 to 30 years old decreased dramatically (Gebo et al 2005). However, reasons for hospitalizations among HIV-infected patients 50 years and older has also changed since the introduction of HAART, with fewer hospitalizations for OIs, but more hospitalizations related to cerebrovascular and ischemic heart diseases. Additionally, older age was associated with higher rates of hospitalizations for liver-related diseases, pneumonia, and diabetes, and higher odds of death during hospitalization compared to younger ages.

Heart disease, diabetes, and cancers are among the most prevalent chronic medical conditions affecting older adults and account for some of the leading causes of death in the US population age 65 years and older (FIARS 2006). Other conditions such as hypertension, hyperlipidemia, cerebrovascular diseases, and declining renal function also become more prevalent as a person ages. Even among

Table 4 Common and/or important adverse effects associated with currently available antiretroviral therapy (Manfredi 2002; Cooper et al 2007; Isentress PI 2007; Lalezari et al 2007; Nelson et al 2007; Selzentry PI 2007; Steigbigel et al 2007; DHHS 2008; Intelence PI 2008)

Antiretroviral drug class	Antiretroviral agent	Common and/or important adverse effects	Clinical considerations
Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine	<ul style="list-style-type: none"> Nausea, vomiting, headache Anemia (macrocytic), neutropenia 	<ul style="list-style-type: none"> Monitor CBC with differential at minimum every 3 months (more frequent if necessary) Consider EPO for anemia, GCSF for neutropenia
	Didanosine	<ul style="list-style-type: none"> Pancreatitis Peripheral neuropathy 	<ul style="list-style-type: none"> Avoid concomitant use with Stavudine, Hydroxyurea, or Ribavirin Reduce dose when coadministered with Tenofovir Peripheral neuropathy: avoid other neurotoxins, limit EtOH; consider treat with Gabapentin, TCAs, Lamotrigine
	Stavudine	<ul style="list-style-type: none"> Peripheral neuropathy Lipodystrophy (primarily fat wasting) Hyperlipidemia 	<ul style="list-style-type: none"> Check for correct weight-based dosing; consider dose reduction or switch to another agent if symptoms Avoid concomitant use with Didanosine Peripheral neuropathy: avoid other neurotoxins, limit EtOH; consider treat with Gabapentin, TCAs, Lamotrigine
	Lamivudine	<ul style="list-style-type: none"> Generally well tolerated Nausea, headache Severe acute exacerbations of HBV upon drug discontinuation 	<ul style="list-style-type: none"> Closely monitor LFTs in HIV/HBV co-infected patients if drug discontinued
	Abacavir	<ul style="list-style-type: none"> Black Box Warning: Hypersensitivity reaction Nausea, vomiting, diarrhea 	<ul style="list-style-type: none"> Recommend screen for HLA-B*5701 (an MCH class I allele) to determine if patient at risk for hypersensitivity reaction; if positive, do not start Abacavir Hypersensitivity reaction should be suspected if patient presents with 2 or more of the following: fever, rash, GI symptoms^a, constitutional symptoms^b, respiratory symptoms^c If hypersensitivity reaction suspected, stop drug immediately and do not rechallenge as fatal reactions can occur upon re-exposure (includes other products containing Abacavir)
	Tenofovir	<ul style="list-style-type: none"> Nausea, vomiting, diarrhea, flatulence Nephrotoxicity (eg, ↑ SCr, proteinuria, Fanconi's syndrome) Severe acute exacerbations of HBV upon drug discontinuation 	<ul style="list-style-type: none"> Avoid other nephrotoxic drugs Monitor SCr, UA, serum potassium and phosphorus (especially in at-risk patients) Closely monitor LFTs in HIV/HBV co-infected patients if drug discontinued
	Emtricitabine	<ul style="list-style-type: none"> Generally well tolerated Nausea, headache Hyperpigmentation of palms, soles Severe acute exacerbations of HBV upon drug discontinuation 	<ul style="list-style-type: none"> Closely monitor LFTs in HIV/HBV co-infected patients if drug discontinued
	Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine	<ul style="list-style-type: none"> Black Box Warning: Severe, life-threatening, and even fatal hepatotoxicity; skin reactions (including Stevens-Johnson Syndrome) Rash, ↑ LFTs Nausea, vomiting, headache
Delavirdine		<ul style="list-style-type: none"> Rash, ↑ LFTs 	

(Continued)

Table 4 (Continued)

Antiretroviral drug class	Antiretroviral agent	Common and/or important adverse effects	Clinical considerations
Protease inhibitors (PIs)	Efavirenz	<ul style="list-style-type: none"> • CNS symptoms^d (very common, >50%) • Rash, ↑ LFTs • False-positive cannabinoid tests • ↑ lipids (including HDL) 	<ul style="list-style-type: none"> • Efavirenz should be taken on an empty stomach (avoid fatty foods); take before bedtime (or 2–3 hours before bedtime) • CNS symptoms usually resolve (or diminish) after 2–4 weeks of therapy; warn patients to limit risky activities until effects are known
	Etravirine	<ul style="list-style-type: none"> • Rash • Nausea 	<ul style="list-style-type: none"> • Etravirine should be taken following a meal as fasting conditions ↓ absorption by 50% • Etravirine tablets may be dispersed in glass of water if patient unable to swallow whole
	Saquinavir	<ul style="list-style-type: none"> • Headache, fatigue, abdominal pain 	<ul style="list-style-type: none"> • For HIV treatment, Saquinavir should only be used combined with Ritonavir (in order to attain adequate drug levels)
	Indinavir	<ul style="list-style-type: none"> • Hyperbilirubinemia • Nephrolithiasis 	<ul style="list-style-type: none"> • Hyperbilirubinemia is usually a result of ↑ indirect (unconjugated) bilirubin; generally asymptomatic, however discontinue drug if concurrent ↑ LFTs and symptoms • Patients should keep hydrated with at least 1.5–2 liters/day of fluid (noncaffeinated preferred) to decrease likelihood of nephrolithiasis
	Ritonavir	<ul style="list-style-type: none"> • Perioral paresthesia • Taste perversion • Asthenia 	<ul style="list-style-type: none"> • Commonly used in low doses combined with other protease inhibitors as a pharmacokinetic enhancer (termed “boosting”)
	Nelfinavir	<ul style="list-style-type: none"> • Diarrhea (very common, up to 50%) 	<ul style="list-style-type: none"> • Consider preemptive antidiarrheals (eg, Loperamide, Diphenoxylate/Atropine) • Calcium tablets, bulk-forming agents (eg, Psyllium), and pancreatic enzymes have been used anecdotally
	Fosamprenavir	<ul style="list-style-type: none"> • Headache • Nausea, vomiting, diarrhea • Rash (sulfa moiety) 	<ul style="list-style-type: none"> • Use with caution, monitor closely in patients with sulfonamide allergy
	Atazanavir	<ul style="list-style-type: none"> • Hyperbilirubinemia • Nephrolithiasis • PR interval prolongation 	<ul style="list-style-type: none"> • Hyperbilirubinemia is usually a result of ↑ indirect (unconjugated) bilirubin; generally asymptomatic, however discontinue drug if concurrent ↑ LFTs and symptoms • Use caution in patients with underlying cardiac conduction abnormalities or taking other medications that can prolong PR interval
	Lopinavir/Ritonavir	<ul style="list-style-type: none"> • Perioral paresthesia, asthenia • ↑ GGT 	<ul style="list-style-type: none"> • GI intolerance much more likely with once-daily dosing than twice-daily dosing
	Tipranavir	<ul style="list-style-type: none"> • Black Box Warning: Clinical hepatitis and hepatic decompensation (including fatal reactions) • Black Box Warning: Intracranial hemorrhage (both fatal and nonfatal) have been reported, however causal relationship not yet established 	<ul style="list-style-type: none"> • For HIV treatment, Tipranavir should only be used combined with Ritonavir (in order to attain adequate drug levels) • Use contraindicated in patients with Child-Pugh class B or C hepatic insufficiency

Note: All PIs have been associated with GI intolerance (nausea, vomiting, diarrhea), ↑ LFTs, hyperglycemia, hyperlipidemia (especially hypertriglyceridemia), and fat maldistribution; increased bleeding episodes may be seen in patients with hemophilia

(Continued)

Table 4 (Continued)

Antiretroviral drug class	Antiretroviral agent	Common and/or important adverse effects	Clinical considerations
		<ul style="list-style-type: none"> • Rash (sulfa moiety) 	<ul style="list-style-type: none"> • Monitor closely for hepatotoxicity in patients co-infected with HBV and/or HCV • Use with caution in patients at increased risk for bleeding
	Darunavir	<ul style="list-style-type: none"> • Rash (sulfa moiety) • Neutropenia • Nasopharyngitis • Headache 	<ul style="list-style-type: none"> • For HIV treatment, Darunavir should only be used combined with Ritonavir (in order to attain adequate drug levels) • Use with caution, monitor closely in patients with sulfonamide allergy
Fusion inhibitors	Enfuvirtide	<ul style="list-style-type: none"> • Injection site reactions^e (very common, >90–95%) • Bacterial pneumonia • Hypersensitivity reaction uncommon 	<ul style="list-style-type: none"> • Patients should be counseled on sterile and administration techniques; rotate injection sites • Massaging injection area may reduce pain, nodules • Warm compress, analgesics, antihistamines may be used as necessary
Entry inhibitors	Maraviroc	<ul style="list-style-type: none"> • Black Box Warning: Hepatotoxicity with allergic-type reaction (eg, pruritic rash, eosinophilia) have been reported • Diarrhea, nausea, vomiting • Postural hypotension, headache • Fever, respiratory symptoms (eg, cough, infection) 	<ul style="list-style-type: none"> • Monitor LFTs, allergic-type reaction (allergic-type reaction may precede hepatotoxicity)
Integrase inhibitor	Raltegravir	<ul style="list-style-type: none"> • Diarrhea, nausea • Headache • ↑ Creatine kinase 	<ul style="list-style-type: none"> • Cancers commonly associated with severe immunodeficiency were reported in clinical trials, however it is unknown at this time if this is directly related to Raltegravir treatment • Caution in patients already at risk for myopathy or rhabdomyolysis

Abbreviations: FDA, Food and Drug Administration; ↑, increase; ↓, decrease; CBC, complete blood count; EPO, erythropoietin; GCSF, filgrastim; TCA, tricyclic antidepressant; EtOH, alcoholic beverages; SCr, serum creatinine; UA, urinalysis; LFTs, liver function tests; HBV, Hepatitis B virus; HCV, Hepatitis C virus; GGT, Gamma-glutamyl transferase.

Notes: ^aGastrointestinal (GI) symptoms may include nausea, vomiting, diarrhea, abdominal pain; ^bConstitutional symptoms may include generalized malaise, fatigue, body aches, loss of appetite; ^cRespiratory symptoms may include dyspnea, cough, pharyngitis; ^dCentral nervous system (CNS) symptoms may include dizziness, somnolence, insomnia, abnormal dreams (eg, nightmares, vivid dreams), confusion, abnormal thinking or difficulty concentrating, amnesia, agitation, hallucinations, euphoria; ^eInjection site reactions may include pain, erythema, induration, nodules, cysts, pruritis.

HIV-infected patients, a higher percentage of older patients have diabetes, chronic respiratory disorders, hypertension, and hyperlipidemia, as well as other cardiac conditions, such as coronary heart disease and heart failure (Skiest et al 1996; Butt et al 2004; Palacios et al 2006). In one study of HIV-infected persons 55 years and older, 89% had one or more co-morbidities, with an average of 2.4 co-morbid conditions per person (Shah et al 2002). Whether any or all of these co-morbid conditions can exacerbate the natural history of HIV infection in older patients, further compound toxicities from HIV therapy, or affect morbidity and mortality in this patient population remains to be determined.

There is limited evidence-based literature to guide therapy of metabolic complications specifically in HIV-infected

patients although various groups have developed general guidelines to assist the clinician in areas of managing metabolic complications associated with HAART (Schambelan et al 2002) and separate guidelines for addressing dyslipidemia in HIV (Dube et al 2003). A brief review of these recommendations and of current HIV clinical practice is provided for the reader under the section titled “Primary care issues.”

As mentioned earlier, declining CD4 cell counts in HIV infection is associated with increased risk for certain types of malignancy. The CDC’s AIDS case definition includes Kaposi’s sarcoma (KS), lymphomas, such as Burkitt’s lymphoma and non-Hodgkin’s lymphoma (NHL), and invasive cervical carcinoma (CDC 1992). Since the introduction

of HAART, the incidences of KS and NHL among AIDS patients have significantly declined (Clifford et al 2005; Engels et al 2006). Nonetheless, regardless of HAART, there are other non-AIDS defining malignancies found in a greater proportion of HIV-infected patients compared to the general population, including lung, liver, brain, and anal cancers (Dal Maso et al 2003; Clifford et al 2005; Engels and Goedert 2005; Engels et al 2006).

Cancer risk also increases with age in non-HIV-infected persons, but very limited data is available evaluating the impact of HIV infection on cancer risk in older persons and vice versa. Using data from the AIDS-Cancer Registry Match study, Engels (2001) determined risk for KS and lung cancer in AIDS patients stratified by age. In AIDS patients 60 years and older, risk for KS was significantly lower than that among patients 30 to 39 years old. The author noted that this trend was quite different from KS previously seen at a higher rate in non-HIV infected elderly European and Mediterranean men. Conversely, the incidence of lung cancer among AIDS patients increased with age from 0.1 per 1,000 persons-years in the 15 to 29 years old age group to 3.7 per 1,000 persons-years in the 60 years and older age group. Even though this mirrored the increasing incidence of lung cancer with aging in the general population, the overall incidence was still higher in AIDS patients than in the age-matched population.

The same study group also sought to determine effects of HIV infection on the cancer risk profile of AIDS patients 60 years and older. Compared to the general population, elderly AIDS patients had a relative risk of 1.3 for all non-AIDS defining cancers (Biggar et al 2004). In this analysis, elderly AIDS patients had a higher risk for Hodgkin's lymphoma, anal cancer, liver cancer, and multiple myeloma. Additionally, lung and stomach cancer risks were higher in this group. One interesting observation was that prostate cancer was negatively associated with AIDS. The authors speculated that this may be due to reduced screening in the elderly HIV/AIDS population. These data demonstrate that information on cancer risk in elderly HIV-infected persons is still evolving, and until more definitive information becomes available, the clinician should be aware of and continue screening for HIV-associated and age-associated malignancies.

Although many factors are associated with the development of osteopenia and osteoporosis, recent studies have suggested that women with HIV infection are at greater risk for this condition, which can be further accentuated when taking certain ARV regimens (Dolan et al 2004; Pan et al 2006; Anastos et al 2007). HIV-infected older men also manifest decreased bone mineral density compared to uninfected men

(Arnsten et al 2007). Whereas some studies have determined that HIV infection and lower CD4 counts result in earlier onset of menopause (Schoenbaum et al 2005), the effect of HIV infection on women's hormonal levels, menstrual cycles and the relationship with resultant osteoporosis is not clear. HIV infection and increasing age in men are also associated with hypogonadism (Crum-Cianflone et al 2007). A multitude of clinical conditions including sexual dysfunction, fatigue, poor appetite and osteopenia are associated with hypogonadism (Klein et al 2005). Androgen replacement and treatment of erectile dysfunction even in elderly men can result in significant improvements in some of these conditions and in quality of life (Crum et al 2005). Practitioners should keep in mind that in HIV-infected patients treated with protease inhibitors, caution should be used with the concurrent administration of phosphodiesterase enzyme inhibitor medications for erectile dysfunction (eg, sildenafil) due to clinically important drug interactions. Protease inhibitors can inhibit the metabolism of the erectile dysfunction agent, thereby leading to high blood levels and increased risk for side effects such as severe hypotension.

Psychiatric disorders may predispose persons to HIV risk behaviors and ultimately HIV infection. HIV infection itself can also increase the likelihood of active psychiatric disorders, including depression, bipolar disorder and mania, psychosis, and anxiety disorders as well as cognitive decline, dementia, and substance abuse disorders. In their review of the literature on psychiatric co-morbidity in HIV-infected older patients, Skapik and Treisman (2007) revealed that HIV-positive older adults had higher rates of depression and poorer cognitive function compared to HIV-negative older adults. Furthermore, it is postulated that various psychiatric disorders may contribute to the progression of HIV disease through a number of interactions leading to further immunosuppression. When managing psychiatric disorders in HIV-infected patients, the clinician should keep in mind that a number of psychotropics (including, but not limited to selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and tricyclic antidepressants) can have significant interactions with antiretroviral therapy and thus dosing titration is key. In addition, Efavirenz can cause psychiatric and neurologic disturbances and should be used with caution; patients should be counseled regarding its potential effects. A number of review articles summarizing the data and treatment considerations on this topic are currently available and the reader is referred to these references for further information as needed (Hinkin et al 2001; Dolder et al 2004; Skapik and Treisman 2007).

Table 5 Significant drug–drug interactions that may be seen in the elderly where concomitant use is contraindicated^a

Drug Class	Cardiovascular agents	Lipid lowering agents	Anti-microbials	Anti-histamines	Gastrointestinal agents	CNS agents ^b	Herbals	Other
Antiretrovirals: Nonnucleoside reverse transcriptase inhibitors								
Nevirapine	–	–	Rifampin Rifapentine	–	–	–	St. John's Wort	–
Delavirdine	–	Lovastatin Simvastatin	Rifampin Rifapentine Rifabutin	Astemizole Terfenadine	Cisapride H ₂ blockers PPI	Alprazolam Midazolam Triazolam Ergot alkaloids	St. John's Wort	Amprenavir Fosamprenavir Carbamazepine Phenobarbital Phenytoin
Efavirenz	–	–	Rifapentine	Astemizole Terfenadine	Cisapride	Midazolam Triazolam Ergot alkaloids	St. John's Wort	Voriconazole
Etravirine	–	–	Rifampin Rifapentine	–	–	–	St. John's Wort	Unboosted PIs Boosted ATV, FPV,TPV Carbamazepine Phenobarbital Phenytoin
Antiretrovirals: Protease inhibitors								
Saquinavir	–	Lovastatin Simvastatin	Rifampin Rifapentine Rifabutin ^c	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	Fluticasone
Indinavir	Amiodarone	Lovastatin Simvastatin	Rifampin Rifapentine	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	Atazanavir
Ritonavir	Amiodarone Bepidil Flecainide Propafenone Quinidine	Lovastatin Simvastatin	Rifapentine	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	Voriconazole ^d
Nelfinavir	–	Lovastatin Simvastatin	Rifampin Rifapentine	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	–
Fosamprenavir	Bepidil	Lovastatin Simvastatin	Rifampin Rifapentine	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	Delavirdine Fluticasone
Atazanavir	Bepidil	Lovastatin Simvastatin	Rifampin Rifapentine	Astemizole Terfenadine	Cisapride PPI	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	Fluticasone Indinavir Irinotecan

(Continued)

Table 5 (Continued)

Drug Class	Cardiovascular agents	Lipid lowering agents	Anti-microbials	Anti-histamines	Gastrointestinal agents	CNS agents ^b	Herbals	Other
Lopinavir/ Ritonavir	Flecainide Propafenone	Lovastatin Simvastatin	Rifampin Rifapentine	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	Fluticasone
Tipranavir/ Ritonavir	Amiodarone Bepridil Flecainide Propafenone Quinidine	Lovastatin Simvastatin	Rifampin Rifapentine	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	St. John's Wort	Fluticasone
Darunavir/ Ritonavir	–	Lovastatin Simvastatin	Rifampin Rifapentine	Astemizole Terfenadine	Cisapride	Pimozide Midazolam Triazolam Ergot alkaloids	–	Carbamazepine Phenobarbital Phenytoin Fluticasone
Antiretrovirals: Entry inhibitor								
Maraviroc ^{a,e}	–	–	Rifampin Rifapentine	–	–	–	St. John's Wort	–

Abbreviations: PPI, proton pump inhibitors; FDA, Food and Drug Administration; PIs, protease inhibitors; ATV, Atazanavir; FPV, Fosamprenavir; TPV, Tipranavir.

Notes: Drugs listed to the right should not be used with the corresponding antiretroviral drug listed in the left hand column; ^aAdapted from publicly available resource (DHHS 2008); ^bCentral nervous system (CNS) agents includes neuroleptics and psychotropics; Midazolam may be used with caution for procedural sedation, otherwise extended concomitant use is contraindicated; ^cRifabutin may be used with Ritonavir-boosted Saquinavir; ^dConcomitant Voriconazole is contraindicated with Ritonavir doses ≥ 400 mg BID; ^eSelzentry PI 2007.

In advanced immunosuppression, symptoms of opportunistic infections that preferentially infect the central nervous system (eg, cryptococcal meningitis and toxoplasma encephalitis) may be difficult to distinguish from age-related neurologic changes. HIV neurologic syndromes, such as AIDS dementia and progressive multifocal leukoencephalopathy (PML), can also manifest as or aggravate underlying dementia symptoms in the elderly. HIV-associated dementia has been found to have higher prevalence and tends to be more severe in HIV-infected patients age 50 years and older than in younger patients (age 20 to 39 years old) (Valcour et al 2004). In contrast, the Veterans Aging Cohort Five-Site Study did not find depression and alcohol/drug abuse to increase with age – in fact, just the opposite, when comparing HIV-infected patients by age group (Justice et al 2004). What the investigators did find was that HIV-infected patients had higher prevalence of depression and alcohol/drug abuse than age-matched non-HIV-infected patients. Regardless of HIV infection status, memory problems were positively correlated with increased age in this study population. Thus, the presence of both psychiatric disorders and cognitive decline can be a significant morbidity in the aging HIV-infected patient.

Adherence issues

In HIV therapy, medication adherence is a very important determinant for the success or failure of treatment (DHHS 2008). Unlike medication therapy for other disease states, medication nonadherence in HIV also creates multi-drug resistant HIV which further compromises treatment options. Antiretroviral adherence studies indicate that greater than 95% adherence to ARV therapy provides optimal efficacy while limiting viral rebound and development of HIV drug resistance, although at least 80% adherence has been used conventionally in non-HIV medication adherence studies (Bangsberg et al 2000; Paterson et al 2000; Gross et al 2001; Maggiolo et al 2005). To achieve a more than 95% adherence rate, a patient cannot miss more than 1 dose per month of a once daily medication, or no more than 2 missed doses per month for a twice daily medication regimen. While some studies suggest that medication adherence may be improved in the older HIV-infected patient, substance abuse and cognitive dysfunction may contribute to poor adherence (Wutoh et al 2003; Hinkin et al 2004). Other factors that can adversely affect medication adherence in elderly patients, which also overlap with factors affecting medication adherence in HIV-infected

persons, include: complex drug regimens (such as frequent dosing, large quantities of pills, and dietary restrictions) and increasing number of prescription medications; increasing number of prescribers (especially for patients seeing generalists and multiple specialists for various medical conditions); high medication costs; differing health beliefs (such as self-efficacy or belief in powerful others, eg, health care providers, who control a person's well-being); medication side effects (including fear of experiencing side effects); lack of social support and living alone; psychiatric conditions (including depression), and cognitive and physical impairments (Wutoh et al 2003; Hughes 2004; Schlenk et al 2004).

Polypharmacy in the older patient is especially concerning, since this patient population is also more likely to have chronic medical conditions for which multiple medications may be prescribed. The average number of prescriptions filled annually among noninstitutionalized Medicare enrollees 65 years and older increased from 18 prescriptions in 1992 to 32 prescriptions in 2002 (FIARS 2006). Furthermore, the number of prescriptions filled annually in this population ranged from an average of 11 prescriptions in those without any chronic medical conditions to an average of 61 prescriptions in persons with 5 or more chronic conditions. HIV medications will add at a minimum 3 additional medications (1–3 prescriptions per month). If antimicrobials for OI prophylaxis or medications to manage HIV medication side effects are required, then an additional 2–5 medications per month over and above other medications for chronic conditions and HIV treatment may be required.

Assessment of medication adherence or nonadherence is essential in HIV therapy, as this information can be correlated with response to antiretroviral therapy as well as be used to identify areas for intervention and for providing focused patient counseling and support. Of note, health care providers were found to be poor predictors of patient medication adherence, misjudging adherence in 30% to 41% patients in one study (Paterson et al 2000). Thus, it is beneficial to utilize various strategies in determining medication adherence, including reviewing pharmacy refill records and conducting focused patient medication adherence interviews. As opposed to asking closed-ended questions that can be answered by either a “yes” or “no” reply (eg, Did you miss any doses of your HIV medications?), open-ended questions can elicit more specific responses (eg, How many doses of your HIV medications have you missed in the past 2 weeks? In the past month?). In addition, it is equally important to assess reasons for medication nonadherence, such as medication side effects or pill fatigue, so that a patient's issues and concerns are addressed sooner rather

than later. This information could also be used to guide the clinician's next steps in managing HIV regimen failure. Medication adherence tools that can be utilized to improve medication adherence include simplifying antiretroviral therapy, pill boxes, social support, and using cues and incorporating dosing into daily routines (eg, taking medications with meals).

Primary care issues

It is likely that older patients being seen for routine medical care by general internists, geriatricians, or family practitioners may be involved in case finding for HIV infection. Some of those patients will test positive for HIV infection. It is important for generalists to recognize certain signs and symptoms that may be suggestive of ongoing HIV infection. HIV testing in the elderly should be offered and counseling provided. HIV infection should be suspected and worked-up in patients with co-morbid conditions that can indicate an increased risk for HIV infection. Elderly patients who have chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or recent history of STDs should have HIV screening performed, if not already done. If prior negative tests for HIV infection have been recorded, renewed testing should be performed in the event that ongoing risk factors are elicited during the visit. Although reactivation of VZV (herpes zoster or shingles) is relatively common in the older adult, multidermatomal disease or dissemination may be an indication for significant immunosuppression possibly as a result of HIV infection. Reactivation of tuberculosis, recurrent herpes simplex (HSV) infections, gastrointestinal parasitosis, mucocutaneous candida and fungal infections or molluscum contagiosum may also indicate ongoing HIV infection. Abnormalities on physical exam that can point to an HIV diagnosis include facial seborrhea, angular cheilitis, thrush, gingivitis, aphthous ulcers, hairy leukoplakia of tongue (highly indicative), diffuse lymphadenopathy, hepatosplenomegaly, onychomycosis and other dermatophytoses. Laboratory abnormalities such as anemia, leukopenia (especially lymphopenia), thrombocytopenia, and elevated total protein, in the absence of other diagnoses, can also suggest HIV infection.

The approach to newly diagnosed HIV-infected patients requires an evaluation that includes an assessment for ongoing sexual activity, medical co-morbidities, mental health issues, and substance abuse issues; complete hematology and chemistry profiles, CD4 cell count, HIV viral load, HIV resistance testing, and serology for hepatitis viruses, syphilis and other STDs; routine vaccinations (except for live vaccines) and screening for cervical and rectal abnormalities

by examination and pap smears; and other routine cancer screening such as mammography and colonoscopy (Aberg et al 2004). Patients should also be assessed for willingness and ability to adhere to HIV medication regimens, their understanding of HIV infection, and risk and harm reduction education. HIV-infected patients are routinely seen every 3–4 months to assess HIV treatment effectiveness, medication side effects, and ongoing medical or psychosocial concerns. In HIV patients who are doing well, many of these routine visits can be accomplished through their primary care providers. In those elderly patients with a more complicated HIV disease course (eg, ARV treatment failure with drug resistance, ongoing OI) care switches back to an HIV specialist.

It is also likely that the generalist will have to balance HIV care with management of other co-morbid conditions commonly associated with aging such as hypertension, diabetes, and hyperlipidemia. For hypertension, blood pressure goals should follow those of the US National High Blood Pressure Education Program Seventh Report of the Joint National Committee (JNC VII) or similar other national guidelines. Renal function should be monitored in patients on either concomitant diuretics or angiotensin-converting enzyme (ACE) inhibitors and Tenofovir. Because calcium channel blockers are metabolized through the CYP 3A4 enzyme to a significant extent, they should be used with caution and dose titrated accordingly when co-administered with protease inhibitors. An additional recommendation exists for Diltiazem: Diltiazem dose should be decreased by 50% in patients also taking Atazanavir.

Treatment of diabetes in the HIV-infected patient should utilize the same treatment strategies and aim for similar blood glucose and HgbA1C goals as those established by the American Diabetes Association and other similar organizations. As discussed earlier in this review, long-term use of protease inhibitors can lead to insulin resistance and glucose intolerance. Thus, insulin sensitizers such as Metformin and thiazolidiones should be considered for the treatment of diabetes in HIV-infected patients as long as no contraindications exist. Consideration may also be given to switching the antiretroviral regimen from a protease inhibitor-based to a NNRTI-based regimen. If a protease inhibitor is used, or required based on viral resistance, then Atazanavir may be an option, as it is not expected to affect blood glucose levels to a very significant degree when compared to other protease inhibitors. There are no specific contraindicated drug-drug interactions between antidiabetic medications and antiretrovirals, but additional monitoring may be necessary due to

overlapping medication toxicities (eg, thiazolidiones/PI and liver toxicity, Metformin/NNRTIs and lactic acidosis). Providers should also watch for potential drug-drug interactions between thiazolidiones and NNRTIs or protease inhibitors resulting in increased effects of the hypoglycemic agent and adjust dosages of the antidiabetic drug as needed.

Lipid goals in HIV-infected patients with hyperlipidemia should follow the goals set by the National Heart, Lung, and Blood Institute's National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines or similar guidelines. Since lipid lowering agents and antiretrovirals can cause hepatotoxicity, close monitoring of LFTs is advised. Providers should also keep in mind that two particular statin agents, Lovastatin and Simvastatin, are contraindicated when co-administered with a protease inhibitor. Alternative statins with limited to no clinically significant drug interactions with PIs include Fluvastatin, Pravastatin, and low-dose Atorvastatin. Another potent statin option available for the management of hyperlipidemia in HIV-negative patients is Rosuvastatin. Because Rosuvastatin is not metabolized through CYP 3A4, it is not expected to have a significant interaction with antiretroviral therapy such as protease inhibitors. Notably, two small pilot studies have found that Rosuvastatin levels were actually increased 1.5- to nearly 5-fold when co-administered with Lopinavir/Ritonavir (van der Lee et al 2007; Kiser et al 2008). At this time no specific Rosuvastatin dose adjustment recommendations exist for concurrent administration with Lopinavir/Ritonavir or other protease inhibitors, and until additional efficacy and safety information becomes available, caution should be used with this combination in HIV-infected patients on HAART.

End of life issues

End of life care is not necessarily any different in the HIV-infected older person than in a younger person with HIV/AIDS or in the uninfected elderly. HIV-infected elderly patients with advanced HIV disease may not wish to disclose their diagnosis to family members or friends and thus may experience fear of abandonment and isolation. Some caregivers or family members may be concerned about the infectious nature of caring for an HIV-infected person who is dying and limit their contact as a consequence. Financial considerations may result in the decision to forgo taking expensive HIV medications. Some elderly patients may be ill-prepared in coping with the diagnosis, because of late diagnosis and already advanced disease and other serious concomitant co-morbid conditions. In addition to other end of life issues that need to be discussed, providers will need

to have discussions with end-stage elderly patients about continued HIV treatment, OI prophylaxis or treatment, and nutritional support in those with HIV-associated wasting syndrome. Palliative care programs, whether home-based or hospital-based, appear to offer benefit in quality of life domains for end-stage AIDS patients (Harding et al 2005).

Conclusions

The course of the HIV epidemic has dramatically changed over the past three decades largely as a result of growing awareness, implementation of prevention strategies, and the availability of potent antiretroviral therapy, especially in developed countries. However, current epidemiologic data show changes in the demographics of the HIV population. As the HIV population ages and the rate of newly detected infections in the elderly rise, clinicians should be aware of the increasing need to balance HIV care and the management of co-morbid conditions commonly associated with aging. To date, no guidelines are available that specifically address the needs of the elderly HIV-infected patient. Additional research is urgently needed to better understand the impact of aging on the course of HIV infection, to develop and implement effective education and prevention measures, and to determine efficacy and safety of antiretroviral therapy in the older HIV-infected patient.

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